

# **Estonian approach: from biobanking to precision medicine**

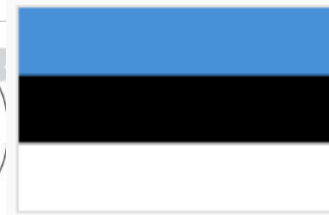
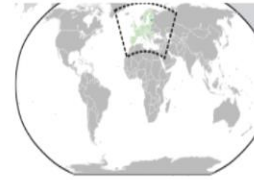
**Andres Metspalu  
Estonian Genome Center  
University of Tartu**

**G2MC 2015 Symposium  
Implementing Genomic Medicine into Practice  
November 6 & 7, 2015  
Singapore**



estonian genome center  
university of tartu

# Republic of Estonia

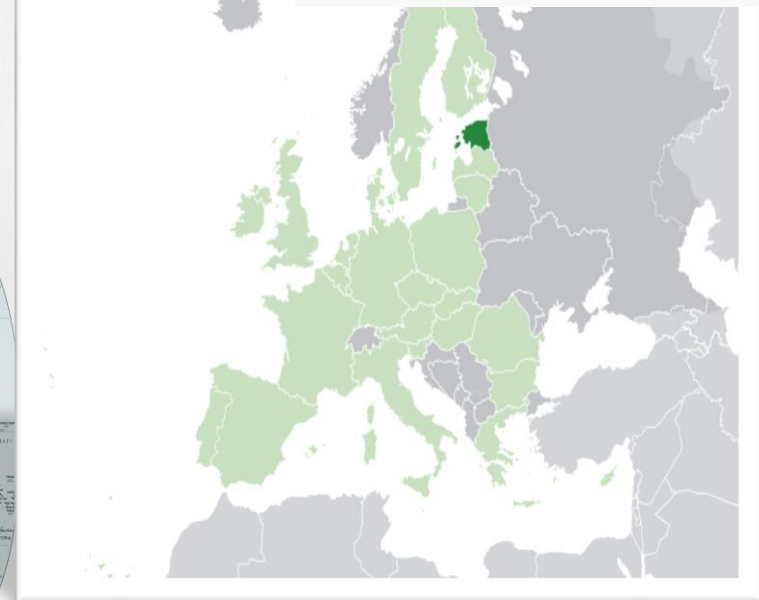


Flag



Coat of arms

Political Map of the World, September 2008



EU & NATO member  
since 2004

Schengen Treaty since  
2007

EUR as our currency  
since 2011

- Population size: ~1.3 million
- Territory: 45 000 km<sup>2</sup>



# Estonian Biobank

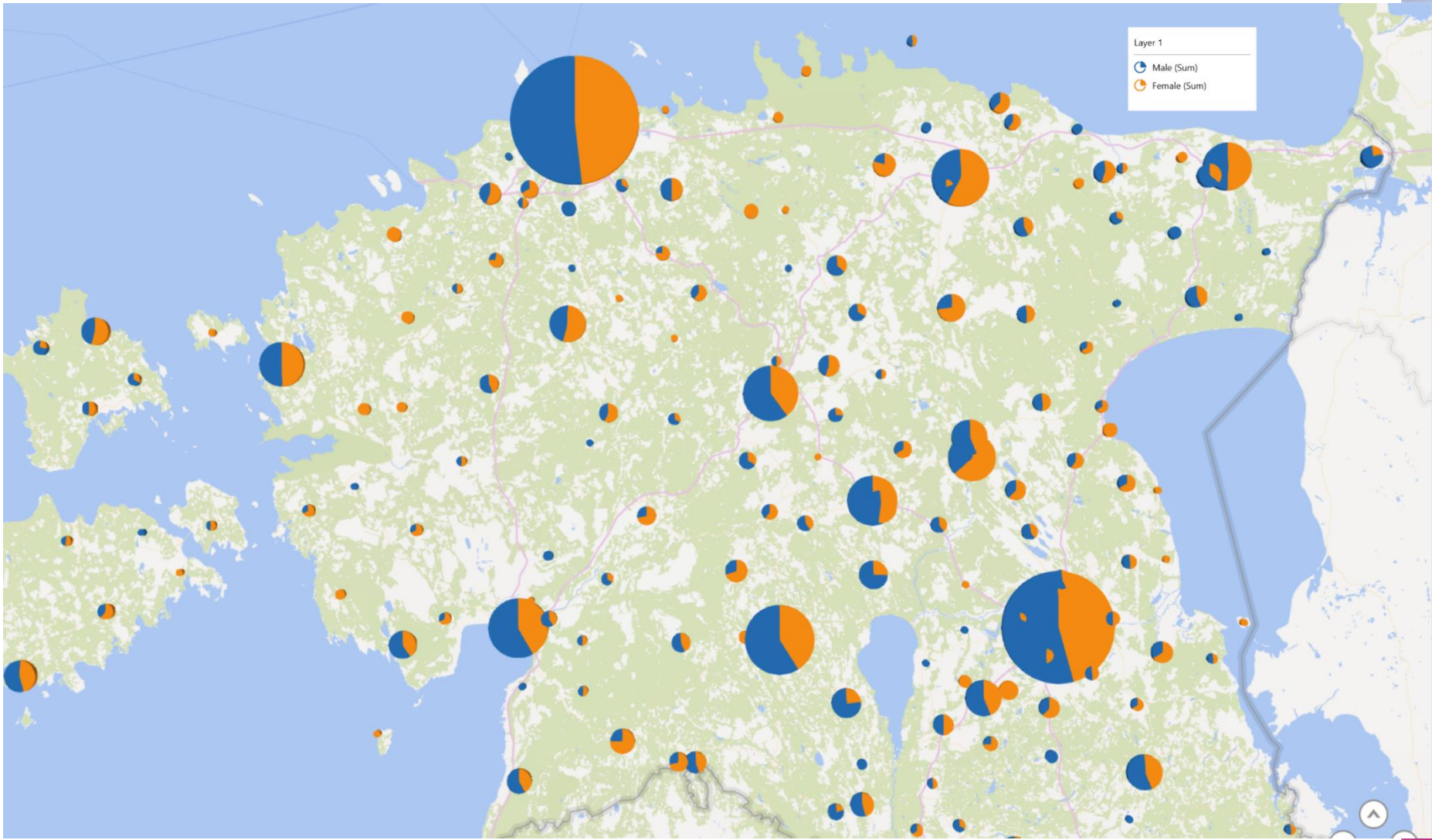
- A prospective, longitudinal, population-based database with health records and biological materials
- 52,000 participants - 5% of the adult population of Estonia
- Individuals are recruited by GPs, physicians in the hospitals and medical personnel in the EGCUT recruitment offices
- Estonian Human Genes Research Act (HGRA)



# WGS project in Estonia

- - samples were selected from the biobank in order to maximize the genetic variation (independent samples, diverse birthplace, estonians, population based)
- - we did the pilot of 50 individuals (Illumina) and 27 individuals (Complete Genomics)
- - sequencing was performed in The Broad Institute, PCR free method was used, 30X
- - ELSI issues are covered by informed consent and HGR Act (biobanking law)
- - using the data in health care will be piloted in 2016-2018. WGS data will be used to impute all array data to the MAF to 0.1%





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# Sample size

2304 samples submitted



4 samples had <1.2 ug input

2300 samples processed



7 samples failed in library preparation 3 times  
(likely sample issue)

2293 samples completed (BAMs delivered)



9 samples with a contamination rate > 10%

2284 samples jointly called

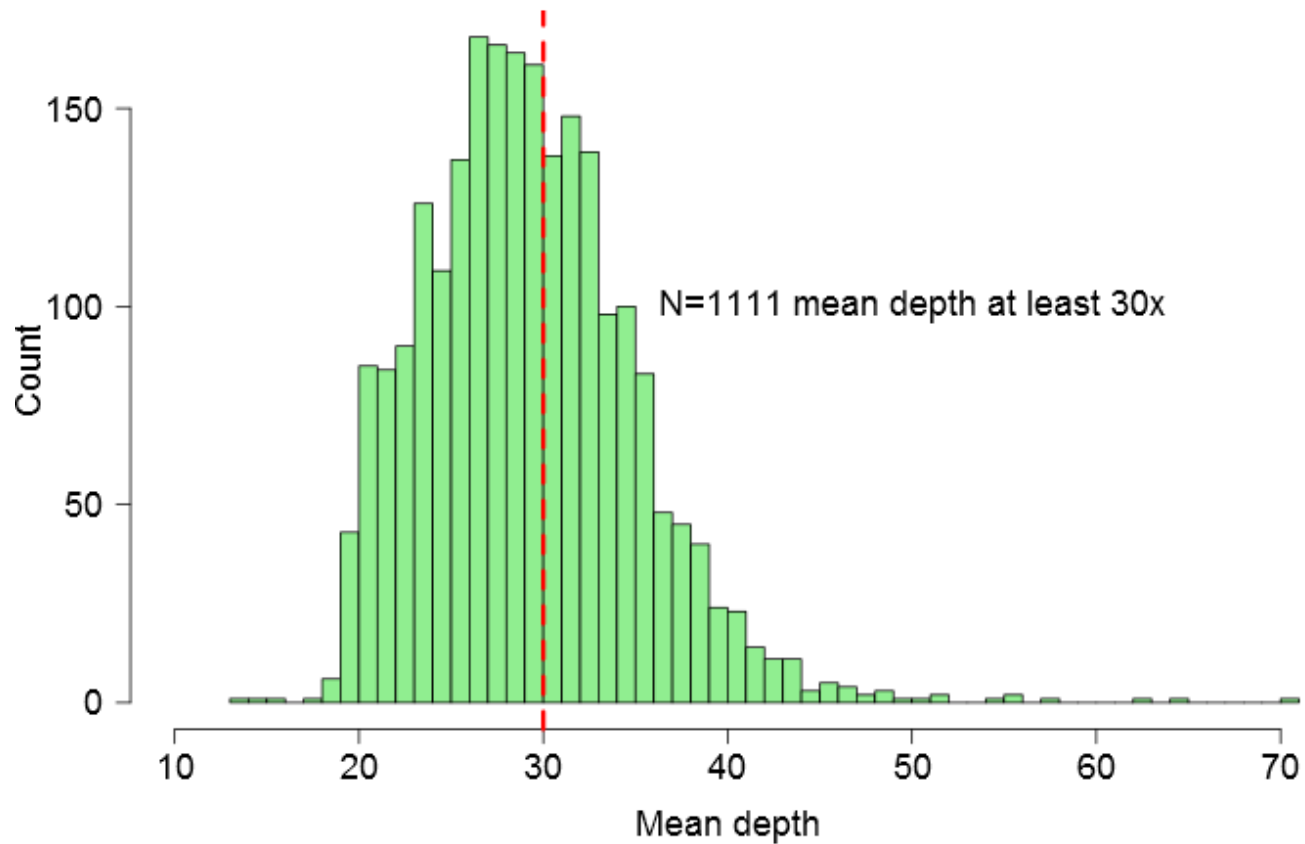


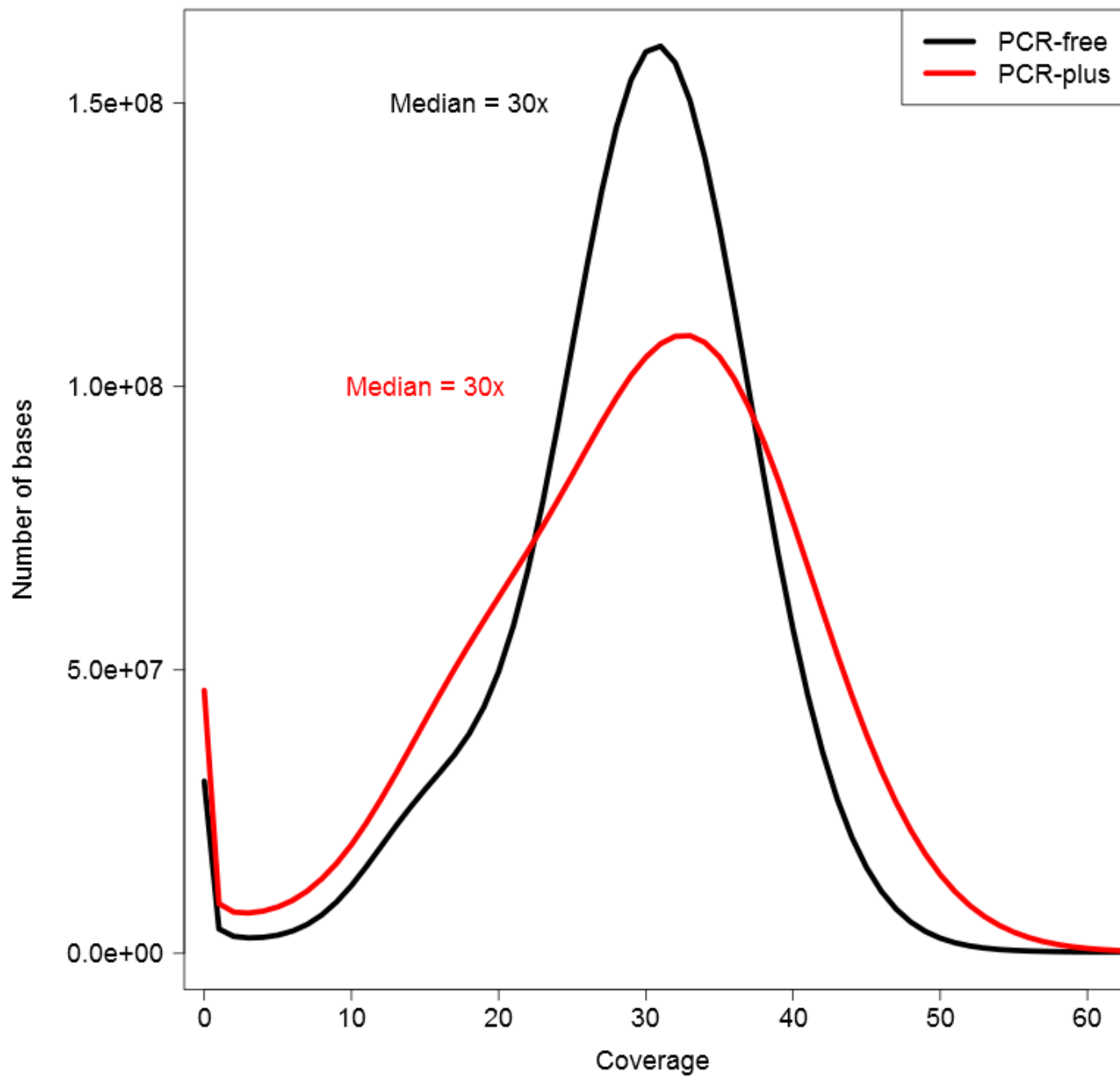
40 samples failed QC

2244 samples passed QC



# Sequencing depth





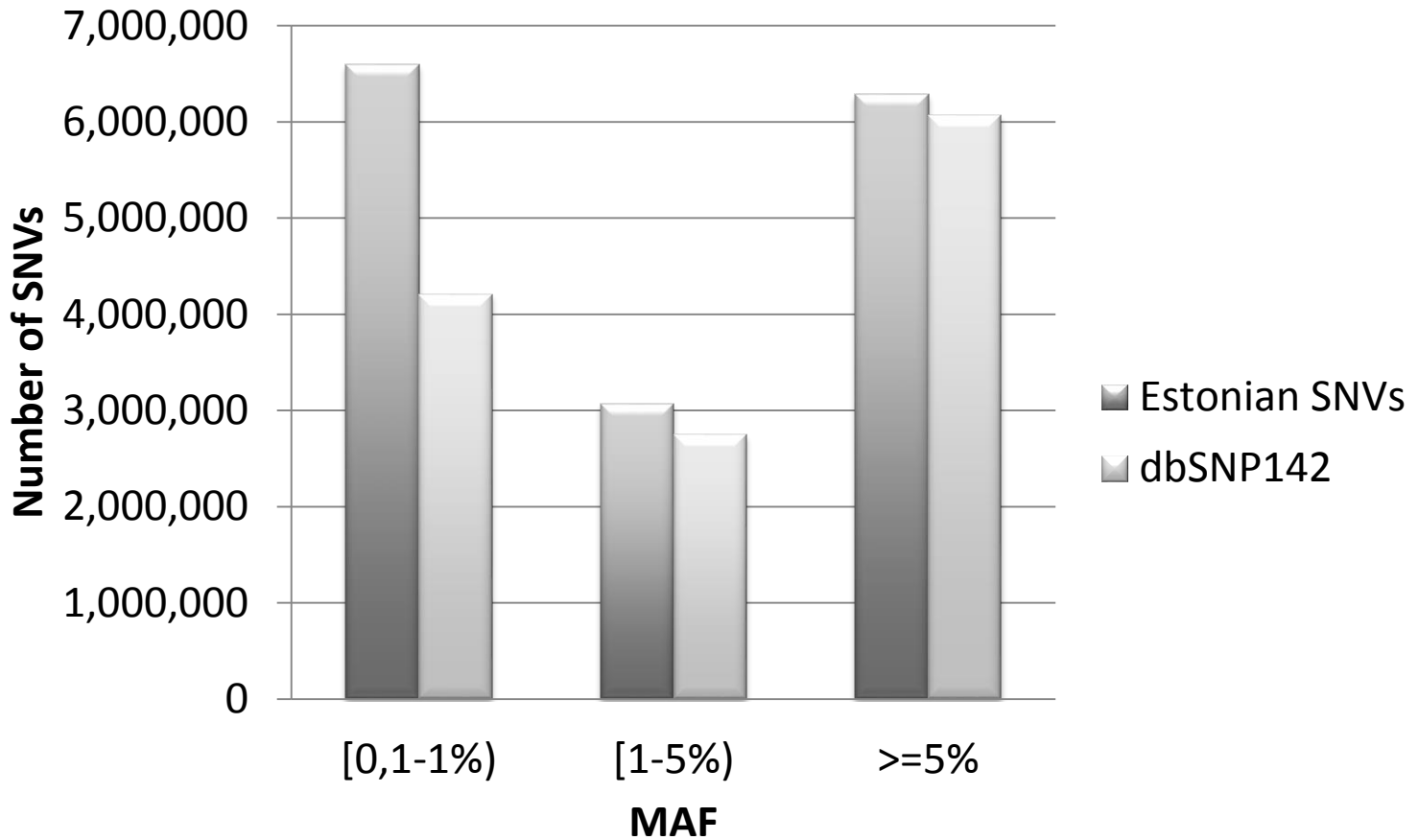
# Novelty versus dbSNP 142

MAF	SNVs	dbSNP%	Indels	dbSNP%
AC>2 - 0,1%	3,086,579	44%	581,703	23%
[0,1-1%)	6,593,280	64%	1,671,433	29%
[1-5%)	3,064,178	90%	1,200,536	40%
>=5%	6,284,187	97%	3,130,531	56%
<b>Total</b>	<b>19,028,224</b>		<b>6,584,203</b>	

AC - Allele Count



## Novelty versus dbSNP 142



# Novelty rate versus ExAC (LoFs)

	SNVs	ExAC_NFE%	Indels	ExAC_NFE%
<b>Total</b>	<b>7,151</b>	<b>35%</b>	<b>7,380</b>	<b>26%</b>
AC=1	4,143	25%	4,089	18%
AC=2	873	36%	1,003	24%
AC>2	2,135	54%	2,288	42%

ExAC\_NFE - Non-Finnish European

AC - Allele Count



CHROM	POS	REF	ALT	AF	Het	Hom_ALT	Consequence	SYMBOL
1	45797982	C	T	0.0002	1	0	STOP_GAINED&SPLICE_SITE	MUTYH
1	55525338	T	C	0.0004	2	0	ESSENTIAL_SPLICE_SITE	PCSK9
2	21226207	C	A	0.0009	4	0	ESSENTIAL_SPLICE_SITE	APOB
2	21228842	C	T	0.0002	1	0	STOP_GAINED	APOB
2	47703631	C	T	0.0002	1	0	STOP_GAINED	MSH2
2	48026217	G	A	0.0002	1	0	STOP_GAINED	MSH6
3	38655514	G	A	0.0002	1	0	STOP_GAINED	SCN5A
3	38663981	G	A	0.0004	2	0	ESSENTIAL_SPLICE_SITE	SCN5A
7	6029430	C	T	0.0002	1	0	ESSENTIAL_SPLICE_SITE	PMS2
7	150645530	A	C	0.0027	12	0	ESSENTIAL_SPLICE_SITE	KCNH2
7	150645949	G	A	0.0002	1	0	STOP_GAINED	KCNH2
13	32945177	C	T	0.0004	2	0	STOP_GAINED	BRCA2
13	32972626	A	T	0.0029	13	0	STOP_GAINED	BRCA2
14	23898437	C	T	0.0002	1	0	ESSENTIAL_SPLICE_SITE	MYH7
15	48784784	C	A	0.0016	7	0	ESSENTIAL_SPLICE_SITE	FBN1
17	41234520	G	A	0.0002	1	0	STOP_GAINED	BRCA1
17	41245708	T	A	0.0002	1	0	STOP_GAINED	BRCA1
18	29118713	G	A	0.0004	2	0	ESSENTIAL_SPLICE_SITE	DSG2
19	39070642	G	A	0.0002	1	0	STOP_GAINED	RYR1

# Clinical Exome Sequencing

In collaboration with Tartu University Hospital

Since 2014 funded by the Estonian Health Insurance Fund

- **Trio whole-exome sequencing (>50x coverage)**
  - Nextera Rapid Capture Exome and HiSeq 2500 (Illumina)
  
- **Illumina Sequencing Panels**
  - Illumina TruSight One
  - Illumina TruSight Cancer Panel



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# Clinical Exome Sequencing

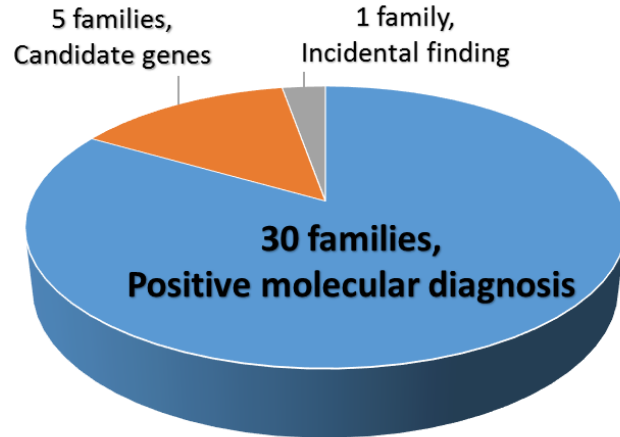
- **Over 250 whole-exomes sequenced in total (patients and their unaffected family members):**
  - Developmental delay
  - Immune system disorders
  - Epilepsy
  - Dental anomalies
  - Bone development abnormalities
- **Diagnostic WES:** 118 exomes covered by the Estonian Health Insurance Fund for pediatric cases, cost per exome 1507,40 EUR
- **Research WES:** 133 exomes covered by research grants



# Clinical Exome Sequencing

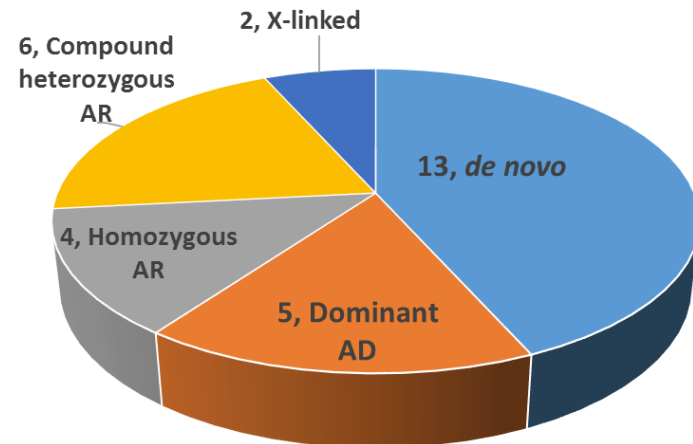
## Diagnostic outcome in 97 families tested with WES

total of 251 exomes analysed



**Diagnostic yield ~31%**

## Inheritance pattern in 30 families with positive diagnosis



**251 exomes sequenced = 97 families**

- 50 parent-offspring trios
- 25 single-cases
- 17 families



# Nationwide Personalised Medicine Pilot Programme

An example of capitalizing big on the (healthcare) IT infrastructure

Genome Bank (Est 2001)  
52 000 donors  
(5% of the population)

+

Digital health data  
from 9 sources  
(>10y history)

+

International investments for  
personalized medicine



**Government decision for Nationwide Personalized Medicine Pilot Project in 2015-2018**

personalized services and stratified health system planning

growth-factor for healthcare R&D and business development

Internationally open  
R&D and  
collaboration platform

Regional  
Personalized  
Medicine centre of  
excellence

Rapid clinical application  
of personalized medicine  
approach and decision-  
support tools



International  
business  
collaboration

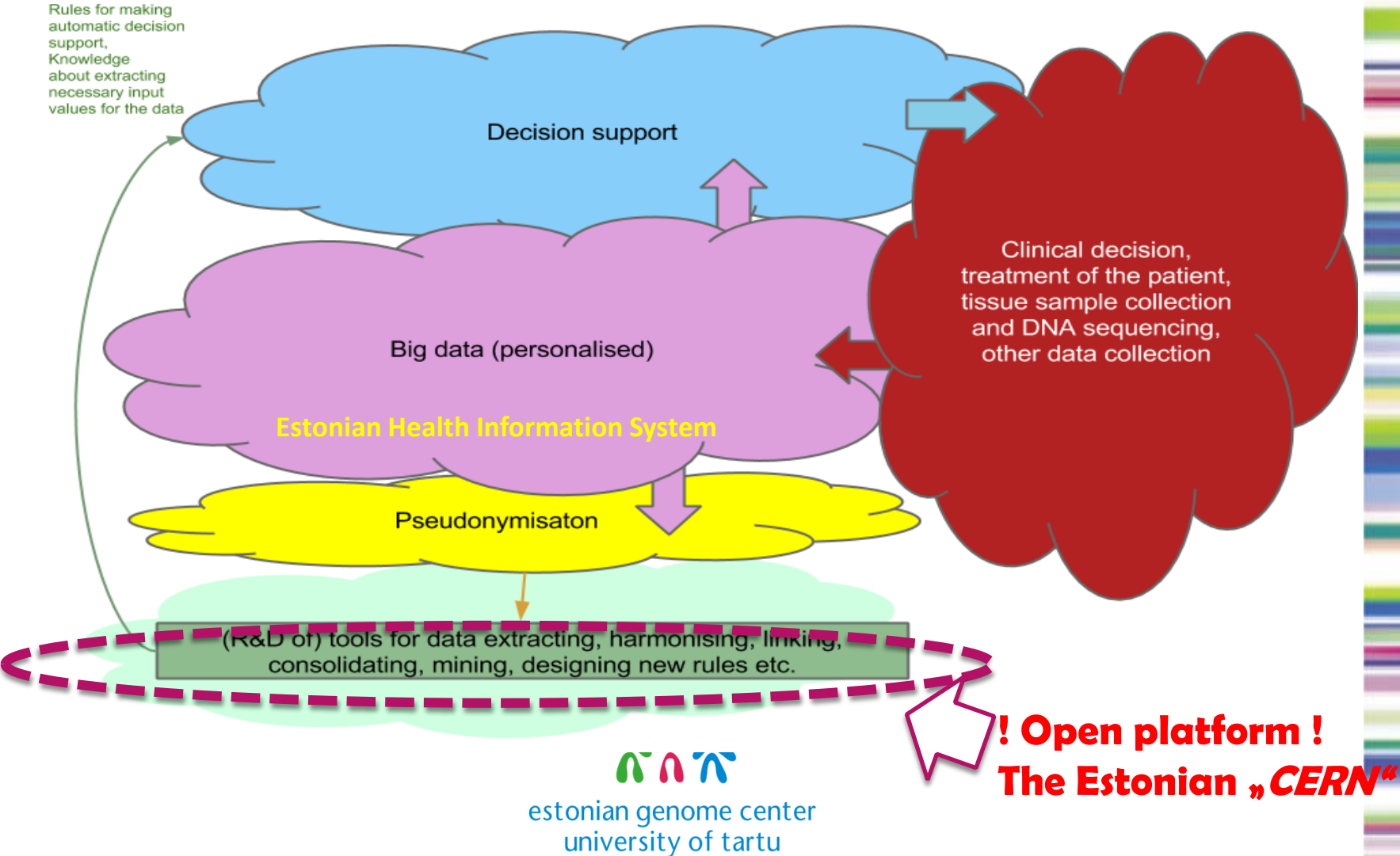
# Goals of the Pilot Programme

**One of the implementation initiatives of the National Research, Development and Innovation Strategy for Health Care**

- 1) validate the feasibility and effectiveness of personalised medicine approach as the basis for clinical patient management for selected health issues;**
- 2) establish informatics and data processing infrastructure for routine practice of personalized (4P) prevention and health care, i.e. based on integrated association analysis of individual genome, health, behavior and environmental data.**
- 3) constitute a comprehensive innovation ecosystem to support universities and companies in translational and applied R&D in the field of personalized (4P) medicine.**



# Personalised medicine infrastructure for Estonia



# Draft PM action plan framework

## **Pilot projects for PM application in clinical settings**

- Competitive selection of clinical pilots
- International expert assessment

## **Basic ecosystem & infrastructure development**

- PM Open Research ja Development Platform
- Decision support service
- Health professional training
- Communication for population and health professionals

## **Expanding engaged population in the biobank (from 50k to 500k)**

## **Management and coordination**

## **Budgeting under preparation**

- initial commitment for 2016
- various sources anticipated (Government, private investors, commercial partnership)



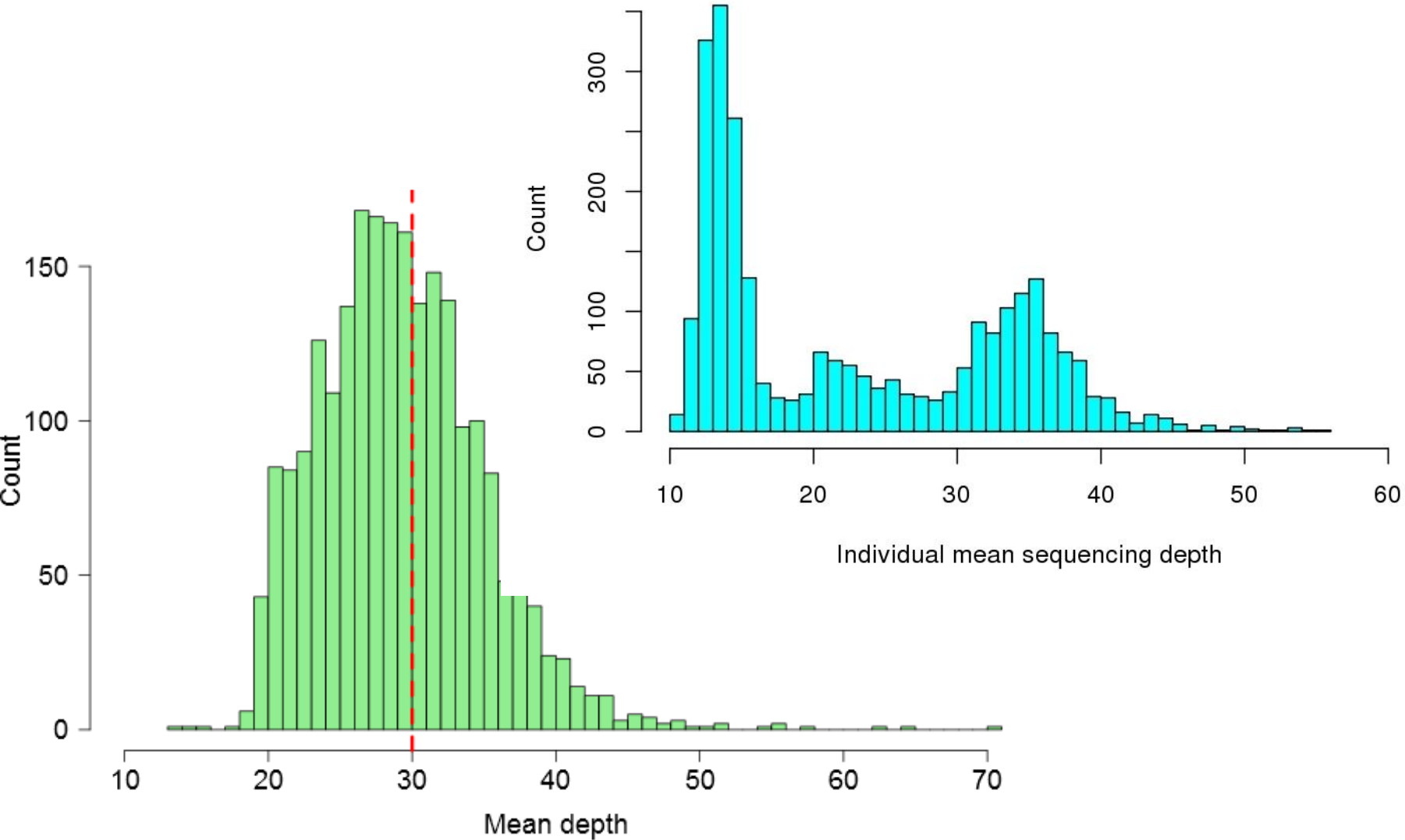


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Thank you!  
[www.biobank.ee](http://www.biobank.ee)

# Sequencing depth



# Distribution of recruiters

