From Biobanking to Precision Medicine

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My genome: our future

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Personalized medicine

- rare disease – precision diagnostics (WES, WGS)
- cancer – precision treatment (mut specific MaB)
- common diseases – personal prevention (PRS)
- Pharmacogenomics (drug response)
Genomics of the common disease (CAD, T2D, etc.) “Estonian approach”

1. Sequence ca 1% of the population and capture maximum amount of the genomic heterogeneity
2. Use arrays for the major part of the population and impute the arrays
3. Use the data for PRS and pharmacogenetics
4. It costs 50€ to recruit and genotype one individual = population scale Per Med
Estonian Biobank (started in 1999!)

1. Prospective, longitudinal, volunteer-based
2. Health records, diet, physical activity, etc. DNA, plasma, 3000 WGS, 2500 WES, all GSA array
3. 52,000 participants from 2002-2011, additional 150 000 2018-2019
5. Open for research: Clear access rules, broad informed consent, GSA array data
6. 200 000 individuals = 20% of the adult (18y and up) population of Estonia
Human Genes Research Act

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.
Secure exchange of health data – cornerstone of Estonian digital health architecture
Figure 3. National registries and databases for enrichment of phenotype data in the Estonian Biobank. The schematic diagram illustrates the different layers of information available in the database of the Estonian Biobank, which is continually being updated by queries to the Estonian Causes of Death Registry, the Estonian Cancer Registry and the Digital Prescription Database of the Estonian Health Insurance Fund, as well as electronic medical records (EMRs) from the databases of the two major hospitals in Estonia. Data generated through research projects must be returned to the Biobank within 5 years of the original data release from the Biobank.
Disease trajectories + treatment info for people in the biobank

Male, born 1944

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**Pentoxifylline**
- Start: 27.02.04 - 19.12.08

**Simvastatin**
- Start: 20.12.08 - 5.12.13

**Glibenclamide**
- Start: 8.08.04 - 5.11.08

**Glimepridine**
- Start: 25.02.09 - 4.07.14

**Isosorbid mononitrates**
- Start: 8.11.04 - 28.11.06

**Rosuvastatin**
- Start: 3.12.04 - 2.10.07

**Ramipril**
- Start: 24.12.04 - 22.04.14

**Metoprolol**
- Start: 24.12.04 - 22.04.14

**Amlodipine**
- Start: 14.02.05 - 7.10.09

**Metformin**
- Start: 10.11.05 - 15.11.11

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Return the data

• Estonian biobank is returning the research data back to the people who want and agree to get it.

• We are inviting back approx. 2000 people, around 1500 have received the polygenetic risk scores (PRS) and 30 min counseling.
3 examples:


• 2. PRS – breast cancer (Läll et al 2018, submitted)

• 3. Pharmacogenetics
FH-linked variant (*LDLR*, *APOB*, *PCSK9* gene) carriers display

- greater than 50 mg/dl (1.3 mmol/L) and a wide spectrum of LDL-C level

Diagnostic LDL-C level cut-off for FH cases >4.9 mmol/L

*Khera et al. J Am Coll Cardiol. 2016*

*Abul-Husn et al. Science 2016*

*Alver et al. (2018) Genetics in Medicine*
FH Summary

• **Under-diagnosis and under-treatment**
  – reclassified 51% from having non-specific hypercholesterolemia to having FH, half of them were on statins, but none had LDL-C below treatment goals
  – identified 32% who had gone unrecognized by the medical system
  – Reliable identification of new FH cases and people with high GRS which has direct impact on family members

• **Insensitivity of current criteria used in FH diagnosis**
  – wide spectrum of LDL-C levels
    • 34% had LDL-C levels ≤4.9 mmol/L
  – visible accumulations of lipid deposits detected in 5% only
  – heterogeneity in clinical expression

  – Cascade
Polygenic risk scores (PRS) weighted: sum of all risk alleles weighted by their effect size

Calculated as $S = w_1X_1 + w_2X_2 + \ldots + w_kX_k$, 

$X_1, \ldots, X_k$ - allele dosages for $k$ independent markers (SNP-s), 

$w_1, w_2, \ldots, w_k$ - weights

Methodological questions:
A) How to select the SNPs – how many and what are the selection criteria?
B) How to select the optimal weights?

Breast Cancer

- No BRACA1 & BRCA2, but ca 900 SNP variants
Breast Cancer risk by GRS quartile
(317 incident cases in 33554 women)

GRS quartile:
- 4 (top 25%)
- 3 (50-75%)
- 2 (25-50%)
- 1 (bottom 25%)
- Whole cohort

Läll et al (2018) submitted
Population vs top 5% GRS based on NIHD data

Cumulative incidence on breast cancer among women
Intervention?

Perhaps for the high risk group start mammography/MRI 10 years earlier?

Clinical study to test it is underway in TU hospital
Importance of pharmacogenomics

98% of Europeans carry $\geq 1$ mutation of pharmacogenetic relevance

Pharmacogenetic study

- Drug prescriptions
- WGS + genome-wide genotyping
- ADR diagnoses
On average 5.5% of individuals in the population use at least one of the 32 drugs associated with the studied genes on a daily basis.
CYP2D6 Loss of function mutation and adverse drug reactions

1. Metoprololum
2. Tamoxifenum

L27.0 = Generalized skin eruption due to drugs and medicaments taken internally

1. Sertralinum
2. Venlafaxinum

M60.8 = Other myositis

1. Escitalopramum

T88.7 = Unspecified adverse effect of drug or medicament
Y57.5 Drugs, medicaments and biological substances causing adverse effects in therapeutic use

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We will determine genotypes of Estonian Biobank participants for variants in 8 genes that have previously been shown to be relevant in response of drugs with certain active substances. They will then receive a pharmacogenetics report and counselling based on peer-reviewed and internationally approved clinical practice guidelines. More specific prescribing decision support will be provided for medical professionals.
Pharmacogenetic feedback

- 33-y female with depression
- CYP2C19 slow metabolizer, dose reduction to 50% recommended
- Sertralin and escitalopram formerly prescribed
- Both withdrawn, due to ADR - agitation, aggressiveness, pharyngitis, etc.
Translating genotype data of 44,000 biobank participants into clinical pharmacogenetic recommendations: challenges and solutions

Sulev Reisberg, MSc\textsuperscript{1,2,3}, Kristi Krebs, MSc\textsuperscript{4,5}, Maarja Lepamets, MSc\textsuperscript{4,5}, Mart Kals, MSc\textsuperscript{4}, Reedik Mägi, PhD\textsuperscript{4}, Kristjan Metsalu, MSc\textsuperscript{4}, Volker M. Lauschke, PhD\textsuperscript{6}, Jaak Vilo, PhD\textsuperscript{1,2,3} and Lili Milani, PhD\textsuperscript{4,7}
Virtuous Cycle of Clinical Decision Support

Registry → Measure

Practice → Guideline

CDS

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

• The next step beyond evidence-based medicine
• The systematic incorporation of research and quality improvement considerations into the organization and practice of healthcare
• To advance biomedical science and thereby improve the health of individuals and populations.
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, urgent need for better databases
• Large work-load to keep database of known risk variance updated
Conclusion

Large prospective biobank cohorts make it possible to move towards personalized risk prediction and to use it in general medical practice – however, there are still many challenges on this road
Thank you!

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