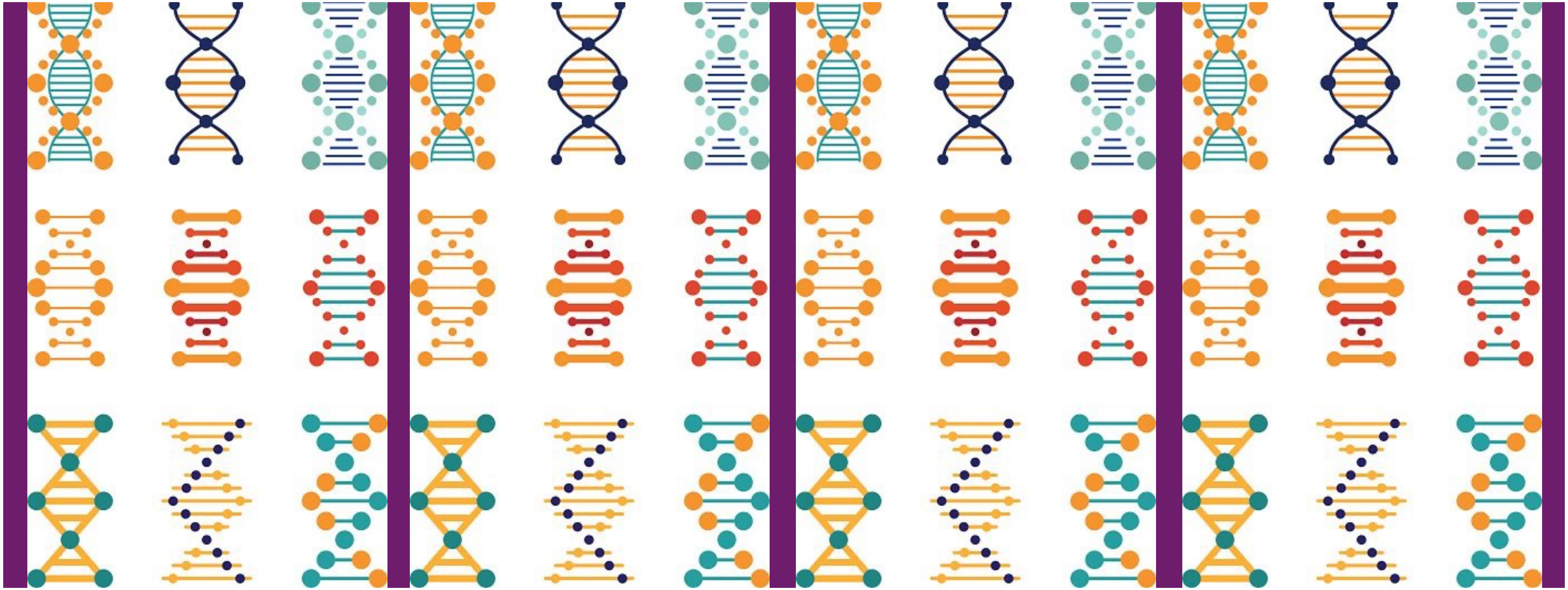


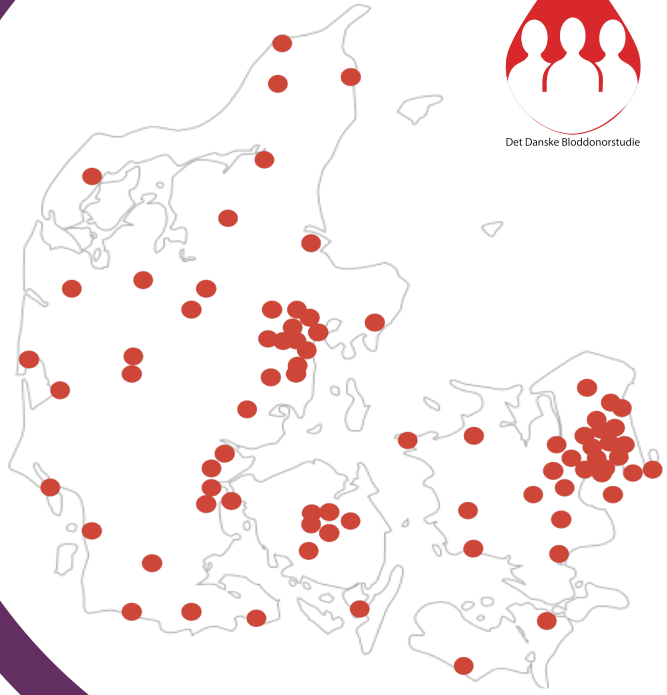
APPLYING ML IN LARGE-SCALE COMMON COMPLEX GENETICS

Karina Banasik
Associate Professor
Novo Nordisk Foundation Center for Protein Research,
University of Copenhagen

THE BIGGEST BIOBANKS WITH GENETICS IN DENMARK

THE DANISH BLOOD DONOR STUDY

- ✓ Nationwide recruitment of blood donors via Danish Blood Banks
- ✓ 206 donation points across Denmark
- ✓ High participation rate: 95%
- ✓ Builds on existing infrastructure
- ✓ 135K blood donors recruited since 2010
- ✓ Donors donate up to four times per year (10 times if plasma donors)
- ✓ EDTA plasma stored in biobank at each donation
- ✓ Data collected on a dedicated secure cloud



Det Danske Bloddonorstudie

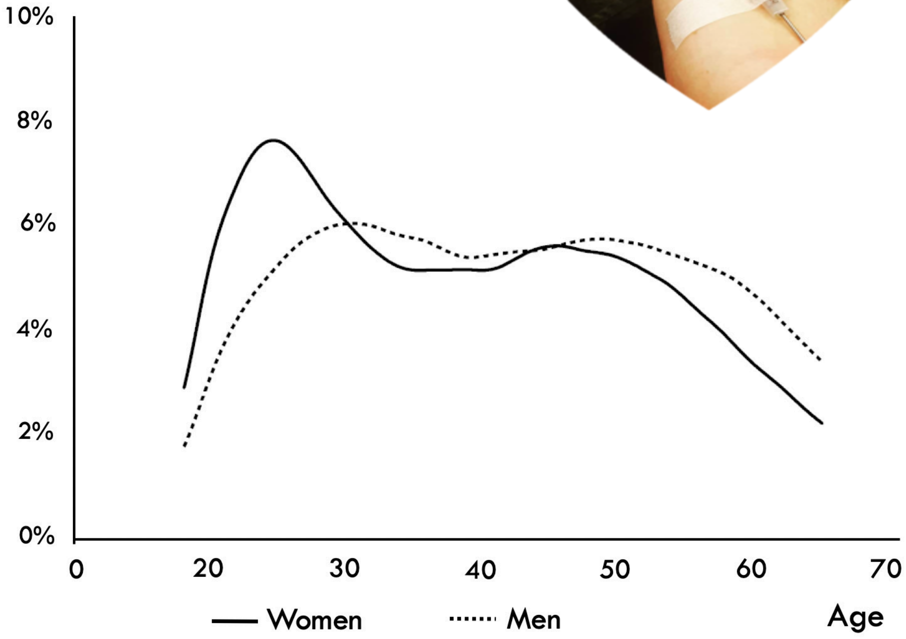
Novo Nordisk Foundation
Center for Protein Research

WHO DONATES BLOOD?

✓ Blood donation is voluntary and unpaid

✓ Inclusion criteria

  - ✓ Physically well
  - ✓ Between 18 and 67 years old
  - ✓ Weigh more than 50 kilos
  - ✓ Speak Danish, have a Danish social security number, and have lived in Denmark for minimum one year



[Burgdorf *et al.* 2017]

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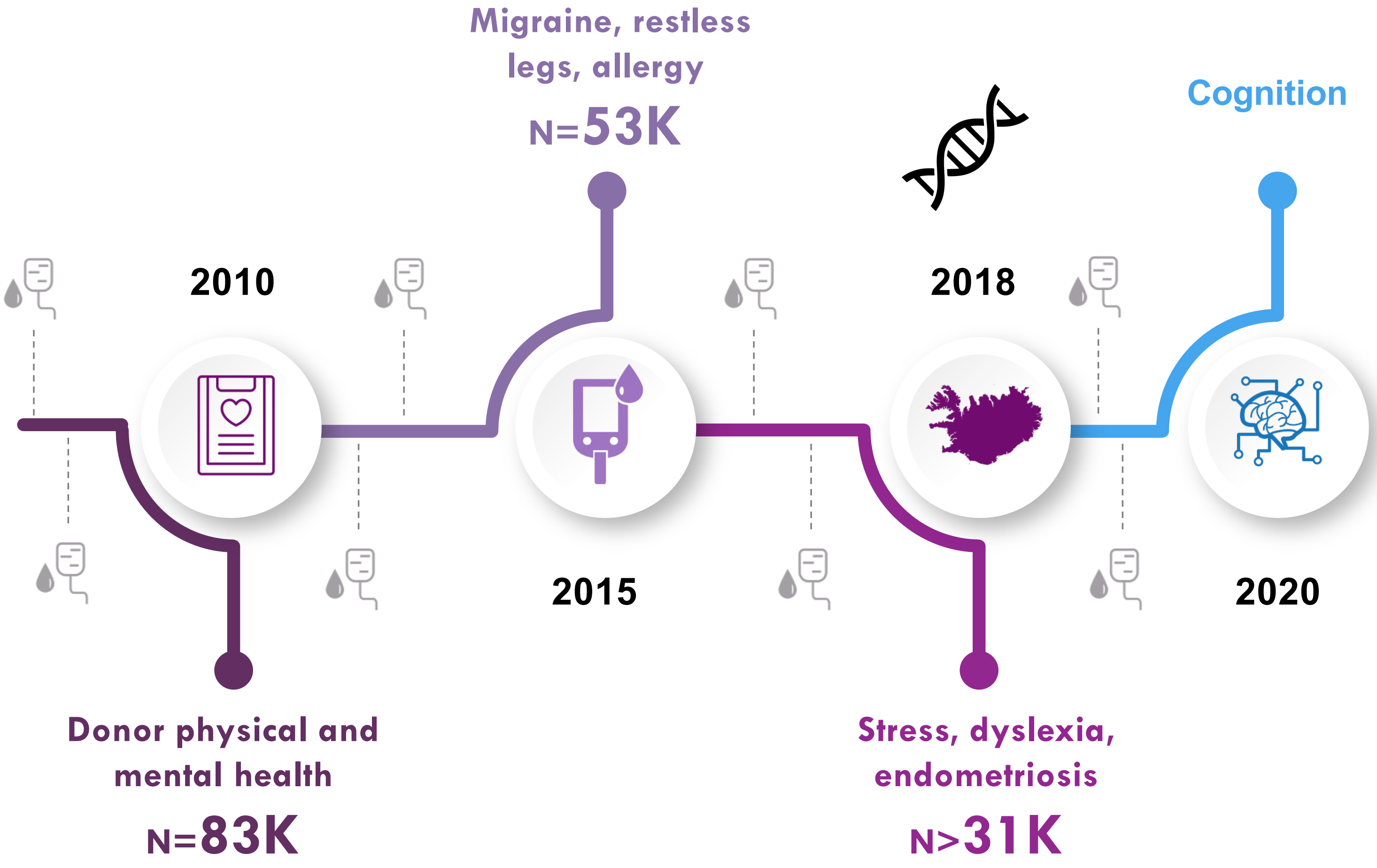
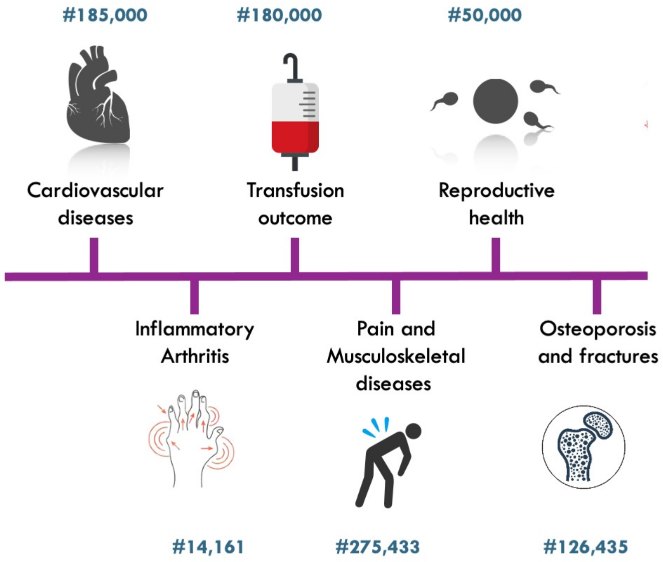
A RICH DATA COLLECTION

- ✓ Illumina GSA chip on 110K in collaboration with deCODE genetics
- ✓ Three questionnaires (basic info: weight, height, smoking etc in all three)
- ✓ 270K unique donations with Sysmex haematology measures
- ✓ >500K EDTA plasma samples in the biobank


Migraine, restless legs, allergy
N=53K
Cognition
2010
2018
2015
2020
Donor physical and mental health
N=83K
Stress, dyslexia, endometriosis
N>31K

COPENHAGEN HOSPITAL BIOBANK

- ✓ Biobank with >430K patients
- ✓ Initiated at Rigshospitalet in Copenhagen in 2009
- ✓ Collection of surplus of EDTA whole blood from the Clinical Immunology department
- ✓ Average age of patients at inclusion >45 years
- ✓ Linkable with Danish national registries and electronic health records
- ✓ Illumina GSA chip in collaboration with deCODE genetics



#185,000
Cardiovascular diseases

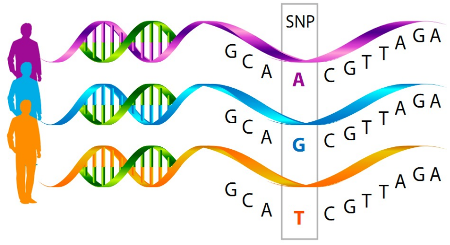
#180,000
Transfusion outcome

#50,000
Reproductive health

Inflammatory Arthritis
#14,161

Pain and Musculoskeletal diseases
#275,433

Osteoporosis and fractures
#126,435



REGION H

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DATA INFRASTRUCTURE ON COMPUTEROME 2.0

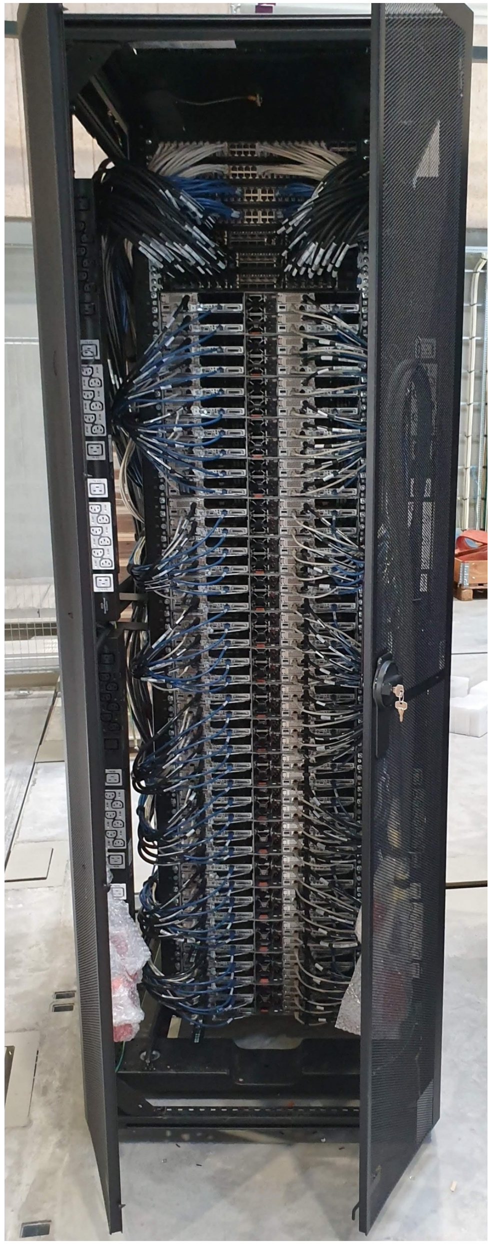
The system is designed to process large amounts of healthcare data with the highest I/O performance using state of the art storage and memory technology

- ✓ 90% of the system is cooled using warm water liquid cooling
- ✓ Heat is re-used
- ✓ Wind power

30K
CPUs

30-40
GPU nodes for machine learning

55
"Fat" nodes with 1.5TB of RAM



GENOME-WIDE ASSOCIATION (GWAS) ANALYSES IN PRECISION MEDICINE

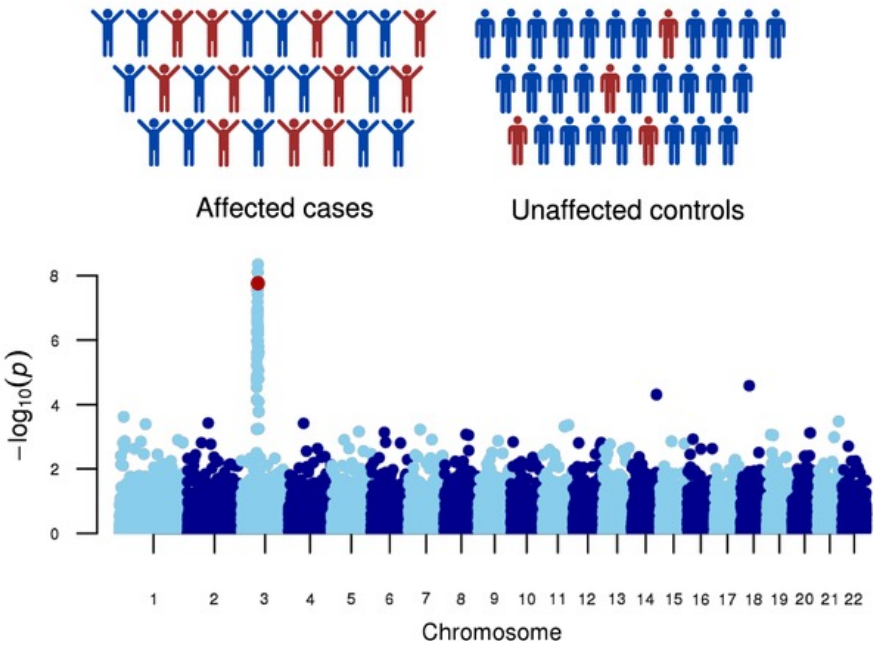
…GATG**C**TTGG…

…GATG**T**TTGG…

An experimental design to discover new genetic variants associated with diseases and traits

In GWAS, allele or genotype frequencies are compared between individuals with a disease (cases) and unaffected individuals (controls)

Since the genetics of complex diseases are driven by a combination of variants with moderate effect sizes, large sample sizes are extremely important!



ADVANTAGES OF BIOBANK-DRIVEN LARGE-SCALE COMMON COMPLEX GENETICS

✓ GWAS can help identify genes that contribute to disease or variation in traits that in turn can be used to develop better prevention and treatment strategies

✓ The biobanks are not unbiased populations, but serves well for making inference about the effects of genetics on disease

✓ The large collection of individuals in the biobanks together with linkable life-course registry data and electronic health records holds great promise in precision medicine in Denmark

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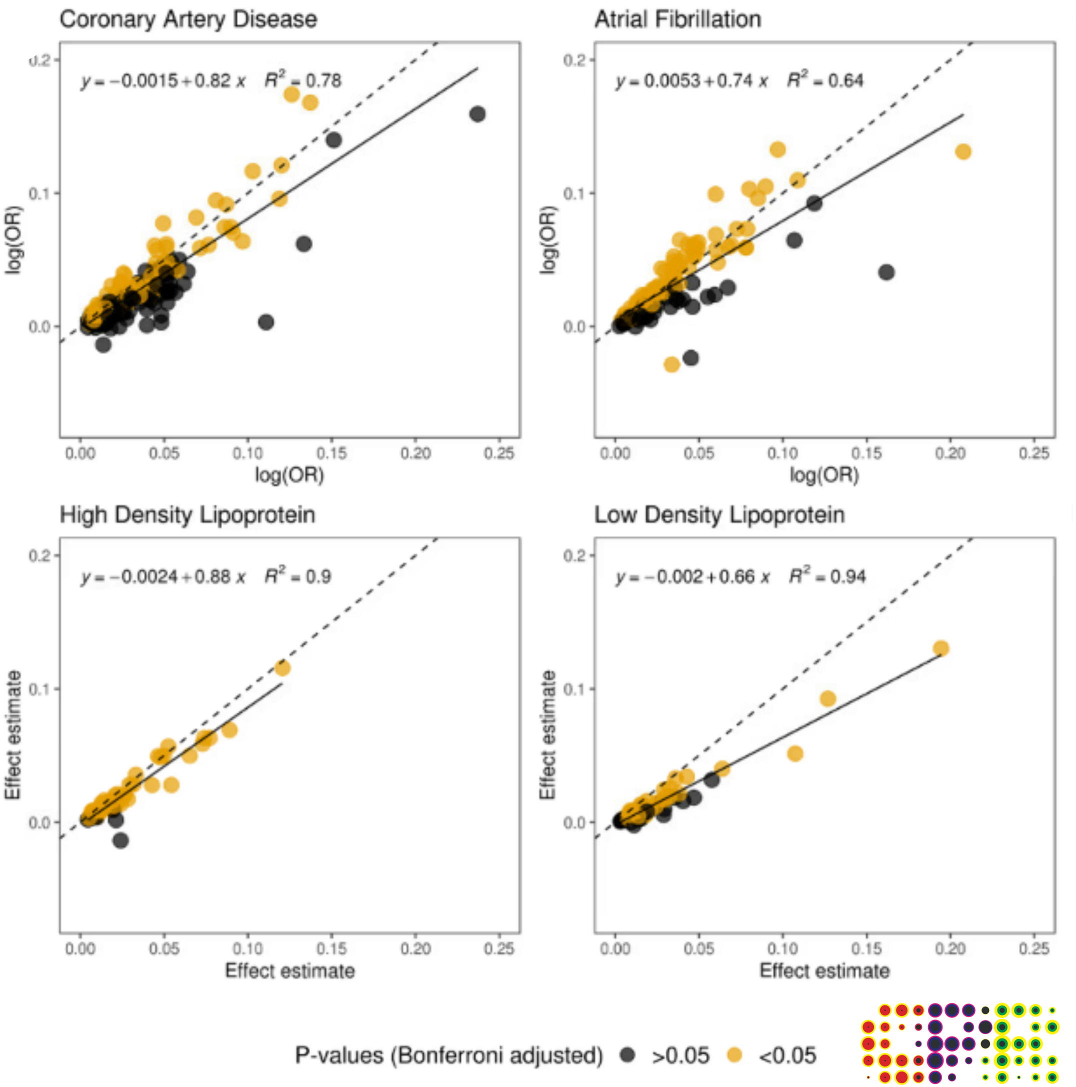
WHAT HAVE WE FOUND SO FAR?

PERFORMANCE MEASURES

Comparison of GWAS effect sizes (weighted by risk allele frequencies) between our study population and a reference population (usually the largest published European GWAS).

Our results are comparable to results from other large genetic cohorts!



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[Laursen et al. in review]

GWAS META-ANALYSIS OF IRON HOMEOSTASIS

Det Danske Bloddonorstudie

Iron is essential for many biological functions and iron deficiency and overload have major health implications – *what makes a great blood donor?*

Sample size is important!

Iceland
(deCODE genetics)

~ 155K samples, ~32 million variants

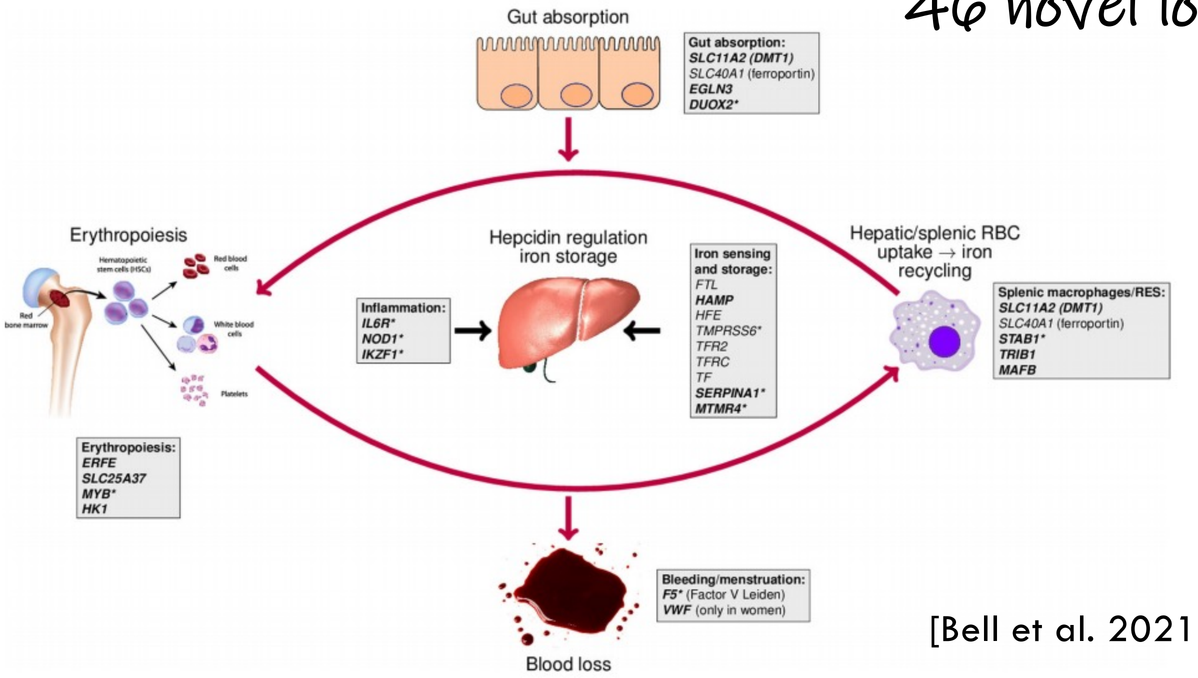
UK
(INTERVAL study)

~ 43K samples, ~19 million variants

Denmark
(Danish Blood Donor Study)

~ 84K samples, ~19 million variants

46 novel loci



Gut absorption:
SLC11A2 (DMT1)
SLC40A1 (ferroportin)
EGLN3
*DUOX2**

Erythropoiesis:
ERFE
SLC25A37
*MYB**
HK1

Inflammation:
*IL6R**
*NOD1**
*IKZF1**

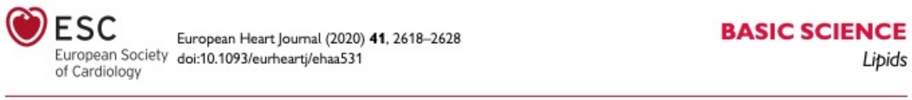
Iron sensing and storage:
FTL
HAMP
HFE
*TMPRSS6**
TFR2
TFRC
TF
*SERPINA1**
*MTMR4**

Splenic macrophages/RES:
SLC11A2 (DMT1)
SLC40A1 (ferroportin)
*STAB1**
TRIB1
MAFB

Bleeding/menstruation:
*F5** (Factor V Leiden)
VWF (only in women)

[Bell et al. 2021]

GENETIC VARIABILITY IN THE ABSORPTION OF DIETARY STEROLS AFFECTS THE RISK OF CORONARY ARTERY DISEASE

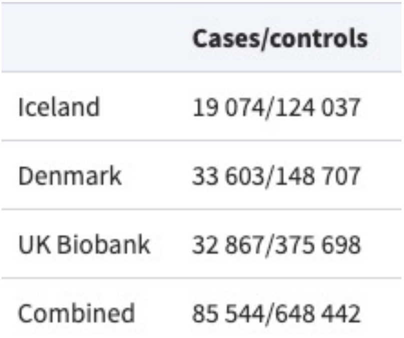

ESC
European Society of Cardiology

European Heart Journal (2020) **41**, 2618–2628
doi:10.1093/eurheartj/ehaa531

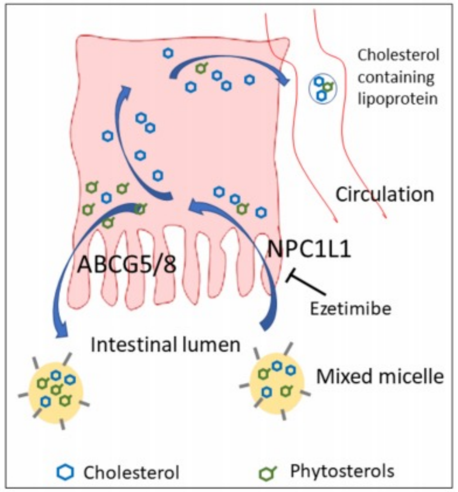
BASIC SCIENCE
Lipids

Genetic variants that decrease function of the ABCG5/8 transporter ***increase uptake*** of both dietary cholesterol and phytosterols into the circulation

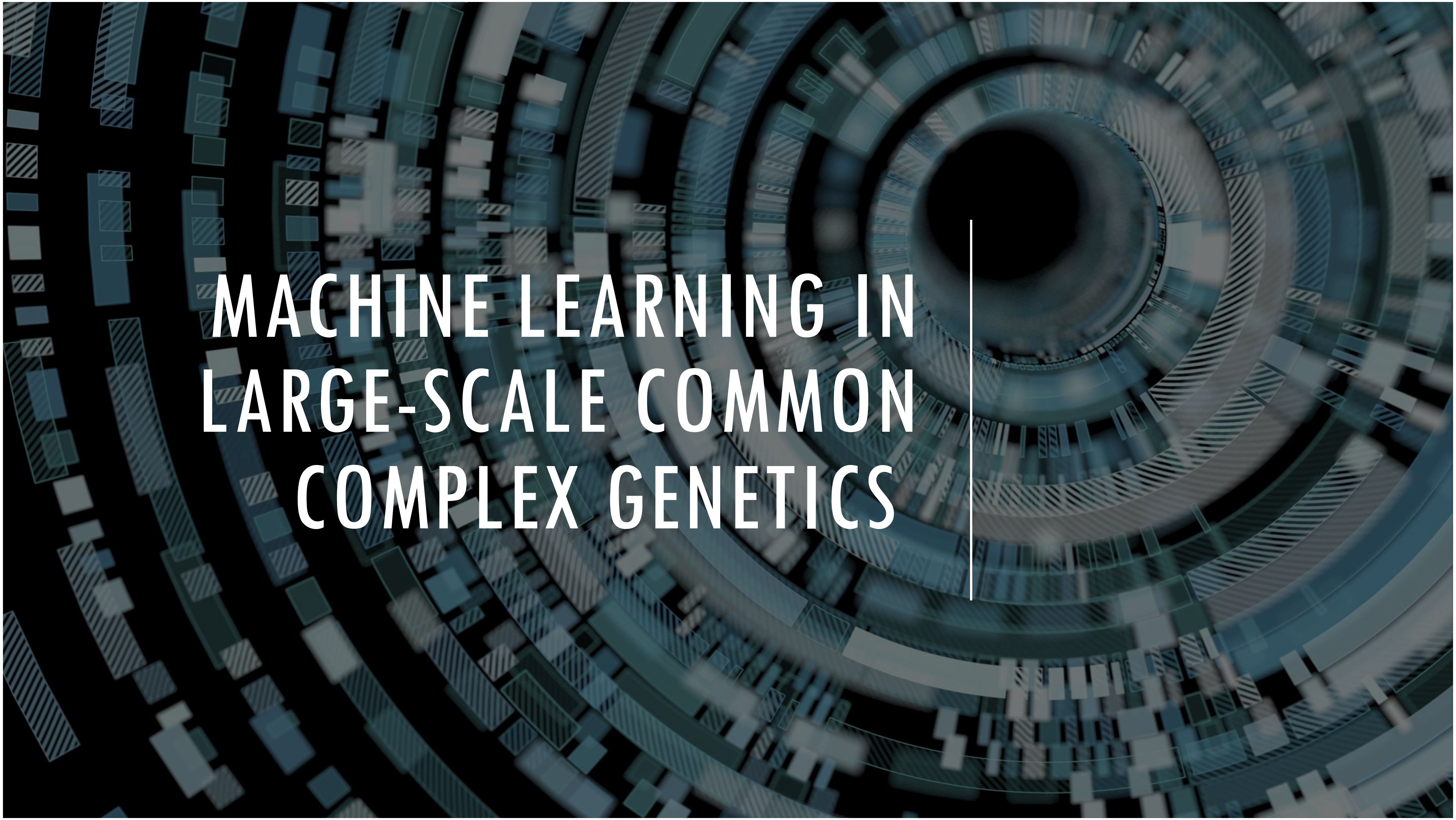
→ increase the risk of coronary artery disease.



	Cases/controls
Iceland	19 074/124 037
Denmark	33 603/148 707
UK Biobank	32 867/375 698
Combined	85 544/648 442



[Helgadottir et al. 2020]



MACHINE LEARNING IN LARGE-SCALE COMMON COMPLEX GENETICS

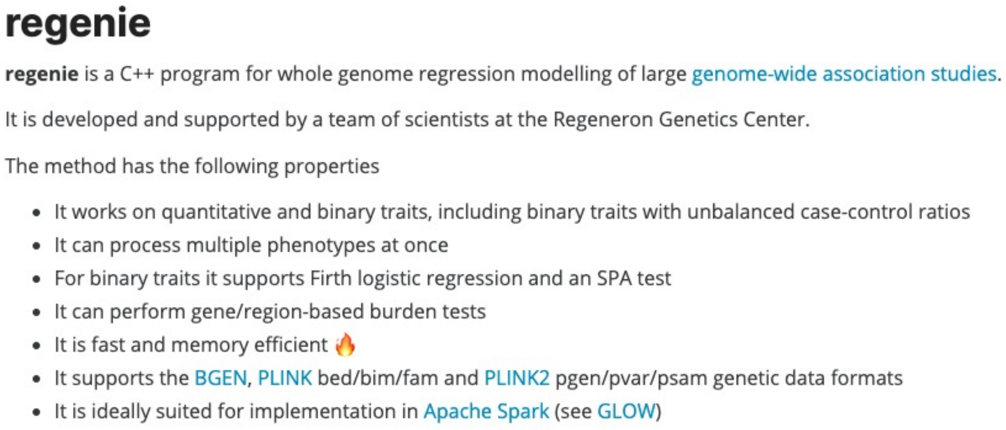
REGENERON®
GENETICS CENTER

ANALYSIS SPEED AND SCALING

- ✓ A GWAS is usually conducted with ~7-32 mio variants (dependendent on imputation depth and allele frequency cut-offs)
- ✓ Very computational demanding in biobank settings with hundreds of thousands of samples!

Computational requirements of running GWAS on 50 binary traits from the UK Biobank with different case-control ratios and distinct missing data patterns:

	CPU (hours)	Elapsed time (hours)
SAIGE	369,417	89,865
REGENIE	46,204	3,348



regenie

regenie is a C++ program for whole genome regression modelling of large genome-wide association studies.

It is developed and supported by a team of scientists at the Regeneron Genetics Center.

The method has the following properties

- It works on quantitative and binary traits, including binary traits with unbalanced case-control ratios
- It can process multiple phenotypes at once
- For binary traits it supports Firth logistic regression and an SPA test
- It can perform gene/region-based burden tests
- It is fast and memory efficient 🔥
- It supports the BGEN, PLINK bed/bim/fam and PLINK2 pgen/pvar/psam genetic data formats
- It is ideally suited for implementation in Apache Spark (see GLOW)

REGENIE is 8x faster in CPU hours

& 26.8x faster in elapsed time

https://rgcgithub.github.io/regenie/

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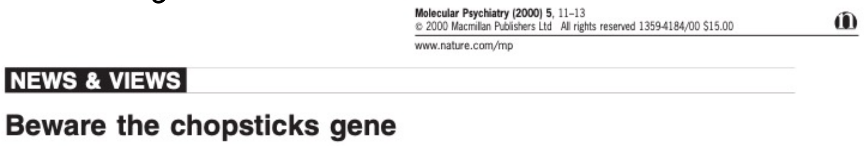
UNSUPERVISED CLUSTERING IN POPULATION ADMIXTURE

✓ Allele frequencies can differ between subpopulations

✓ Population stratification can lead to false positive associations and/or mask true associations.

Why do some people eat with chopsticks and others do not?

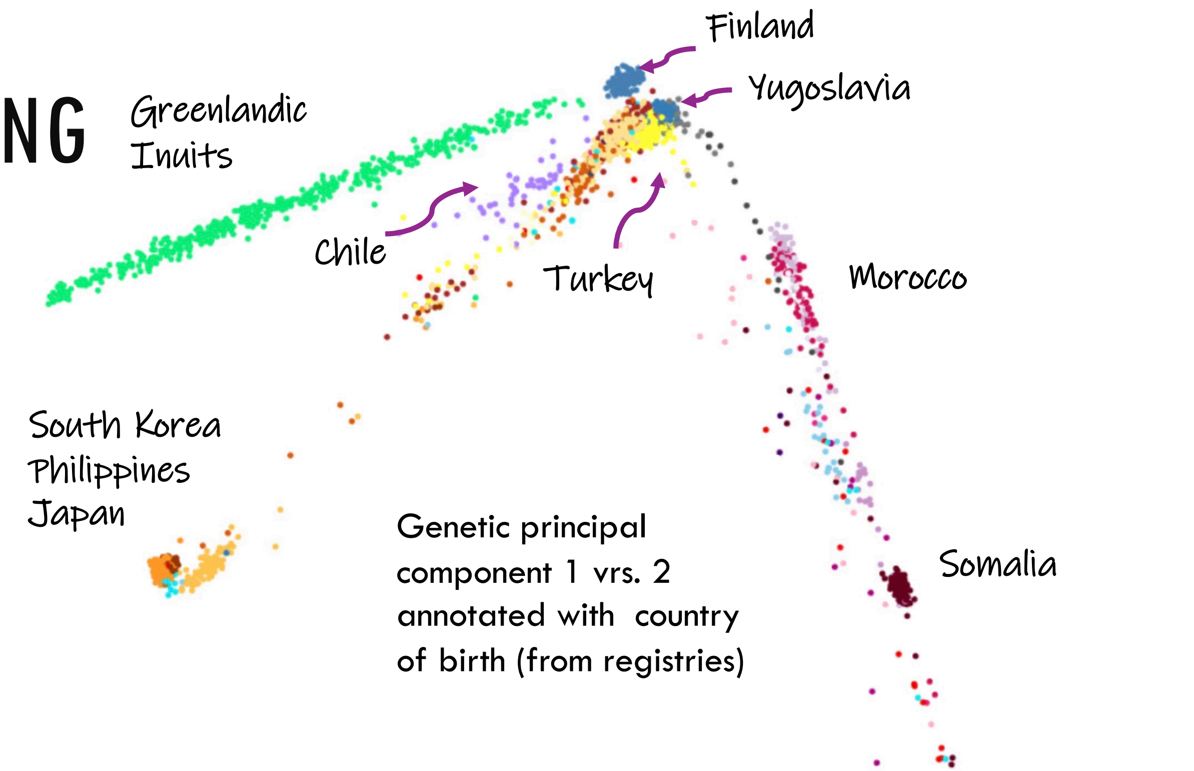
Differences in allele frequencies in Asians and Caucasians, led to the discovery of the 'successful-use-of-selected-handinstruments gene' (SUSHI) which was driven by the fact that these two populations differ in chopstick use for purely cultural rather than biological reasons.



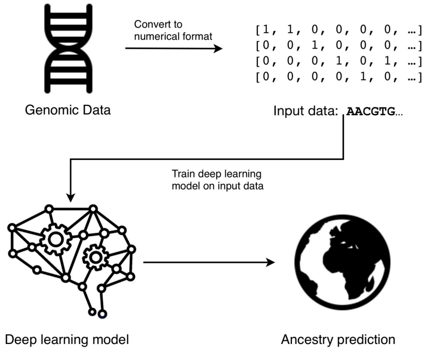
Molecular Psychiatry (2000) 5, 11–13
© 2000 Macmillan Publishers Ltd All rights reserved 1359-4184/00 $15.00
www.nature.com/mp

NEWS & VIEWS

Beware the chopsticks gene



Genetic principal component 1 vrs. 2 annotated with country of birth (from registries)



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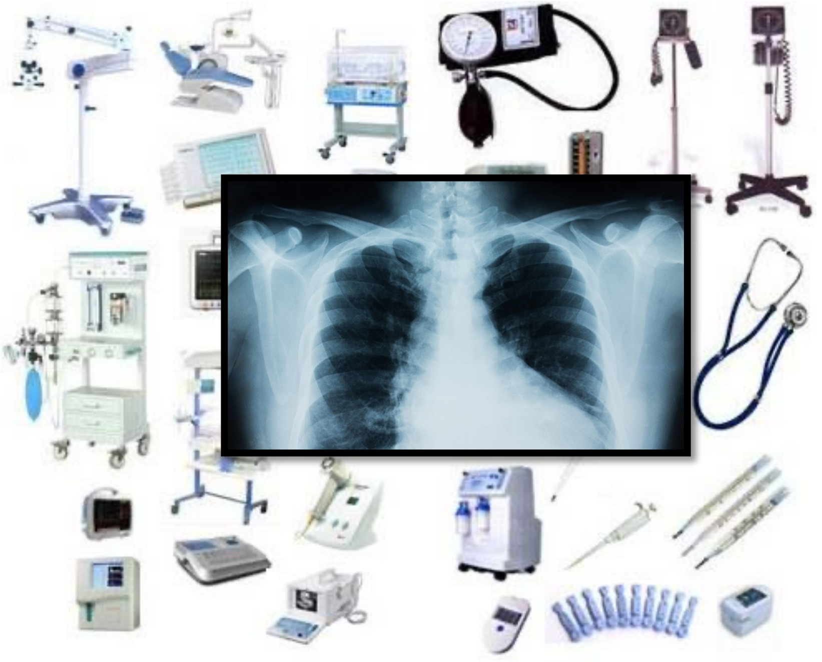
DEEP PHENOTYPING FOR PATIENT CHARACTERIZATION

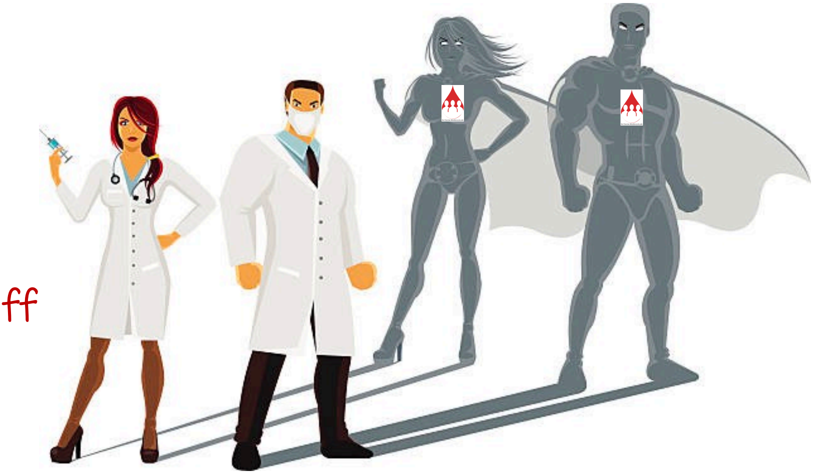
Unstructured data – "the other 80 percent of all data"

Systematically extract and preprocess features from data generated by machines



ACKNOWLEDGEMENTS

Blood Bank staff



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deCODE genetics

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Hilma Hólm
Bragi Walters

...and even more importantly:

Thanks to all the generous
blood donors who donate much more
than blood and truly make a difference!

novo nordisk fonden

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Thank you for the attention!