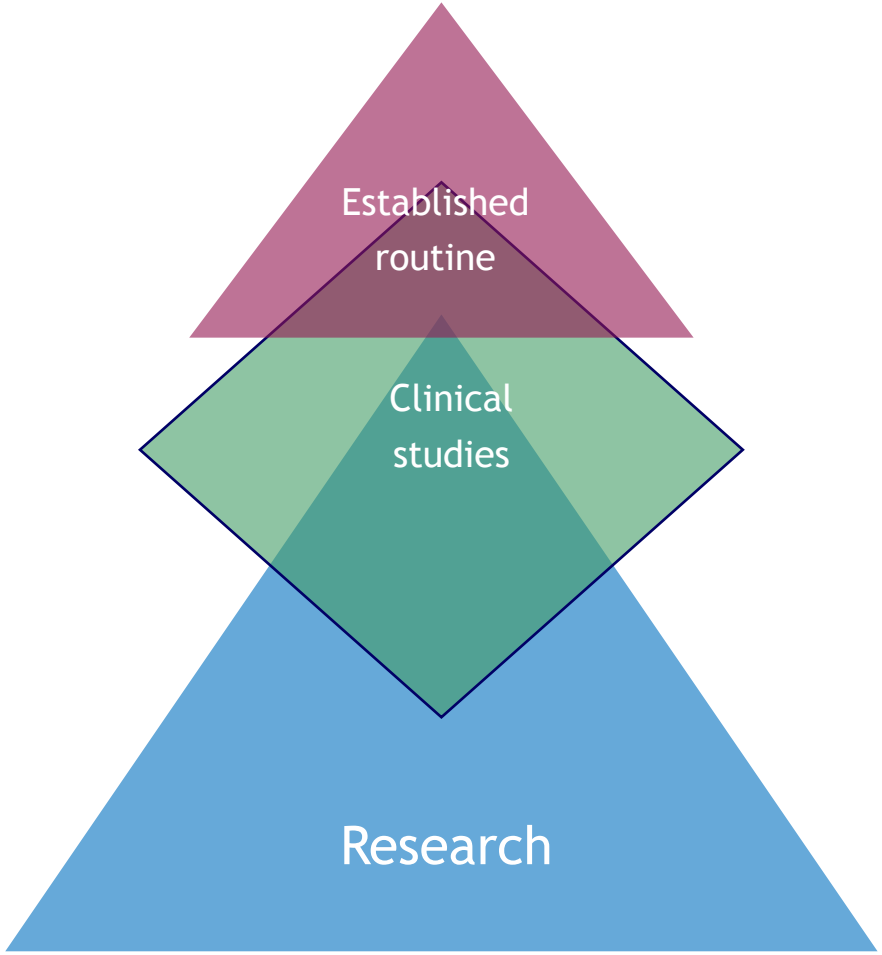
# Towards implementation of precision medicine across countries

Eivind Hovig

# Precision medicine – Precision diagnostics

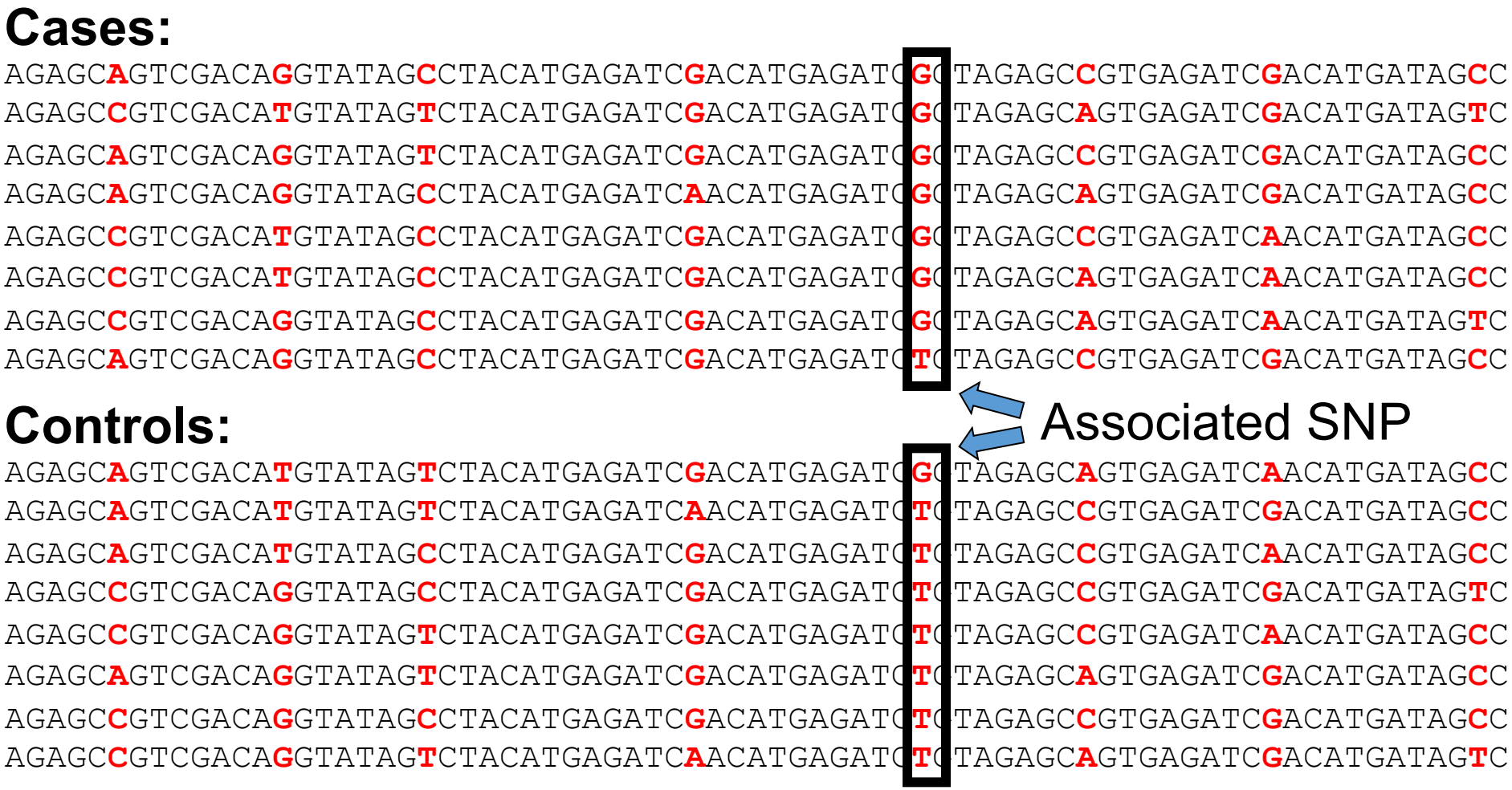
- Routine molecular diagnostics
- Molecular diagnostics for selection to clinical trials
- Molecular diagnostics in clinical trials
- Molecular diagnostics for PM targeted treatment
- Next generation molecular diagnostics



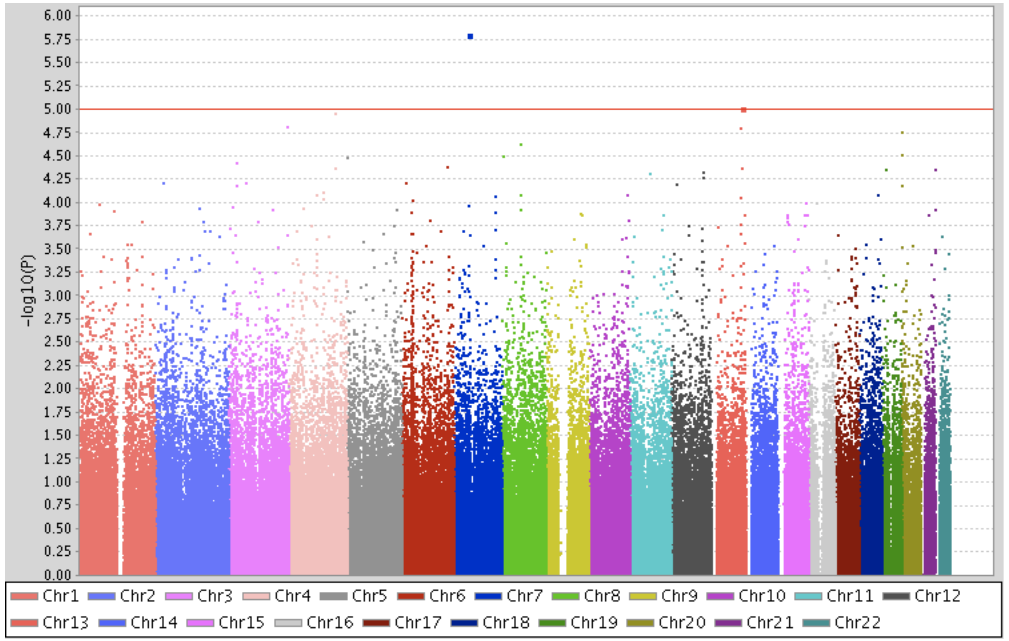
# Genome wide association studies

- Goal: find connections between:
  - A phenotype: height, type-I diabetes, etc., known to be heritable
  - Whole-genome genotype
    - Usually SNP arrays: Sampled points along the genome known to vary between individuals
    - Can be whole genome sequencing (mostly rare due to cost)
  - Mostly case-control comparing variant frequencies at each position to identify deviating frequencies indicating a hit along the genome
  - A hit is an association, not a direct hit
  - Need to huge numbers of individuals for statistical significance

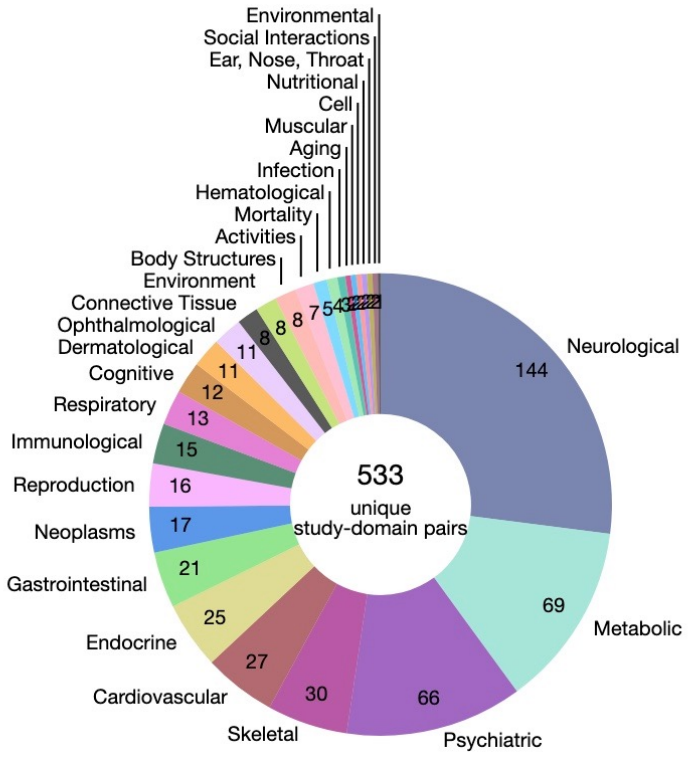
# Find the associated SNP

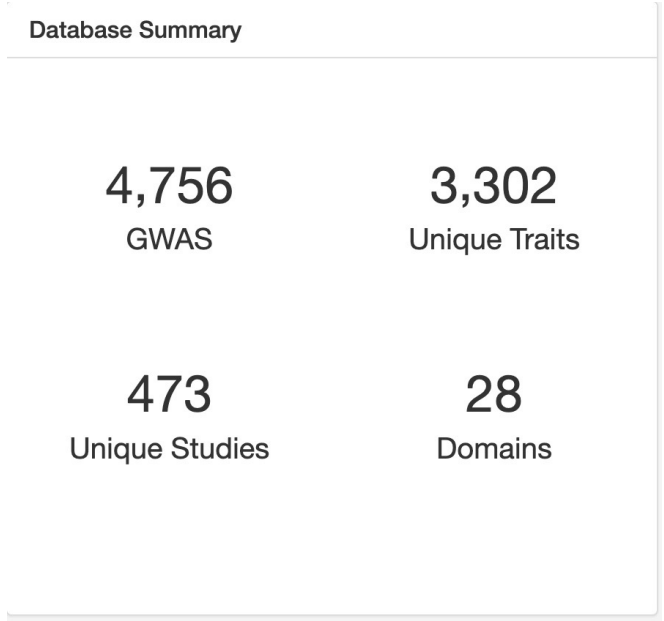


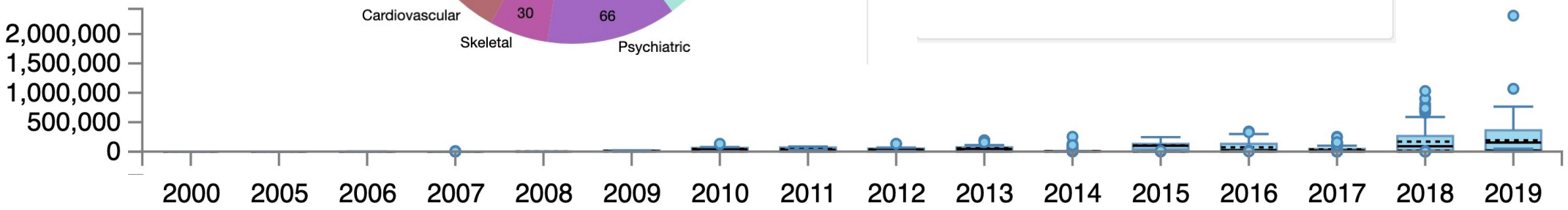
# “Manhattan plot” of GWAS results



# GWAS: A large undertaking



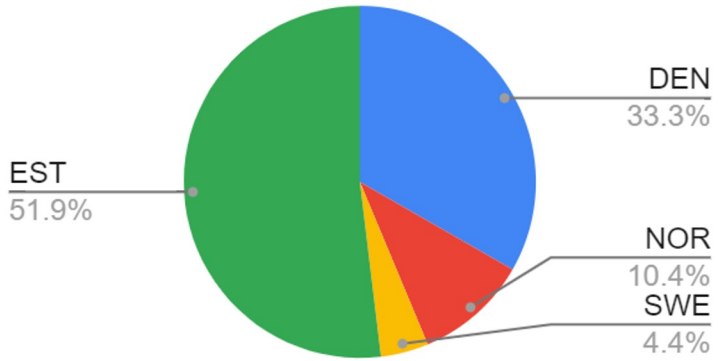




https://atlas.ctglab.nl/

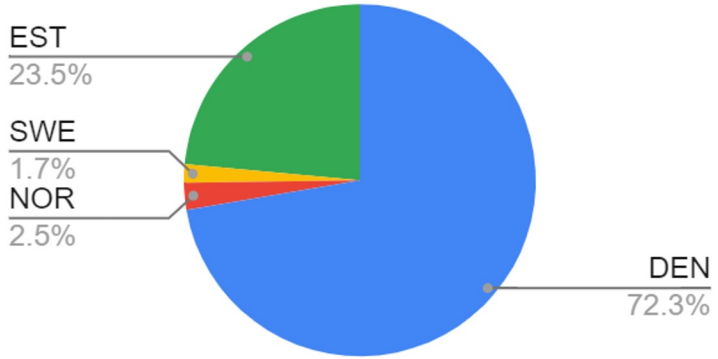
# Sample size for cohorts used in an ongoing study on Major Depression Disease

| Name | N MDD | N eoMDD | N control | Covariates |
|---|---|---|---|---|
| iPSYCH2012 | 20,804 | 18,429 | 23,854 | Sex, birthyear, 25PCs |
| iPSYCH2015 | 10,487 | 8,105 | 15,772 | Sex, birthyear, 25PCs |
| EstBB | 48,804 | 8,768 | 127,395 | Sex, birthyear, 10PCs |
| MoBa | 8,824 | 908 | ~128,000 | Sex, birthyear, 20PCs, batch |
| PREFECT | 1,796 | 470 | 6,613 | 4PCs |
| UKB | 76,828 | 21,499 | 418,765 | Sex, 20PCs |

Major Depression disease

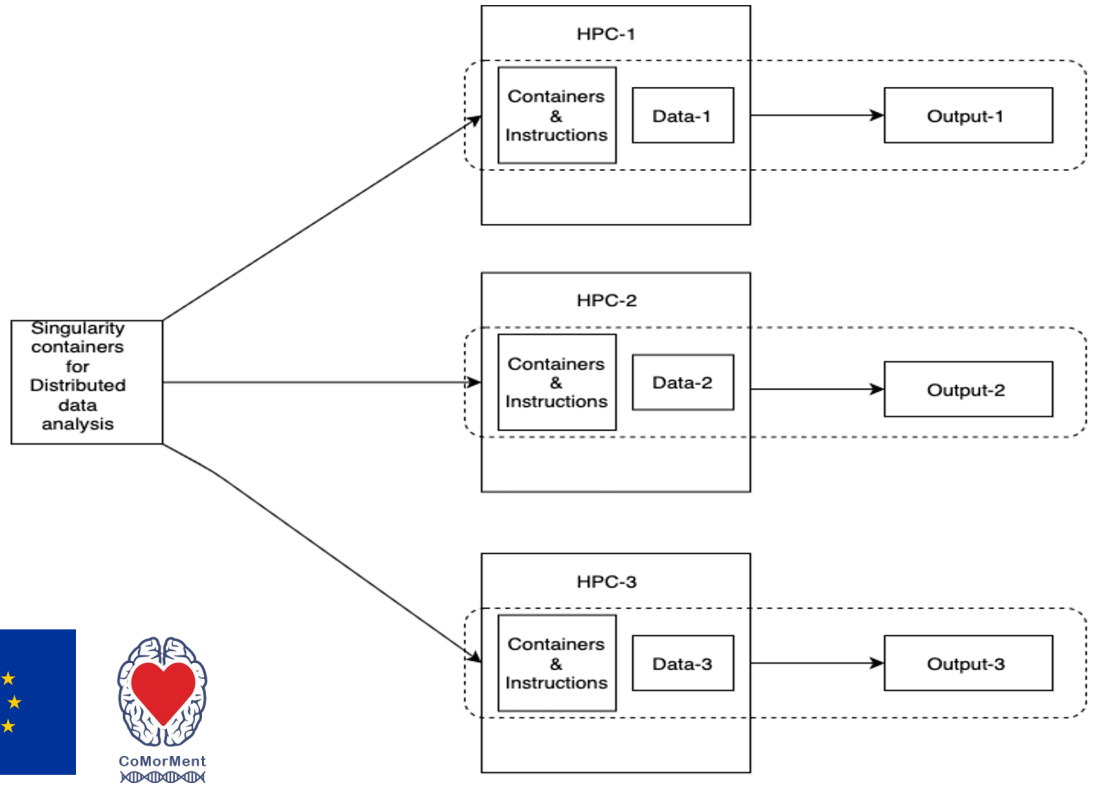



early onset Major Depression disease




CoMorMent

# Distributed & standardized procedure for uniform handling




System requirements have been defined and approved by sites

Available for download : https://github.com/comorment/containers/tree/main/singularity

Inclusion of tools for GWAS and post-GWAS analysis and visualization and available sample datasets and reference data

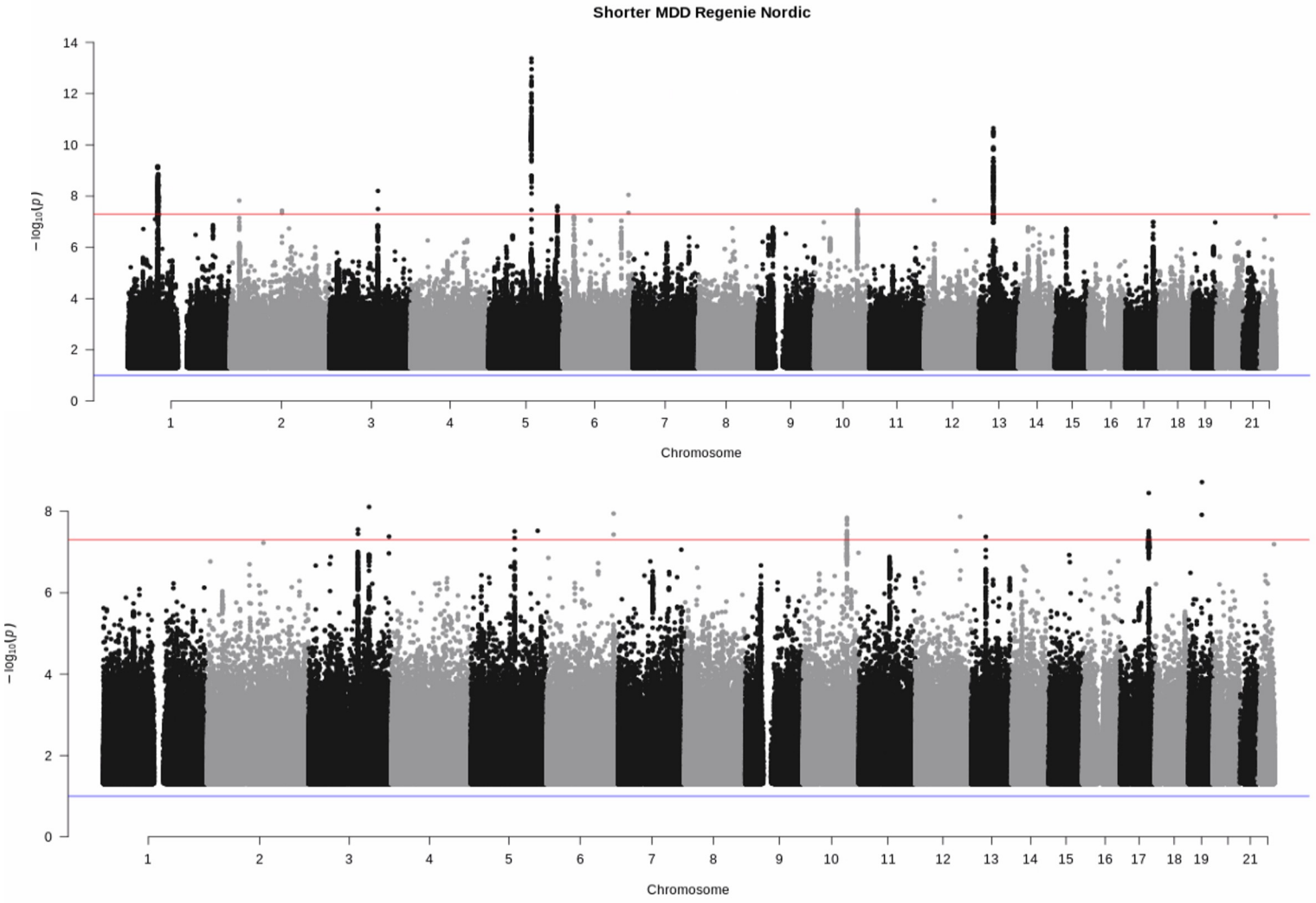
instructions for use cases : https://github.com/comorment/containers/tree/main/usecases

# Container content

| container | tool |
|---|---|
| hello.sif | demo example |
| gwas.sif | plink |
| gwas.sif | plink2 |
| gwas.sif | plink2_avx2 |
| gwas.sif | PRSice_linux |
| gwas.sif | simu_linux |
| gwas.sif | bolt |
| gwas.sif | gcta64 |
| gwas.sif | gctb |
| gwas.sif | king |
| gwas.sif | metal |
| gwas.sif | vcftools |
| gwas.sif | bcftools |
| gwas.sif | flashpca_x86-64 |
| gwas.sif | regenie |
| gwas.sif | GWAMA |
| gwas.sif | magma |
| gwas.sif | shapeit2 |
| gwas.sif | impute4 |
| gwas.sif | minimac4 |
| gwas.sif | bgenix |
| gwas.sif | cat-bgen |
| gwas.sif | edit-bgen |
| python3.sif | python3 |
| python3.sif | ldpred |
| python3.sif | mixer |
| python3.sif | python_convert |
| r.sif | R |
| r.sif | seqminer |
| r.sif | rareGWAMA |
| r.sif | GenomicSEM |
| r.sif | TwoSampleMR |
| r.sif | GSMR |
| r.sif | LAVA |
| r.sif | LAVA partitioning |
| saige.sif | SAIGE |
| enigma-cnv.sif | PennCNV |

CoMorMent

# Nordic MDD and eoMDD show significant loci




NORMENT
Norwegian Centre for
Mental Disorders Research

*The CoMorMent project has received funding form the European Union's Horizon2020 Research and Innovation Action under Grant agreement 847776.*

CoMorMent

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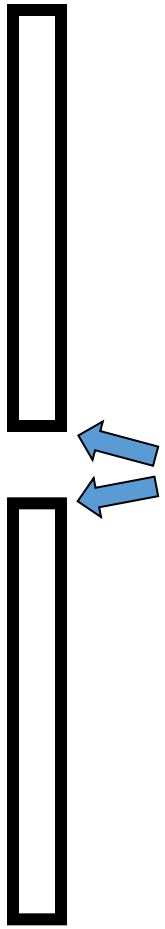
# Find the associated SNP

**Cases:**

AGAGCAGTCGACAG
AGAGCCGTCGACAT
AGAGCAGTCGACAG
AGAGCAGTCGACAG
AGAGCCGTCGACAT
AGAGCCGTCGACAT
AGAGCCGTCGACAG
AGAGCAGTCGACAG

**Controls:**

AGAGCAGTCGACAT
AGAGCAGTCGACAT
AGAGCAGTCGACAT
AGAGCCGTCGACAG
AGAGCCGTCGACAG
AGAGCAGTCGACAG
AGAGCCGTCGACAG
AGAGCCGTCGACAG

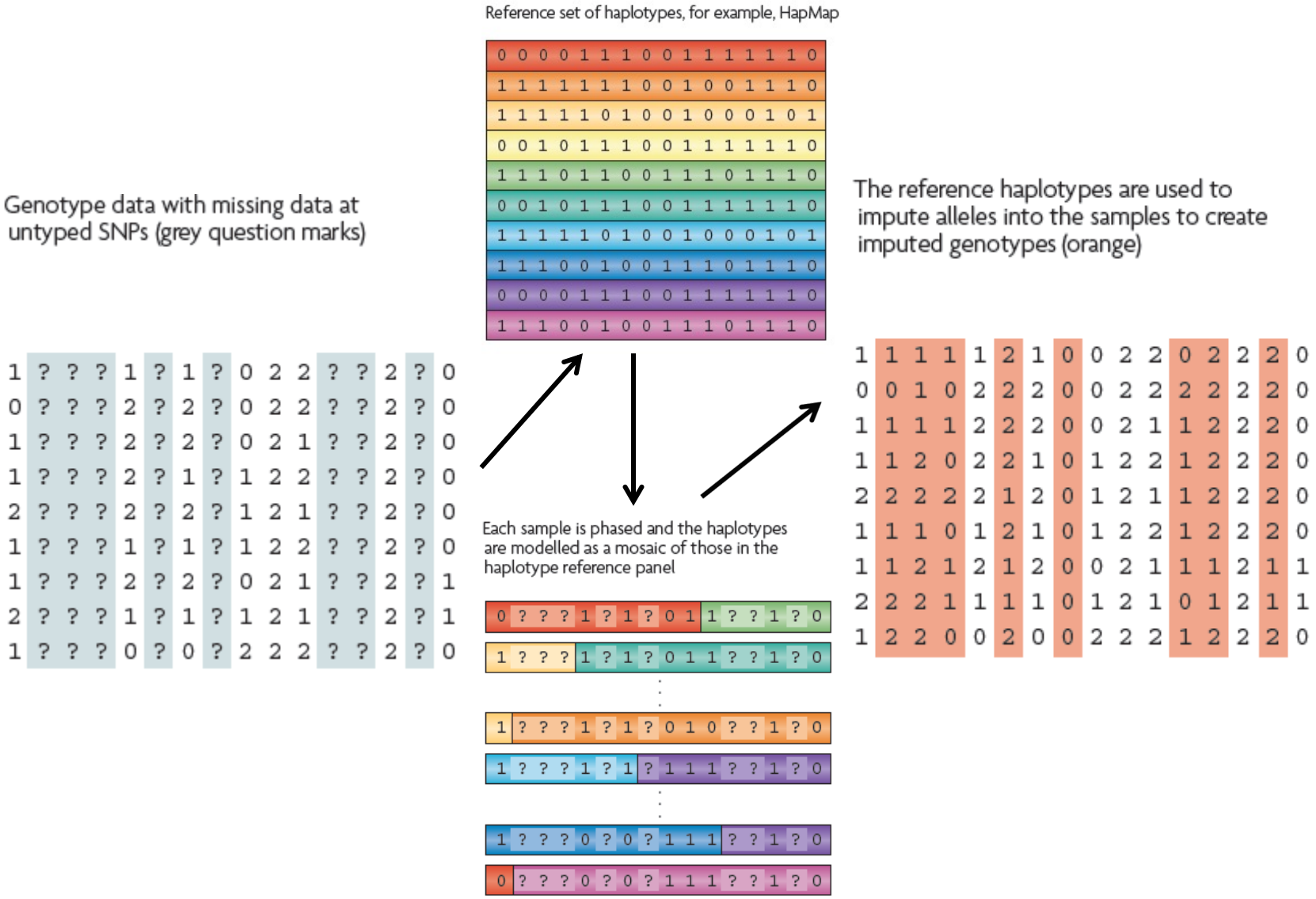


CGTGAGATCGACATGATAGCC
AGTGAGATCGACATGATAGTC
CGTGAGATCGACATGATAGCC
AGTGAGATCGACATGATAGCC
CGTGAGATCAACATGATAGCC
AGTGAGATCAACATGATAGCC
AGTGAGATCAACATGATAGTC
CGTGAGATCGACATGATAGCC

Associated SNP

AGTGAGATCAACATGATAGCC
CGTGAGATCGACATGATAGCC
CGTGAGATCAACATGATAGCC
CGTGAGATCGACATGATAGTC
CGTGAGATCAACATGATAGCC
AGTGAGATCGACATGATAGCC
CGTGAGATCGACATGATAGCC
AGTGAGATCGACATGATAGTC

# Imputation…

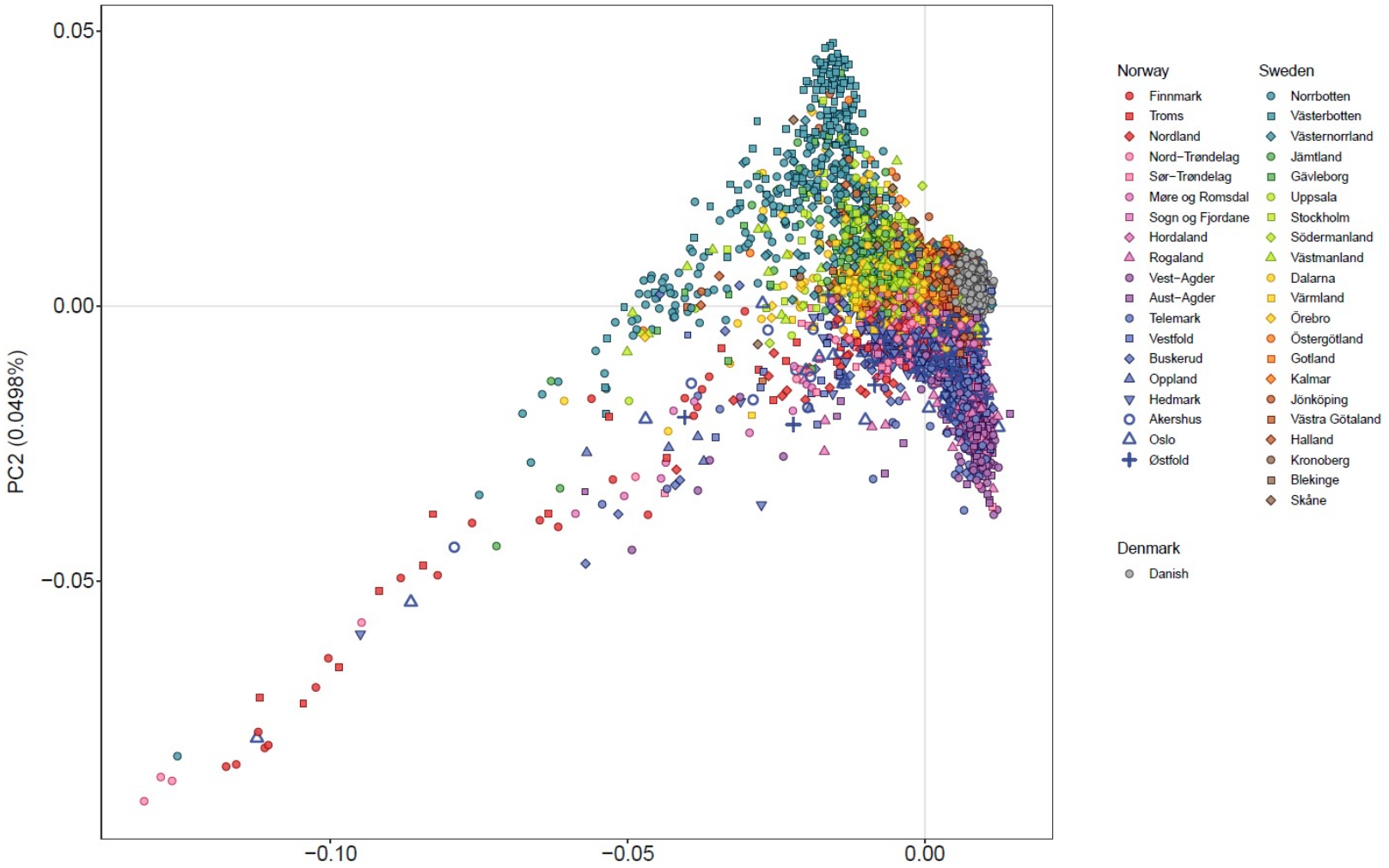



(Marchini & Howie 2010)

# Genetic structure in the Nordics

2985 Norwegians
3519 Swedes
1606 Danes

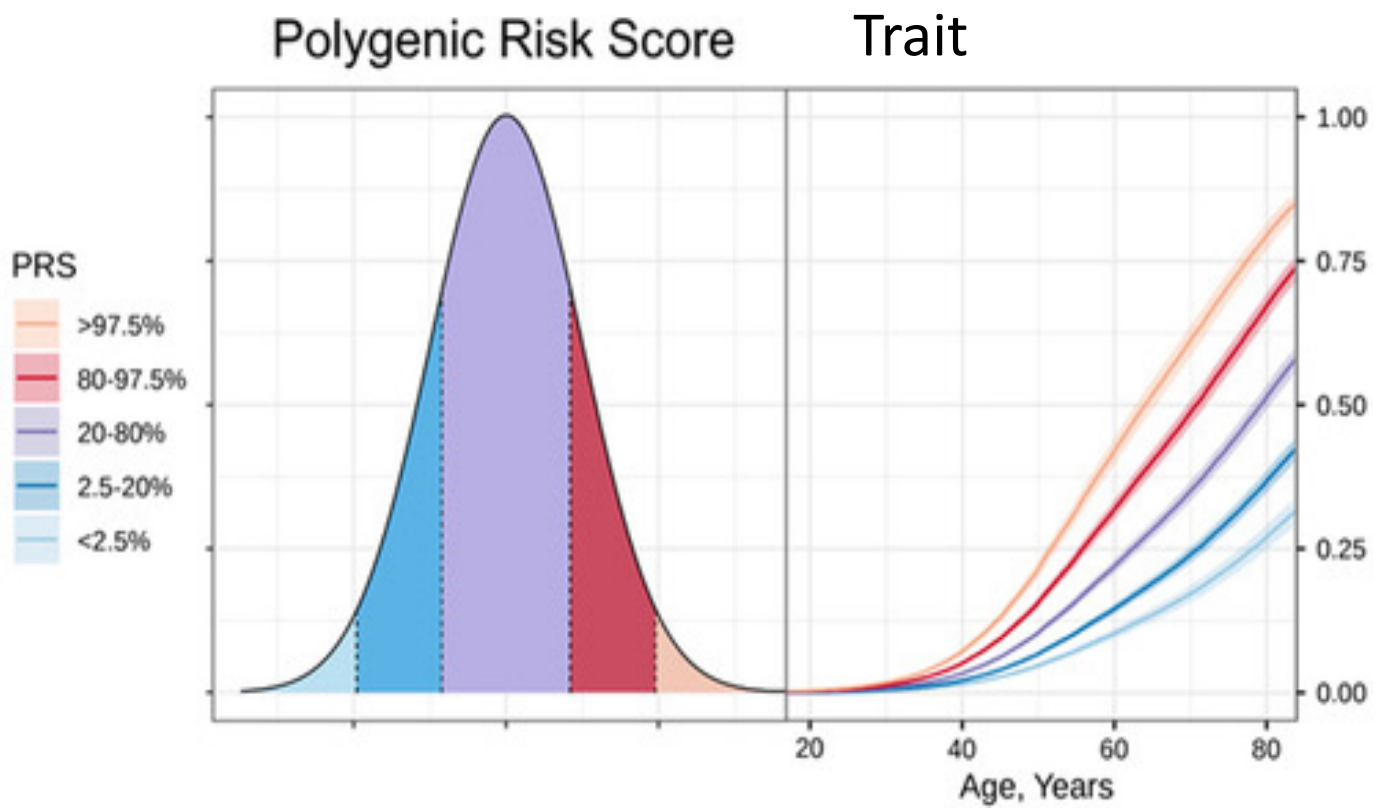
PCA plot



# Example imputation

| chr1 | Estonian | HRC | NORGENE |
|---|---|---|---|
| N imputed SNPs | 2,203,149 | 3,066,134 | 1,768,482 |
| N imputed SNPs (INFO > 0.8) | 863,824 | 1,498,665 | 1,084,341 |
| N imputed SNPs (MAF 1%) | 672,704 | 610,806 | 854,52 |
| Median INFO | 0.56 | 0.73 | 0.89 |
| | | | |
| N imputed SNPs (INFO > 0.8 & MAF > 1%) | 601,772 | 598,272 | 768,197 |
| MEDIAN INFO (INFO > 0.8 & MAF > 1%) | 0.9900 | 0.9982 | 0.9960 |
| | | | |
| Overlap (position and change, no imp qc) | Estonian | NORGENE | 874,791 |
| | HRC | NORGENE | 1,111,409 |
| | HRC | Estonian | 1,936,512 |

# Polygenic risk score




Polygenic risk score:

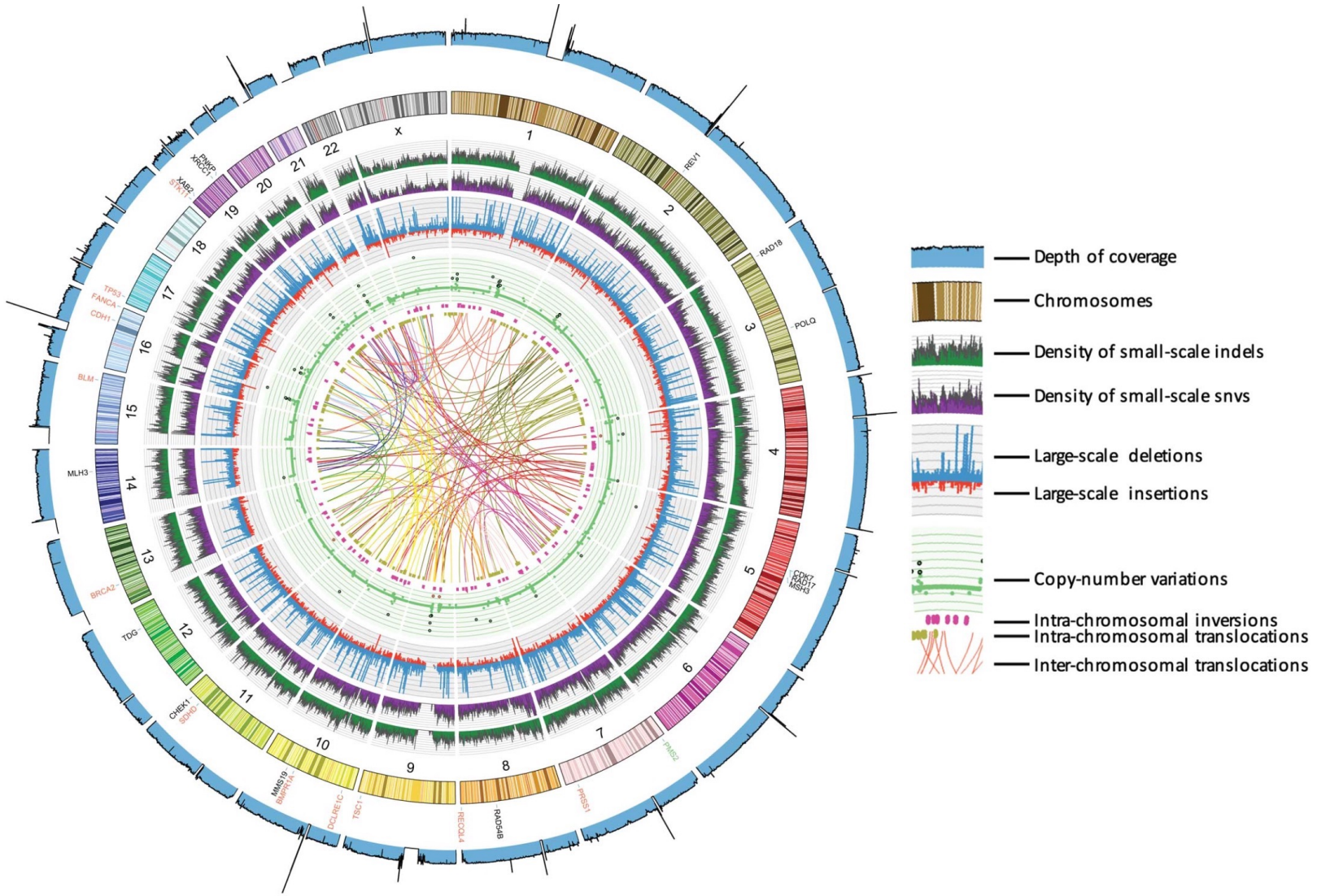
A set of SNPs that collectively
may predict a risk, based on GWAS studies

e.g.: Does an individual have a high risk that warrants monitoring or treatment

May depend on the population

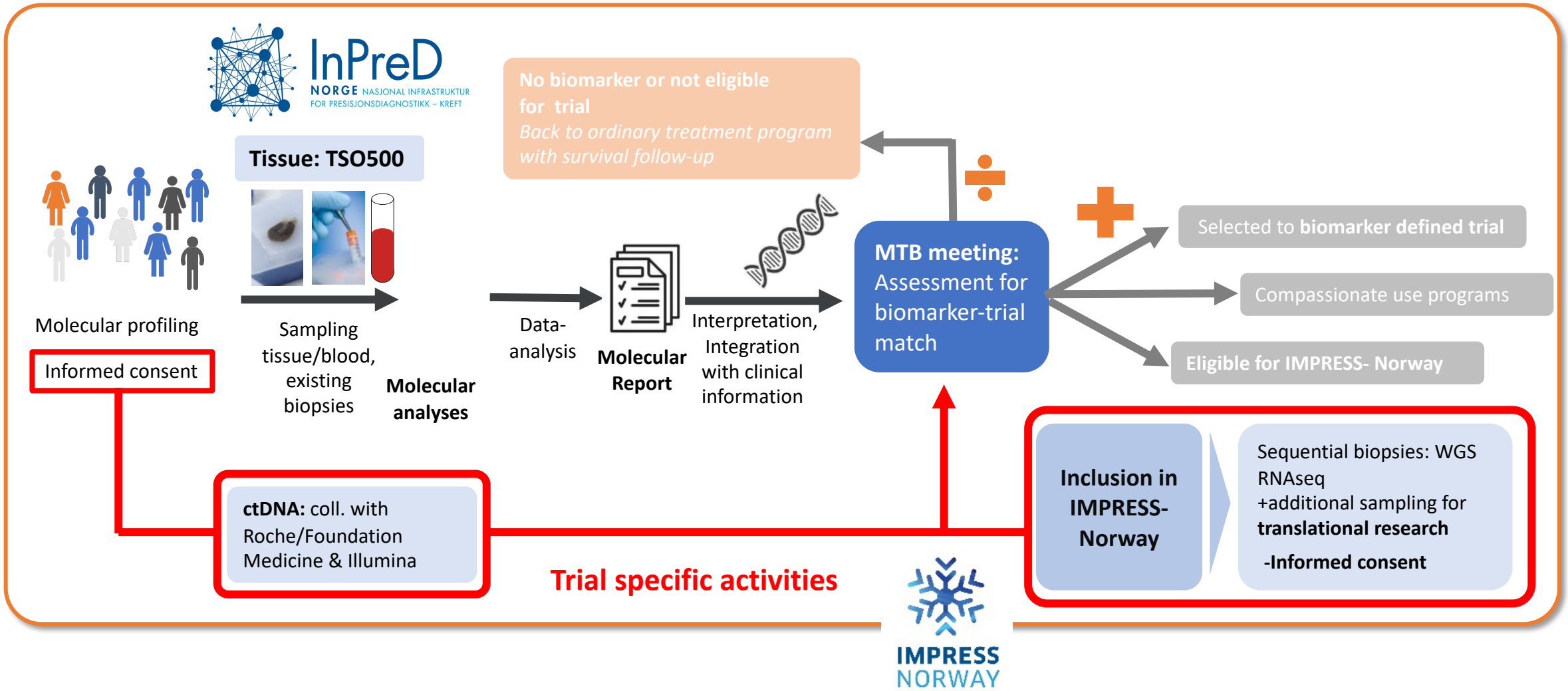
Cancer risks, diabetes, etc

# Cancer: Many layers of perturbation




Genetics
Epigenetics

# The interaction between InPreD and IMPRESS – Norway



MDT OUS

# IPD-XXX

*Papillary thyroid carcinoma*

TSO500 DNA RNA | Jan 2022 | MDT Report

Version string: 2.2.0.12/21-06-07/0.9.1/0.6.1/hg19/T

Patient: F/XXy

Radium

Tumor type: Papillary thyroid cancer

Y of D: 20xx

Bio-material: Distal met post-treatment FFPE

Xx-xxxx

Tumor content: 40%

F1 Liquid CDx

Gene Alterations

Overlap TSO500: YES

Add. biomarkers: YES

PIK3CA E545K, E542K

InPreD Infrastructure for Precision Diagnostics @OUS

VAF=variant allele fraction , CN=copy number

Level of evidence = ESCAT guidelines

## SUMMARY OF KEY FINDINGS

| | | | | | |
|---|---|---|---|---|---|
| **SNVs/ indels** | *Total nr of SNVs/indels* in protein coding sequence: **alter protein coding sequence** | 15<br>12<br>9 | **Copy number variants** | None > 6 copies<br>Loss of CDKN2A/2B | **Gene fusions** RNA: CCDC6-RET |
| TMB | Mut/ Mb: 7.8 (Low 5 / Intermediate 20 / High) Potentially overestimated TMB* | | MS status | Stable | |

## Biomarkers and variant/gene-drug association

| **Biomarkers potentially relevant for immune therapy** | None reported |
|---|---|

| Gene | Variant | Type | VAF/ CN | Variant GoF/ LoF | Pathway/ function | Therapeutic context: Sensitive | Therapeutic context: Resistant | Level of Evidence: Patient's tumor type | Level of Evidence: Other tumor type |
|---|---|---|---|---|---|---|---|---|---|
| **RET** | CCDC6 -RET | fusion | | GoF | MAPK Pi3K/AKT | TKI | | 1 | |
| **PIK3CA** (F1 Liquid) | E545K<br>E542K | missense | 1,2%<br>1.2% | GoF | Pi3K/AKT | PI3Ki | | 3 | 1 |

| | |
|---|---|
| *Variant classification (RET)* | The fusion CCDC6 (exon 2 ) and RET (exon 12) was assessed to be in frame and kinase domain intact. The fusion is a known oncogenic variant with constitutive kinase activation. RET fusion is a biomarker for RET targeted therapy in subtypes of thyroid and lung cancers. Clinical data is emerging from trials with RET-selective inhibitors*. |
| *Variant classification (PIK3CA)* | The PIK3CA hotspot variants lead to constitutively activated PI3K/AKT pathway. The low variant allele frequency (F1 Liquid) suggest subclones, possibly as a result of treatment resistance. Targeting PIK3CA is app. for a subgroup of breast cancer but the variants have no clear treatment implication in thyroid cancer. |

## Additional results: Variants of unknown significance in treatment relevant genes

| Gene/Variant | Comments |
|---|---|
| **RAD51C** R370Q | RAD51C is involved in HR DNA repair. The variant is in the C terminal domain of the gene but of unknown biological significance. |

## Variants that alter protein coding sequence (N=10)

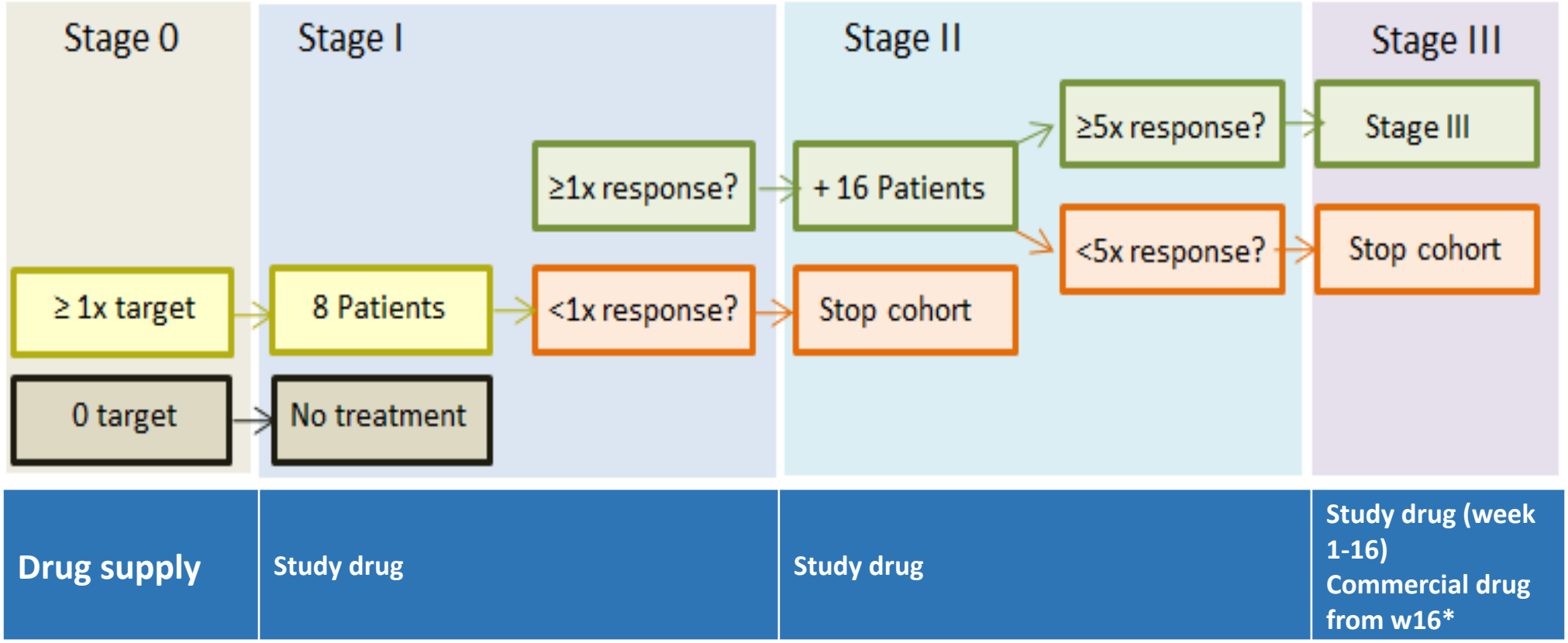
| Gene Symbol | Protein change | Coding status | VAF tumor |
|---|---|---|---|
| **DICER1** | E1705Q | missense | *0.024* |
| **IRF4** | G202D | missense | 0.323 |
| **SOX17** | D131N | missense | 0.358 |
| **MST1R** | X1401= | stop_retained | *0.062* |
| **PPP6C** | E237K | missense | 0.357 |
| **C11ORF30** | R840H | missense | 0.485 |
| **IGF1R** | S752R | missense | 0.473 |
| **NSD1** | Q784E | missense | 0.437 |
| **RAD51C** | R370Q | missense | 0.336 |
| **TERT** | c.-124 C>T | Non-coding | 0.471 |

*According to ESMO guidelines, recommendation for genetic counseling does not apply for the variants reported by TSO500 for this sample.*

Mutation hotspot

*; Registrational results of LOXO-292 in patients with RET-altered thyroid cancers - ScienceDirect ; and PMID: 32846061.

# Novel reimbursement models for PCM - from a trial setting to implementation




*The design of stage III is a phase 1 (week 1 to 16) where patients will be treated with the investigational products (IP), provided by the manufacturer. If clinical benefit (defined as confirmed objective response or stable disease at 16 weeks and measured more than once, at least 28 days apart) is observed for an individual patient at 16 weeks, treatment for that individual patient with the IP will continue in phase 2

# Shared study-design across Nordic – DRUP collaboration based on tumor-agnostic approach

- Individual treatment approach
- Targeted treatment

DRUP the Drug Rediscovery Protocol
Expanded use of existing anticancer drugs

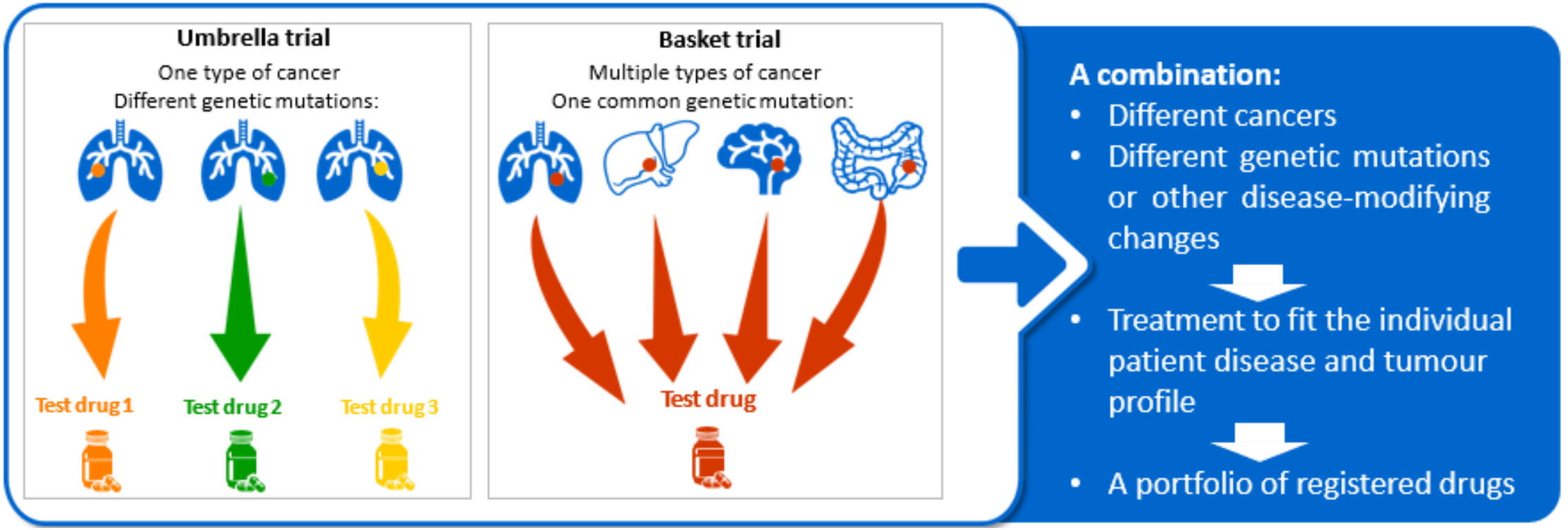
TAPUR Targeted Agent and Profiling Utilization Registry Study | ASCO
Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

ProTarget
A Danish Nationwide Clinical Trial on Targeted Anti-Cancer Treatment based on Molecular Profiling

MEGALiT

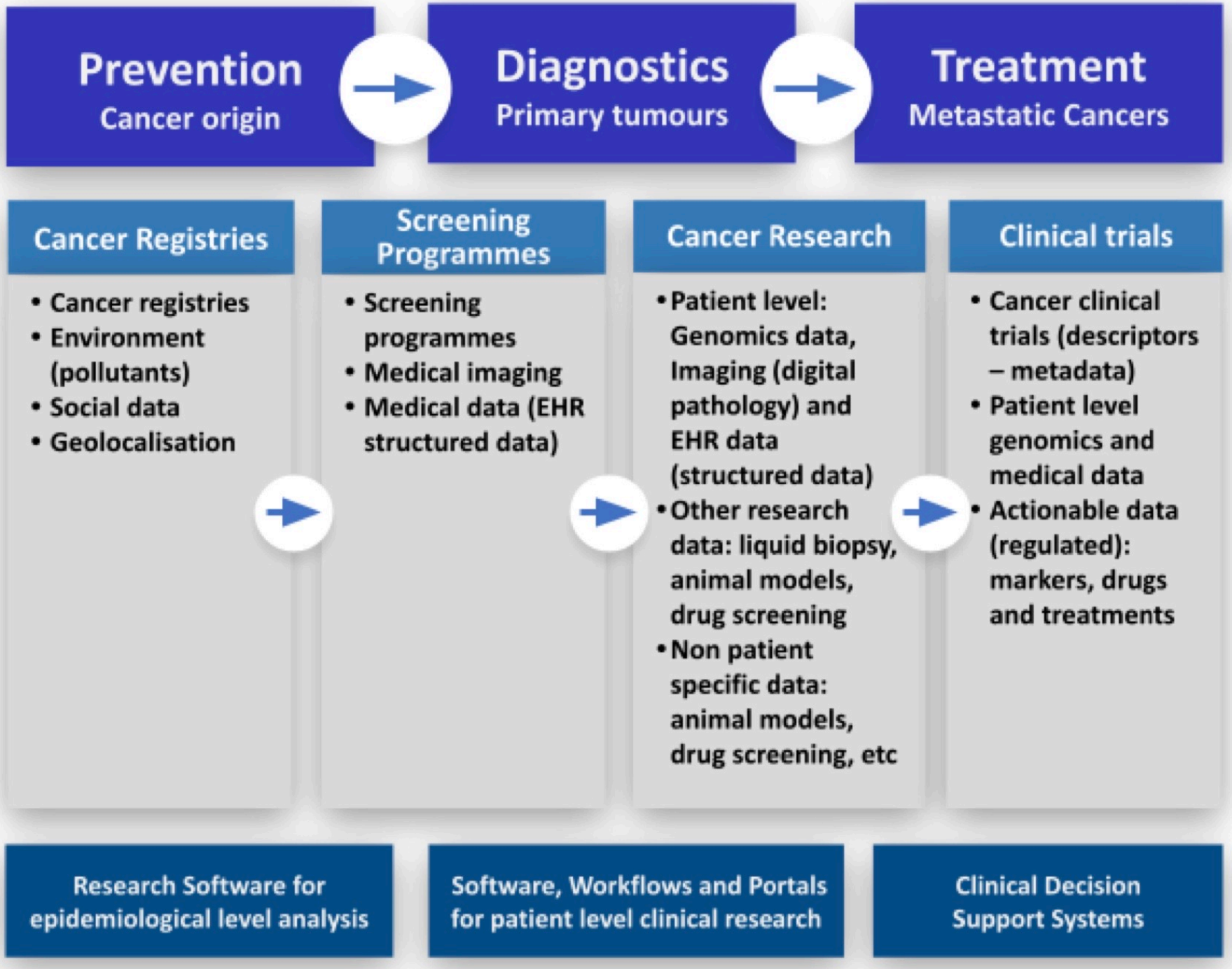
IMPRESS NORWAY

FINPROVE
DRUG REDISCOVERY PROGRAM IN FINLAND



# EOSC4Cancer

Starting EU project



http://ega.elixir.no

Federated European Genome-phenome Archive Norway

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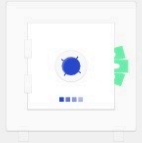
# Federated EGA Norway node

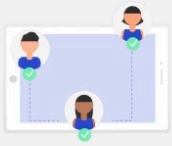
LS LOGIN

The Federated EGA (European Genome-phenome Archive) is a distributed solution for sharing and exchange of human -omics data across national borders. Federated instance collects metadata of -omics data collections stored in national or regional archives and make them available for search through the main EGA portal.

Searchable



Secure



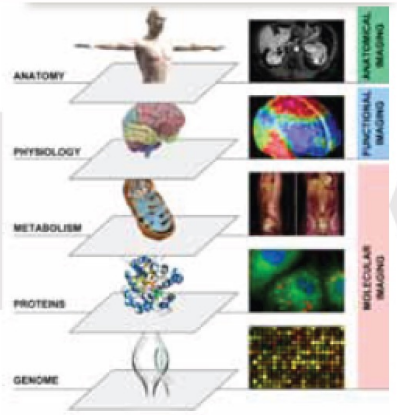
Shareable

# Big Data

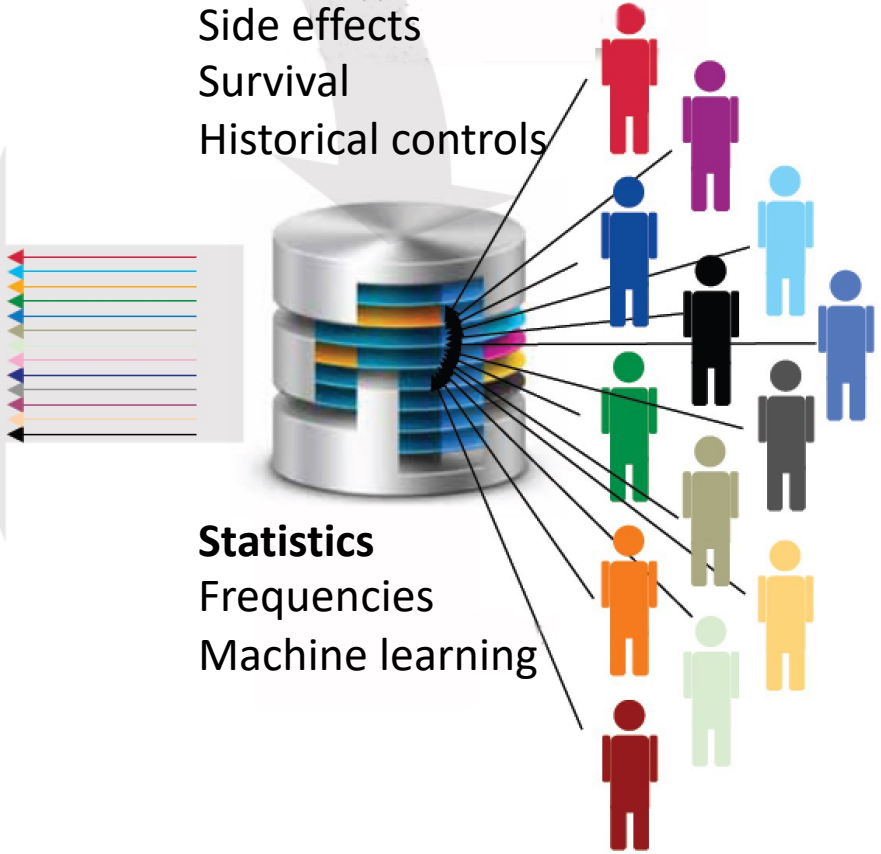
Individual

Big data in health

Biomarkers
Treatment
Reponse eval.
Side effects




**Database**
Biomarkers
Treatment
Reponse
Side effects
Survival
Historical controls



**Statistics**
Frequencies
Machine learning

BACKGROUND DOCUMENT

# Proposal for a regulation - The European Health Data Space

COM(2022) 197/2

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## Details

| | |
|---|---|
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| **Author** | Directorate-General for Health and Food Safety |

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