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# Ethical issues with predictions based on OMICS or imaging data

Baptiste Couvy-Duchesne  
**IMind Master**

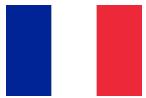
[baptiste.couvy@icm-institute.org](mailto:baptiste.couvy@icm-institute.org)  
<https://github.com/baptisteCD>

@BaptisteCouvy 

# A bit about me

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2010-2012:



Dual degree in **statistics and epidemiology**

*ENSAI, Rennes 1 University*

2013-2017:



PhD in **neuroimaging genetics**

*Queensland Brain Institute*

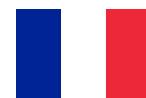
2017-2019:



Post-doctorate in **complex trait genetics**

*Institute for Molecular Bioscience*

2019-Now:



NHMRC Fellowship, CNRS, INRIA - **neuroimaging**

*Institute for Molecular Bioscience*

*ARAMIS-lab, Paris Brain Institute*

*INRIA*



Margaret Wright



Peter Visscher  
Naomi Wray  
Jian Yang



Olivier Colliot

# Prediction - train and test samples

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**Train algorithm**

Estimate parameters of the model



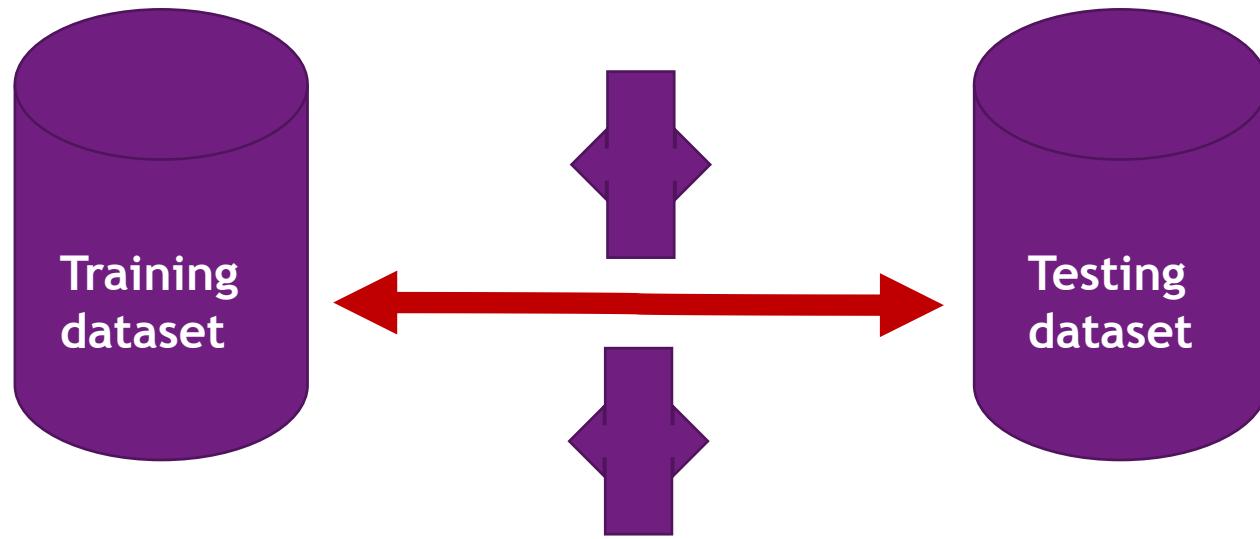
**Evaluate prediction accuracy**

Prediction metric (AUC, sensitivity, specificity, correlation, R<sup>2</sup>, MAE)

# Prediction - data leakage

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**Data leakage** - (part of) test dataset used or seen in training

- e.g. feature selection, unsupervised learning, separate visits of same individual

**Risk : inflated prediction accuracy, overfitting**

**Can be quite common in ML articles (e.g. Ansart et al., 2021)**

# Prediction metrics

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Trait of interest	Predictor	Metric
Binary	Binary	Sensitivity, specificity, balanced accuracy, OR
Binary	Continuous	AUC, OR, R <sup>2</sup>
Continuous	Binary / Continuous	Correlation, R <sup>2</sup> , MAE

Prediction	Pred-control	Pred-case
Trait		
Control	TN	FP
Case	FN	TP

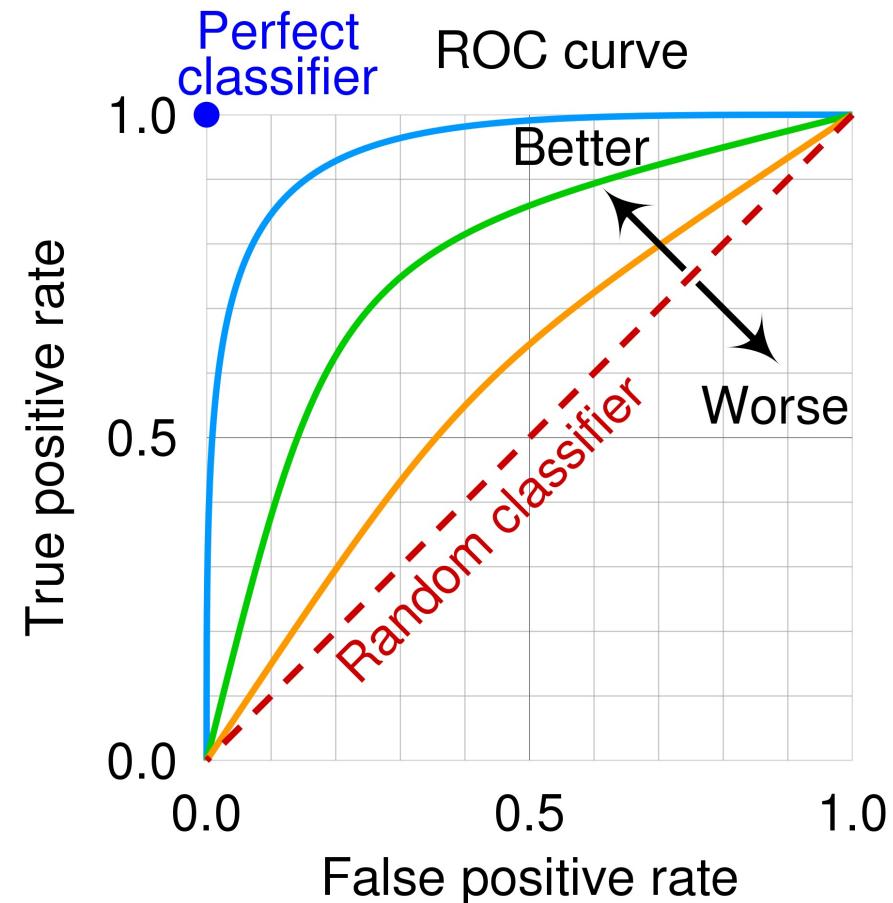
$$\text{TPR / Recall / Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

# Prediction metrics

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Trait of interest	Predictor	Metric
Binary	Binary	Sensitivity, specificity, balanced accuracy, OR
Binary	Continuous	AUC, OR, R <sup>2</sup>
Continuous	Binary / Continuous	Correlation, R <sup>2</sup> , MAE



# Prediction metrics

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Trait of interest	Predictor	Metric
Binary	Binary	Sensitivity, specificity, balanced accuracy, OR, R <sup>2</sup>
Binary	Continuous	AUC, OR, R <sup>2</sup>
Continuous	Binary / Continuous	Correlation, R <sup>2</sup> , MAE

$$TraitOfInterest \sim \mu + \beta \times Predictor + \alpha \times Covariate + \epsilon$$

*Logistic regression:* OR = exp( $\beta$ )

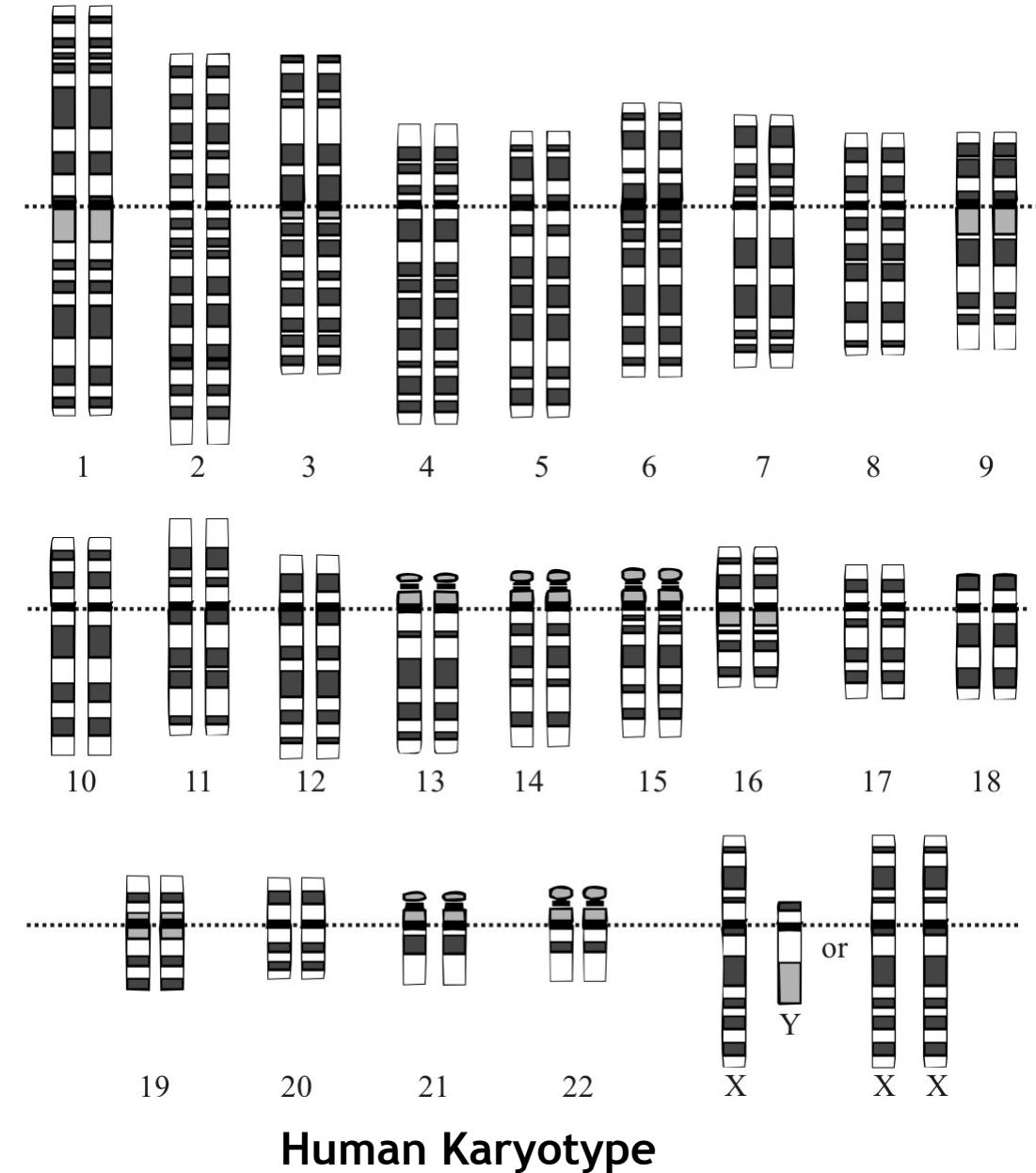
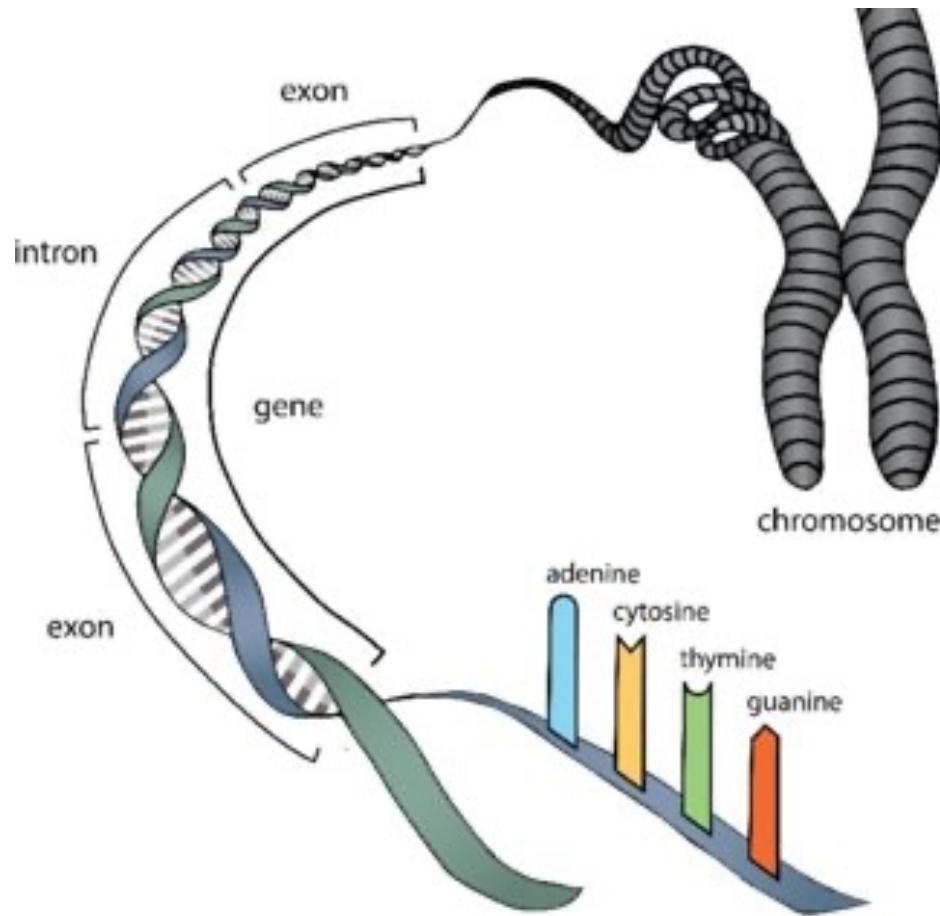
*Logistic regression:* pseudo – R<sup>2</sup> from likelihood

$$Gaussian\ regression: cor = \frac{\beta \times \sigma_{TraitOfInterest}}{\sigma_{Predictor}}$$

*Gaussian regression:* R<sup>2</sup> = cor<sup>2</sup>

# Prediction - Genetic data

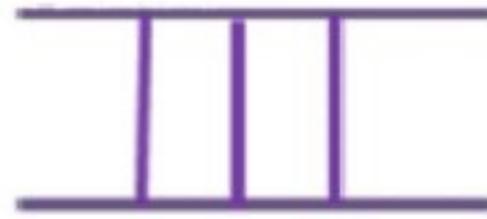
8



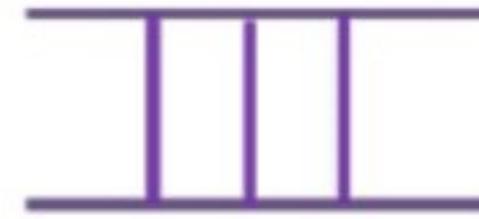
# Single Nucleotide Polymorphism (SNP)

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DNA



GC<sub>GA</sub>  
CGCT

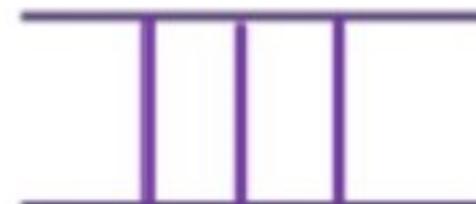


SNP

Polymorphism  
(SNP)



GT<sub>GA</sub>  
CACT



rsNumber  
Chromosome:BasePair

Reference Allele: C  
Alternate Allele: T

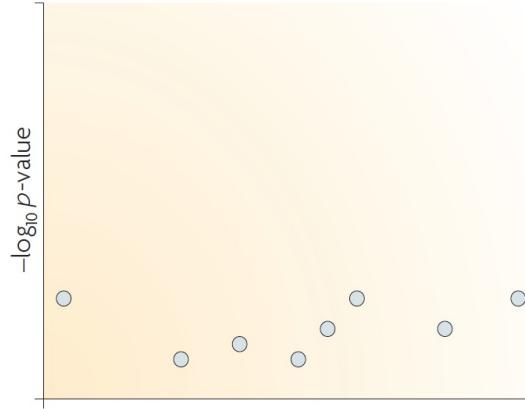
SNP value: 0 - 1 - 2  
CC - CT / TC - TT

# Genetic data in practice - structured

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## Box 1 | How genotype imputation works

**b** Testing association at typed SNPs may not lead to a clear signal



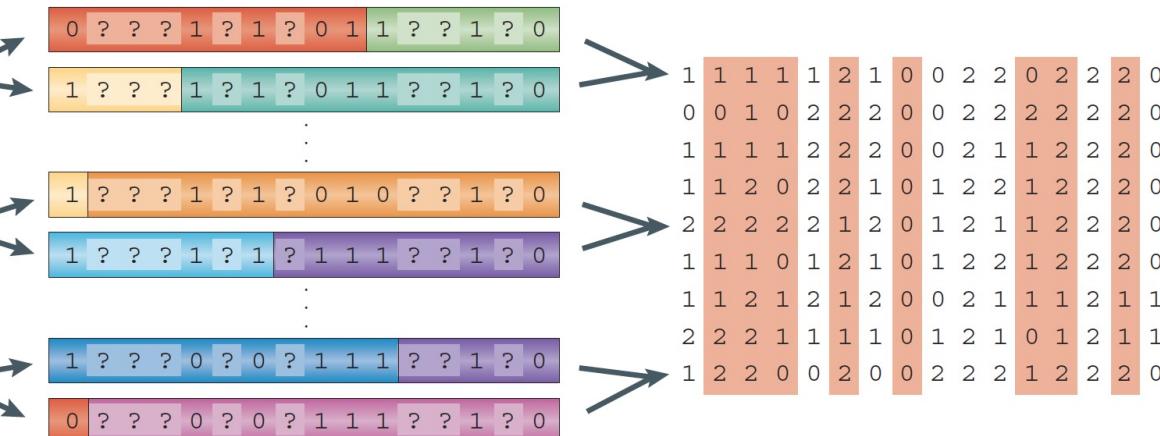
**a** Genotype data with missing data at untyped SNPs (grey question marks)

1	?	?	?	1	?	1	?	0	2	2	?	?	2	?	0
0	?	?	?	2	?	2	?	0	2	2	?	?	2	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	0
1	?	?	?	2	?	1	?	1	2	2	?	?	2	?	0
2	?	?	?	2	?	2	?	1	2	2	?	?	2	?	0
1	?	?	?	1	?	1	?	1	2	2	?	?	2	?	0
2	?	?	?	2	?	2	?	1	2	1	?	?	2	?	0
1	?	?	?	1	?	1	?	2	2	2	?	?	2	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	2	?	1
2	?	?	?	1	?	1	?	1	2	1	?	?	2	?	1
1	?	?	?	0	?	0	?	1	1	1	?	?	1	?	0

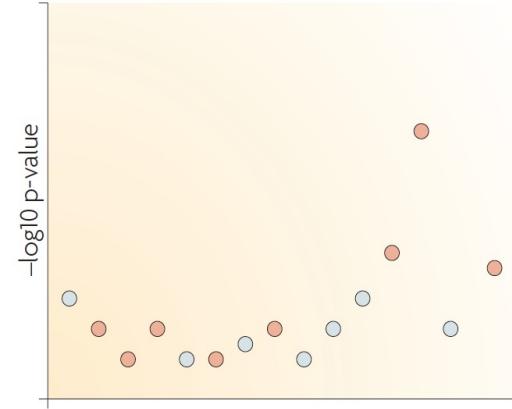
**d** Reference set of haplotypes, for example, HapMap

0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	1	1	1	1	0	0	1	0	0	1	1	1	0
1	1	1	1	1	1	0	1	0	0	1	0	0	0	1	0
0	0	1	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	0	1	1	0	0	1	1	1	0	1	1	1	0
0	0	1	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	1	1	0	1	0	0	1	0	0	0	1	0	1
1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0
0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	0
1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0

**c** Each sample is phased and the haplotypes are modelled as a mosaic of those in the haplotype reference panel



**f** Testing association at imputed SNPs may boost the signal



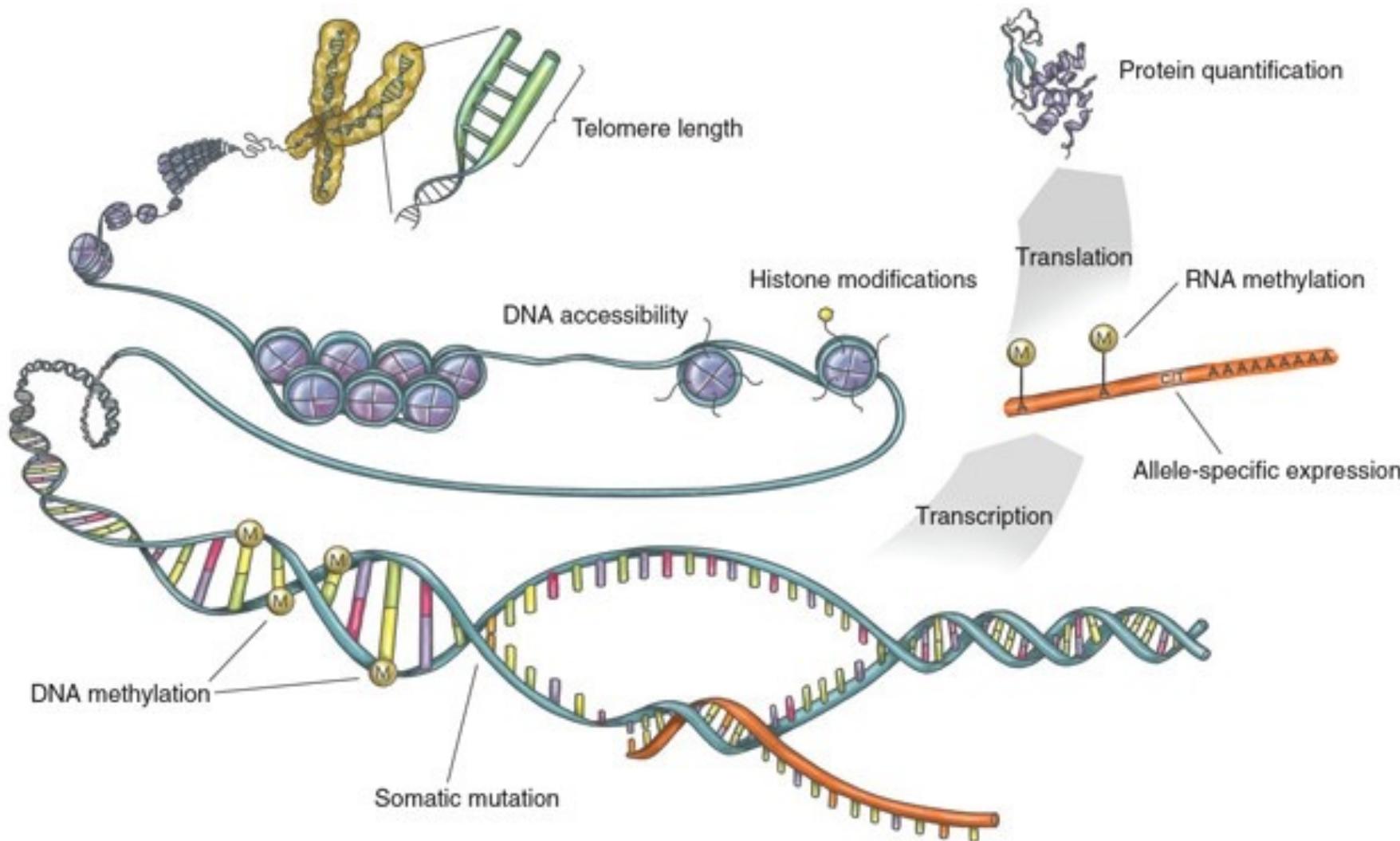
*Genotype imputation for genome-wide association studies.*  
Marchini et al., 2010.

**Other genetic variants:**  
Indels, CNVs, tri-allelic SNPs.

Of note SNPs may be population specific

# Methylation & Gene Expression data

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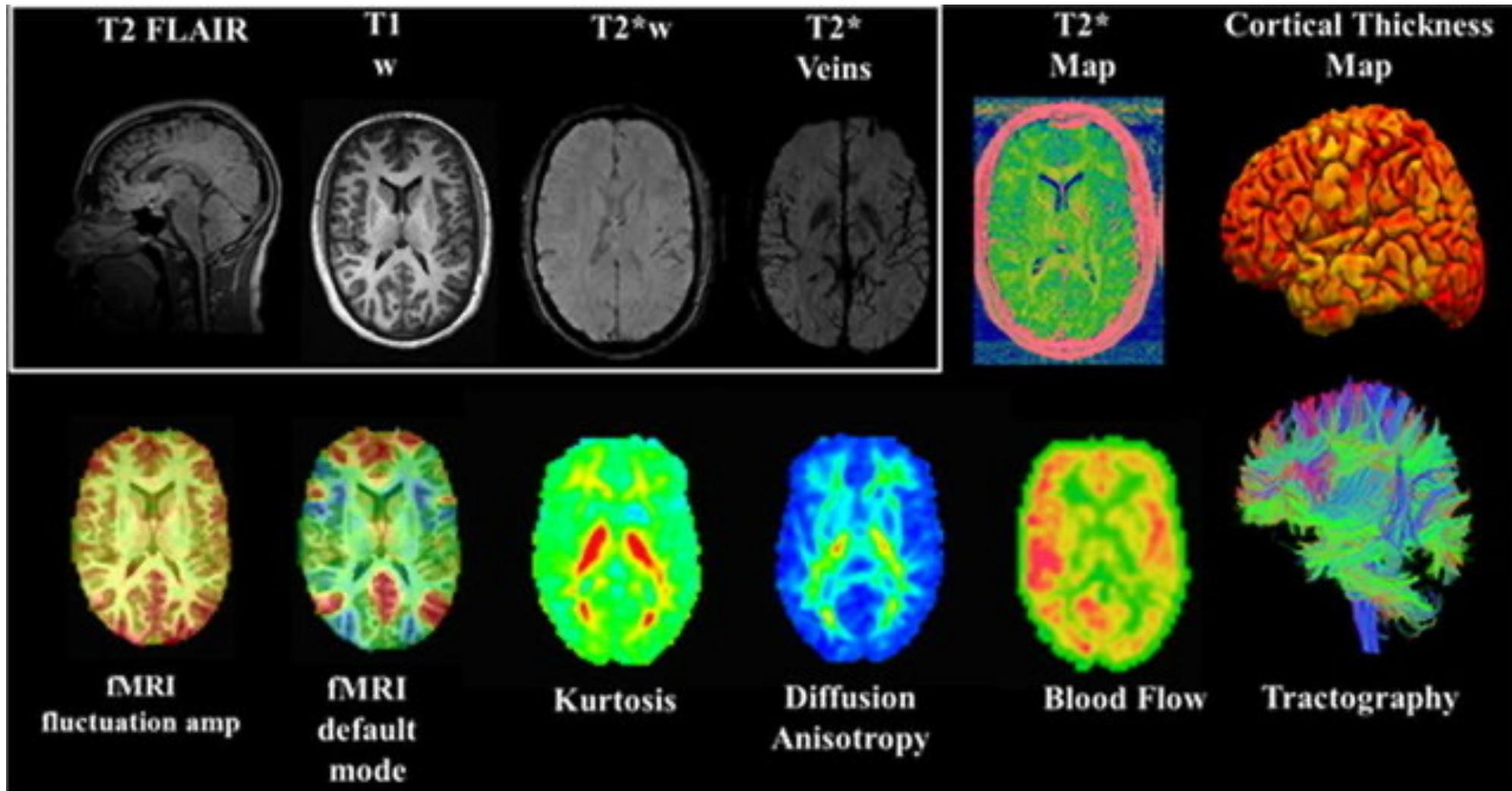


**Methylation of CpG sites  
(tissue / cell specific)**

**Gene expression  
(tissue specific)**

# Brain MRI images and features

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A National Study on the Effects of Concussion in Collegiate Athletes and US Military Service Academy Members: The NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium Structure and Methods. Broglio et al., 2017.

# Known confusion factors & confounders

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	Genetic	Omics	Brain MRI
Demographics	Age, sex	Age, sex	Age, sex, body size, head size
Technical	Site, batch, genotyping chip	Site, batch, assay	Site, MRI machine, study, field strength
Specific	Genetic ancestry,	Genetic ancestry, sample composition (e.g. cells), tissue type	Head motion, magnet drift

**How to take them into account:**

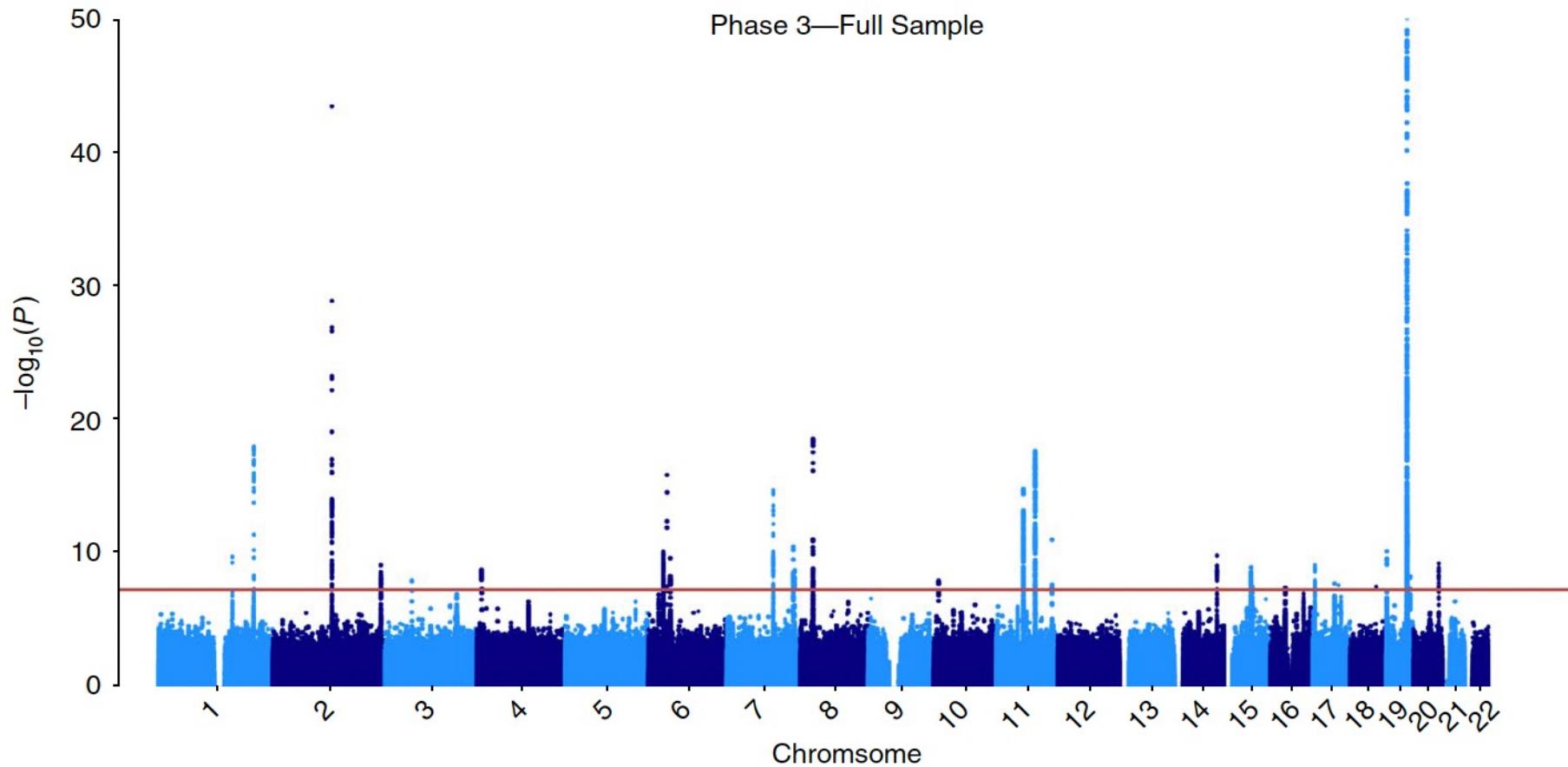
- Covariates, in training
- Representativity of trait/test samples
- Generalisability of prediction

# Polygenic Risk Scores - Manhattan plot

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Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk.  
Jansen et al., 2019

71,880 cases;  
383,378 controls



**Fig. 2 | GWAS meta-analysis for AD risk ( $N = 455,258$ ).** Manhattan plot displays all associations per variant ordered according to their genomic position on the x axis and showing the strength of the association with the  $-\log_{10}$ -transformed  $P$  values on the y axis. The y axis is limited to enable visualization of non-APOE loci. For the phase 3 meta-analysis, the original  $-\log_{10} P$  value for the APOE locus is 276.

## Risk prediction of late-onset Alzheimer's disease implies an oligogenic architecture

Qian Zhang<sup>1</sup>, Julia Sidorenko<sup>1</sup>, Baptiste Couvy-Duchesne<sup>1</sup>, Riccardo E. Marioni<sup>2</sup>, Margaret J. Wright<sup>3,4</sup>, Alison M. Goate<sup>5,6</sup>, Edoardo Marcora<sup>5,6</sup>, Kuan-lin Huang<sup>5,6</sup>, Tenielle Porter<sup>7</sup>, Simon M. Laws<sup>7,8</sup>, & Australian Imaging Biomarkers and Lifestyle (AIBL) Study\*, Perminder S. Sachdev<sup>9,10</sup>, Karen A. Mather<sup>9,11</sup>, Nicola J. Armstrong<sup>12</sup>, Anbupalam Thalamuthu<sup>9,11</sup>, Henry Brodaty<sup>9,13</sup>, Loic Yengo<sup>1</sup>, Jian Yang<sup>1</sup>, Naomi R. Wray<sup>1,3</sup>, Allan F. McRae<sup>1</sup> & Peter M. Visscher<sup>1</sup>✉

Genetic association studies have identified 44 common genome-wide significant risk loci for late-onset Alzheimer's disease (LOAD). However, LOAD genetic architecture and prediction are unclear. Here we estimate the optimal *P*-threshold ( $P_{\text{optimal}}$ ) of a genetic risk score (GRS) for prediction of LOAD in three independent datasets comprising 676 cases and 35,675 family history proxy cases. We show that the discriminative ability of GRS in LOAD prediction is maximised when selecting a small number of SNPs. Both simulation results and direct estimation indicate that the number of causal common SNPs for LOAD may be less than 100, suggesting LOAD is more oligogenic than polygenic. The best GRS explains approximately 75% of SNP-heritability, and individuals in the top decile of GRS have ten-fold increased odds when compared to those in the bottom decile. In addition, 14 variants are identified that contribute to both LOAD risk and age at onset of LOAD.

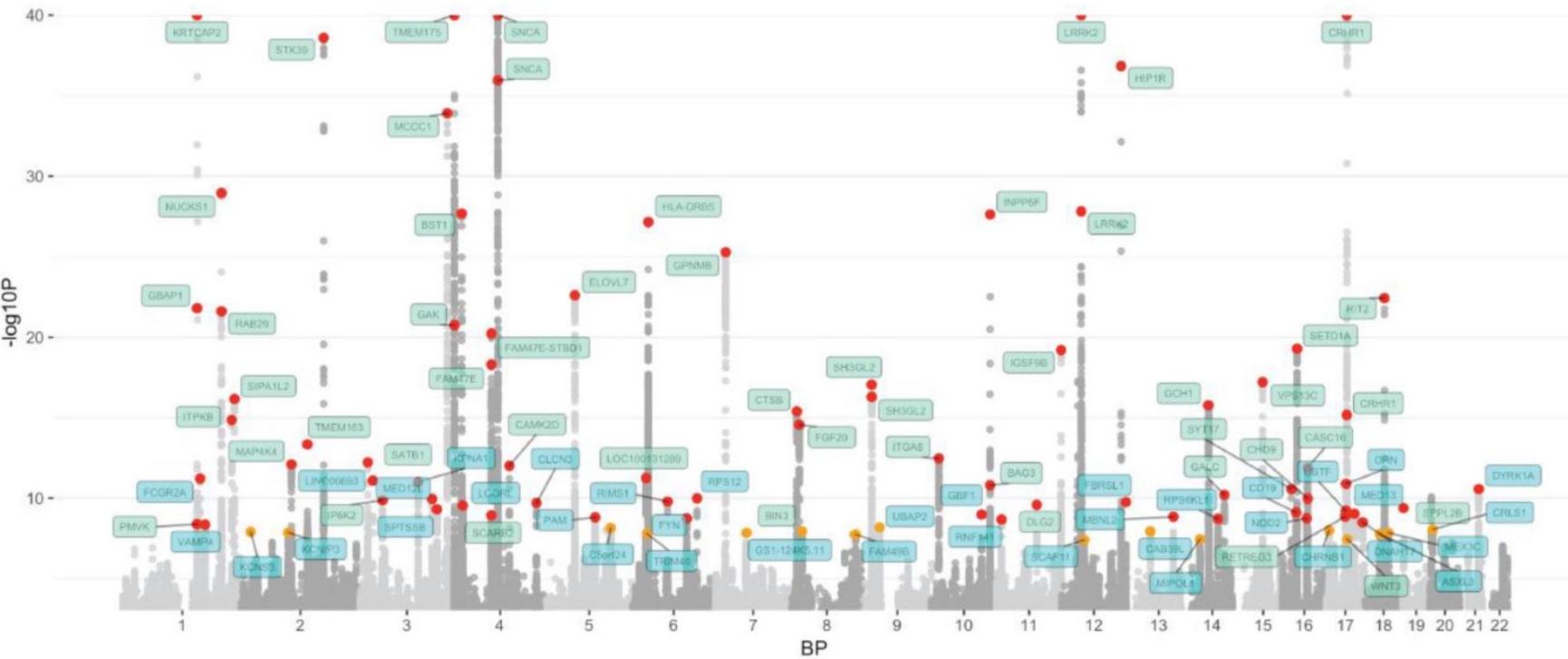
# Parkinson's disease - Manhattan plot

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Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-genome wide association study

Nalls et al.,

analysis of 7.8M SNPs in 37.7K cases, 18.6K UK Biobank proxy-cases (having a first degree relative with PD), and 1.4M controls



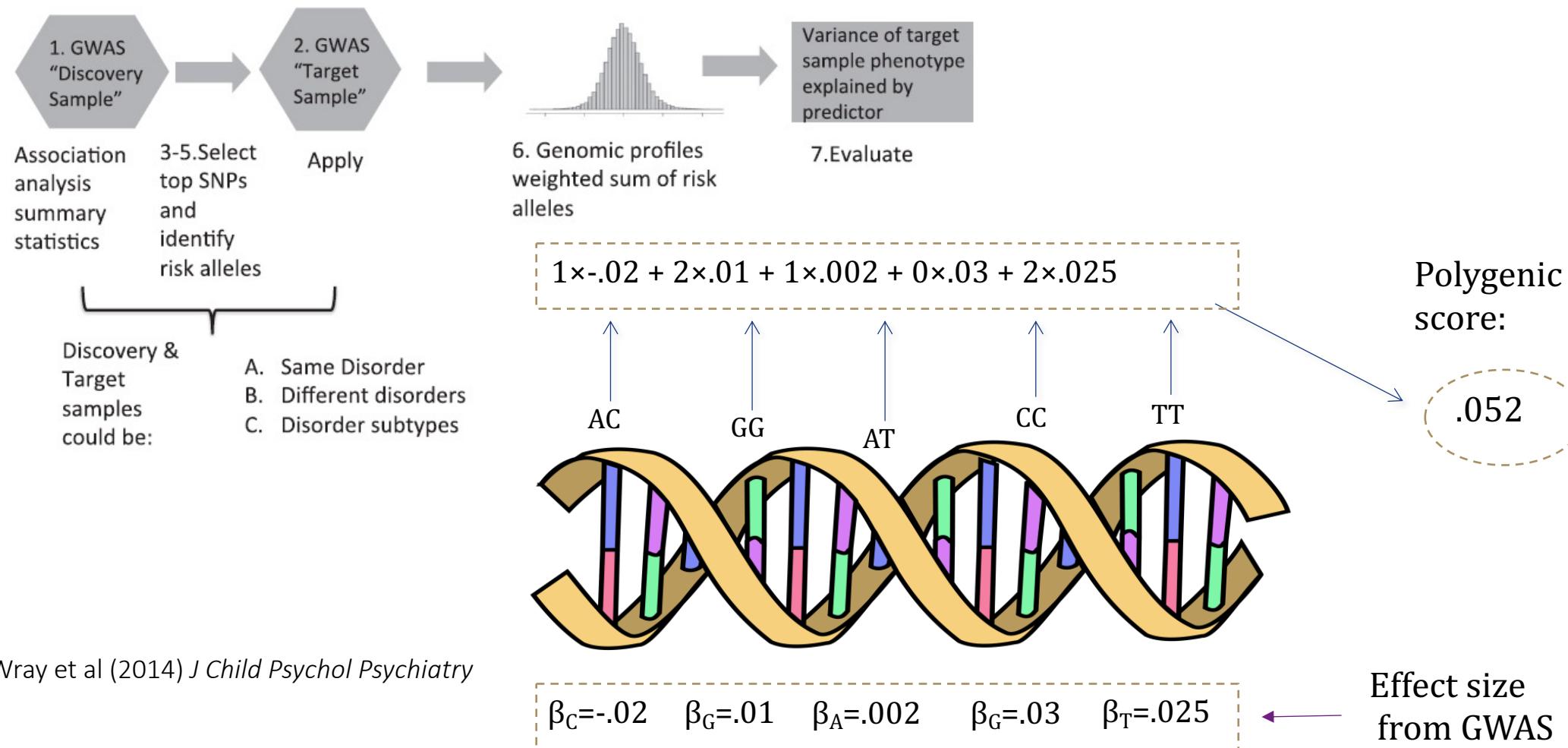
**Figure 2: Manhattan plot.**

The nearest gene to each of the 90 significant variants are labeled in green for previously-identified loci and in blue for novel loci.  $-\log_{10} P$  values were capped at 40. Variant points are color coded red and orange, with orange representing significant variants at  $P = 5 \times 10^{-8}$  and  $5 \times 10^{-9}$  and red representing significant variants at  $P < 5 \times 10^{-9}$ . The X axis represents the base pair position of variants from smallest to largest per chromosome (1-22).

<https://pdgenetics.shinyapps.io/GWASBrowser/>

# Polygenic Risk Scores - calculation

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Wray et al (2014) *J Child Psychol Psychiatry*

Slightly more complex methods may enhance prediction accuracy

A Comparison of Ten Polygenic Score Methods for Psychiatric Disorders Applied Across Multiple Cohorts, Ni et al., 2021

# Heritability

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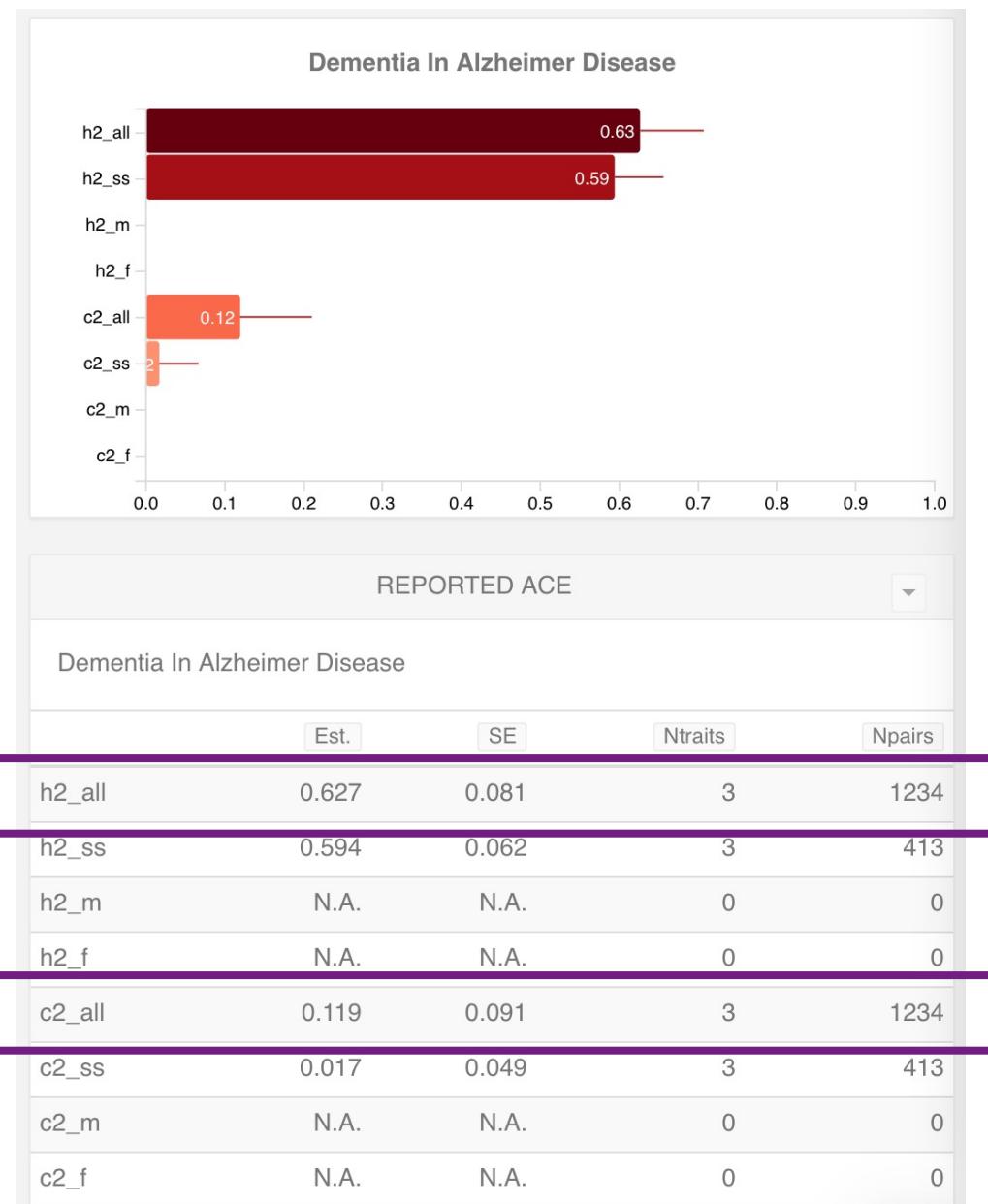
Proportion of individual differences (variance) that may be accounted for by genetic differences

=> Maximal prediction accuracy from PRS

<https://match.ctglab.nl>

Estimation from twin/familial design

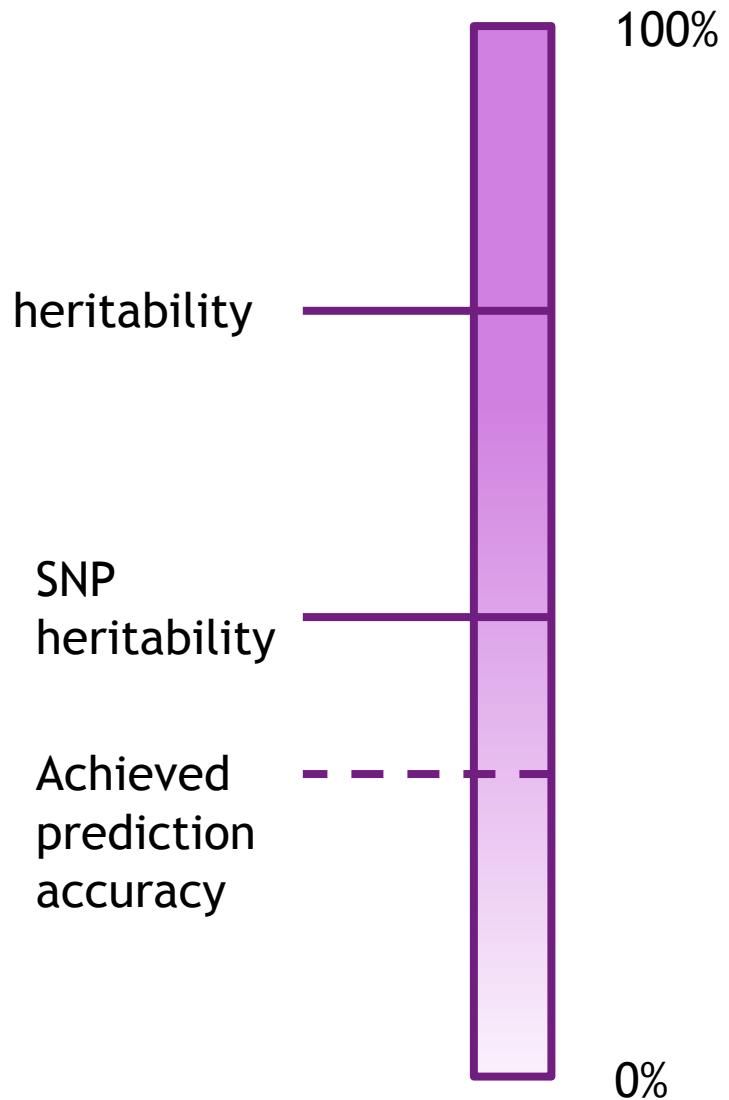
- Genetics
- Shared environment
- Unique environment



- Heritability
- Lack of rare variants  
=> (common) SNP heritability
- Imperfect LD / tagging
- Imperfect imputation
- Finite training sample

## Implications:

PRS measures risk - not fully predictive or diagnostic



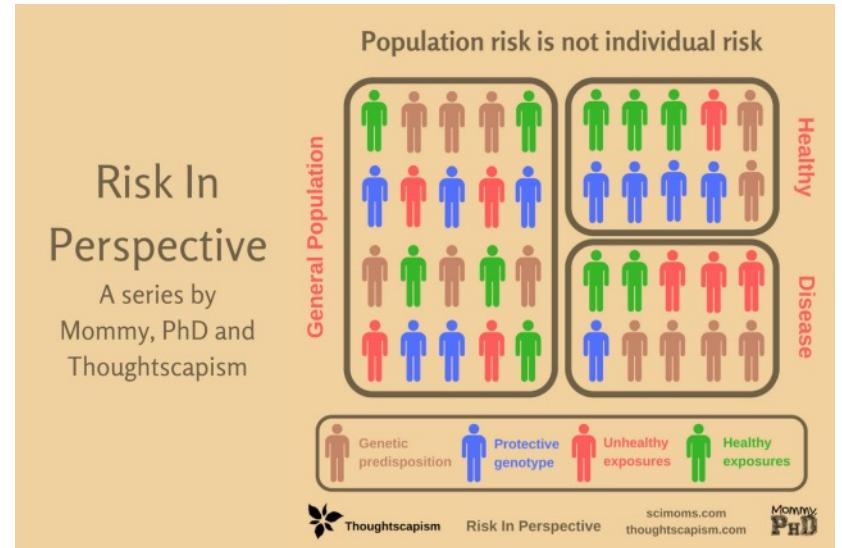
# PRS use (in research)

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PRS : genetic susceptibility to trait / disease

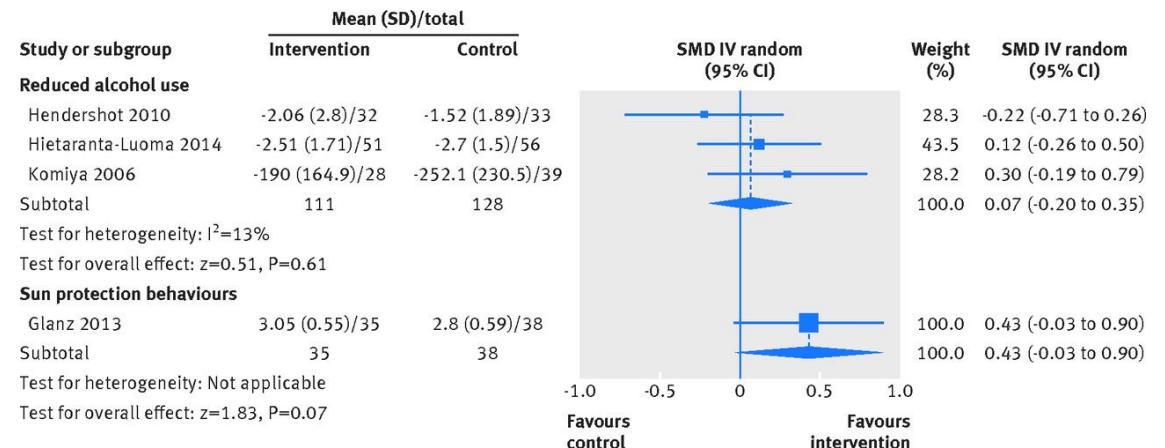
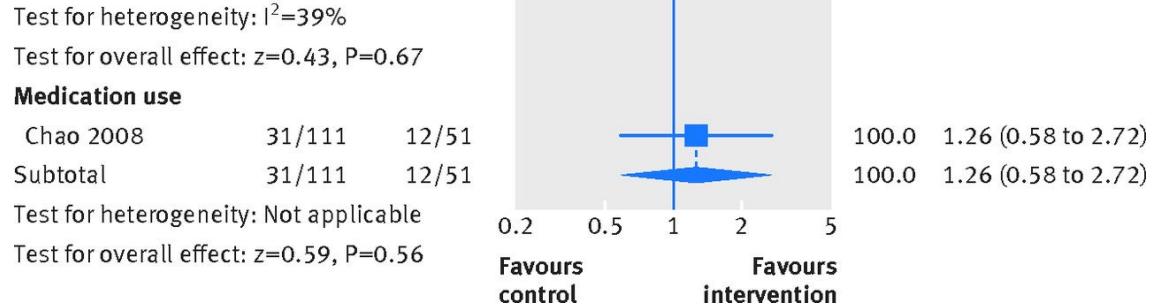
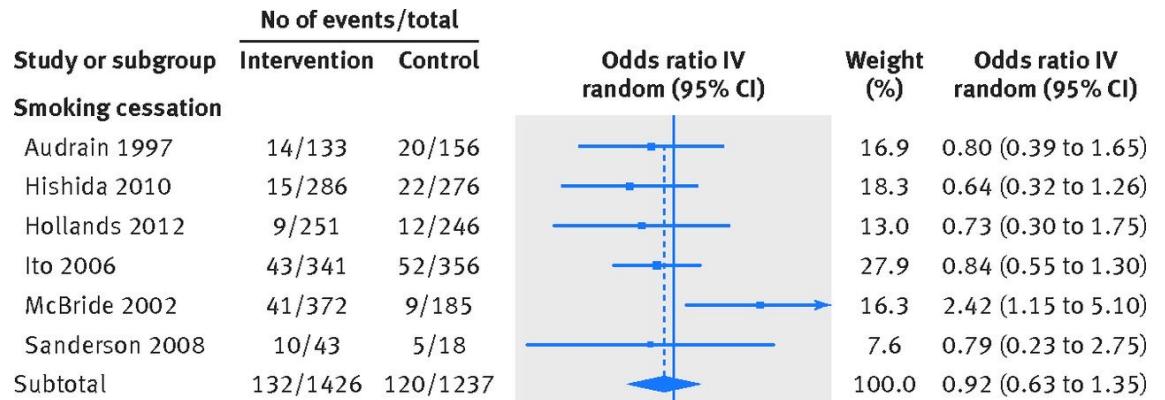
Continuous measure of risk in the population - (sub clinical)

- Apply in samples where clinical information partial/not known
- More predictive than family history for some well studied traits
- Study correlation with other disorders / risk factors  
Draw link - genetic correlation
- Use in recruitment of at risk individuals in studies, clinical protocols, prevention evaluation
- Clinical use for some pathologies, e.g. breast cancer where prevention (mammograms) may be adapted, and several treatment may be available whose benefit risk/ratio may differ based on individual genetics



# Genetic risk knowledge

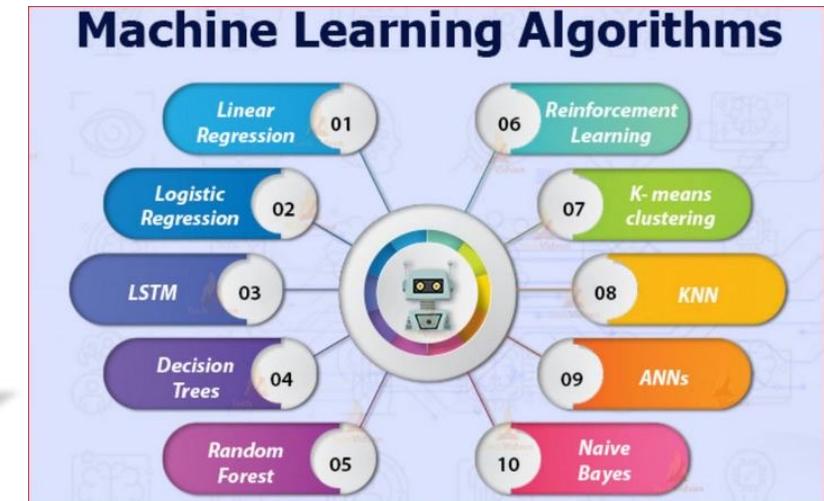
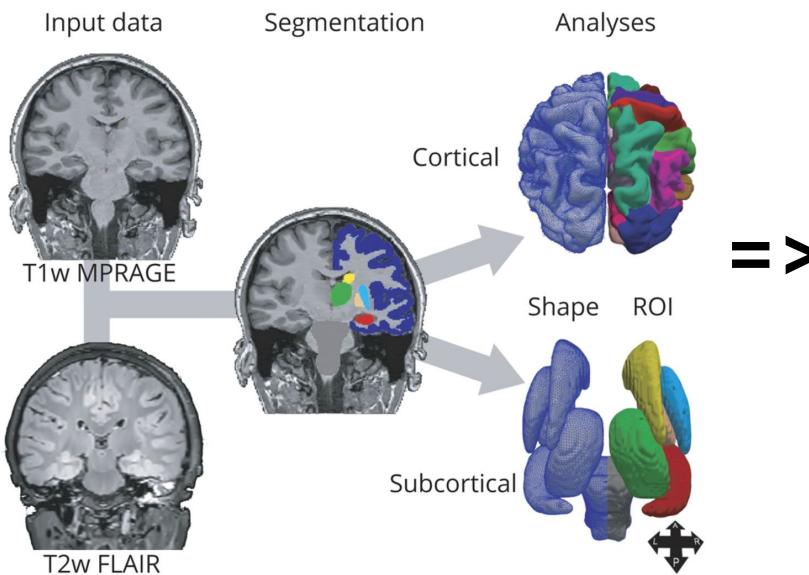
21



The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis, Holland et al., 2016

# Brain imaging prediction - structured data

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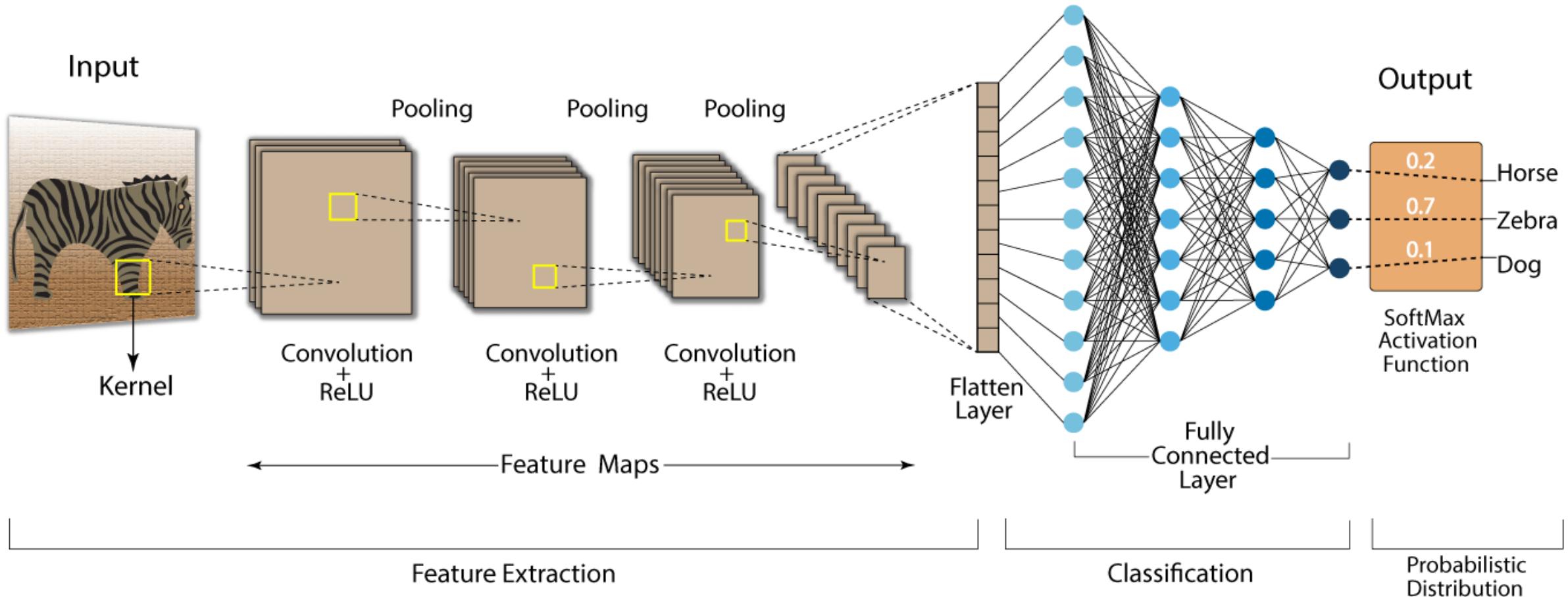
MRI processing - extract feature of interest (e.g. voxel, vertex)

Complexity depends on data reduction, and ML algorithm used. Very quickly non-linear with high number of parameters.

# Convolutional Neural Network (CNN) - unstructured

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## Convolution Neural Network (CNN)



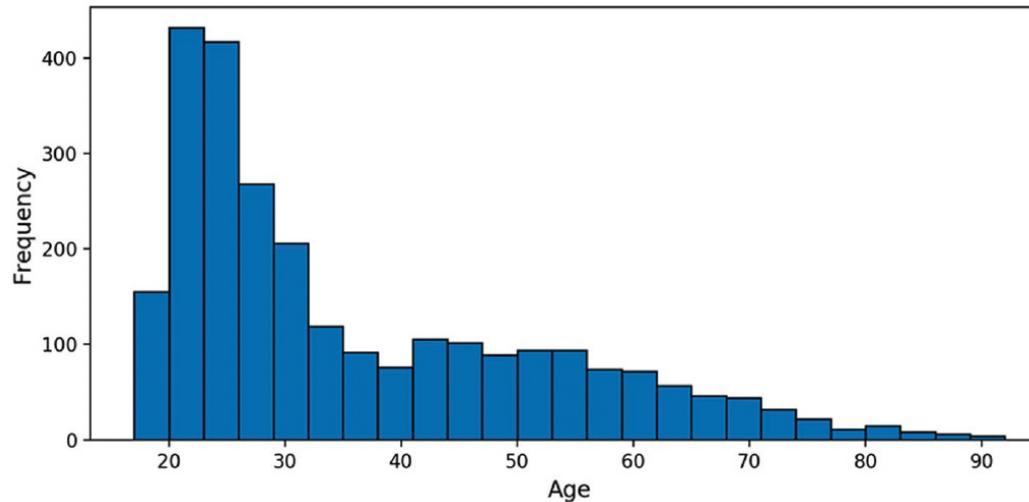
There has been an increasing trend in healthcare and criminal justice to leverage machine learning (ML) for high-stakes prediction applications that deeply impact human lives. Many of the ML models are black boxes that do not explain their predictions in a way that humans can understand. The lack of transparency and accountability of predictive models can have (and has already had) severe consequences; there have been cases of people incorrectly denied parole<sup>1</sup>, poor bail decisions leading to the release of dangerous criminals, ML-based pollution models stating that highly polluted air was safe to breathe<sup>2</sup> and generally poor use of limited valuable resources in criminal justice, medicine, energy reliability, finance and in other domains<sup>3</sup>.

Rather than trying to create models that are inherently interpretable, there has been a recent explosion of work on ‘explainable ML’, where a second (post hoc) model is created to explain the first black box model. This is problematic. Explanations are often not reliable, and can be misleading, as we discuss below. If we instead use models that are inherently interpretable, they provide their own explanations, which are faithful to what the model actually computes.

# Problems behind explicability

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- Not necessarily a trade-off between complexity and performance (structured data)



	6-layer CNN	Age spe. 6-layer CNN	ResNet	Inception V1	Linear model (BLUP)
MAE (SE)	4.18 (0.16)	4.01 (0.15)	4.02 (0.15)	3.82 (0.14)	3.91 (0.14)

*Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead, Rudin et al., 2021  
Ensemble Learning of Convolutional Neural Network, Support Vector Machine, and Best Linear Unbiased Predictor for Brain Age Prediction: ARAMIS Contribution to the Predictive Analytics Competition 2019 Challenge, Couvy-Duchesne et al., 2020*

# Problems behind explicability

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- Explainable ML methods provide explanations that may not be faithful to what the original model computes.
- Explanations often do not make sense or do not provide enough detail to understand what the black box is doing.

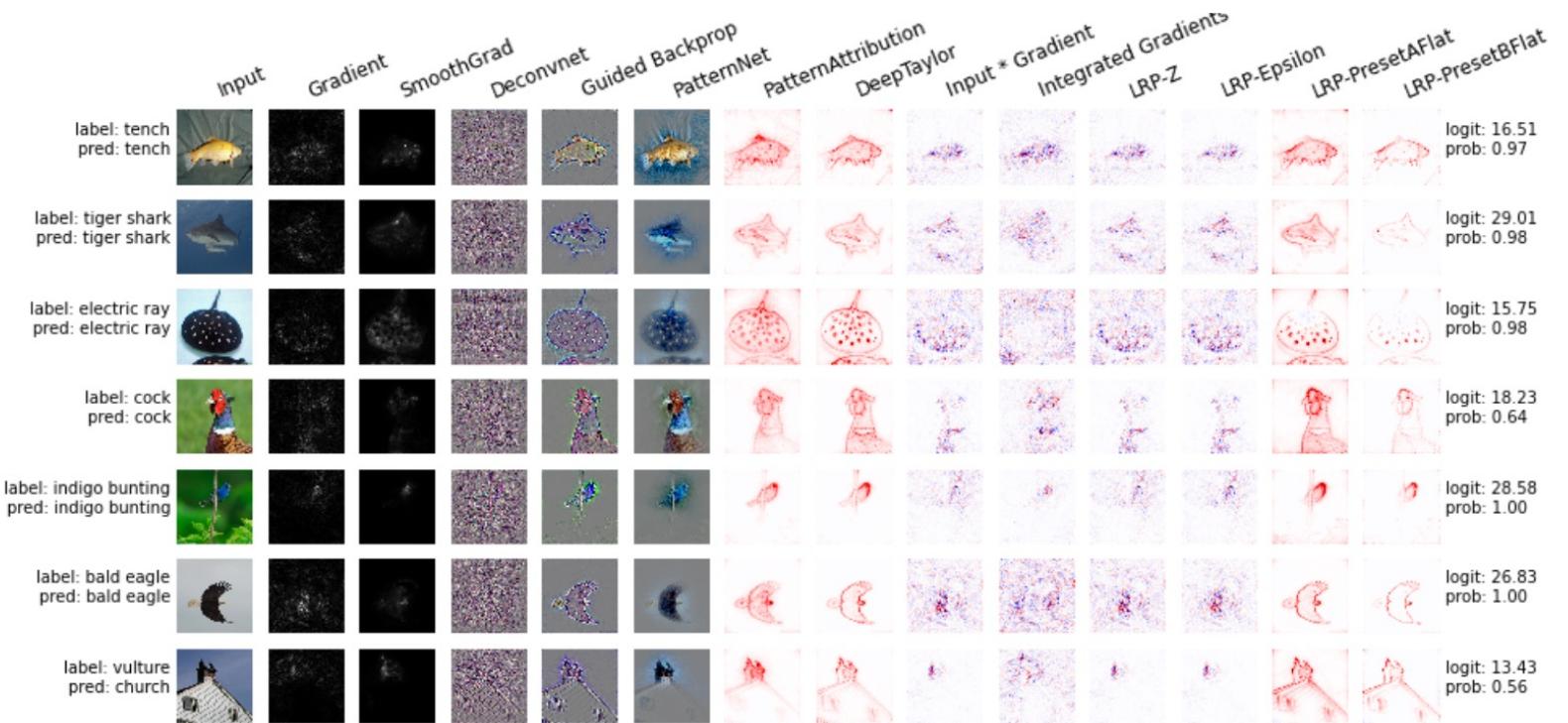


Figure 3. Comparison of Interpretability Methods to Explain Deep Learning Models on ImageNet sample images, using the innvestigate package.

# Problems behind explicability

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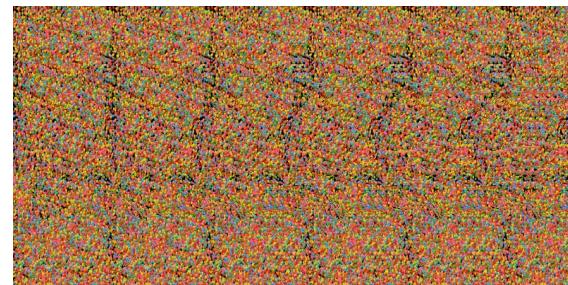
27

- Black box models are often not compatible with situations where information outside the database needs to be combined with a risk assessment.
- Black box models with explanations can lead to an overly complicated decision pathway that is ripe for human error.

# Advantages of a “black box”?

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- Corporations can make profits from the intellectual property afforded to a black box.
  - Technical black box
  - Proprietary black box
- Interpretable models can entail significant effort to construct in terms of both computation and domain expertise.
- Black box models seem to uncover ‘hidden patterns’.



## Encouraging responsible ML governance

Currently, the European Union's revolutionary General Data Protection Regulation and other AI regulation plans govern 'right to an explanation', where only an explanation is required, not an interpretable model<sup>34</sup>, in particular 'The data subject shall have the right not to be subject to a decision based solely on automated processing, including profiling, which produces legal effects concerning him or her or similarly significantly affects him or her' (Article 22 of GDPR regulations from <http://www.privacy-regulation.eu/en/22.htm>). If one were to provide an explanation for an automated decision, it is not clear whether the explanation is required to be accurate, complete or faithful to the underlying model (for example, see ref. <sup>35</sup>). Less than satisfactory explanations can easily undermine these new policies.

- 6) **Safety:** AI systems should be safe and secure throughout their operational lifetime, and verifiably so where applicable and feasible.
- 7) **Failure Transparency:** If an AI system causes harm, it should be possible to ascertain why.
- 8) **Judicial Transparency:** Any involvement by an autonomous system in judicial decision-making should provide a satisfactory explanation auditable by a competent human authority.
- 9) **Responsibility:** Designers and builders of advanced AI systems are stakeholders in the moral implications of their use, misuse, and actions, with a responsibility and opportunity to shape those implications.
- 10) **Value Alignment:** Highly autonomous AI systems should be designed so that their goals and behaviors can be assured to align with human values throughout their operation.
- 11) **Human Values:** AI systems should be designed and operated so as to be compatible with ideals of human dignity, rights, freedoms, and cultural diversity.
- 12) **Personal Privacy:** People should have the right to access, manage and control the data they generate, given AI systems' power to analyze and utilize that data.
- 13) **Liberty and Privacy:** The application of AI to personal data must not unreasonably curtail people's real or perceived liberty.
- 14) **Shared Benefit:** AI technologies should benefit and empower as many people as possible.
- 15) **Shared Prosperity:** The economic prosperity created by AI should be shared broadly, to benefit all of humanity.
- 16) **Human Control:** Humans should choose how and whether to delegate decisions to AI systems, to accomplish human-chosen objectives.
- 17) **Non-subversion:** The power conferred by control of highly advanced AI systems should respect and improve, rather than subvert, the social and civic processes on which the health of society depends.
- 18) **AI Arms Race:** An arms race in lethal autonomous weapons should be avoided.

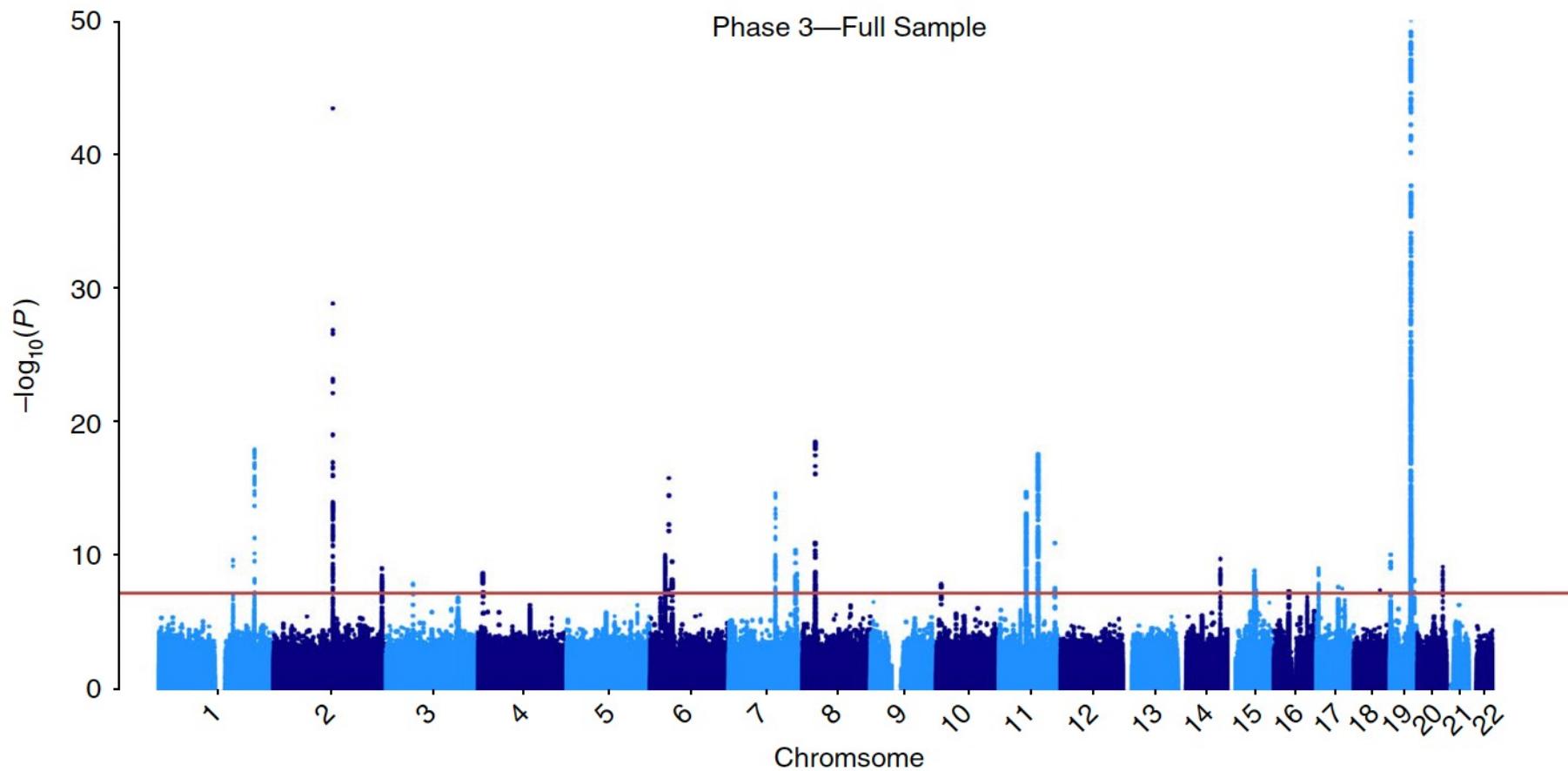


# Late Onset Alzheimer's risk score

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Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk.  
Jansen et al., 2019

71,880 cases;  
383,378 controls



**Fig. 2 | GWAS meta-analysis for AD risk ( $N = 455,258$ ).** Manhattan plot displays all associations per variant ordered according to their genomic position on the x axis and showing the strength of the association with the  $-\log_{10}$ -transformed  $P$  values on the y axis. The y axis is limited to enable visualization of non-APOE loci. For the phase 3 meta-analysis, the original  $-\log_{10} P$  value for the APOE locus is 276.

# Case example - discussion

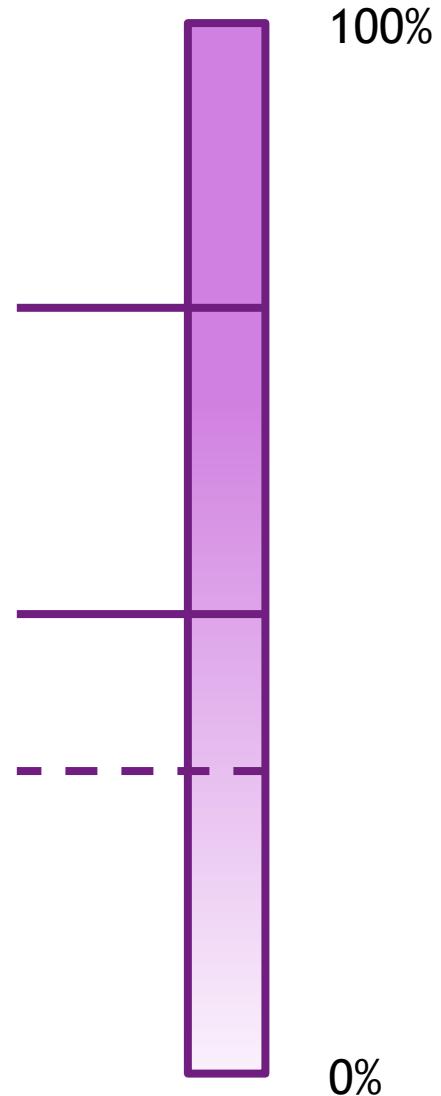
32

Aim - information, population screening, diagnostic, prognosis

Heritability : 0.63 (SE=0.08)

SNP heritability

Achieved  
prediction  
accuracy



# Case example - discussion

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<b>Objective:</b>	Information, population screening, diagnostic, prognosis
<b>Performance:</b>	Prediction accuracy level fair - adapted metrics
<b>Data:</b>	Input data - type, structured, unstructured, missingness, errors Proprietary / Open, Public Participant consent Train / test data (bias ? Under/over representation? Data leakage) Generalisability (performance in practice or on specific groups)
<b>Algorithm:</b>	Complexity Interpretability Explicability
<b>Use:</b>	Risk of misinformation, distress (direct to consumer?) Risk of self medication / treatment options ? Stigma for having a “disease risk variant” Risk of false positive - e.g. no APOE yet high genetic risk Pertinence: no treatment or prevention that target high risk individuals Should APOE4 + individuals have healthy lifestyle?

**Algorithmes, modèles et méthodes pour les images et les signaux du cerveau humain  
(ARAMIS lab)**

Inria

Paris Brain Institute

**Program for Complex Trait Genomics (PCTG)**

Institute for Molecular Bioscience, the University of Queensland

Looking for M2 student(s) - Internships in analysis of big data neuroimaging - statistics, computing - 2022

<https://github.com/baptisteCD>

@BaptisteCouvy 

baptiste.couvy@icm-institute.org

Let's talk about

## Late-Onset Alzheimer's Disease

### What is late-onset Alzheimer's disease?

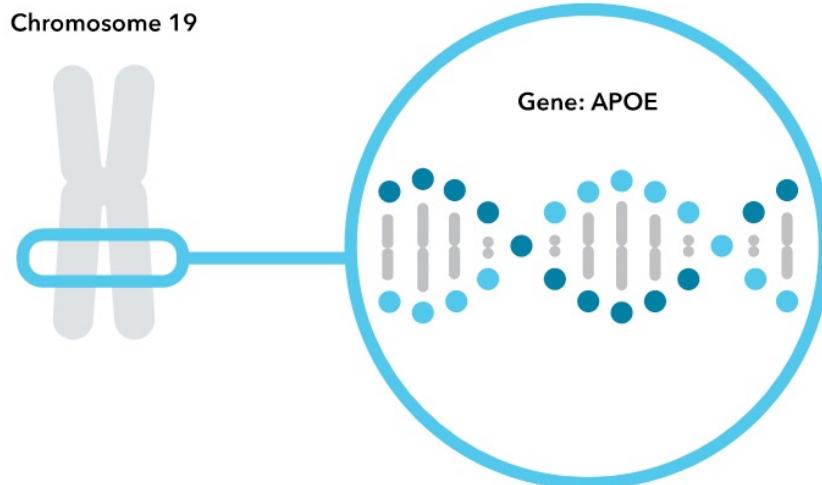
Late-onset Alzheimer's disease is a condition characterized by memory loss, cognitive decline, and personality changes developing after the age of 65. One in ten Americans age 65 and older is affected by Alzheimer's disease.

# Late Onset Alzheimer's risk score

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## Is late-onset Alzheimer's disease genetic?

Late-onset Alzheimer's disease is influenced by genetics. The  $\epsilon 4$  variant in the APOE gene is the most common genetic variant associated with the disease. This means that people with at least one copy of the  $\epsilon 4$  variant may have an increased risk of developing late-onset Alzheimer's disease.



rs429358	rs7412	Name
C	T	$\epsilon 1$
T	T	$\epsilon 2$
T	C	$\epsilon 3$
C	C	$\epsilon 4$