NORMENT
Norwegian Centre for
Mental Disorders Research

Towards CNS Precision Medicine: Progress and Challenges

CNS Precision Medicine: from research to real-world impact

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UiO : University of Oslo

Oslo University Hospital

Conflict of interest

- Consultant Cortechs.ai and Precision Health
- Speaker’s honorarium Janssen, Lundbeck, Otsuka, Sunovion
- National PI for Janssen, COMPASS, MAPS, Boehringer RCT

Cell
Leading Edge

CellPress

Commentary

Precision medicine in 2030—seven ways to transform healthcare

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https://doi.org/10.1016/j.cell.2021.01.015

Precision medicine promises improved health by accounting for individual variability in genes, environment, and lifestyle. Precision medicine will continue to transform healthcare in the coming decade as it expands in key areas: huge cohorts, artificial intelligence (AI), routine clinical genomics, phenomics and environment, and returning value across diverse populations.

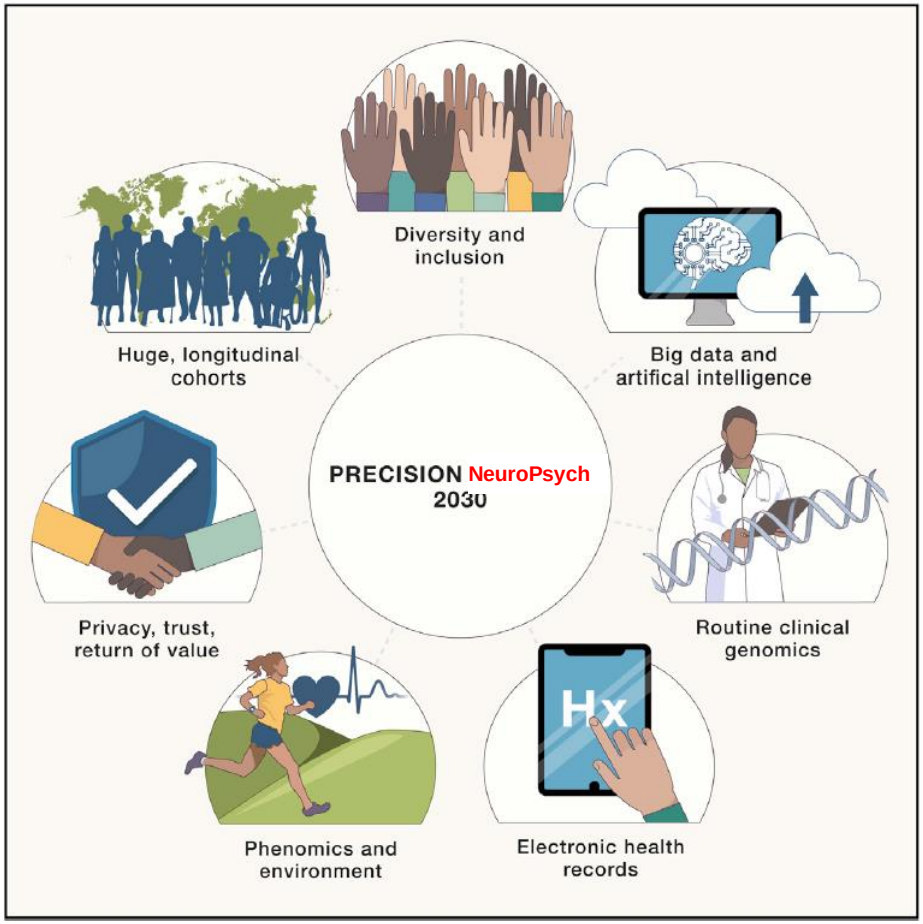


Figure 1. Seven opportunities for precision medicine by 2030

Denny Collins 2021

comment

Roadmap for a precision-medicine initiative in the Nordic region

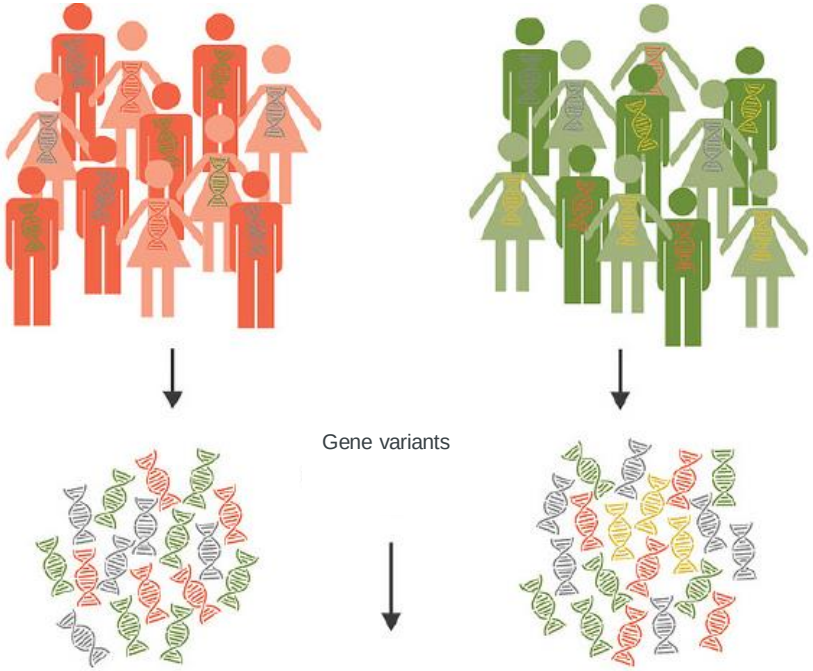
The Nordic region, comprising primarily Denmark, Estonia, Finland, Iceland, Norway and Sweden, has many of the necessary characteristics for being at the forefront of genome-based precision medicine. These include egalitarian and universal healthcare, expertly curated patient and population registries, biobanks, large population-based prospective cohorts linked to registries and biobanks, and a widely embraced sense of social responsibility that motivates public engagement in biomedical research. However, genome-based precision medicine can be achieved only through coordinated action involving all actors in the healthcare sector. Now is an opportune time to organize scientists in the Nordic region, together with other stakeholders including patient representatives, governments, pharmaceutical companies, academic institutions and funding agencies, to initiate a Nordic Precision Medicine Initiative. We present a roadmap for how this organization can be created. The Initiative should facilitate research, clinical trials and knowledge transfer to meet regional and global health challenges.

Pål Rasmus Njølstad, Ole Andreas Andreassen, Søren Brunak, Anders D. Børglum, Joakim Dillner, Tõnu Esko, Paul W. Franks, Nelson Freimer, Leif Groop, Hakon Heimer, David M. Hougaard, Eivind Hovig, Kristian Hveem, Anu Jalanko, Jaakko Kaprio, Gun Peggy Knudsen, Mads Melbye, Andres Metspalu, Preben Bo Mortensen, Juni Palmgren, Aarno Palotie, Wenche Reed, Hreinn Stefánsson, Nathan O. Stitziel, Patrick F. Sullivan, Unnur Thorsteinsdóttir, Marc Vaudel, Eero Vuorio, Thomas Werge, Camilla Stoltenberg and Kári Stefánsson

Genetic ‘revolution’ in neuropsychiatry

- Reduced genotyping costs – massive genotyped samples
  - Polygenic architecture
  - Multiple small effects
- «Genotyping your DNA is cheaper than parking at the hospital»

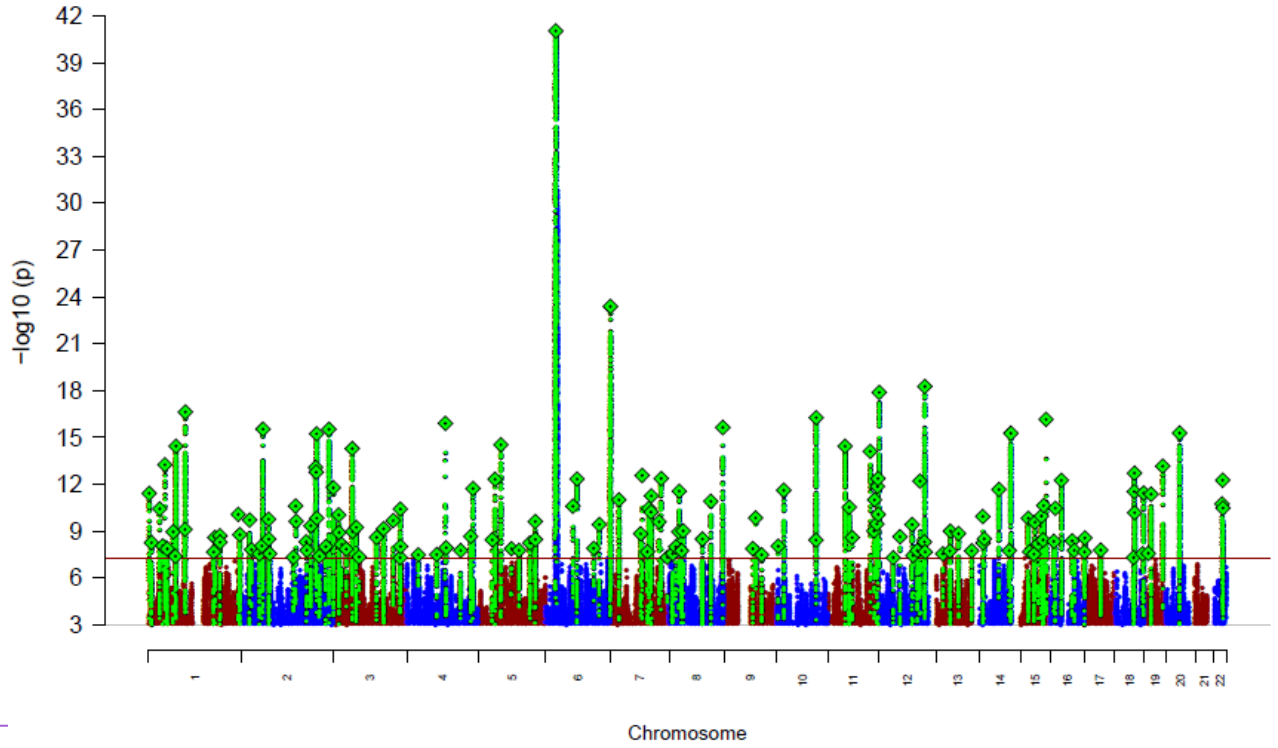
Case-control (GWAS)



Gene variants

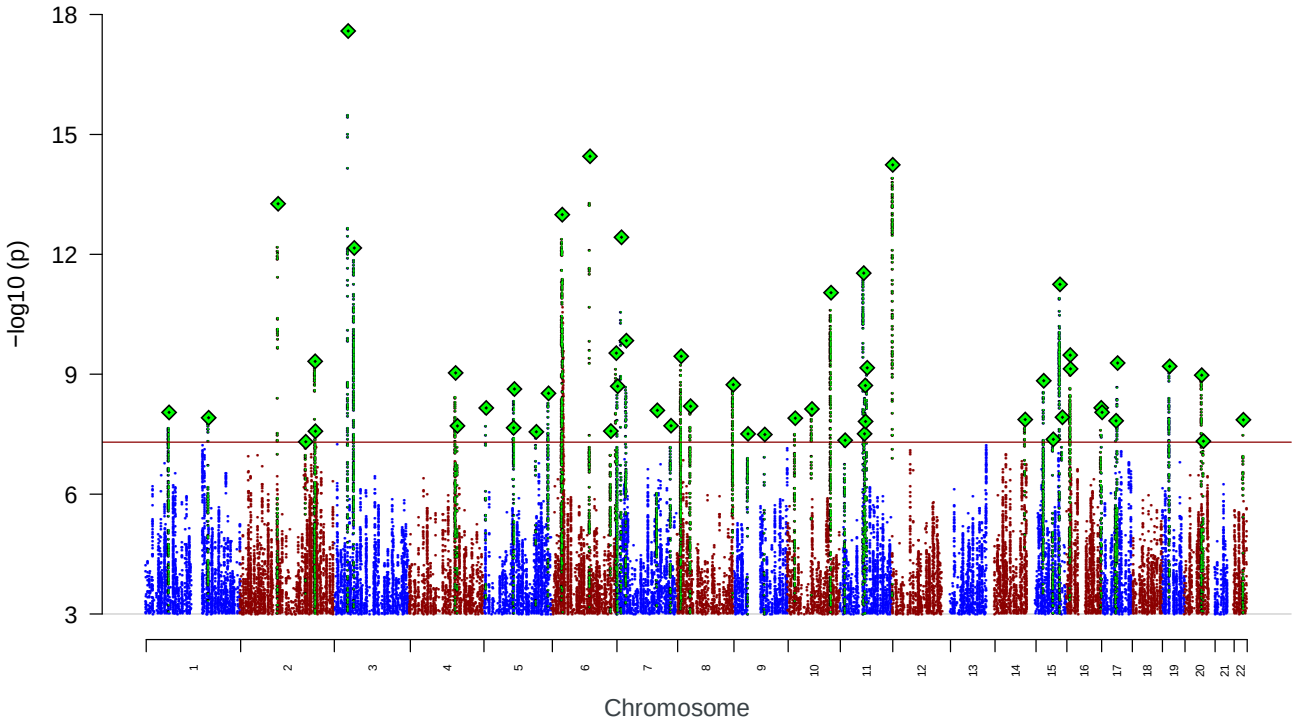
Flickr

2022: schizophrenia - 270 loci



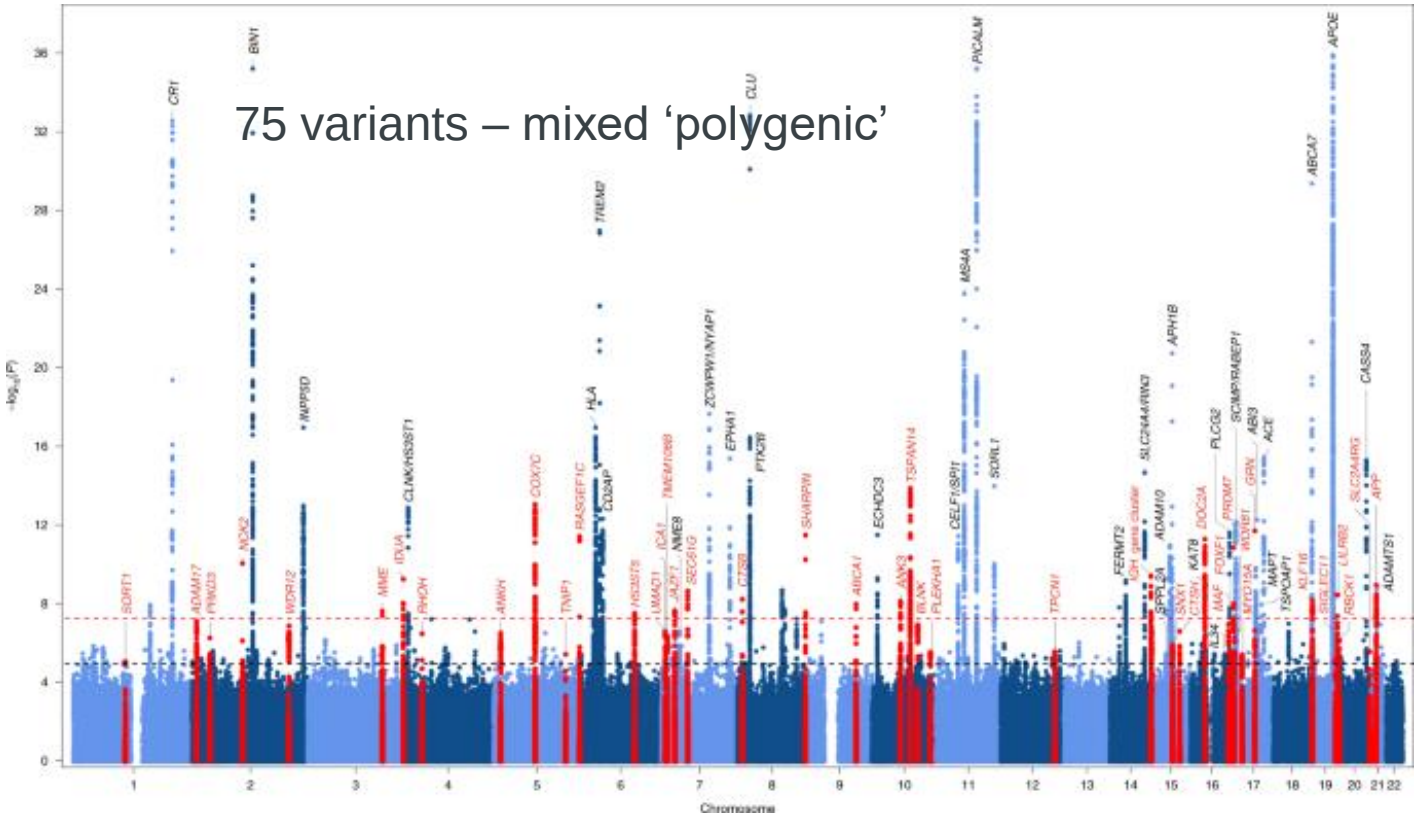
Trubetskoy et al *Nature 2022*

2024: Bipolar disorder - 298 loci



O'Connell et al.,medRxiv
https://www.medrxiv.org/content/10.1101/2023.10.07.23296687v1

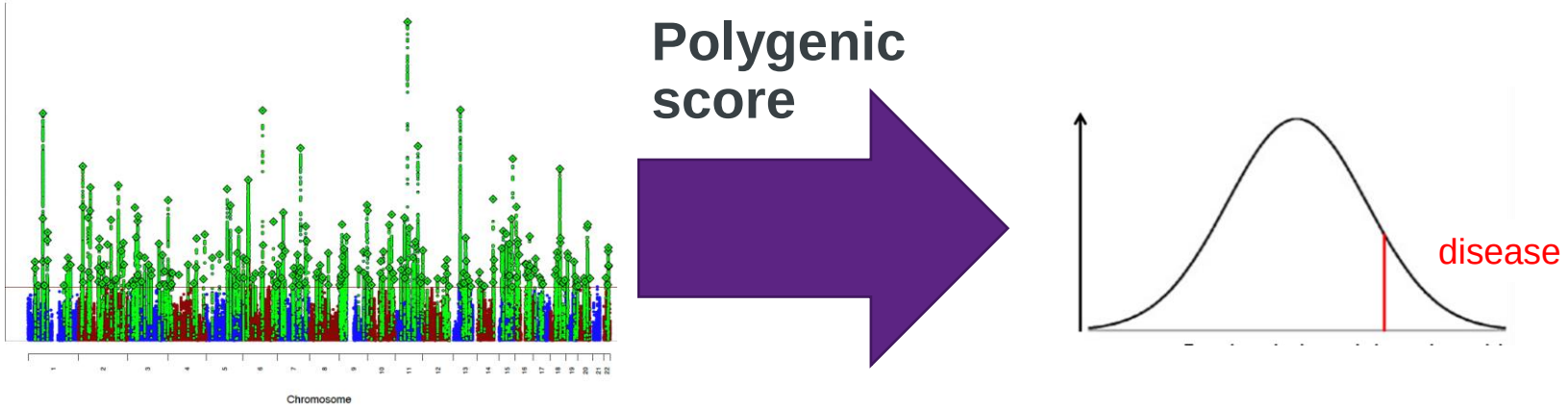
2022: Alzheimer’s disease



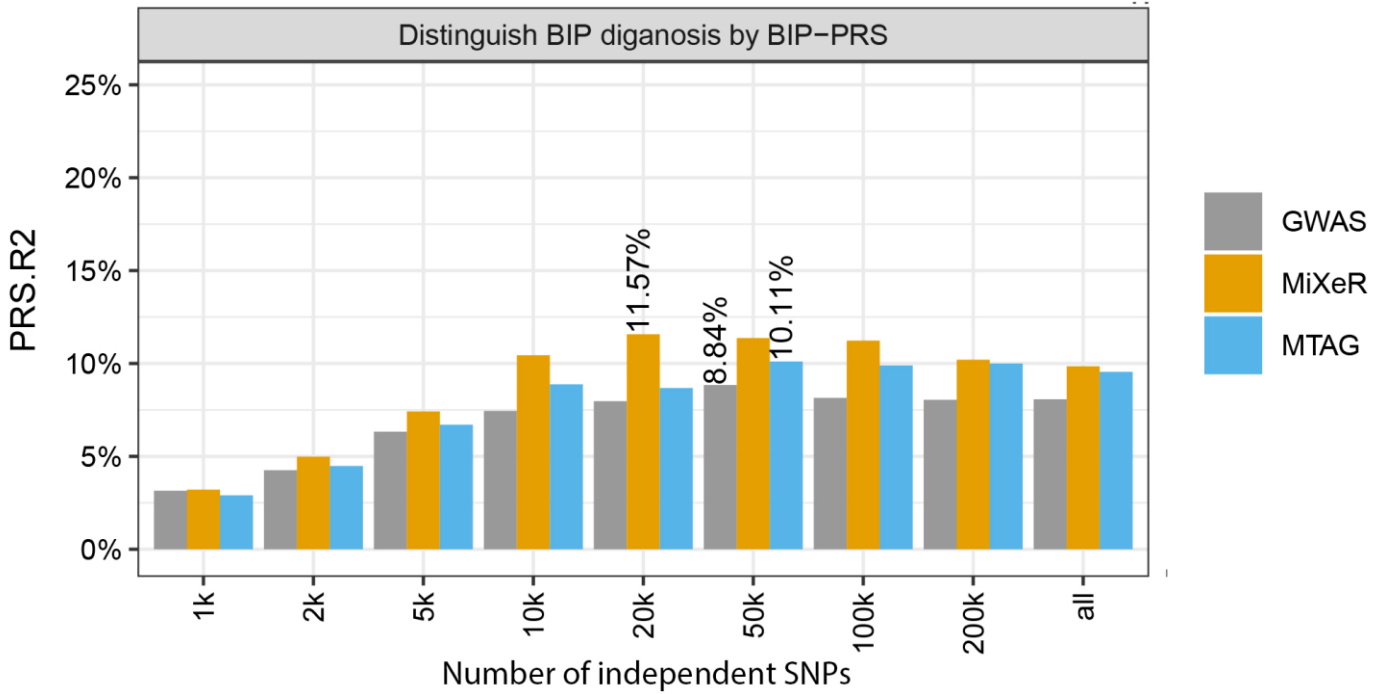
Bellenguez et al *Nat Genet* 2022

Polygenic score

- Cummulative effect of all small genetic variants
  - Genotype individual – calculate risk of disease



Polygenic prediction bipolar disorder



Parker, Frei et al. *subm*

Genetics and drug response – «Stratification»

- Large variation in treatment response
- Large variation in adverse effects
- Trial-and-error approach

Can genetic variants predict response/adverse effects of psychopharmacology agents?
- precision medicine in psychiatry

- Need large training data (GWAS)

Meerman et al. *J Affect Disord 2022, McIntyre et al. Lancet 2020, Jauhar et al. Lancet 2022*

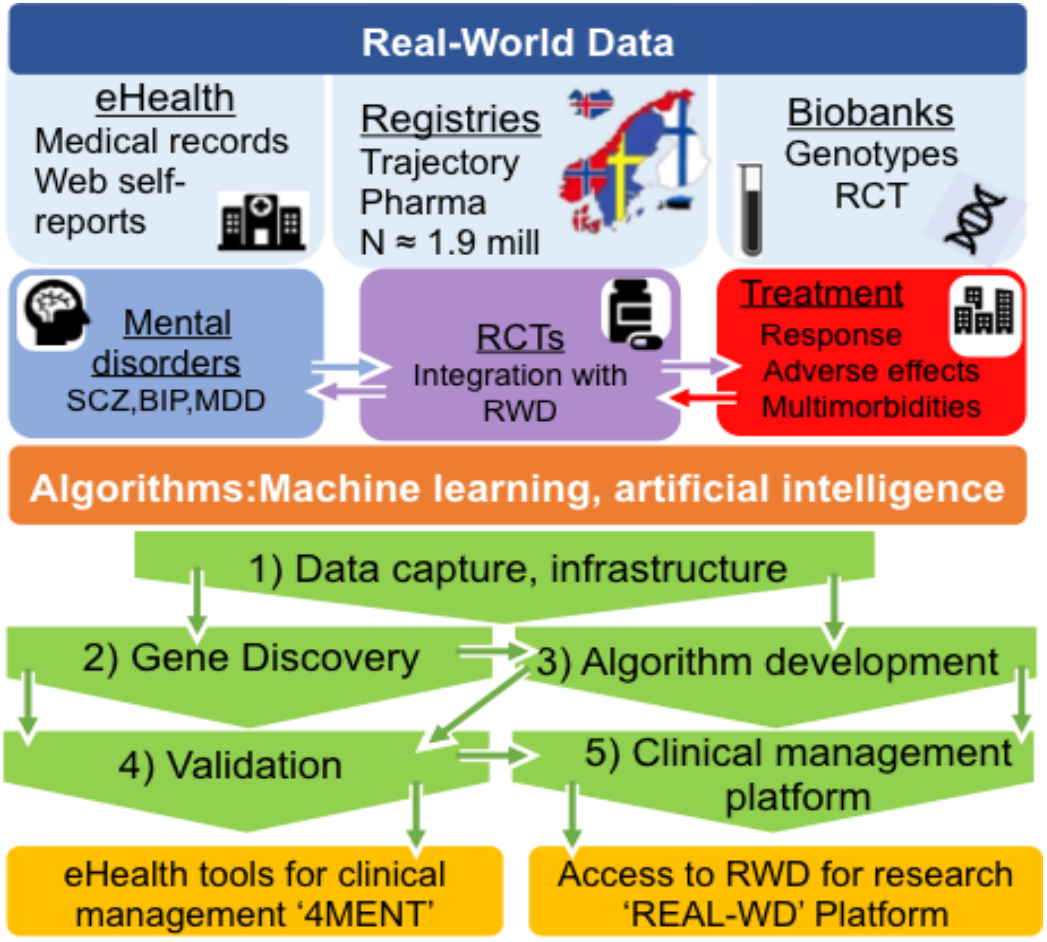
Biological Psychiatry
A Journal of Psychiatric Neuroscience and Therapeutics
Biological Psychiatry

REVIEW | ARTICLES IN PRESS

How real-world data can facilitate the development of precision medicine treatment in psychiatry

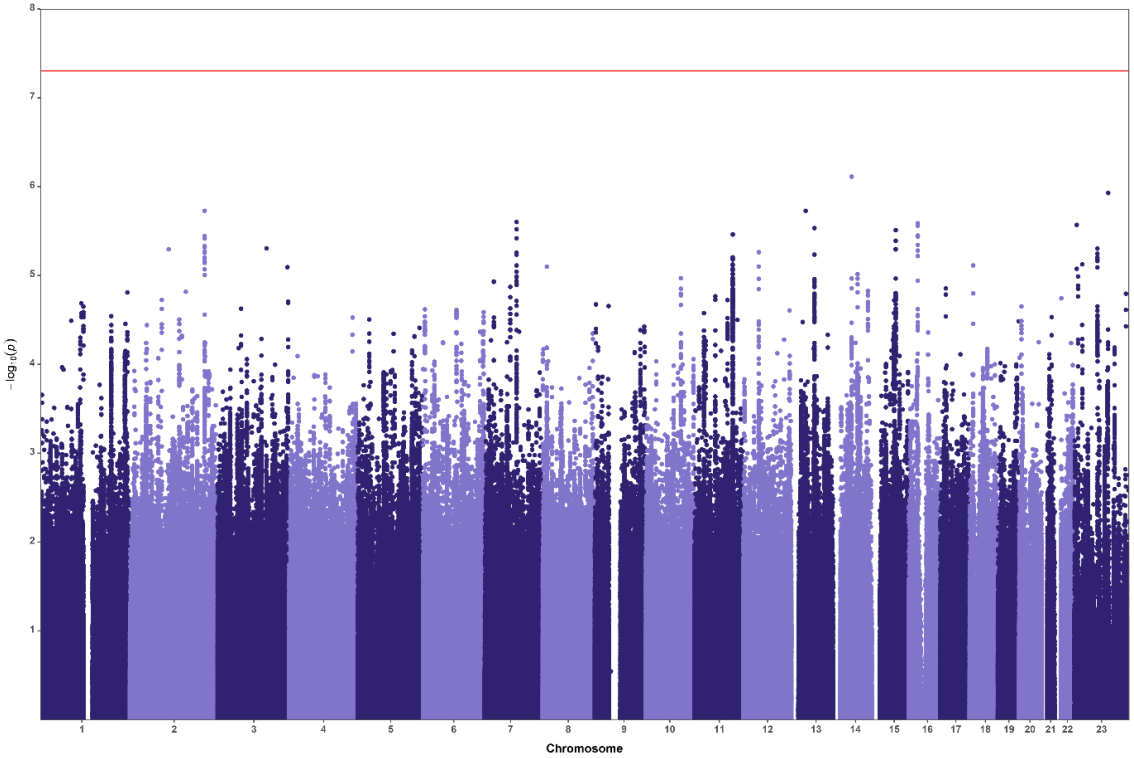
Elise Koch • Antonio F. Pardiñas • Kevin S. O'Connell • Pierluigi Selvaggi • José Camacho Collados • Aleksandar Babic • Serena E. Marshall • Erik Van der Eycken • Cecilia Angulo • Yi Lu • Patrick F. Sullivan • Anders M. Dale • Espen Molden • Danielle Posthuma • Nathan White • Alexander Schubert • Srdjan Djurovic • Hakon Heimer • Hreinn Stefánsson • Kári Stefánsson • Thomas Werge • Ida Sønderby • Michael C. O'Donovan • James T.R. Walters • Lili Milani • Ole A. Andreassen • Show less

Open Access • Published: January 05, 2024 • DOI: https://doi.org/10.1016/j.biopsych.2024.01.001



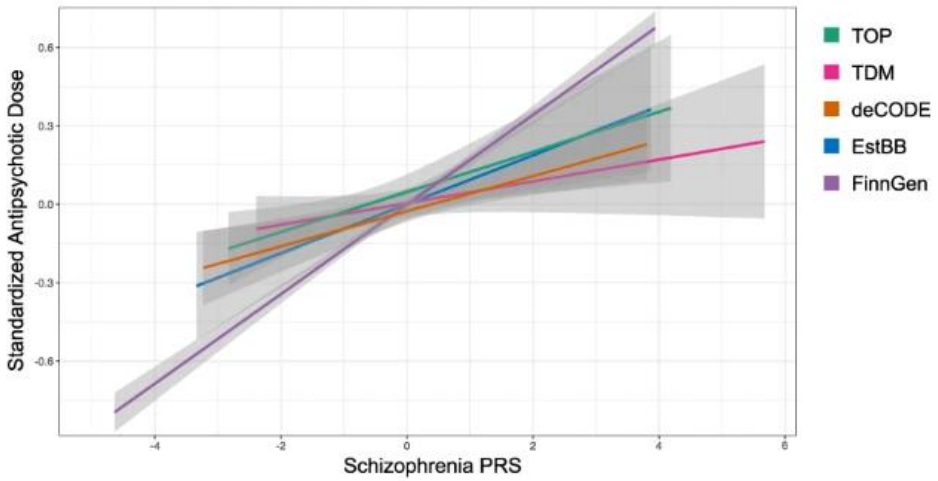
This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant agreement No. 964874

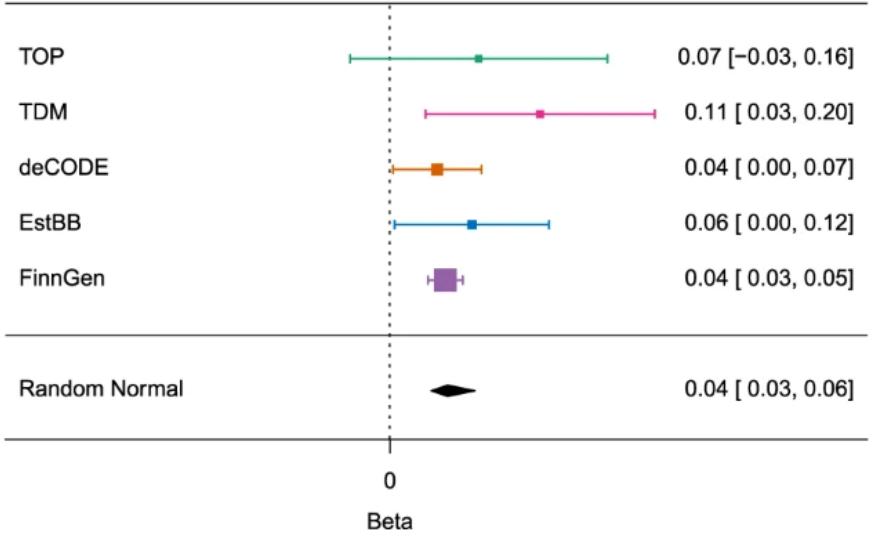
Genetic variants associated with antipsychotic non-response



Pardinas et al., *JAMA Psychiatry* 2022

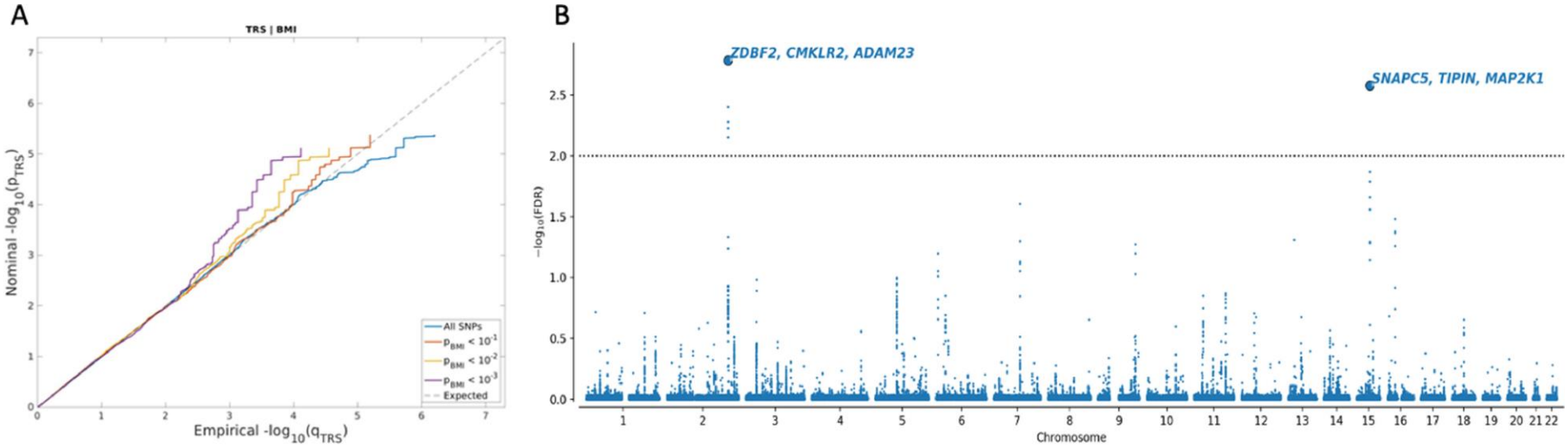
Association between schizophrenia polygenic risk score (PRS) and standardized antipsychotic dosage (DDD method) across all antipsychotics





Koch et al. *Neuropsychopharmacology* 2024

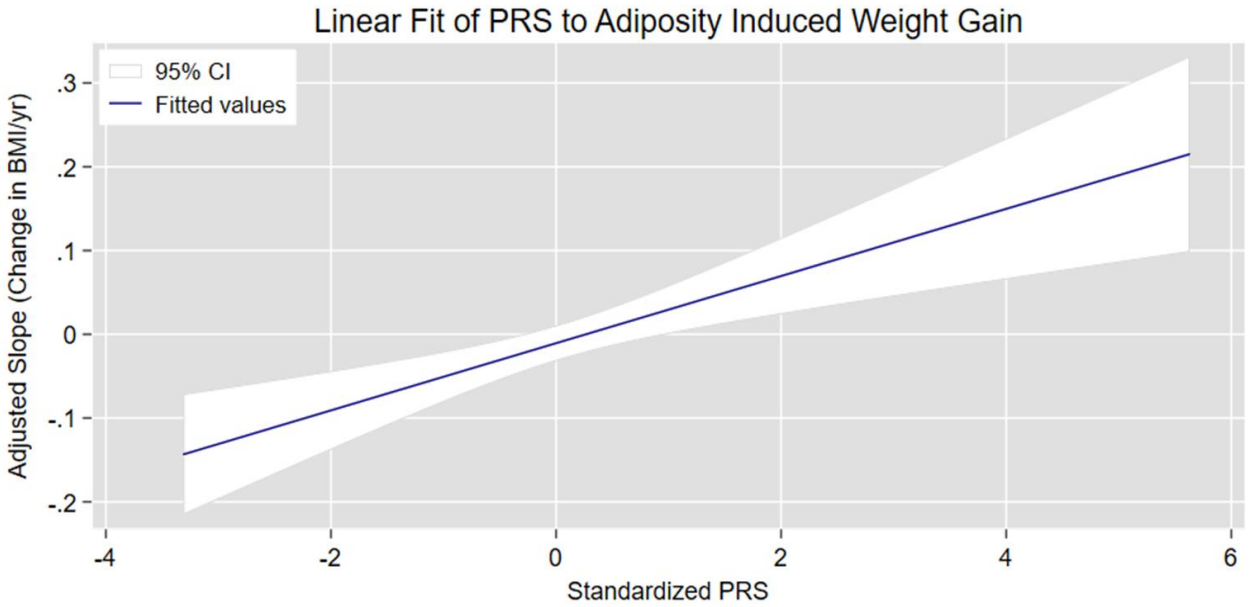
Polygenic overlap with body-mass index improves prediction of treatment-resistant schizophrenia (TRS)



O'Connell et al. *Psychiatry Res* 2023

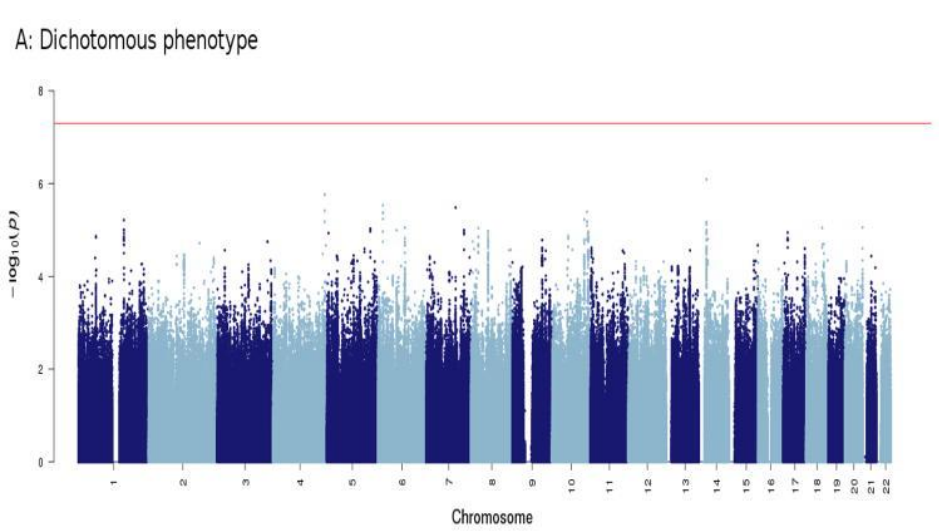
Genetics of Antipsychotic-Induced Weight Gain

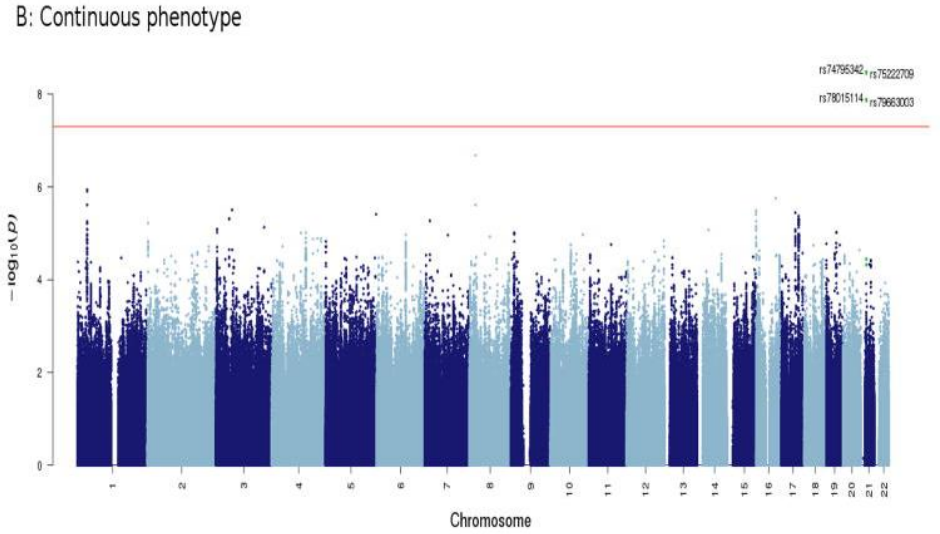
After correcting for other risk factors, the BMI PRS is positively associated with antipsychotic-induced weight gain.



Nicol et al., *WCPG* 2023

Genetic variants associated with lithium response





Hou et al., *Lancet* 2016

Response
TO LITHIUM NETWORK

90

Journal of Affective Disorders 304 (2022) 1–11

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

The Potential of Polygenic Risk Scores to Predict Antidepressant Treatment Response in Major Depression: A Systematic Review

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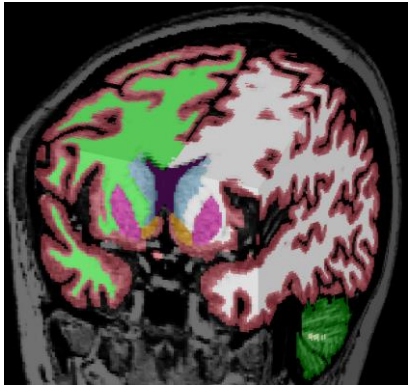
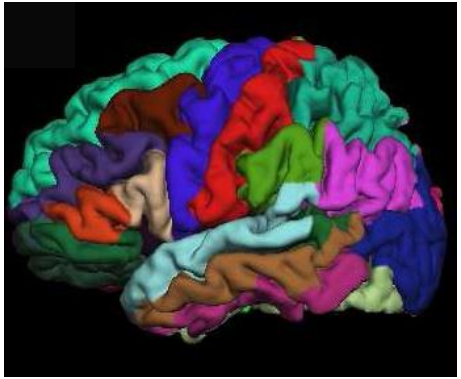
[b] Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherland
[c] Department of Human Genetics, Radboud Institute for Health Sciences, Radboud university medical center, Internal mail 855, Geert Grooteplein-Zuid 10, Nijmegen 6500, Netherlands

Currently, it is too early to incorporate PRSs in strategies to identify MDD patients at risk for poor treatment response or the development of treatment resistant depression.

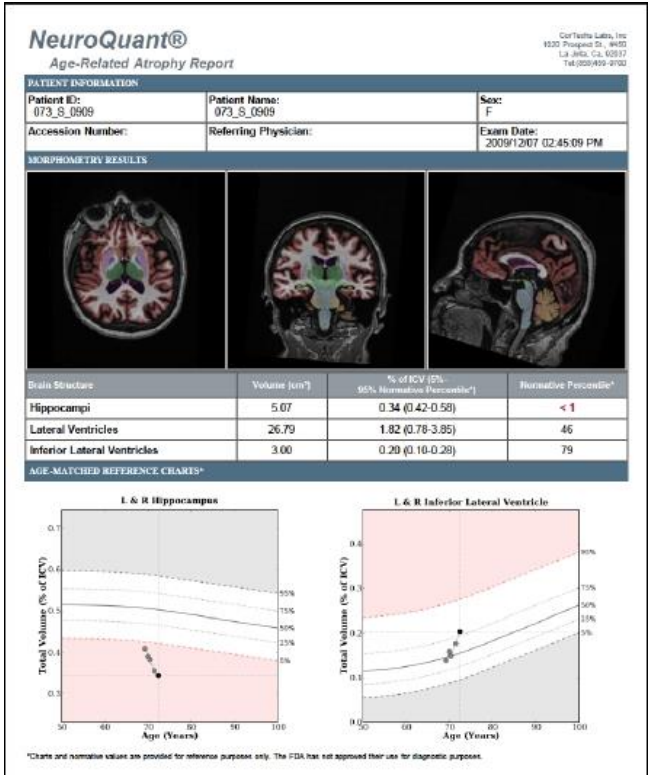
Stratification use case: Memory Clinic

- Start treatment before neurodegeneration (Alzheimer's Disease)
  - Selected for intervention?
- Multi Hazard Score (MHS), genetics, brain MRI, clinical
- *Multimodal* approach – to capture more variation





Quantitative Volumetrics: Imaging Hazard Score AD



NeuroQuant®
Age-Related Atrophy Report

PATIENT INFORMATION

Patient ID:	Patient Name:	Sex:
073_S_0909	073_S_0909	F
Accession Number:	Referring Physician:	Exam Date:
		2009/12/07 02:45:09 PM

MORPHOMETRY RESULTS

Brain Structure	Volume [cm³]	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	5.07	0.34 (0.42-0.58)	< 1
Lateral Ventricles	26.79	1.82 (0.78-3.85)	46
Inferior Lateral Ventricles	3.00	0.20 (0.10-0.28)	79

AGE-MATCHED REFERENCE CHARTS*

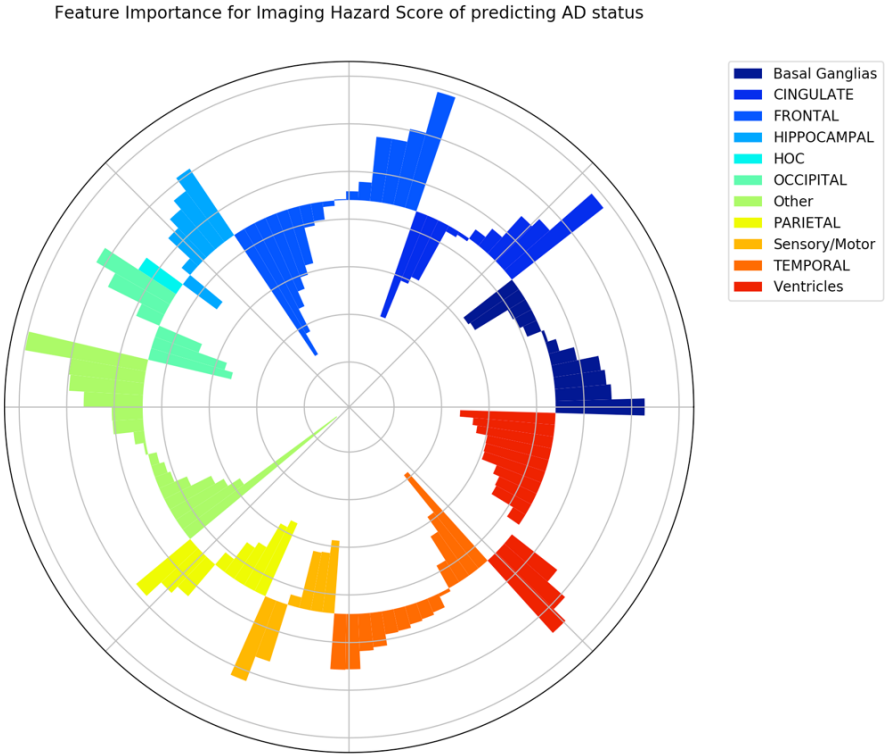
L & R Hippocampus

L & R Inferior Lateral Ventricle

Total Volume (% of ICV)

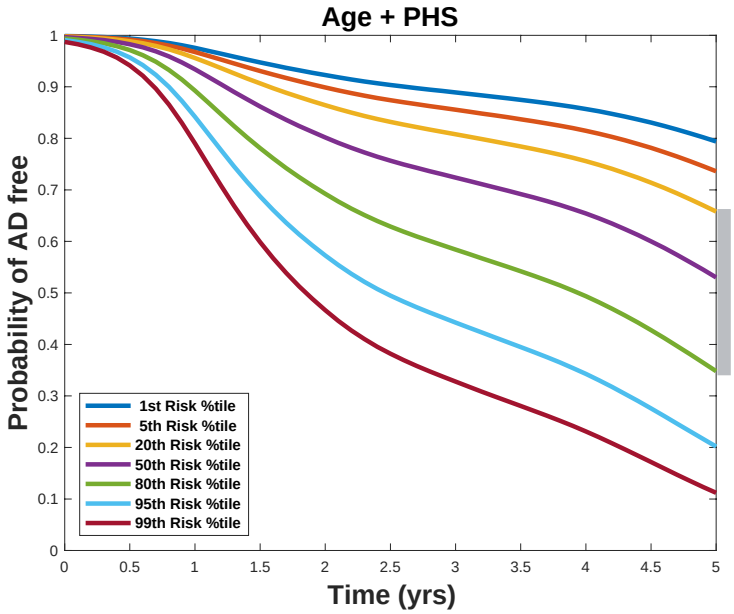
Age (Years)

*Charts and normative values are provided for reference purposes only. The FDA has not approved their use for diagnostic purposes.



Reas et al. *Alzheimers Dement*, 2023

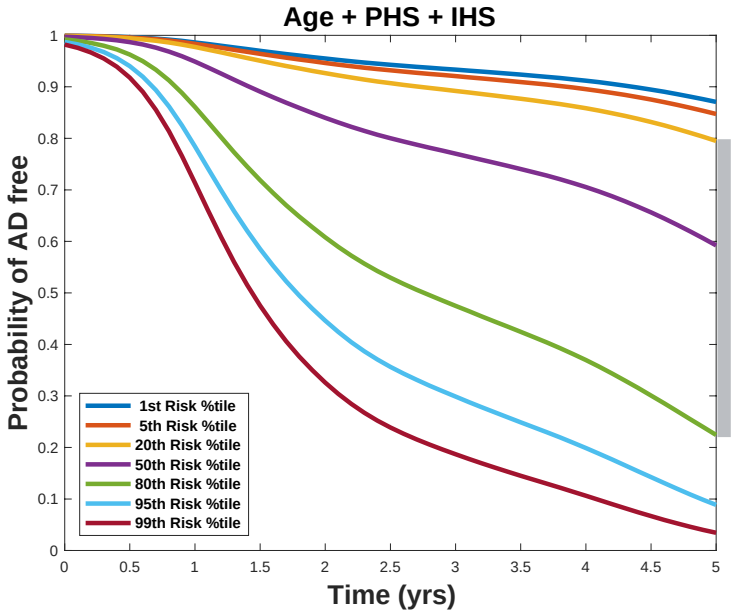
Memory clinic: who will develop Alzheimer's?
Polygenic Hazard Score



$OR_{80/20}$ = 3.57

Reas et al. *Alzheimers Dement*, 2023

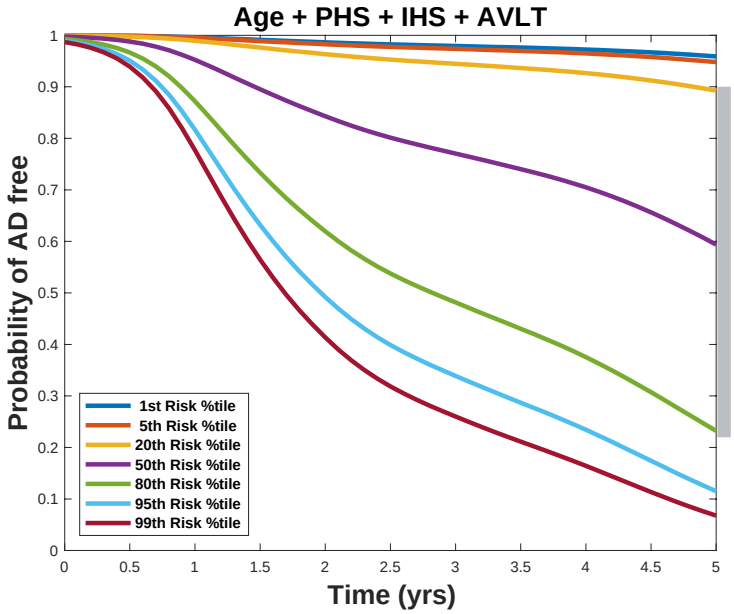
Polygenic Hazard Score and brain MRI



$OR_{80/20}$ = 13.16

Reas et al. *Alzheimers Dement*, 2023

Polygenic Hazard Score, brain MRI and cognitive test



$OR_{80/20}$ = 27.03

Reas et al. *Alzheimers Dement*, 2023

WORLD VIEW | 31 May 2022

Fix the process that led to Alzheimer's drug fiasco

Reforms to accelerated approval should focus on securing reli information in the present and clinical evidence for the future

Jason Karlawish

The morning of 7 June 2021 was a shock. The US Food and Drug Administratior approved aducanumab, the first treatment targeting β-amyloid, a protein asso Alzheimer's disease.

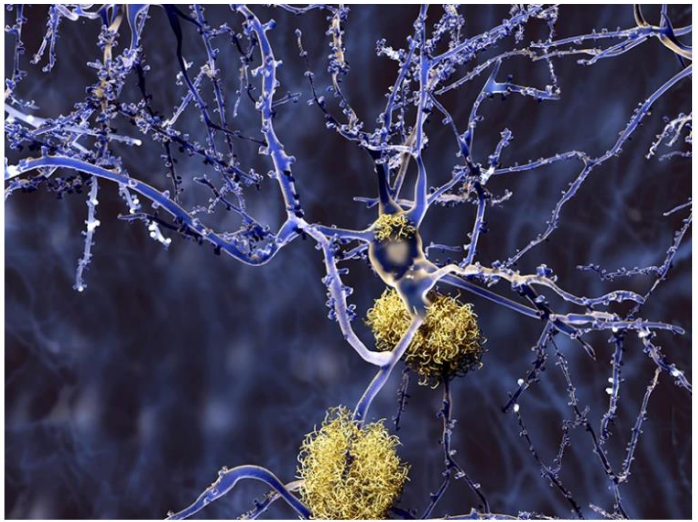
Although some celebrated the approval of the first Alzheimer's drug in nearly were aghast at the lack of demonstrated efficacy: ten members of a panel of ex assembled by the FDA had voted against approving it, with the one remaining 'uncertain'. Three quit in protest when the drug was approved.

NEWS | 07 January 2023 | Correction 10 January 2023

FDA approves Alzheimer's drug lecanemab amid safety concerns

Reports of deaths potentially linked to the treatment have cast a shadow on what many hail as a landmark approval.

Sara Reardon



Protein clumps called amyloid plaques (gold, among blue neurons in this computer illustration) are a hallmark of Alzheimer's disease. Credit: Juan Gaertner/SPL

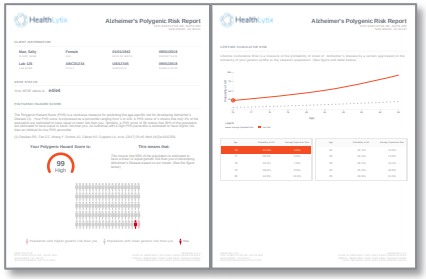
Enrich clinical trials with MHS – Stratify RCTs

Model	Relative sample size
• Age	0.713
• Age + PHS	0.522
• Age + PHS + MRI	0.356
• MHS: Age + PHS + MRI + RAVLT	0.333

Reas et al. *Alzheimers Dement,* 2023

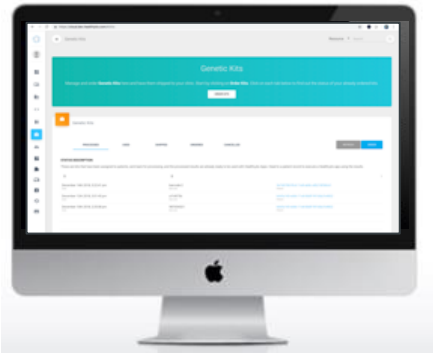
Doctor’s “Dashboard” - Neuropsychiatric disorder

Polygenic Risk Report



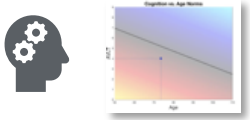
CLIA-certified

Physician Portal

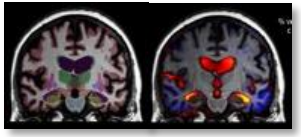


Integrated Risk Report

Genotypes
Biomarkers
Cardiometabolic
(Blood sampling)



Clinical -CVD



Radiology AI/ML

Real-world data quality and access?

- Standardization initiatives real-world data (Nordic registries, UK Biobank, All-of-Us and many others)
- Validation in RCT data (collaboration with industry partners)
  - Cross industry opportunities?
- Data access – sensitive data
  - Tryggve – federated data analytical pipeline
  - Developing academia-industry infrastructures, e.g. FinnGen
- FDA/EMA real-world data for drug approvals?
- Ethical challenges with precision psychiatry

(Fusar-Poli et al. *Eur Neuropsychopharm* 2022)

Acknowledgements

- Study participants
- TOP, BUPGEN
- DemGene
- HUSK, HUNT, MoBa
- UCSD – Anders Dale
- PGC, ENIGMA, deCODE

Funding:

RCN, Health Authorities

EU H2020, Horizon Europe

NIH, Wellcome Trust

KG Jebsen

CoMorMent, RealMent

CoMorMent

The CoMorMent project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant agreement 847776

PGC Psychiatric Genomics Consortium

REALMENT

This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant agreement No. 964874