NORMENT
Norwegian Centre for
Mental Disorders Research

CLINICAL APPLICATIONS AND PERSONALIZED MEDICINE

Kevin O`Connell

October 21st 2019

UiO : University of Oslo

Oslo University Hospital

UNIVERSITY OF BERGEN

Haukeland University Hospital

Norwegian Centre of Excellence
The Research Council of Norway

OUTLINE

- Polygenic risk scores (PRS)
  - Cancer
  - Alzheimer’s
- Polygenic hazard scores (PHS)
  - Cancer
  - Alzheimer’s
- PRS in Psychiatric Disorders
  - Sub-phenotype prediction
  - Schizophrenia Treatment Resistance

Schizophrenia GWAS

2014: 108 loci
2019: ~250 loci (in prep)

How can we use this genetic information in the clinic?

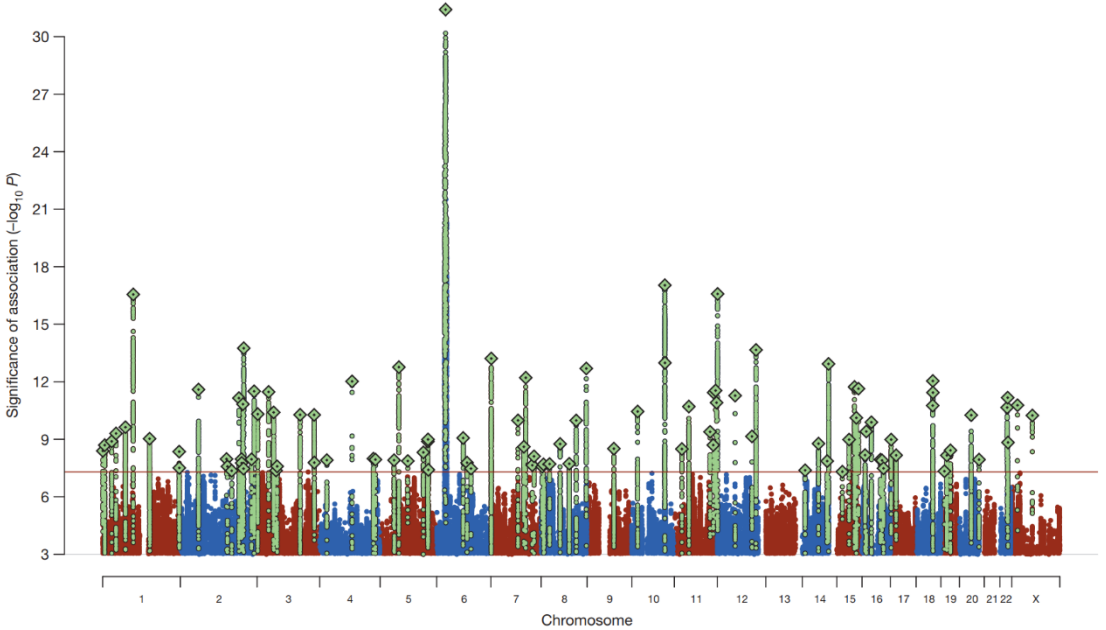


Figure 1 | Manhattan plot showing schizophrenia associations. Manhattan plot of the discovery genome-wide association meta-analysis of 49 case control samples (34,241 cases and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios). The *x* axis is chromosomal position and the *y* axis is the significance ($-\log_{10} P$; 2-tailed) of association derived by logistic regression. The red line shows the genome-wide significance level (5×10^{-8}). SNPs in green are in linkage disequilibrium with the index SNPs (diamonds) which represent independent genome-wide significant associations.

Polygenic risk score (PRS) [Polygenic score]

- $PRS_i = \sum_{j \epsilon SNPs} \beta_i d_{ij}$
- PRS for an individual i is calculated as the sum over the risk-allele frequencies (d_{ij}) of each SNP j. Most PRS models assume that SNPs have an additive effect on the disease risk. In this case, the frequency (d_{ij}) takes values 0, 1, or 2, depending on the number of risk alleles present in the gene.
- One cannot assume SNP influences are equal
- Here, the PRS is expressed as the sum over the weighted (β_i) number of alleles per SNP. The most commonly used weight is the GWAS Odds Ratio, or the univariate linear regression coefficient.

Supplementary Table 2: 128 genome-wide significant associations for schizophrenia

Rank	Index SNP	A12	Frq_{case}	$Frq_{control}$	Chr	Position	Combined		Discovery		Replication	
							OR (95% CI)	P	OR	P	OR	P
54	rs4648845	TC	0.533	0.527	1	2,372,401-2,402,501	1.072 (1.049-1.097)	8.7e-10	1.071	4.03e-9	1.088	8.85e-2

C is effect allele

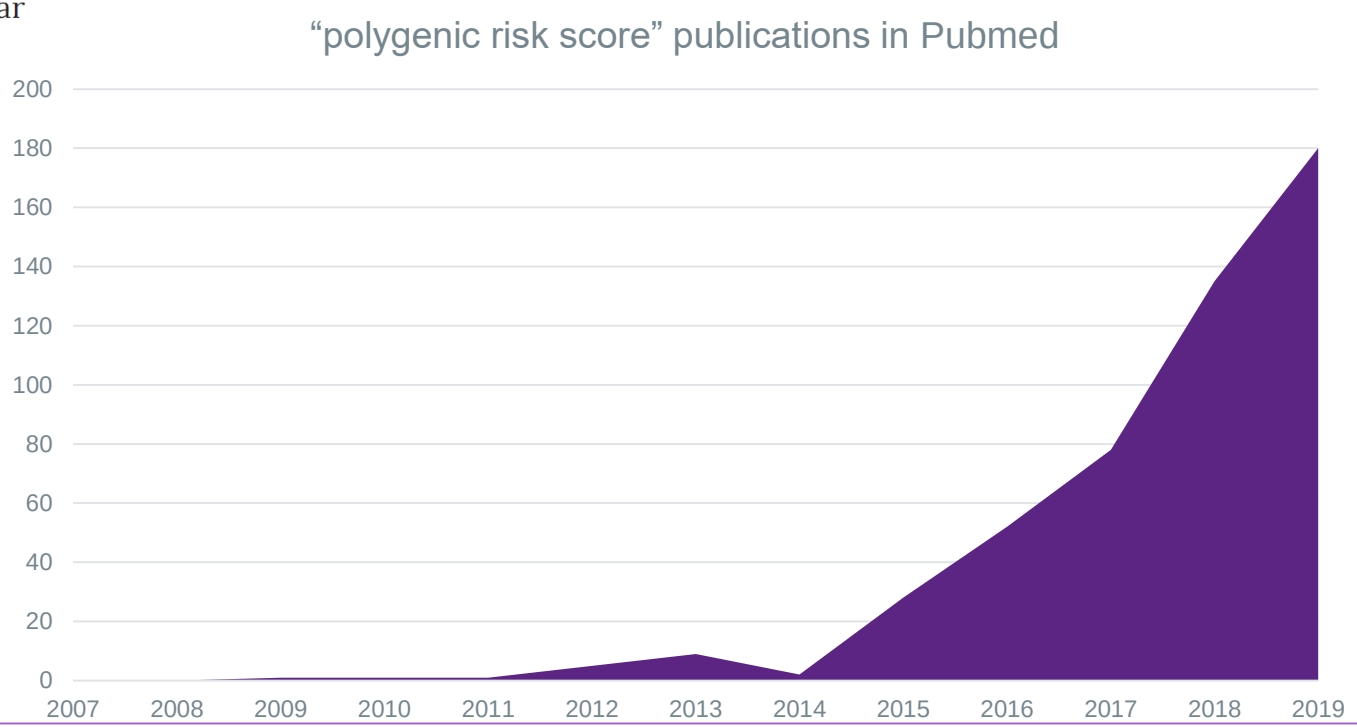
TT genotype = 0*1.071 = 0
TC genotype = 1*1.071 = 1.071
CC genotype = 2*1.071 = 2.142

Polygenic risk score (PRS) [Polygenic score]

Common polygenic variation contributes to risk of schizophrenia and bipolar disorder

The International Schizophrenia Consortium

Nature **460**, 748–752 (06 August 2009) | Download Citation

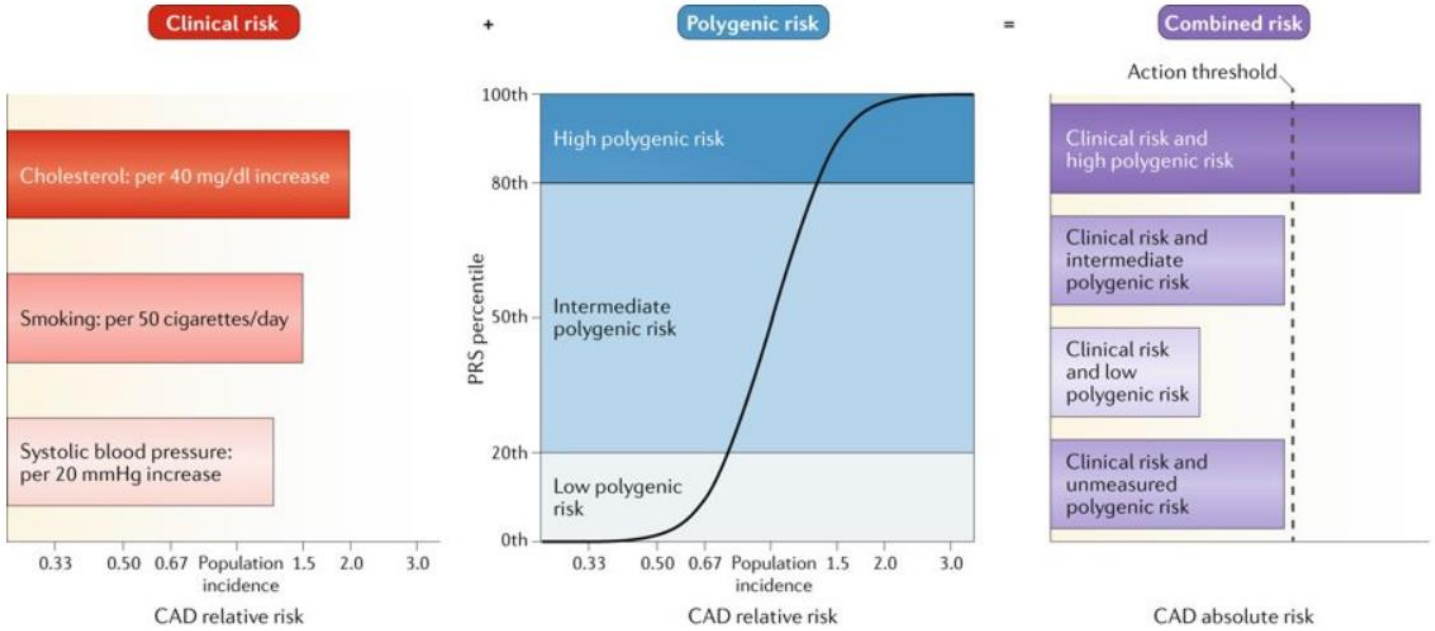


Review Article | Published: 22 May 2018

The personal and clinical utility of polygenic risk scores

Ali Torkamani ✉, Nathan E. Wineinger & Eric J. Topol

Nature Reviews Genetics **19**, 581–590 (2018)



Am J Hum Genet. 2018 Jun 7;102(6):1048-1061. doi: 10.1016/j.ajhg.2018.04.001. Epub 2018 May 17.

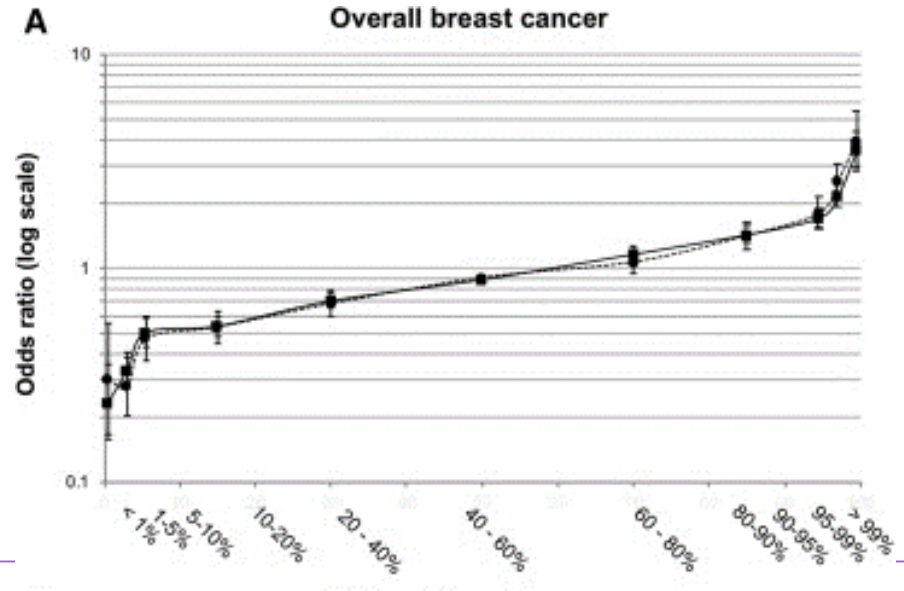
Association of Polygenic Risk Scores for Multiple Cancers in a Phenome-wide Study: Results from The Michigan Genomics Initiative.

Fritsche LG[1], Gruber SB[2], Wu Z[3], Schmidt EM[4], Zawistowski M[5], Moser SE[6], Blanc VM[7], Brummett CM[8], Kheterpal S[8], Abecasis GR[5], Mukherjee B[9].

Am J Hum Genet. 2019 Jan 3;104(1):21-34. doi: 10.1016/j.ajhg.2018.11.002. Epub 2018 Dec 13.

Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes.

Mavaddat N[1], Michailidou K[2], Dennis J[3], Lush M[3], Fachal L[4], Lee A[3], Tyrer JP[4], Chen TH[5], Wang Q[3], Bolla MK[3], Yang X[3], Adank MA[6], Ahearn T[7], Aittomäki K[8], Allen J[3], Andrulis IL[9], Anton-Culver H[10], Antonenkova NN[11], Arndt V[12], Aronson KJ[13], Auer PL[14], Auvinen P[15], Barrdahl M[16], Beane Freeman LE[7],



NIH U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies

Home > Search Results > Study Record Detail

Clinical Implementation of a Polygenic Risk Score (PRS) for Breast Cancer

Study Design

Study Type :	Observational
Estimated Enrollment :	2000 participants
Observational Model:	Case-Crossover
Time Perspective:	Prospective
Official Title:	Clinical Implementatior
Actual Study Start Date :	September 21, 2018
Estimated Primary Completion Date :	September 21, 2020
Estimated Study Completion Date :	September 21, 2025

Neurobiology of Aging
Volume 49, January 2017, Pages 214.e7-214.e11

Genetic report abstract
Brief communication

Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease

Valentina Escott-Price [a], Maryam Shoai [b], Richard Pither [c], Julie Williams [a], John Hardy [b]

Mol Psychiatry. 2019 Mar;24(3):421-430. doi: 10.1038/s41380-018-0030-8. Epub 2018 Feb 27.

Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s.

Logue MW[1,2,3], Panizzon MS[4,5], Elman JA[4,5], Gillespie NA[6], Hatton SN[4,5], Gustavson DE[4,5], Andreassen OA[7,8], Dale AM[4,5,9,10], Franz CE[4,5], Lyons MJ[11], Neale MC[6], Reynolds CA[12], Tu X[13], Kremen WS[14,15,16].

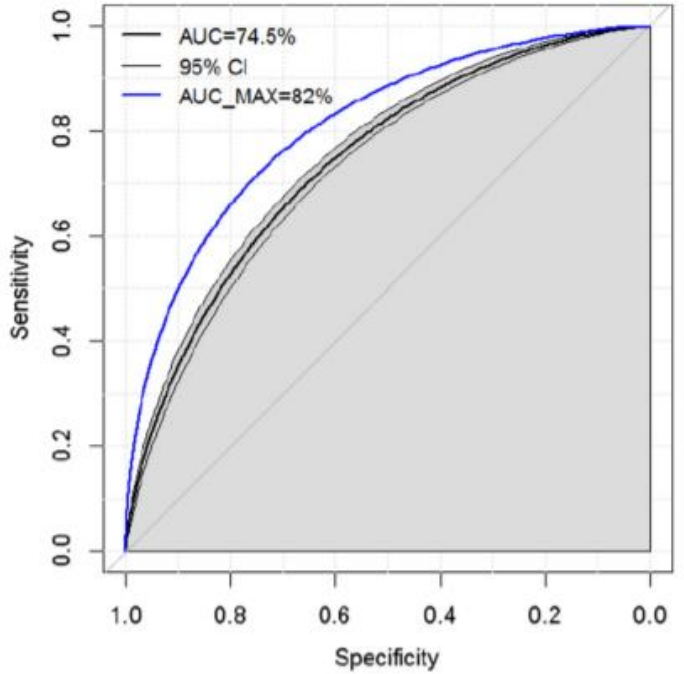


Fig. 1. Polygenic Risk score based estimation of AUC and AUC_{max} for 2% lifetime prevalence of AD. Abbreviations: AD, Alzheimer's disease; AUC, area under the curve.

ORIGINAL RESEARCH ARTICLE

Front. Neurosci., 08 October 2018 | https://doi.org/10.3389/fnins.2018.00699

The Molecular and Neuropathological Consequences of Genetic Risk for Alzheimer's Dementia

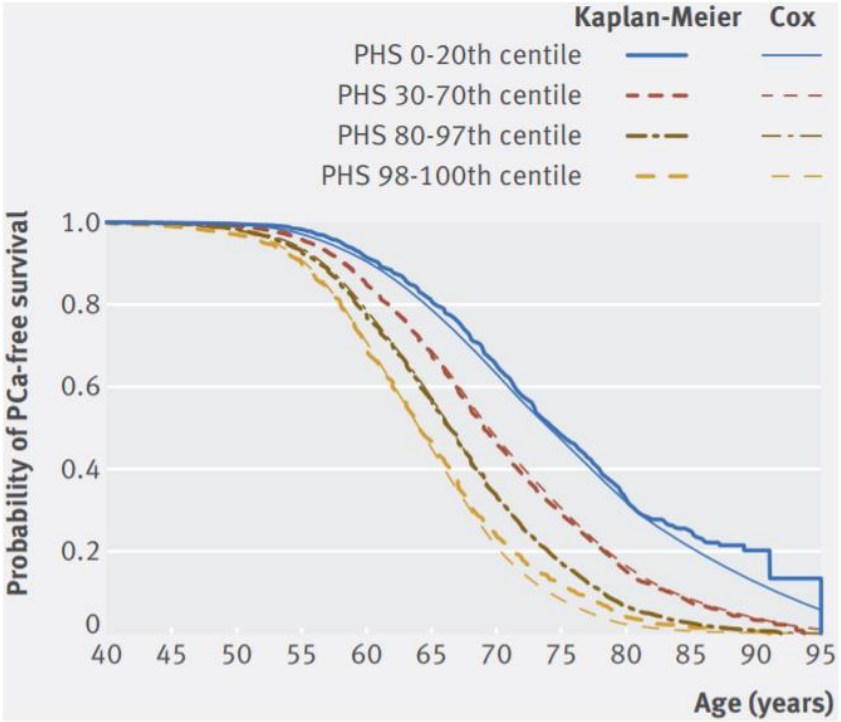
Shinya Tasaki[1,2*], Chris Gaiteri[1,2], Sara Mostafavi[3], Philip L. De Jager[4,5] and David A. Bennett[1,2]

Polygenic hazard score (PHS)

- $PHS_i = \sum_{j \epsilon SNPs} \beta_i d_{ij}$
- Recent studies have introduced the Cox-derived Hazard Ratio as an alternative weight, to account for the time to event, which is otherwise ignored when using the GWAS OR.
- Age-of-onset

Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts

Tyler M Seibert,[1,2] Chun Chieh Fan,[1,3] Yunpeng Wang,[4] Verena Zuber,[4,5] Roshan Karunamuni,[1,2]



Ann Neurol. 2017 September ; 82(3): 484–488. doi:10.1002/ana.25029.

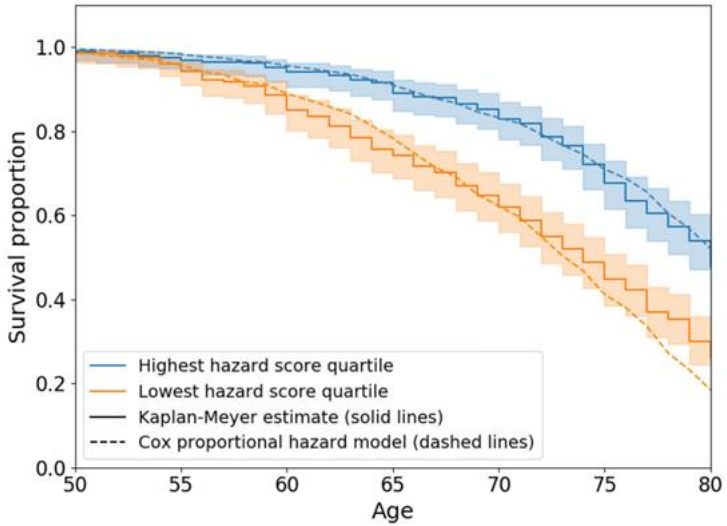
Polygenic hazard scores in preclinical Alzheimer's disease

Chin Hong Tan, PhD[1,#], Bradley T. Hyman, MD, PhD[2], Jacinth J. X. Tan, PhD[3], Christopher P. Hess, MD, PhD[1], William P. Dillon, MD[1], Gerard D. Schellenberg, PhD[4], Lilah M. Besser, PhD[5], Walter A. Kukull, PhD[5], Karolina Kauppi, PhD[6], Linda K. McEvoy, PhD[6], Ole A. Andreassen, MD, PhD[7], Anders M. Dale, PhD[6,8,9], Chun Chieh Fan, MD[10,*], and Rahul S. Desikan, MD, PhD[1,10,*,#]

Acta Neuropathol. 2018 January ; 135(1): 85–93. doi:10.1007/s00401-017-1789-4.

Polygenic hazard score: an enrichment marker for Alzheimer's associated amyloid and tau deposition

Chin Hong Tan[1], Chun Chieh Fan[2], Elizabeth C. Mormino[3], Leo P. Sugrue[1], Iris J. Broce[1], Christopher P. Hess[1], William P. Dillon[1], Luke W. Bonham[4], Jennifer S. Yokoyama[4], Celeste M. Karch[5], James B. Brewer[6,7,8], Gil D. Rabinovici[4], Bruce L. Miller[4], Gerard D. Schellenberg[9], Karolina Kauppi[7], Howard A. Feldman[6], Dominic Holland[6], Linda K. McEvoy[7], Bradley T. Hyman[10], David A. Bennett[11], Ole A. Andreassen[12,13], Anders M. Dale[2,6,7], Rahul S. Desikan[1,4], and For the Alzheimer's Disease Neuroimaging Initiative



Improving PHS

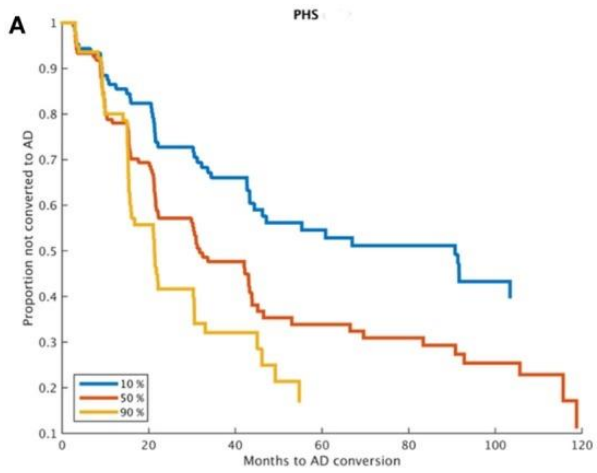
- Prediction accuracy increases when we combine PHS with imaging (atrophy score) and clinical data (MMSE - mini-mental state exam)

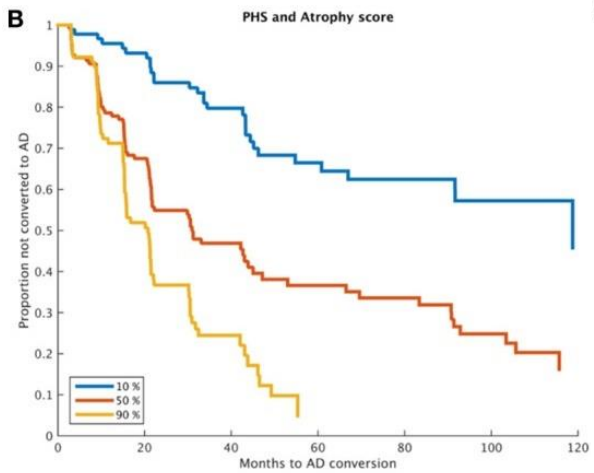
frontiers in Neuroscience

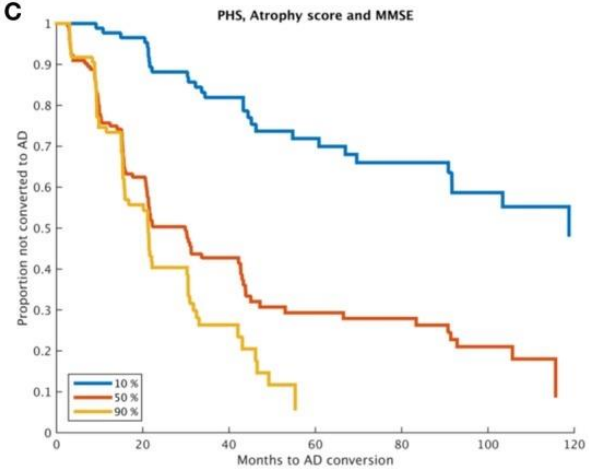
ORIGINAL RESEARCH
published: 30 April 2018
doi: 10.3389/fnins.2018.00260

Combining Polygenic Hazard Score With Volumetric MRI and Cognitive Measures Improves Prediction of Progression From Mild Cognitive Impairment to Alzheimer's Disease

Karolina Kauppi[1,2], Chun Chieh Fan[1,3], Linda K. McEvoy[1], Dominic Holland[4], Chin Hong Tan[5], Chi-Hua Chen[1], Ole A. Andreassen[6,7], Rahul S. Desikan[5], and Anders M. Dale[1,3,4]* for the Alzheimer's Disease Neuroimaging Initiative[†]*

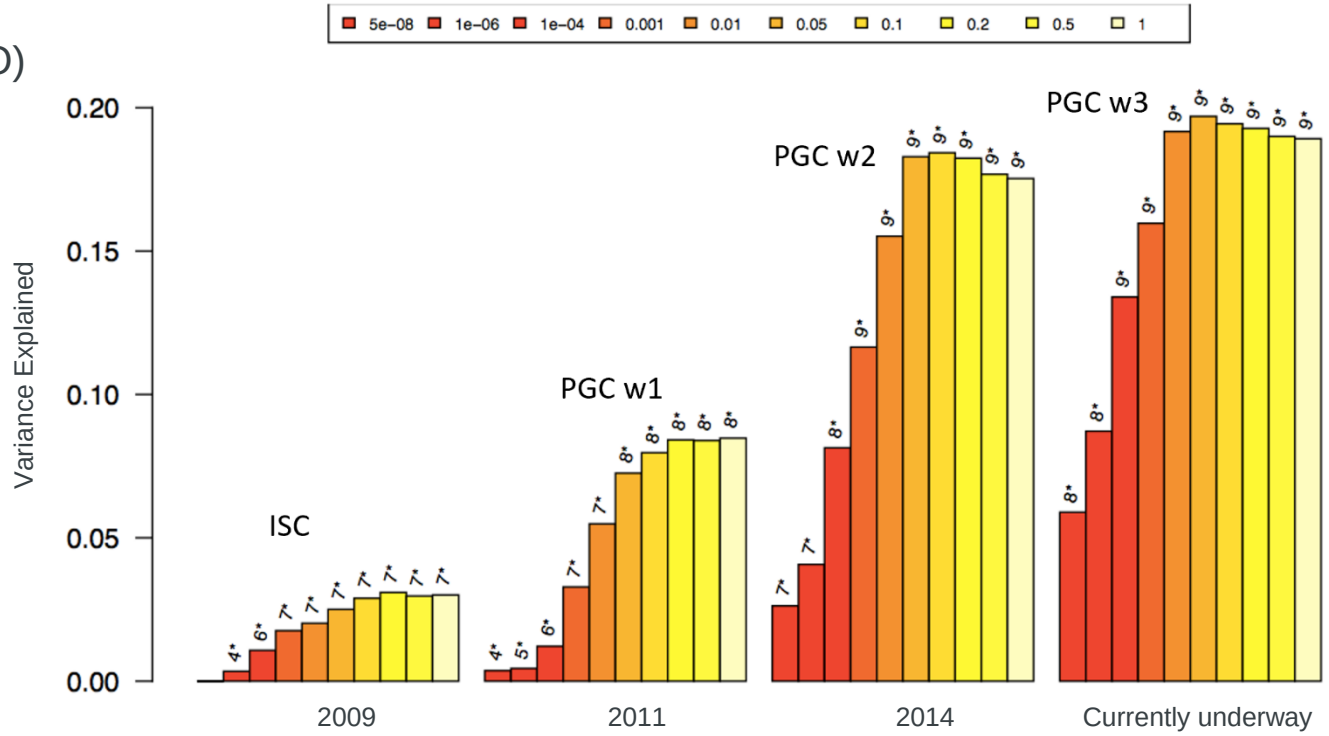






PRS in Psychiatric Disorders

- PGC-SCZ
- Leave-one-out (LOO)



PRS in Psychiatric Disorders

- Independent smaller SCZ cohorts
- PRS explains small % of variance
- Similar in other psychiatric disorders
- Vast improvement required before clinically useful

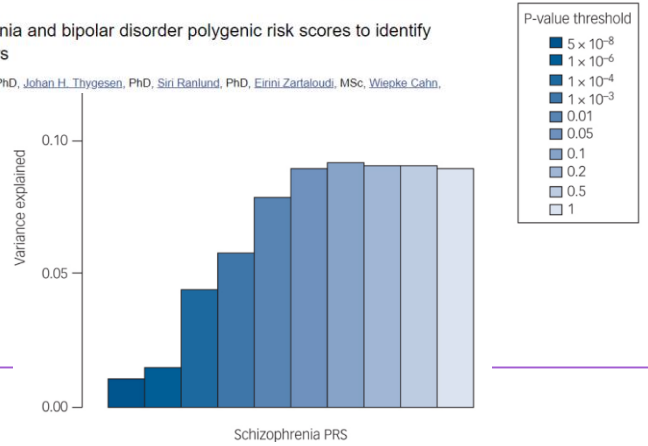
THE BRITISH JOURNAL OF PSYCHIATRY
Cambridge University Press

Br J Psychiatry. 2018 Sep; 213(3): 535–541.
doi: 10.1192/bjp.2018.89

PMCID: PMC6130805
EMSID: EMS77123
PMID: 30113282

Use of schizophrenia and bipolar disorder polygenic risk scores to identify psychotic disorders

Maria Stella Calafato, MD, PhD, Johan H. Thygesen, PhD, Siri Ranlund, PhD, Eirini Zartaloudi, MSc, Wiepke Cahn,

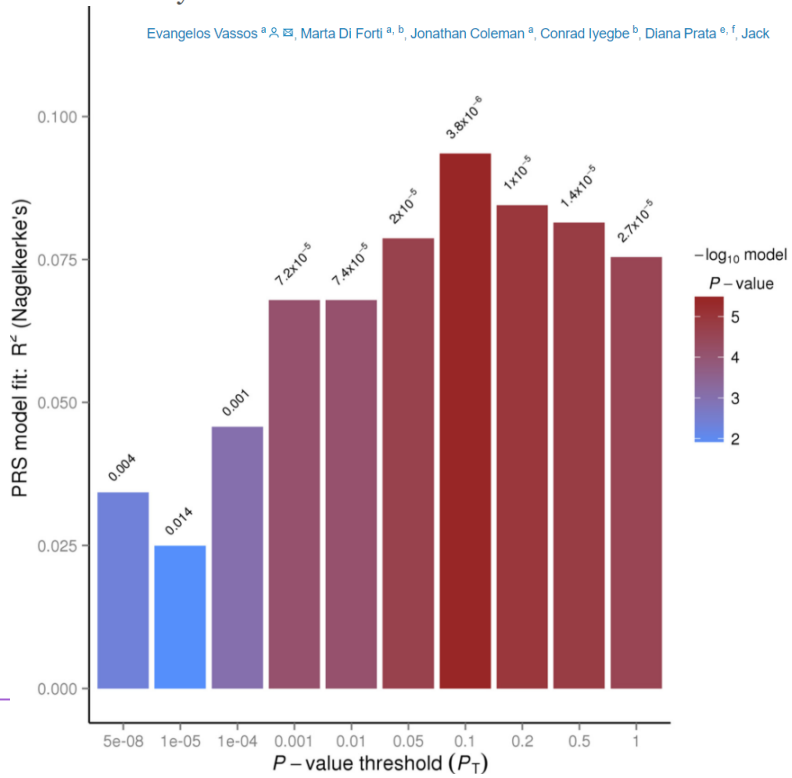


Biological Psychiatry
Volume 81, Issue 6, 15 March 2017, Pages 470-477

Priority Communication

An Examination of Polygenic Score Risk Prediction in Individuals With First-Episode Psychosis

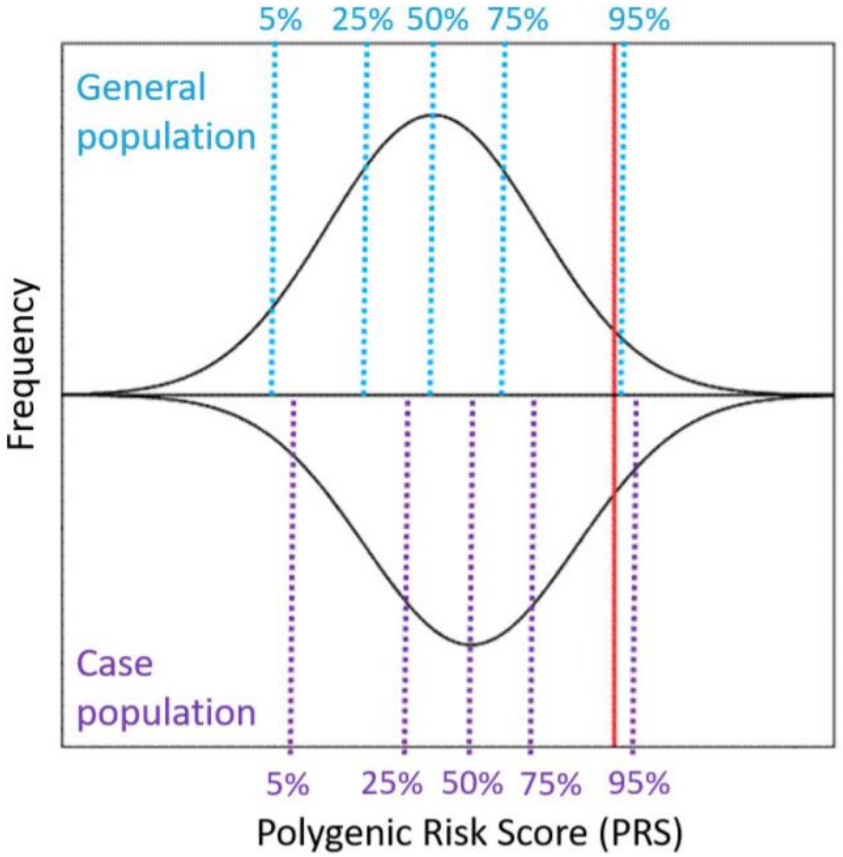
Evangelos Vassos [a], Marta Di Forti [a, b], Jonathan Coleman [a], Conrad Iyegbe [b], Diana Prata [e, f], Jack



PRS in Psychiatric Disorders

- What PRS can do
  - Differentiate case/control at group level
  - Inform research on endophenotypes
  - Provide information on phenotypic correlations

- What PRS cannot do now
  - Inform diagnosis on individual level
  - Substitute for family history in clinical assessment



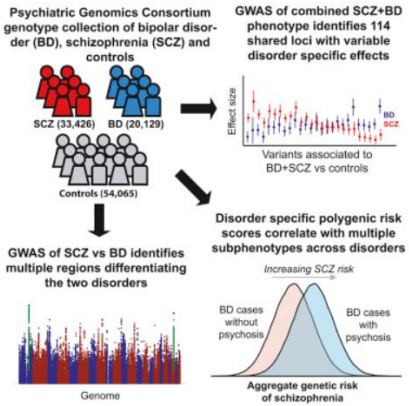
Sub-phenotype Prediction

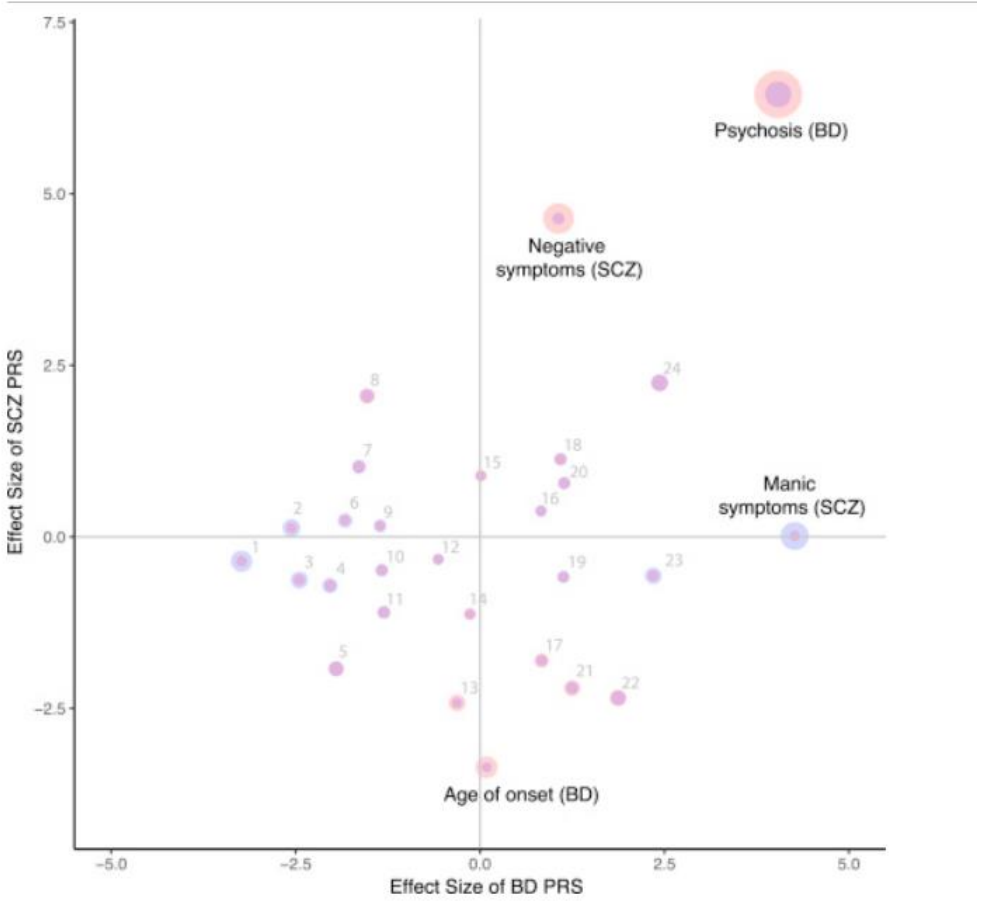
Cell
Volume 173, Issue 7, 14 June 2018, Pages 1705-1715.e16

Article

Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes

Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium





Schizophrenia Treatment Resistance

- 30-50% of SCZ patients are classified as having a treatment resistant disorder[1]. Thus, there is a great need for improved treatment regimens.
- Known genetic overlap; SCZ risk genes and antipsychotic target genes
  - pharmacological mechanisms polygenic
- Perturbations in one gene can propagate to affect other proteins in the protein-protein interaction (PPI) network, i.e. the interactome.
- Protein products of genes that are associated with a disease tend to interact with each other and converge on related biological and functional networks (disease module) [2,3].
- We characterized a SCZ disease module
- Examined the interactome link between antipsychotic drug targets and SCZ risk genes through protein-protein interactions.

1. Meltzer, H.Y. *Curr Med Res Opin* **14**, 1-20 (1997).
2. Menche, J. *et al. Science* **347**, 1257601 (2015).
3. Barabasi, A.L., *et al.*. *Nat Rev Genet* **12**, 56-68 (2011).

Connection Between SCZ Risk Genes and Antipsychotic Drug targets.

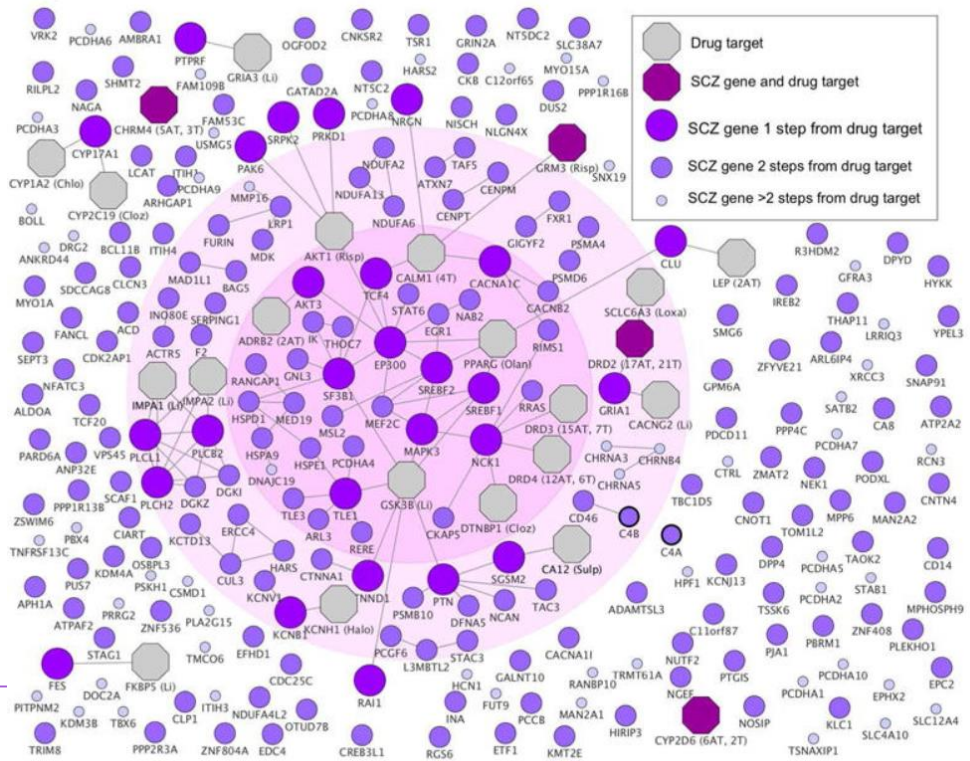
- SCZ risk genes
- Antipsychotic drug targets
- ADME (absorption, distribution, metabolism, and excretion) genes

All of their interactors

Am J Psychiatry. 2018 Jul 1; 175(7): 674–682. PMID: 29495895
Published online 2018 Mar 2. doi: 10.1176/appi.ajp.2017.17040410

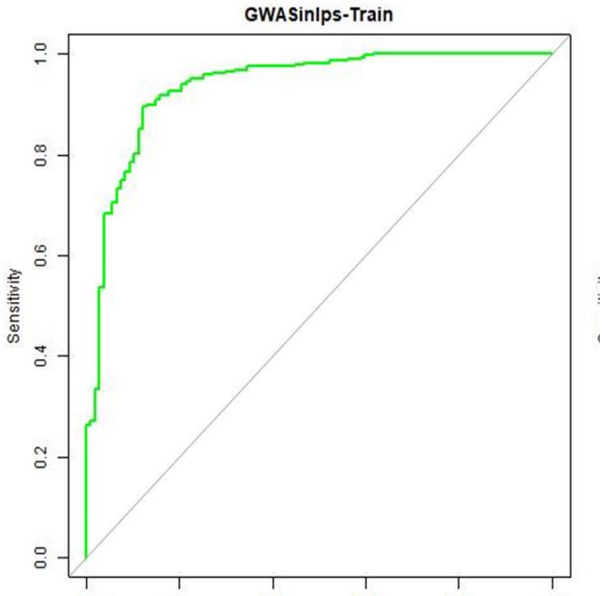
Revisiting antipsychotic drug actions through gene networks associated with schizophrenia

Karolina Kauppi, PhD,[1,2] Sara Brin Rosenthal, PhD,[3] Min-Tzu Lo, PhD,[1] Nilotpal Sanyal, PhD,[1] Mian Jiang,[1] Ruben Abagyan, PhD,[4] Linda K McEvoy, PhD,[1] Ole A Andreassen, PhD,[5] and Chi-Hua Chen, PhD[1]



Prediction of Treatment Resistance

- Preliminary analyses provides strong evidence for the strength of this approach
- ~67,000 SNPs from identified gene networks.
- Novel Bayesian non-local prior method[1], including confounding covariates in the model (i.e., sex, age, and four principal components of genetic population structures).
- Preliminary findings show high prediction rates
  - Training data (85.80%)
  - Testing data (81.96%)



ROC curve. Correct classification in 85.8%.
Gani et al in prep.

1. Sanyal, N. *et al. Bioinformatics* (2018).

NORMENT
Norwegian Centre for
Mental Disorders Research

Thank you

NORMENT
Oslo University Hospital HF
Division of Mental Health and Addiction
Psychosis Research Unit/TOP
Ullevål Hospital, building 49
P.O. Box 4956 Nydalen
N-0424 Oslo
Norway