The University Of Queensland AUSTRALIA | CREATE CHANGE

Polygenic risk prediction: schizophrenia

Naomi Wray

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Program in Complex Trait Genomics

The University Of Queensland AUSTRALIA | IMB
Institute for Molecular Bioscience

The University Of Queensland AUSTRALIA | QBI
Queensland Brain Institute

First mention of polygenic risk prediction

Marker loci associated with highly significant additive effects on the character can be included in a net molecular score, m, which for any individual is the sum of the additive effects on the character associated with these markers. Use of the net molecular score,

Genetics, 1990

Efficiency of Marker-Assisted Selection in the Improvement of Quantitative Traits

Russell Lande* and Robin Thompson†

This paper also proposes genome-wide association studies.
Earlier considered "marker assisted selection", first paper (to my knowledge) that proposes polygenic prediction by exploiting LD (between markers and QTLs) and using a whole genome approach.

Genomic Selection

Genetics, 2001

Prediction of Total Genetic Value Using Genome-Wide Dense Marker Maps

T. H. E. Meuwissen,* B. J. Hayes† and M. E. Goddard†,‡

- Anticipates the arrival of dense SNP arrays
- Proposes multi-SNP advanced statistical models to estimate SNP effects
- To select the best plants/animals from marker data means first making a prediction on how good they are → polygenic prediction

PNAS, 2016

Changes in genetic selection differentials and generation intervals in US Holstein dairy cattle as a result of genomic selection

Adriana García-Ruiz[a,b], John B. Cole[b], Paul M. VanRaden[b], George R. Wiggans[b], Felipe J. Ruiz-López[a], and Curtis P. Van Tassell[b,1]

HIGHLIGHTED ARTICLE

GENETICS | GENOMIC PREDICTION

GENOMIC PREDICTION

Complex Trait Prediction from Genome Data: Contrasting EBV in Livestock to PRS in Humans

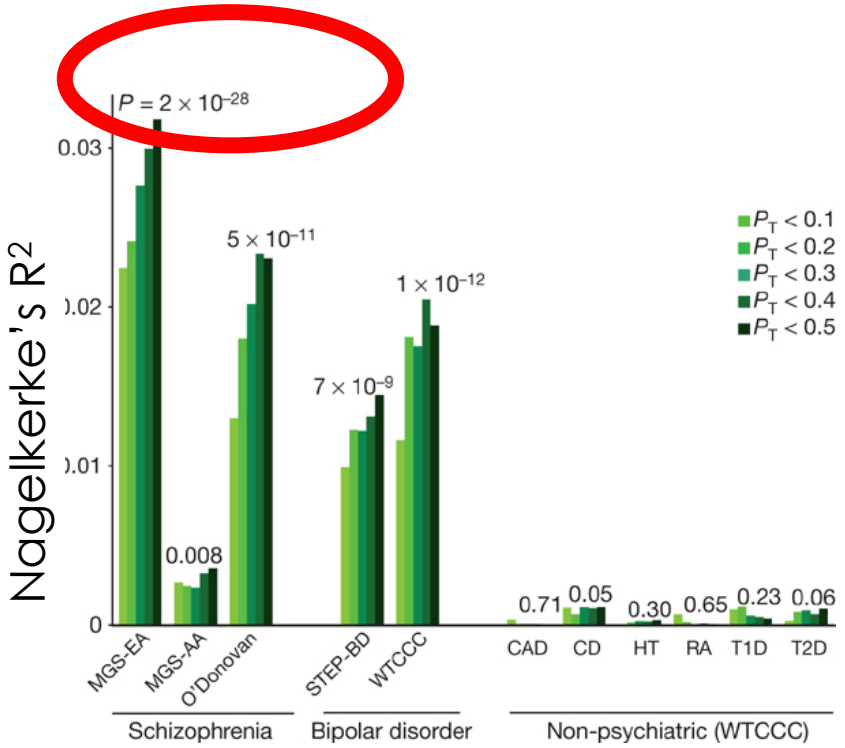
Naomi R. Wray,*,†,1 Kathryn E. Kemper,* Benjamin J. Hayes,‡ Michael E. Goddard,§,** and Peter M. Visscher*,†

Risk Prediction

Prediction of individual genetic risk to disease from genome-wide association studies

Naomi R. Wray,[1,4] Michael E. Goddard,[2,3] and Peter M. Visscher[1]

Simulation
Genome Research, 2007



Shaun Purcell

Pamela Sklar

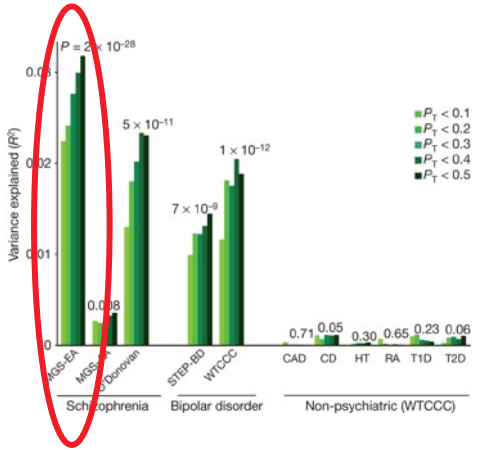
Peter Visscher

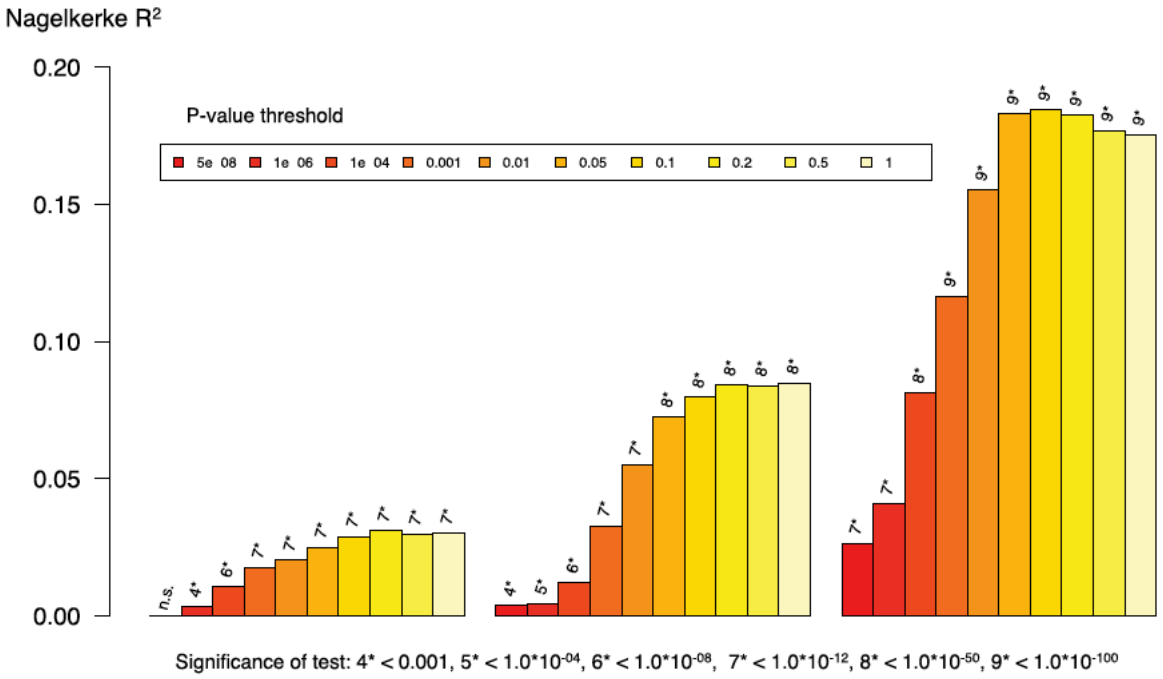
Stuart Macgregor

PLINK --score

Purcell, Wray et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder *Nature* 2009

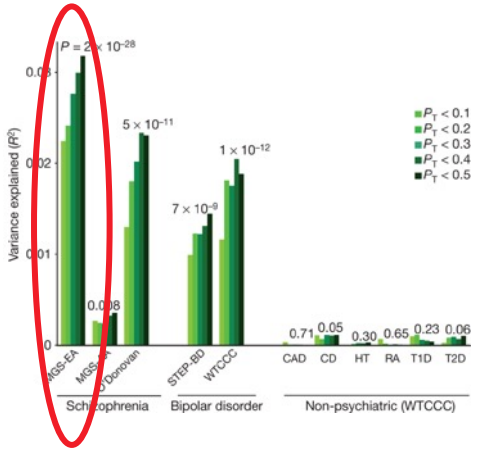
Schizophrenia prediction

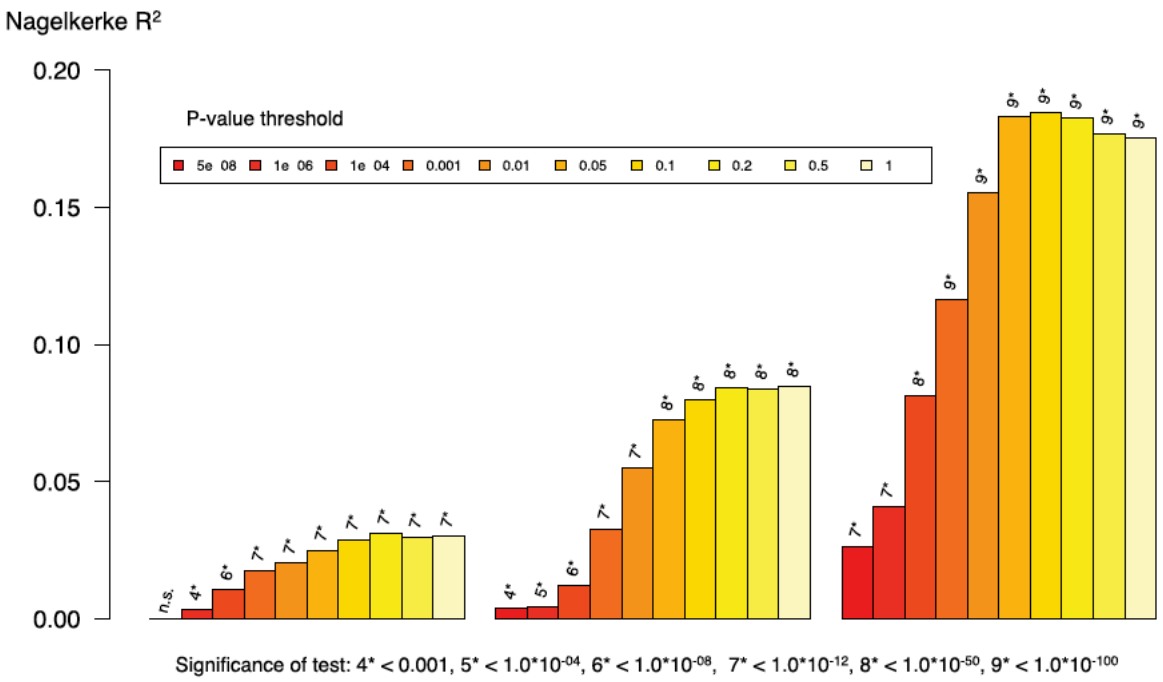


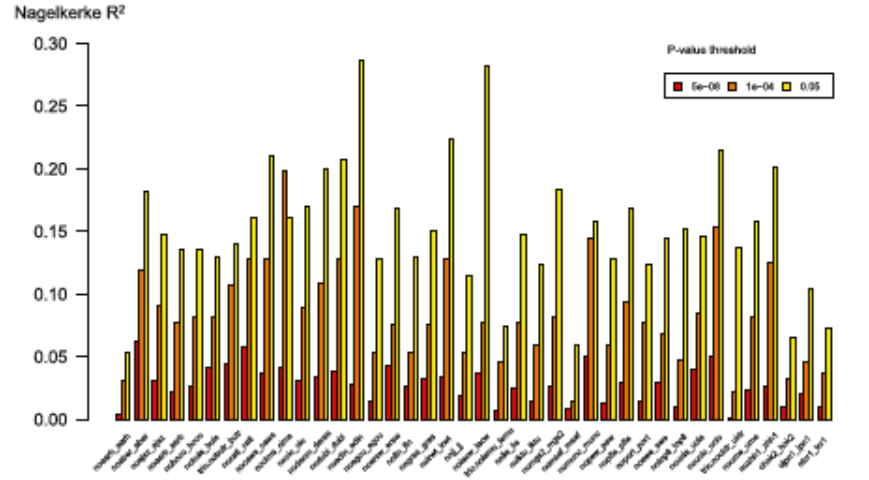


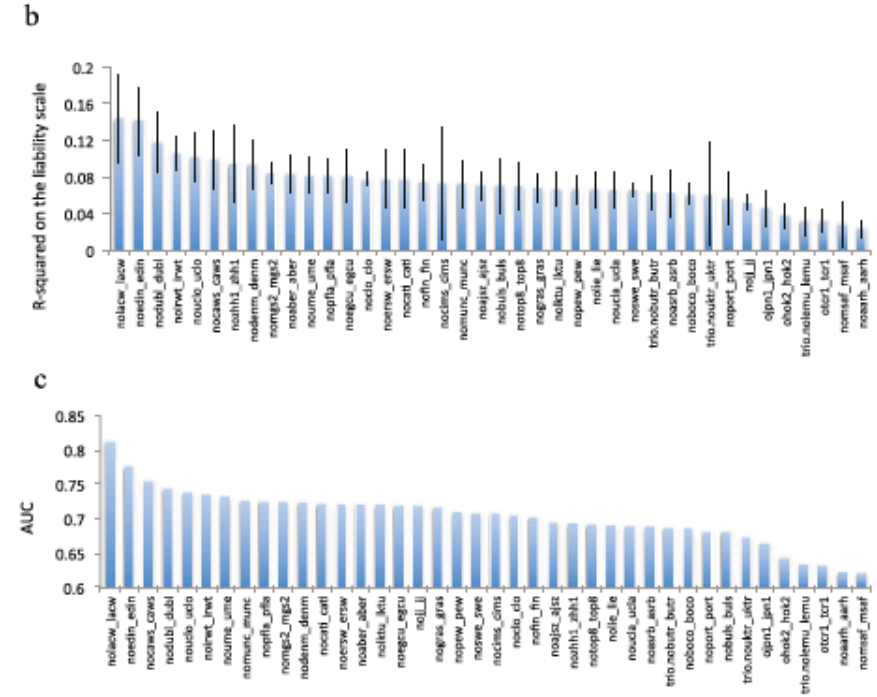
PGC-SCZ 2014 Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia prediction









PGC-SCZ 2014 Biological insights from 108 schizophrenia-associated genetic loci

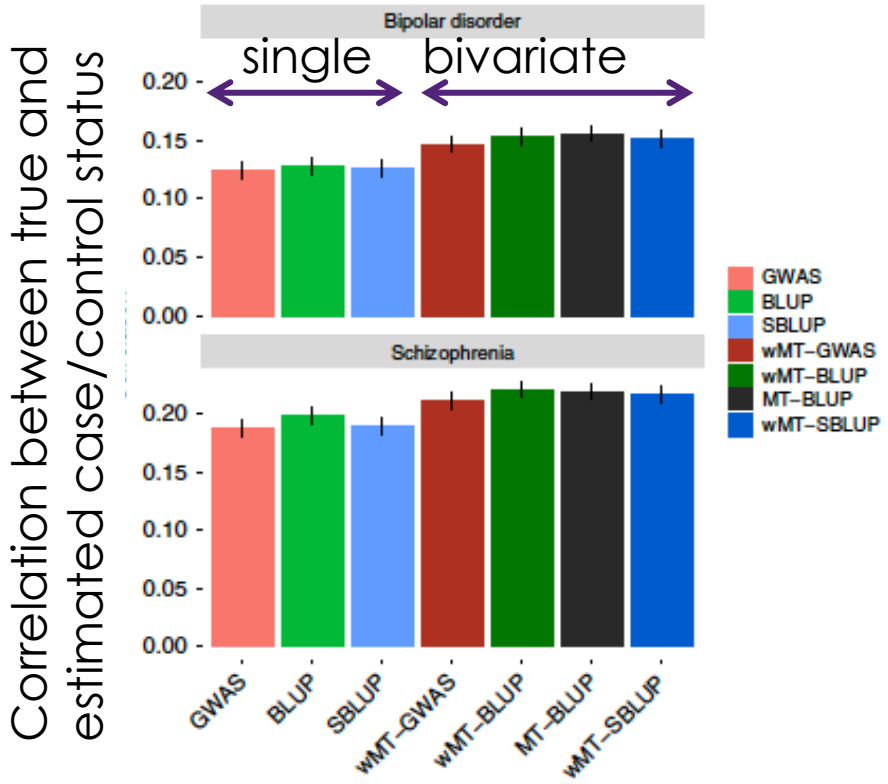
nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-02769-6 OPEN

Improving genetic prediction by leveraging genetic correlations among human diseases and traits

Robert M. Maier[1,2,3], Zhihong Zhu[4], Sang Hong Lee[1,5], Maciej Trzaskowski[4], Douglas M. Ruderfer[6], Eli A. Stahl[7], Stephan Ripke[2,3,8], Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Naomi R. Wray[1,4], Jian Yang[1,4], Peter M. Visscher[1,4] & Matthew R. Robinson[4,9,10]

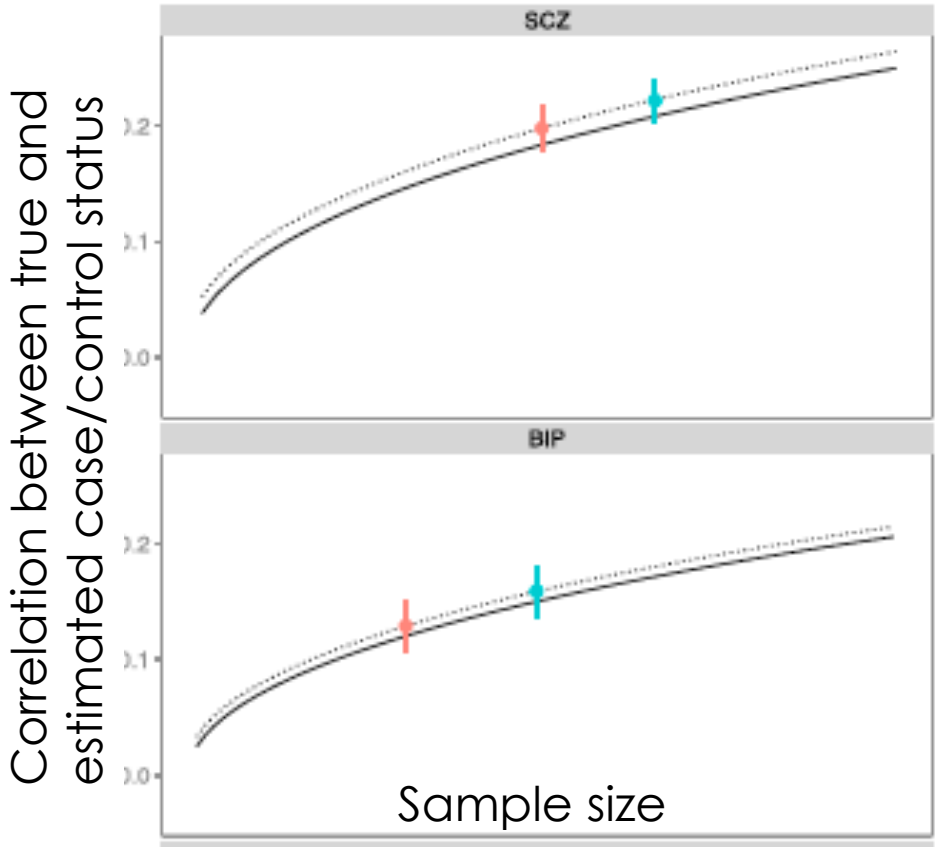


REPORT

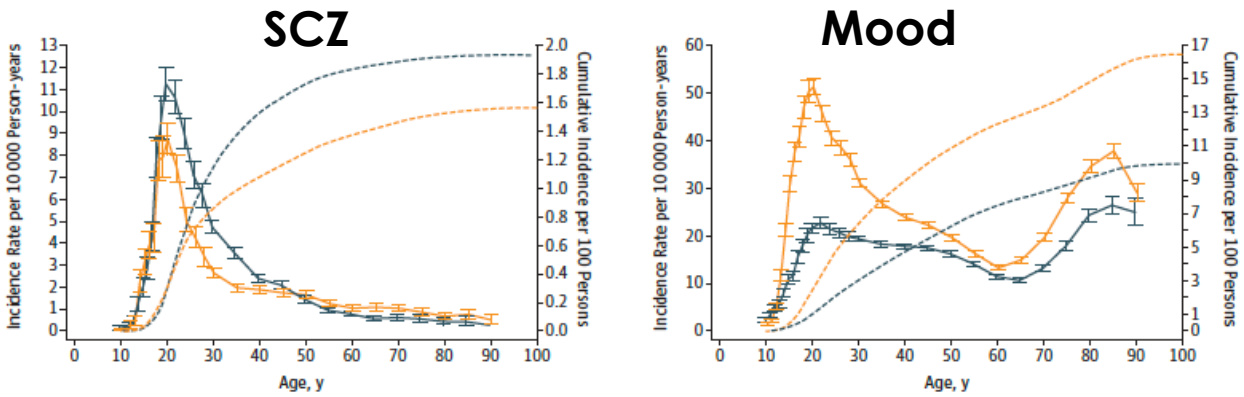
Joint Analysis of Psychiatric Disorders Increases Accuracy of Risk Prediction for Schizophrenia, Bipolar Disorder, and Major Depressive Disorder

AJHG 2015

Robert Maier,[1] Gerhard Moser,[1] Guo-Bo Chen,[1] Stephan Ripke,[2] Cross-Disorder Working Group of the Psychiatric Genomics Consortium, William Coryell,[3] James B. Potash,[3] William A. Scheftner,[4] Jianxin Shi,[5] Myrna M. Weissman,[6] Christina M. Hultman,[7] Mikael Landén,[7,8] Douglas F. Levinson,[9] Kenneth S. Kendler,[10] Jordan W. Smoller,[11] Naomi R. Wray,[1] and S. Hong Lee[1,*]



A need for risk prediction for schizophrenia?

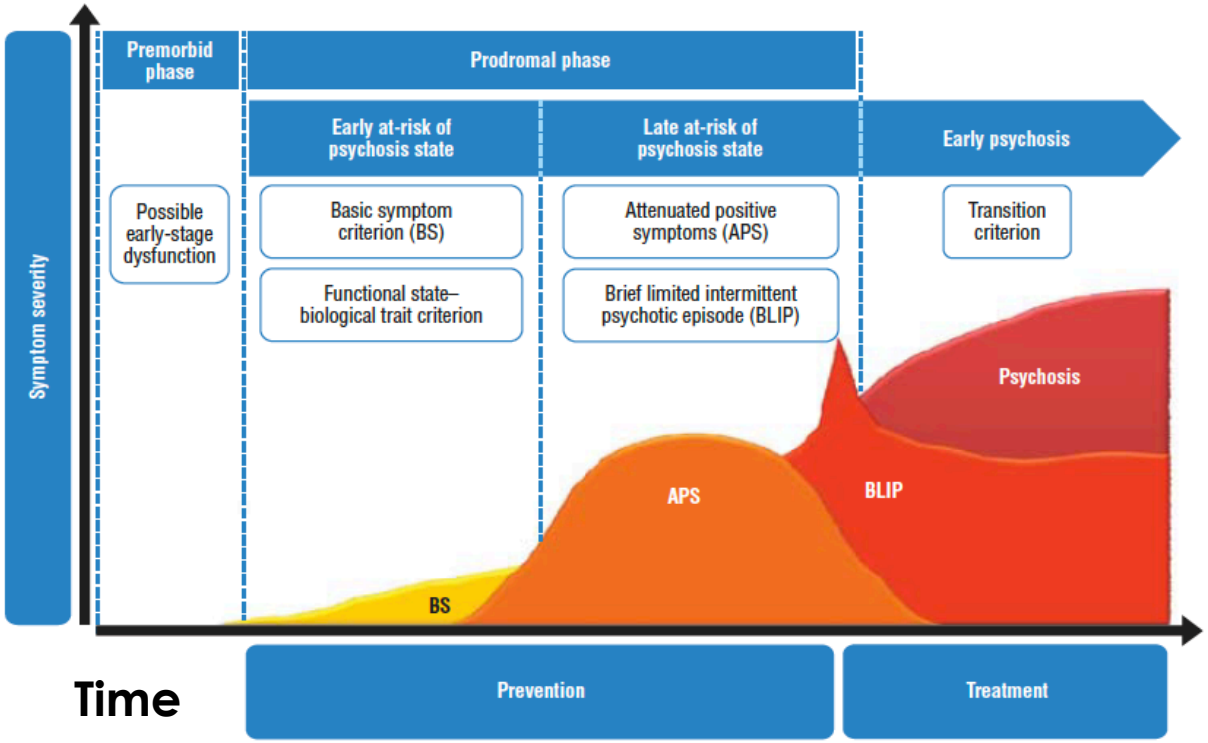


Original Investigation

A Comprehensive Nationwide Study of the Incidence Rate and Lifetime Risk for Treated Mental Disorders

Carsten Bøcker Pedersen, DrMedSc; Ole Mors, PhD; Aksel Bertelsen, MD; Berit Lindum Waltoft, MSc; Esben Agerbo, DrMedSc; John J. McGrath, MD; Preben Bo Mortensen, DrMedSc; William W. Eaton, PhD

JAMAP 2014



REVIEW

The Psychosis High-Risk State

A Comprehensive State-of-the-Art Review

Paolo Fusar-Poli, MD, PhD; Stefan Borgwardt, MD, PhD; Andreas Bechdolf, MD; Jean Addington, PhD; Anita Riecher-Rössler, MD, PhD; Frauke Schultze-Lutter, PhD; Matcheri Keshavan, MD; Stephen Wood, MD, PhD; Stephan Ruhrmann, MD, PhD; Larry J. Seidman, MD, PhD; Lucia Valmaggia, MSc, PhD; Tyrone Cannon, PhD; Eva Velthorst, MSc, PhD; Lieuwe De Haan, MD, PhD; Barbara Cornblatt, MBA, PhD; Ilaria Bonoldi, MD; Max Birchwood, DSc; Thomas McGlashan, MD; William Carpenter, MD; Patrick McGorry, MD; Joachim Klosterkötter, MD, PhD; Philip McGuire, MD, PhD; Alison Yung, MD

JAMAP 2013

Any use of risk prediction for schizophrenia?

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Therapeutic signposts: using biomarkers to guide better treatment of schizophrenia and other psychotic disorders

Richard Banati and Ian B Hickie

Molecular Psychiatry (2012) 1 – 6

www.nature.com/mp

PERSPECTIVE

Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?

S Kapur[1], AG Phillips[2] and TR Insel[3]

CONCLUSION

Biological psychiatry and the related neurosciences have changed mankind's view of itself and of mental illness, but have yet to provide biomedical tests for routine clinical practice. The delay is understandable given the later start than the rest of medicine, the complexity of the brain, the nascence of neuroscientific techniques and the evolving nature of psychiatric nosology. On the other hand, the opportunity afforded by the progress in genomics and imaging combined with the computational abilities is unprecedented and could deliver useful clinical tests. These tests will identify homogenous populations for whom one could develop targeted new therapeutics thus realising a vision of a new stratified psychiatry that cuts across the traditional diagnostic boundaries while simultaneously transforming them.

Editorials

MJA 198 (9) · 20 May 2013

Clinical staging for mental disorders: a new development in diagnostic practice in mental health

Matching the timing and intensity of interventions to the specific needs of patients

Ian B Hickie
Jan Scott
Patrick D McGorry

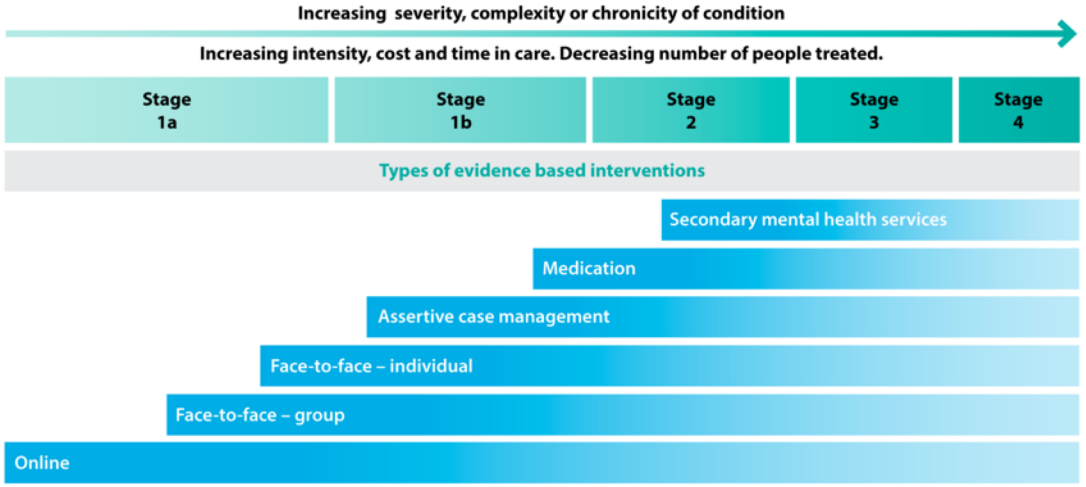
The release of the fifth edition of the *Diagnostic and statistical manual of mental disorders* (DSM-5)[1] classification system, scheduled for May 2013, will

major mental disorders begin between 15 and 25 years of age, a focus on enhanced care and novel clinical research during this critical developmental phase is a timely test of

We propose that a refinement to traditional diagnostic practice — clinical staging — is more likely to improve clinical care and inform future research into the causes of mental disorders.[2-5] Further, clinical staging draws the practice of clinical psychiatry closer to general medicine, especially with regard to chronic disease management.

For many decades, DSM and other international systems strived to enhance the reliability of psychiatric diagnoses. Recent field trials for DSM-5 indicate that acceptable reliability remains elusive.[6] However, even diagnostic categories with modest reliability have limited validity. A major

dromes (stage 1; eg, brief episodes of psychotic or hypomanic symptoms) from those meeting threshold diagnostic criteria (stage 2) or with established or persisting illness (stage 3). Importantly, staging suggests that disorders emerge via a limited set of overlapping and



Application to real youth mental health cohort

1483 12-30yrs "broad" youth mental health service, clinics & *headspace*

209 participation in neurobiology phenotyping

182 with DNA genomewide genotypes passing QC

176 European

Ian Hickie

Early Intervention in Psychiatry 2013; 7: 31–43 doi:10.1111/j.1751-7893.2012.00366.x

Original Article

Applying clinical staging to young people who present for mental health care

Ian B. Hickie,[1] Elizabeth M. Scott,[1] Daniel F. Hermens,[1] Sharon L. Naismith,[1] Adam J. Guastella,[1] Manreena Kaur,[1] Anna Sidis,[1] Bradley Whitwell,[1] Nicholas Glozier,[1] Tracey Davenport,[1] Christos Pantelis,[2] Stephen J. Wood[2,5] and Patrick D. McGorry[3,4]

Clinical staging model framework for psychotic and severe mood disorders

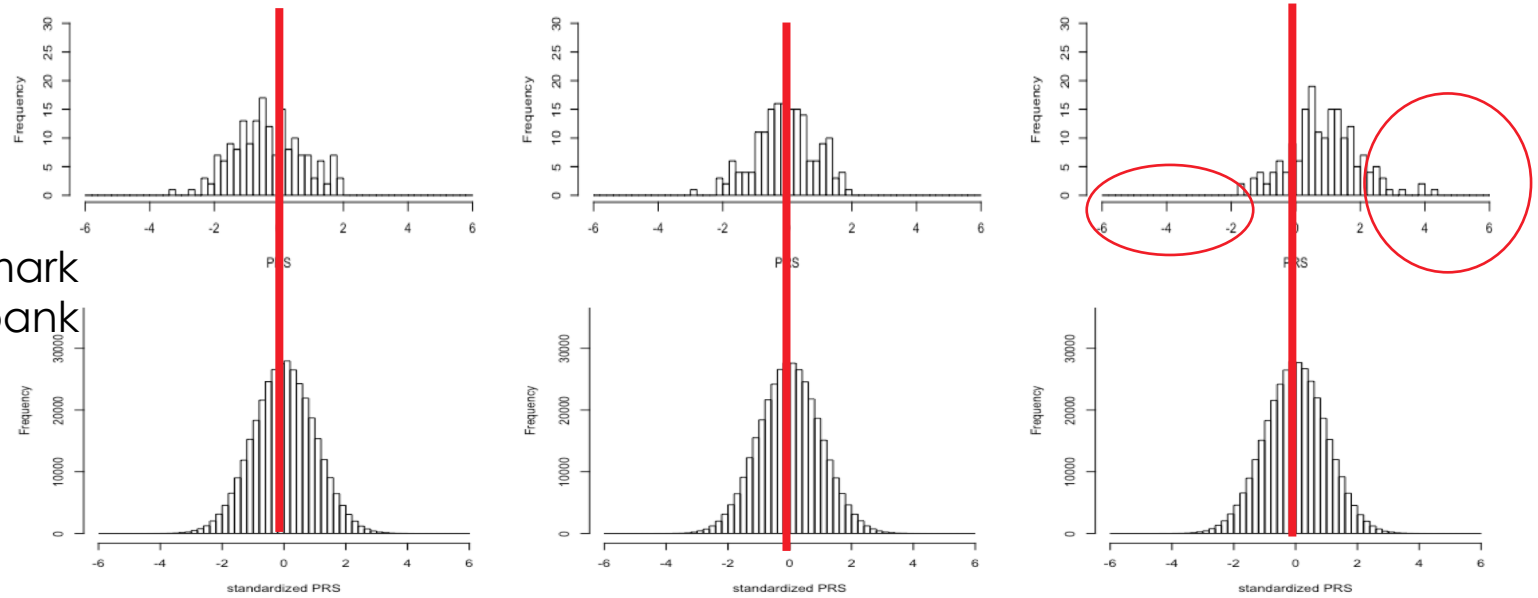
Stage	Definition	Target populations and referral sources	Potential interventions
0	Increased risk of psychotic or severe mood disorder No symptoms currently	• First-degree teenage relatives of probands	• Improved mental health literacy • Family education, drug education • Brief cognitive skills training
1a	Mild or non-specific symptoms (including neurocognitive deficits) of psychosis or severe mood disorder. Mild functional	• Screening of teenage populations • *Referral by*: primary care physicians; school	• Formal mental health literacy • Family psychoeducation, formal CBT
1b	Ultra high risk: moderate but subthreshold symptoms, with moderate neurocognitive changes and functional decline to caseness (GAF, < 70)	• *Referral by*: educational agencies; primary care physicians; emergency departments; welfare agencies	• Family psychoeducation, formal CBT • Active substance misuse reduction • Omega-3 fatty acids • Atypical antipsychotic agents • Antidepressant agents or mood stabilisers
2	disorder Full threshold disorder with moderate to severe symptoms, neurocognitive deficits and functional decline (GAF, 30–50)	emergency departments; welfare agencies; specialist care agencies; drug and alcohol services	• Active substance misuse reduction • Atypical antipsychotic agents • Antidepressant agents or mood stabilisers • Vocational rehabilitation

McGorry et al. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust.* 2007 Oct 1;187(7 Suppl):S40-2.

Height BMI Schizophrenia

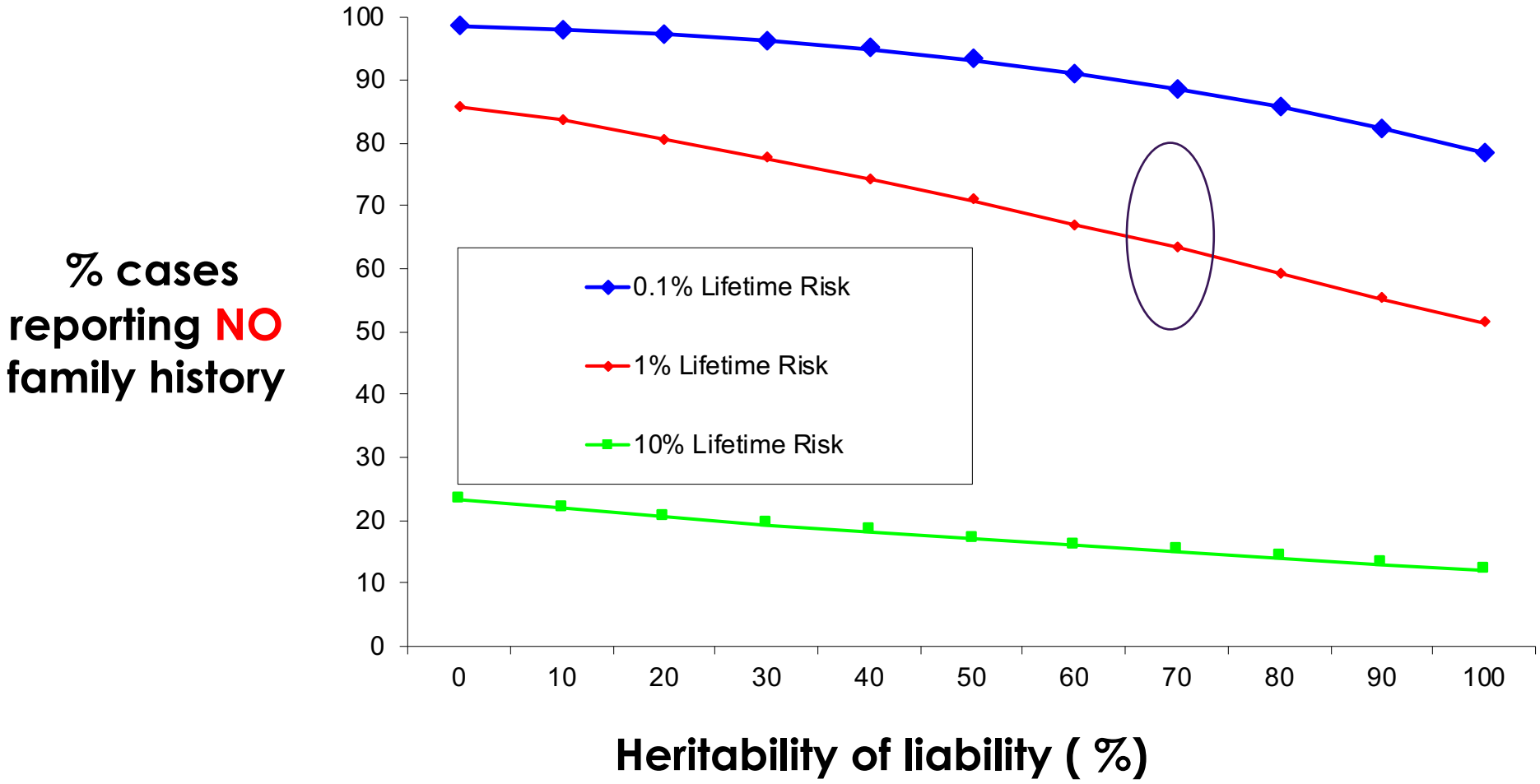
YMH N=176

Benchmark UK biobank N=400K



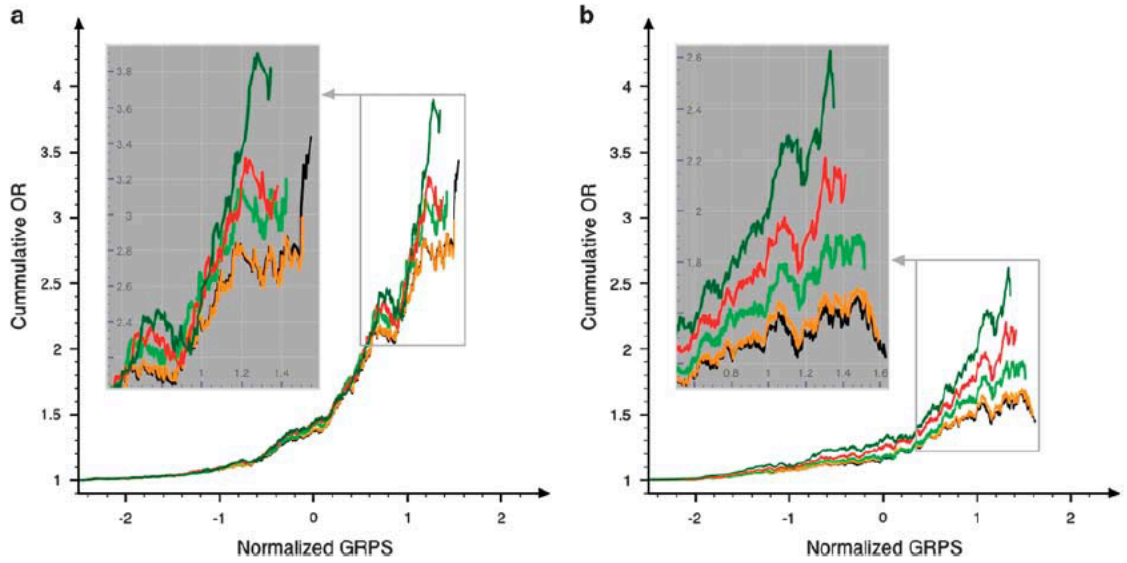
Polygenic risk score in SD units

Most cases of common disease are "sporadic"



Yang, Visscher & Wray (2009) Sporadic cases are the norm for complex disease. Eur J Human Genetics

Schizophrenia PRS applications



Schizophrenia Research 197 (2018) 2–8

Contents lists available at ScienceDirect

Schizophrenia Research

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

The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review

Sumit Mistry [a,*], Judith R. Harrison [a], Daniel J. Smith [b], Valentina Escott-Price [a], Stanley Zammit [a,c]

Inpatient ≥ 4 times SCZ

Inpatient ≥ 4 times any psych disorder

≥ 4 in/out patient main SCZ

≥ 4 in/out any pscyh

Remainder SCZ

DENMARK

Molecular Psychiatry (2016) 21, 969–974

www.nature.com/mp

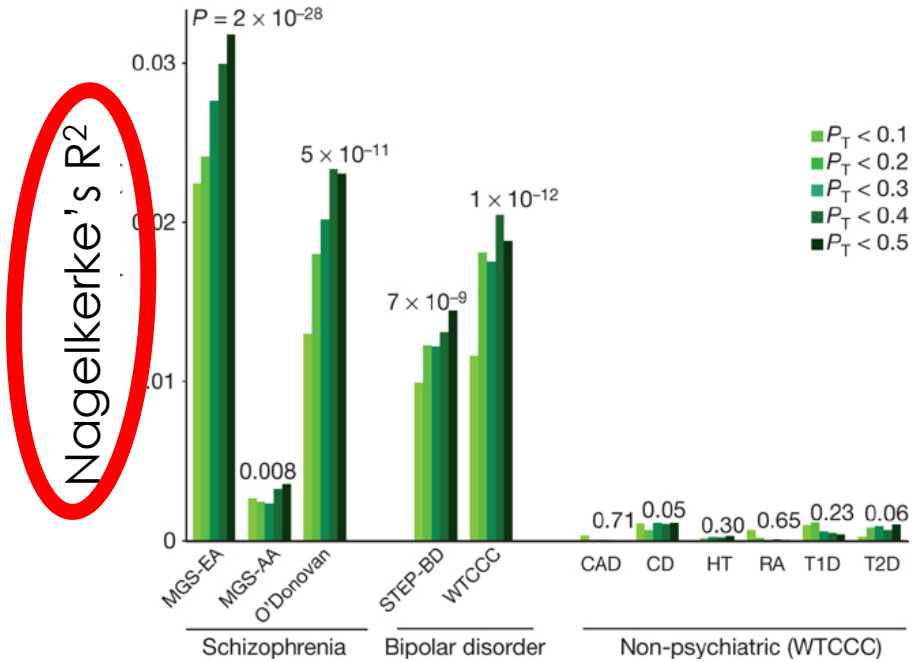
ORIGINAL ARTICLE

High loading of polygenic risk in cases with chronic schizophrenia

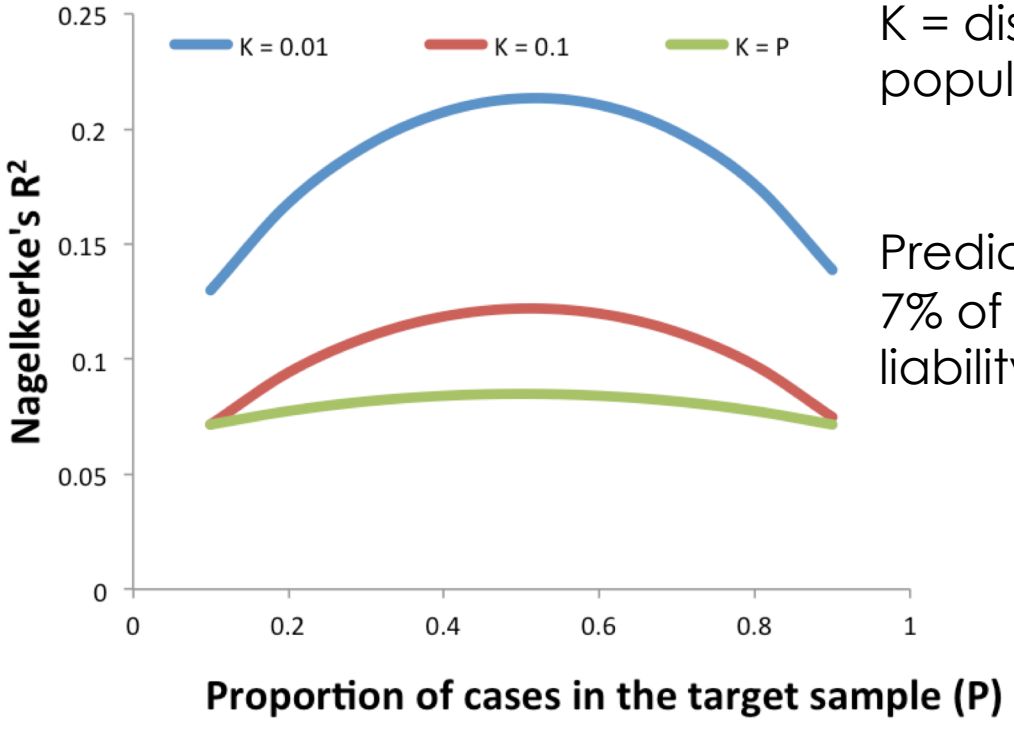
SM Meier[1,2,3], E Agerbo[1,2,4], R Maier[5], CB Pedersen[1,2,4], M Lang[3], J Grove[2,6,7,8], MV Hollegaard[9], D Demontis[2,6,8], BB Trabjerg[1,2], C Hjorthøj[2,10,11], S Ripke[12,13], F Degenhardt[14,15], MM Nöthen[14,15], D Rujescu[16], W Maier[17], MooDS SCZ Consortium[20], T Werge[2,10], O Mors[2,18], DM Hougaard[9], AD Børglum[2,6,8,18], NR Wray[5], M Rietschel[3], M Nordentoft[2,10,16], PB Mortensen[1,2,4,8,19] and M Mattheisen[2,6,8,14,15,19]

Recognise schizophrenia GWAS sample may be over-ascertained for schizophrenia patients treated with clozapine and interpret PRS results accordingly

Criteria for assessing polygenic risk scores



Purcell, Wray et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder *Nature* 2009



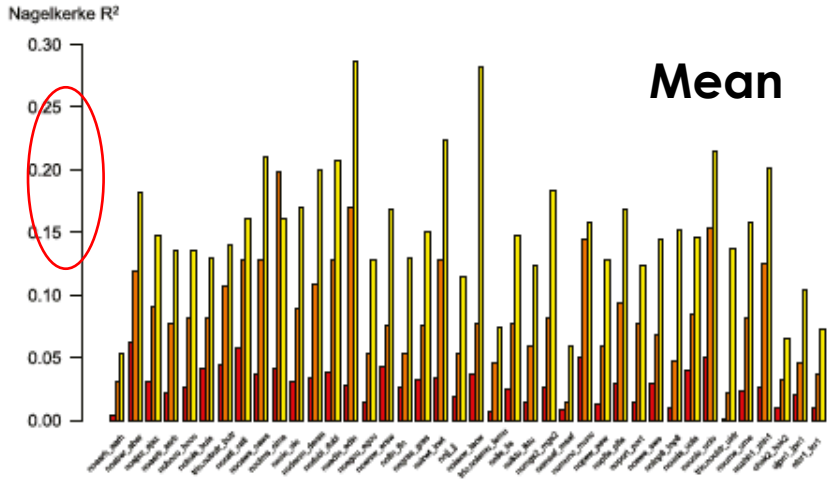
K = disease risk in population

Predictor explains 7% of variance in liability

Schizophrenia prediction

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Nagelkerke's R^2



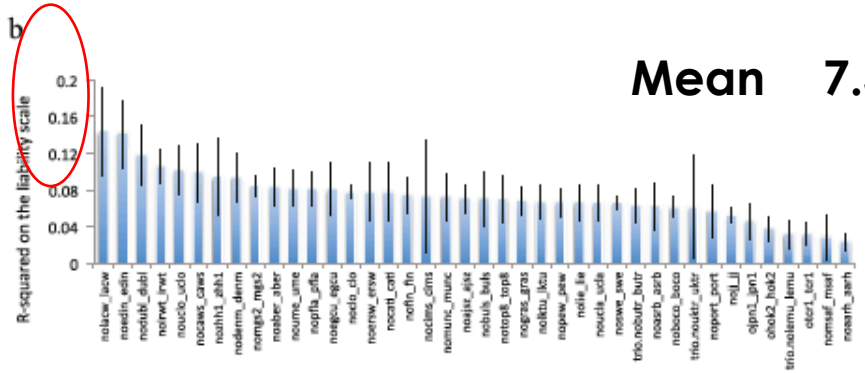
Mean 15%

Genetic Epidemiology 36 : 214–224 (2012)

A Better Coefficient of Determination for Genetic Profile Analysis

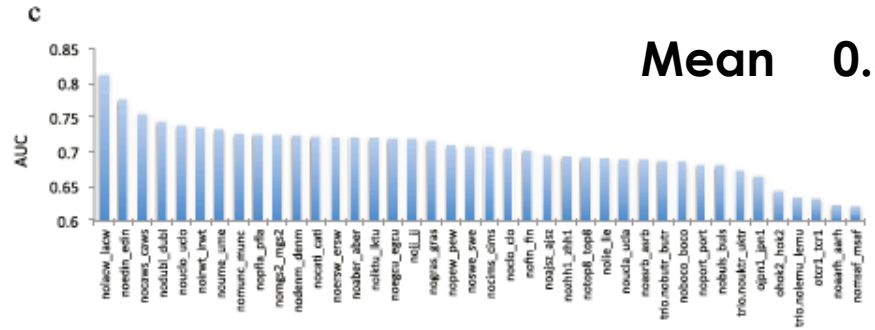
Sang Hong Lee,[1,2*] Michael E Goddard,[3,4] Naomi R Wray,[1,2] and Peter M Visscher[1,2,5]

Liability R^2



Mean 7.3%

AUC



Mean 0.61

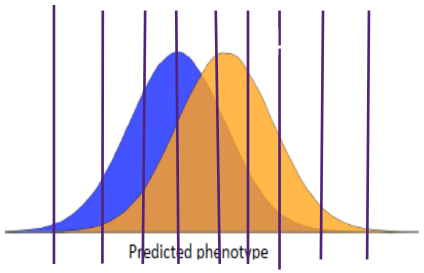
OPEN ACCESS Freely available online PLoS GENETICS

The Genetic Interpretation of Area under the ROC Curve in Genomic Profiling

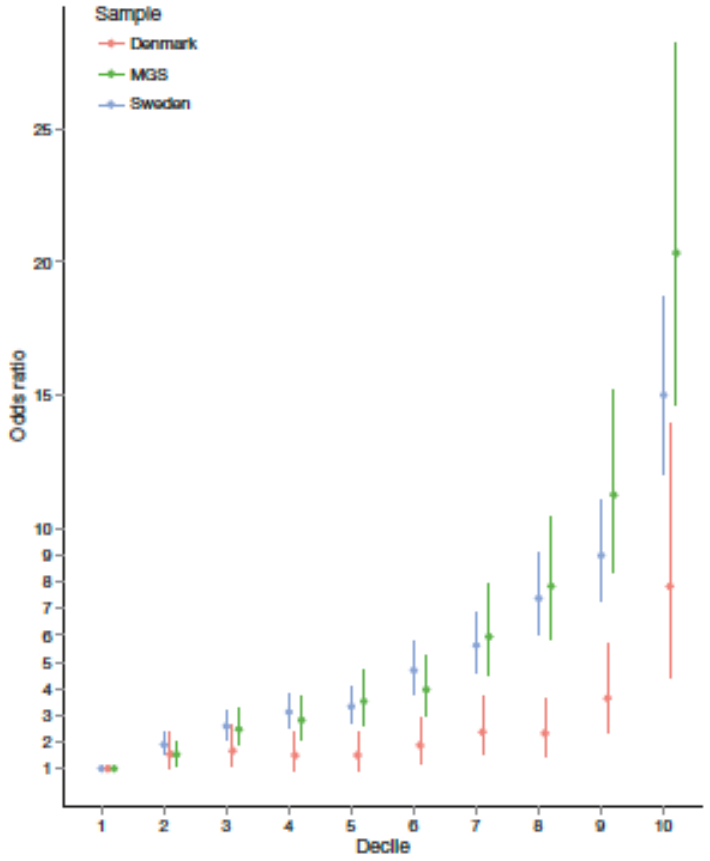
Naomi R. Wray[1]*, Jian Yang[1], Michael E. Goddard[2,3], Peter M. Visscher[1]

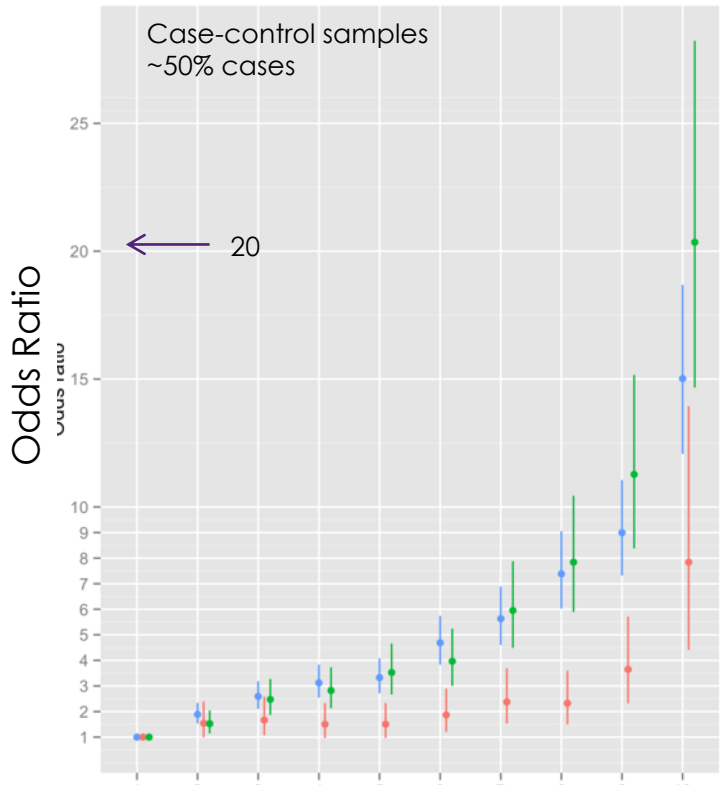
PGC-SCZ 2014 Biological insights from 108 schizophrenia-associated genetic loci

Response as decile odds ratio

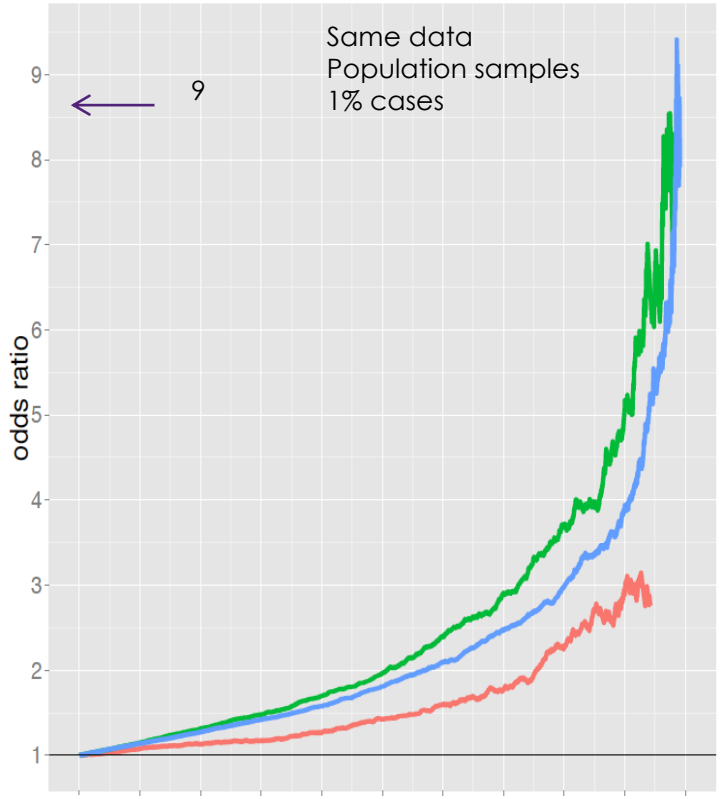


Odds of disease decile vs 1st decile





Risk score decile in case-control sample



Risk score in population

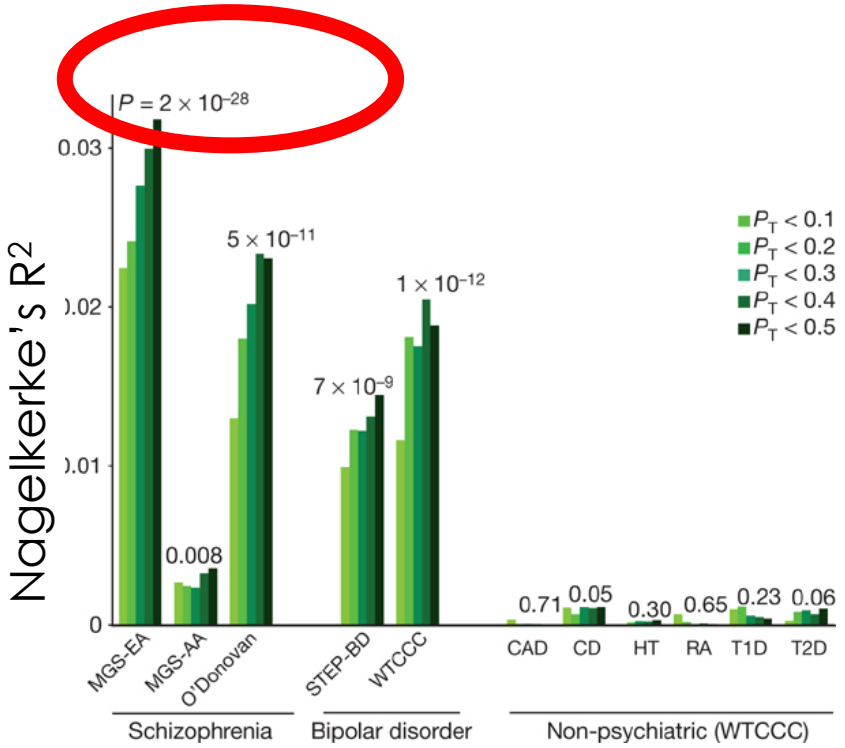
PGC-SCZ 2014 Biological insights from 108 schizophrenia-associated genetic loci

Risk Prediction

Prediction of individual genetic risk to disease from genome-wide association studies

Naomi R. Wray,[1,4] Michael E. Goddard,[2,3] and Peter M. Visscher[1]

Simulation
Genome Research, 2007



Total variance explained by all SNPs from simulation: 0.3

= SNP-based heritability

Shaun Purcell

Pamela Sklar

Peter Visscher

Stuart Macgregor

PLINK --score

Purcell, Wray et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder *Nature* 2009

What is the maximum variance explained?

Variance explained by predictor

$$R^2_{y,\hat{y}} = \frac{cov(y,\hat{y})^2}{Var(y)Var(\hat{y})}$$

$$R^2_M = \frac{h^2_M}{1 + M/(Nh^2_M)}$$

True variance explained by the M SNPs

Number of M SNPs

GWAS discovery sample size

infinitesimal model assumptions

Daetwler et al (2008) Accuracy of Predicting the Genetic Risk of Disease Using a Genome-Wide Approach. PLoS One
Visscher, Yang, Goddard (2010) Commentary on Yang et al (2010)
Wray et al (2013) Pitfalls of predicting complex traits from SNPs. Nature Genetics
Dudbridge (2013) Power and Predictive Accuracy of Polygenic Risk Scores. Plos Genetics
Pasanuic & Price (2017) Dissecting the genetics of complex traits using summary association statistics. Nat Rev Gen

Predicted vs observed for schizophrenia

$$h_M^2 = 0.23$$

$$R_M^2 = \frac{h_M^2}{1 + M/(Nh_M^2)}$$

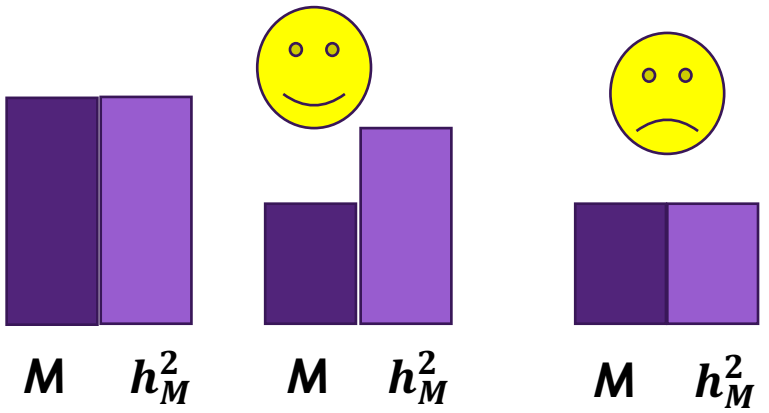
M = effective number of SNPs
= $\frac{\text{total numbers of SNPs}}{\text{Mean LD score}}$

If we use all SNPs from a GWAS,
M = 50,000

From WGS, M is MUCH larger

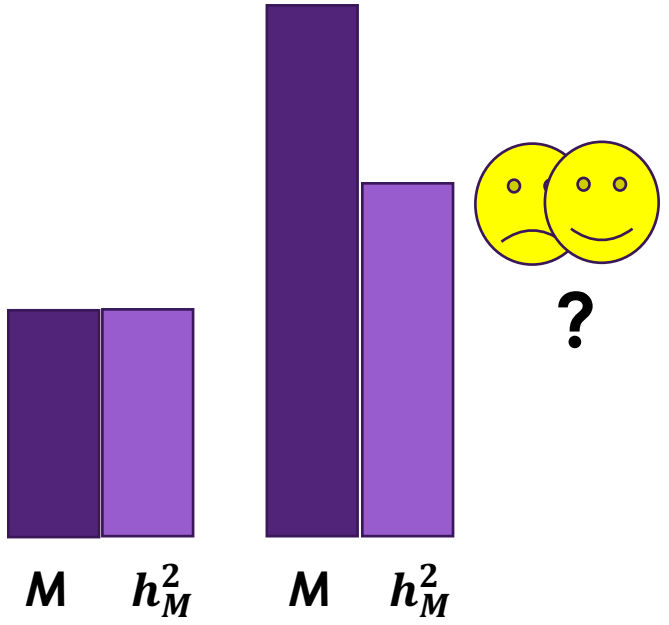
How can we increase prediction from our data

$$R_M^2 = \frac{h_M^2}{1 + M/(N h_M^2)}$$



Can we chose a smaller set of SNPs? The true h_M^2 they explain may be smaller but the balance of h_M^2 to M may lead to a higher R^2?

With WGS, h_M^2 may approach h2, but the increase in M may kill the ratio

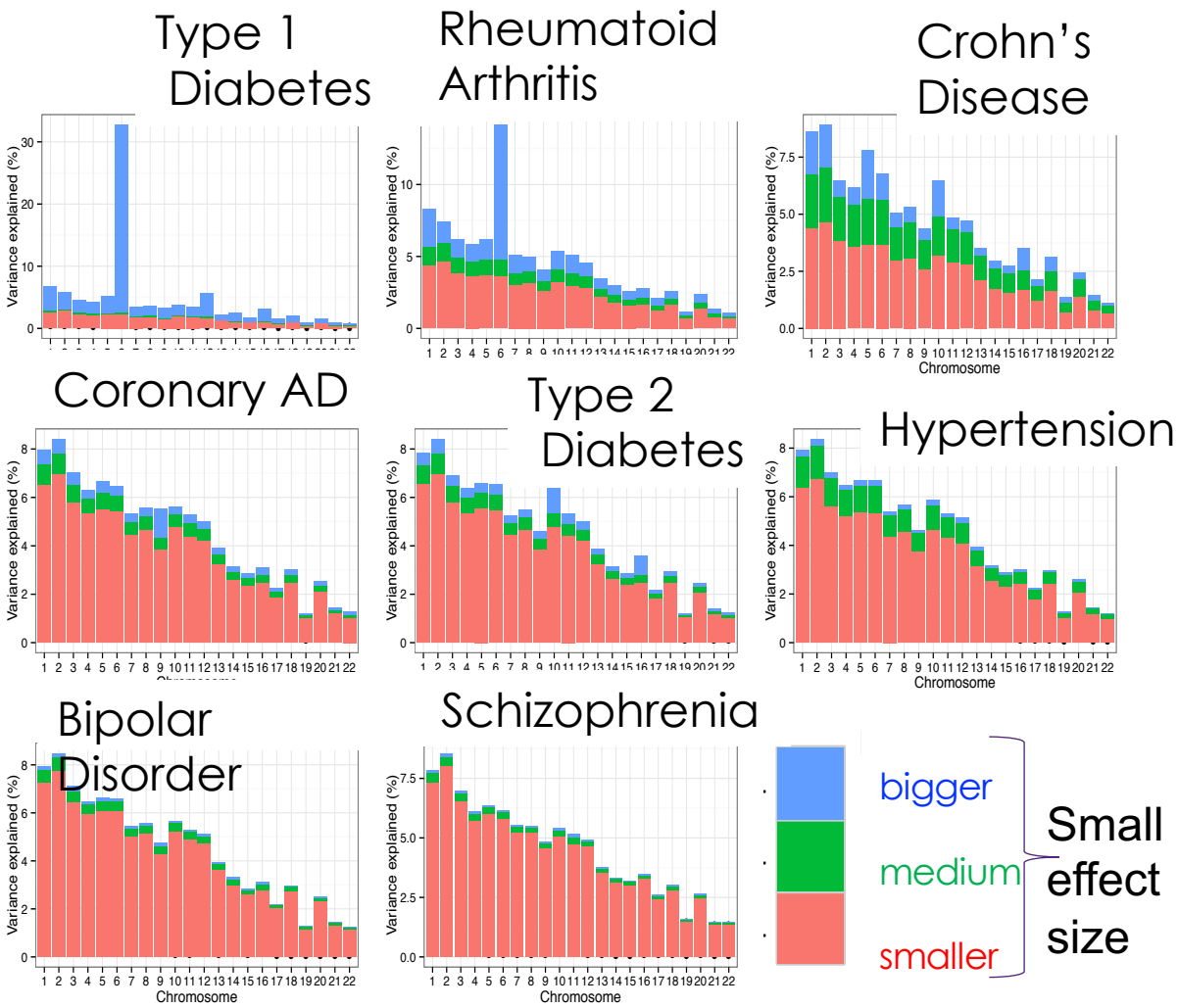


Wray et al (2019) Complex trait prediction from genome data. Genetics

Genetic architecture visualised

- The genetic architecture of the disease
  - ➢ How many risk loci
  - ➢ How big the effect sizes
  - ➢ Relative contribution of genetic factors to risk compared to non-genetic factors

The methodology that optimises risk prediction likely depends on genetic architecture, which is different for different diseases.



Moser et al 2015 Plos Genetics

Summary

Applications of risk prediction methods to schizophrenia have led the field

Risk prediction for psychiatric disorders less likely to be applied in population screening

There is a real need for diagnostic biomarkers in psychiatry

PRS provide a solid foundation stone to build a biomarker risk scheme

Having blood samples collected routinely would pave the way for further developments in risk prediction.

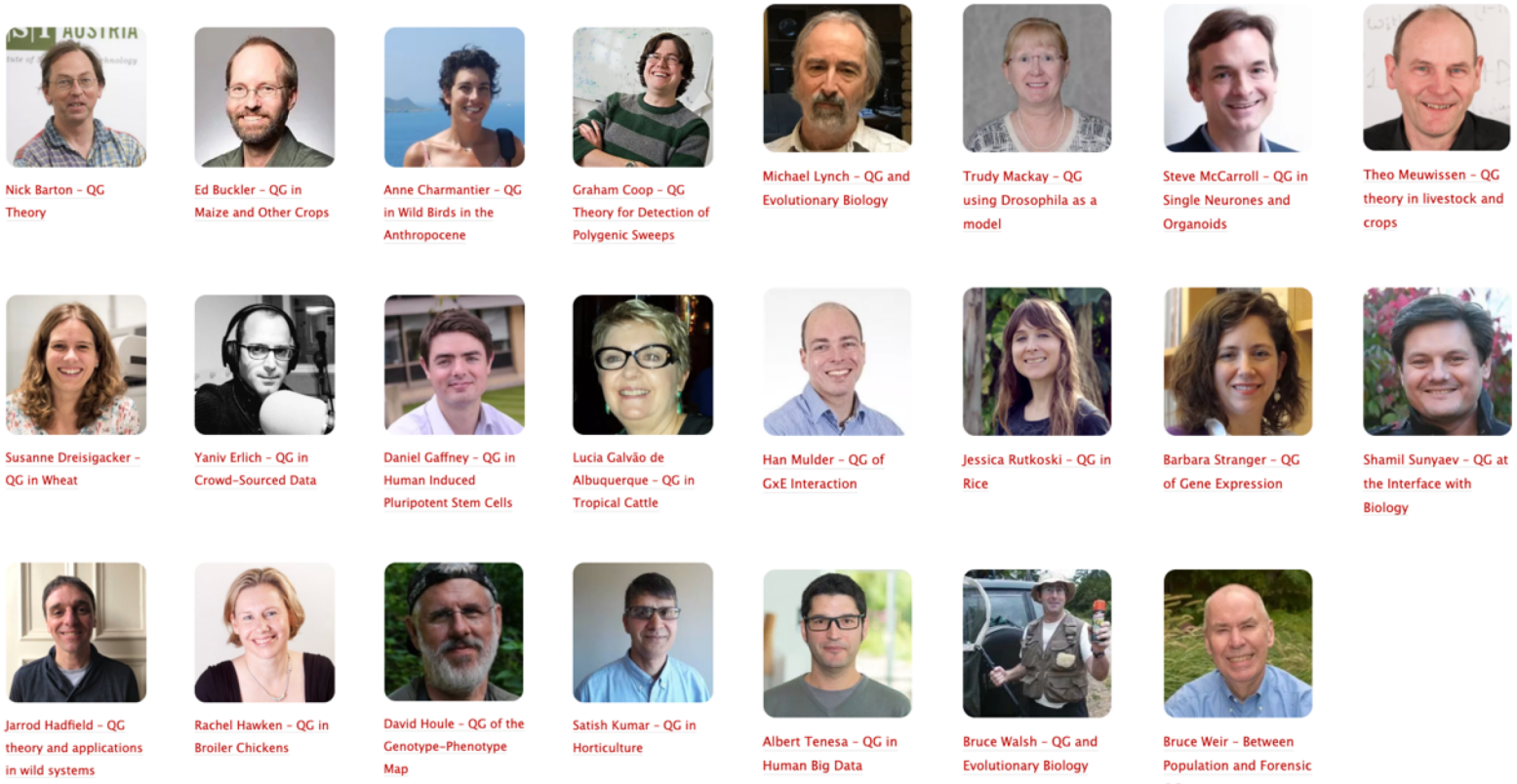
Realism – management of expectations

A recurring theme is about when are samples big enough for GWAS genetic discovery – larger samples are needed for more accurate estimation of individual effect sizes for risk prediction.

Larger samples with better phenotyping…..

icqg6.org
Plan Ahead!
International Congress of Quantitative Genetics
Brisbane June 2020

Including pre- conference student/postdoc workshops



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