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Polygenic risk scores for psychiatry

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Background

JAMA Psychiatry | Review

From Basic Science to Clinical Application of Polygenic Risk Scores
A Primer

Naomi R. Wray, PhD; Tian Lin, PhD; Jehannine Austin, PhD; John J. McGrath, MD, PhD; Ian B. Hickie, MD; Graham K. Murray, MD, PhD; Peter M. Visscher, PhD

Peter Visscher, UQ

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JAMA Psychiatry | Review

Could Polygenic Risk Scores Be Useful in Psychiatry?
A Review

Graham K. Murray, MD, PhD; Tian Lin, PhD; Jehannine Austin, PhD; John J. McGrath, MD, PhD; Ian B. Hickie, MD; Naomi R. Wray, PhD

Graham Murray, UoCambridge

Ian Hickie, UoSydney

Jehannine Austin, UoBritish Columbia

John McGrath, UQ

Methods

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] 2007

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Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Genetics & Development

Prediction of individual genetic risk of complex disease

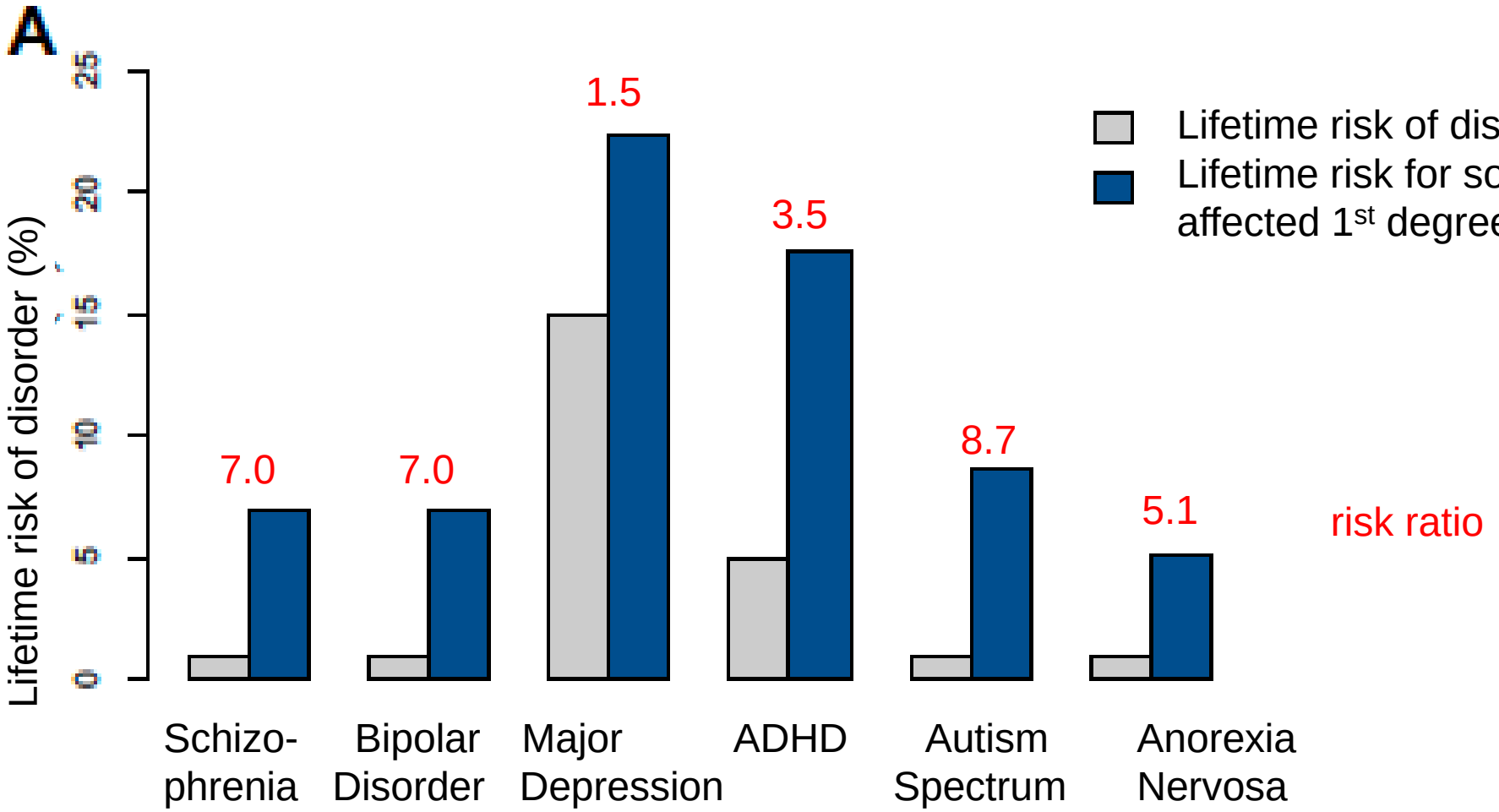
Naomi R Wray[1], Michael E Goddard[2] and Peter M Visscher[1] 2008

Risk predictors have led to polar-opposite opinions for decades.
Reality is in middle ground

Head in the clouds Head in the sand

Source: My undergrad text book: Strachan & Read Human Molecular Genetics 3.

Evidence for a genetic contribution to psychiatric disorders

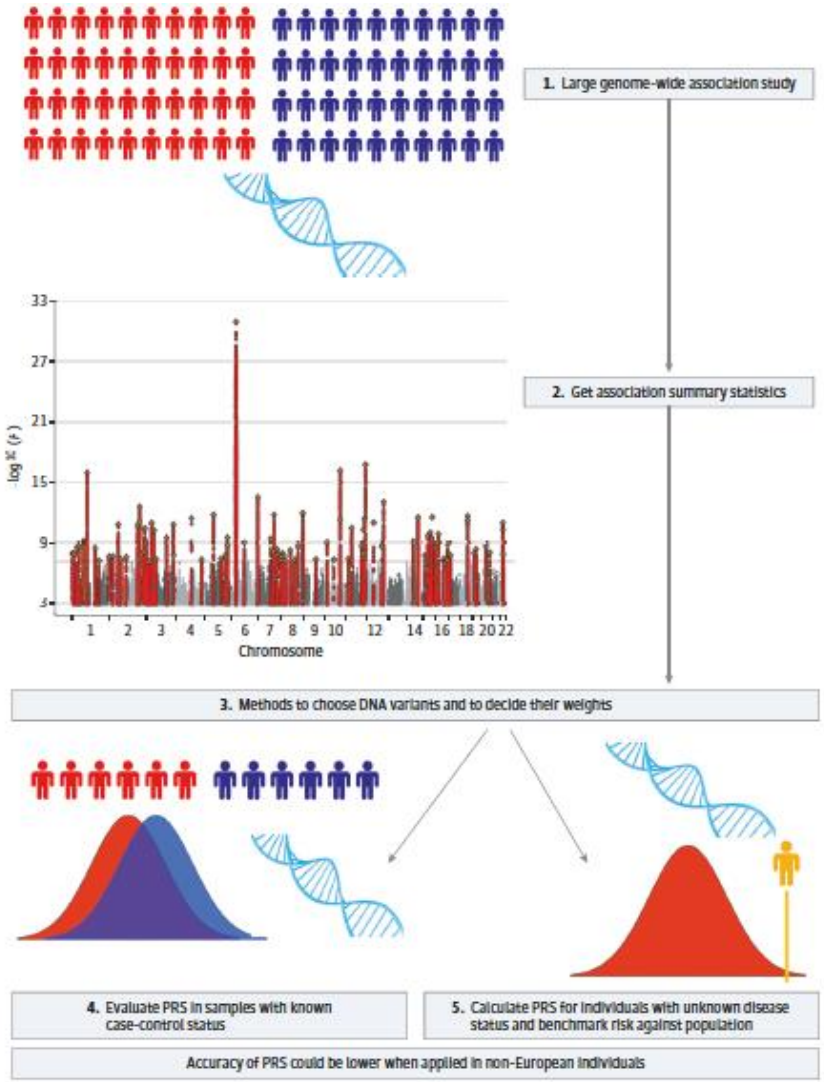


	Schizo-phrenia	Bipolar Disorder	Major Depression	ADHD	Autism Spectrum	Anorexia Nervosa
Heritability:	70%	70%	35%	75%	80%	55%

Proportion of variation attributable to genetic factors

Baselmans et al (2020) Biological Psychiatry

Polygenic risk scores



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Prediction of individual genetic risk of complex disease

Naomi R Wray[1], Michael E Goddard[2] and Peter M Visscher[1] 2008

"The value from predicting individual disease risk from multiple associated variants could be reaped long before the causal mechanism of each is determined."

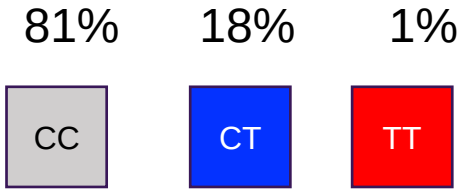
- What constitutes a polygenic risk score for an individual?
- What does the variation in polygenic risk scores between individuals look like?

This understanding needed to answer key questions, e.g.:

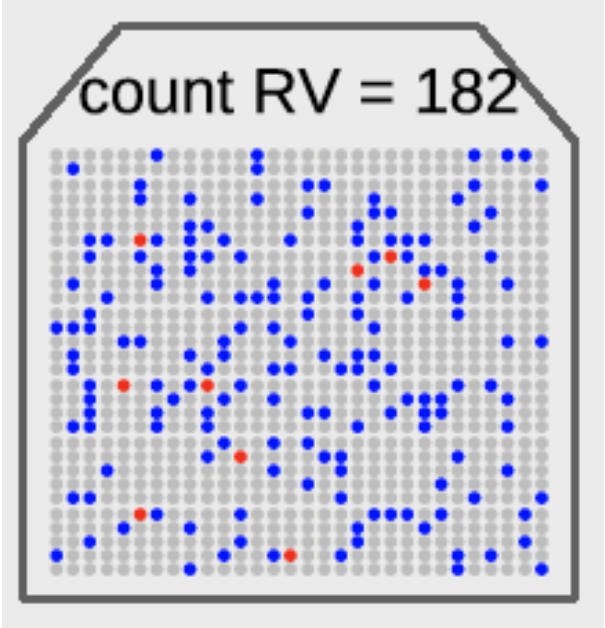
- Will someone **with family history** have a high polygenic risk score?
- Can someone **without family history** have a high polygenic risk score?

Wray et al (2020) From Basic Science to clinical application of polygenic risk scores. JAMA Psychiatry

Polygenic disease for an individual



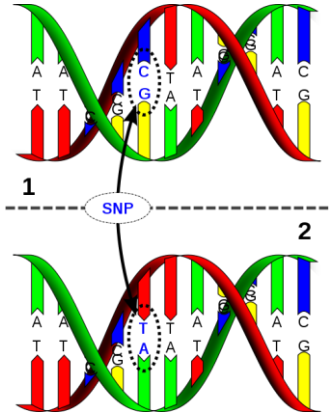
e.g. risk allele T
Frequency 0.1



900 DNA polymorphisms associated with disease risk

RV =risk variant

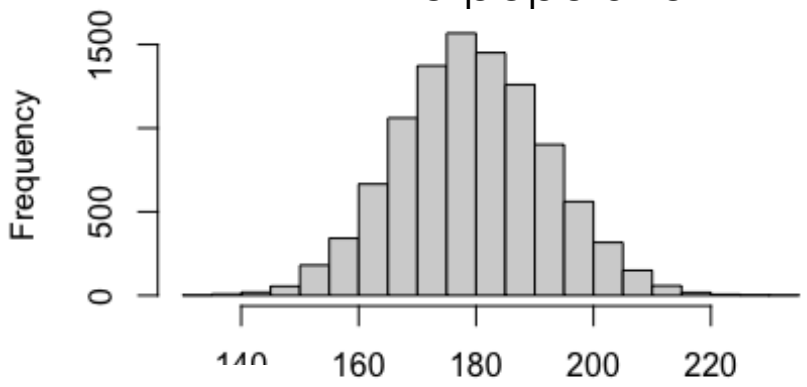
Frequency of risk variant at each site: 0.1



Average person 900*2*0.1 = 180 risk variant

Mean +/- 3SD: 142 to 218

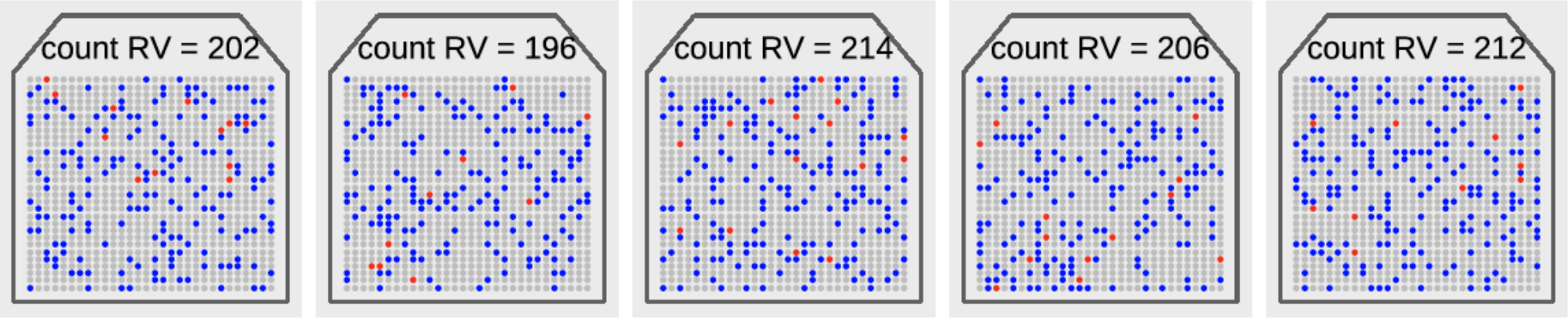
Genetic variation in the population



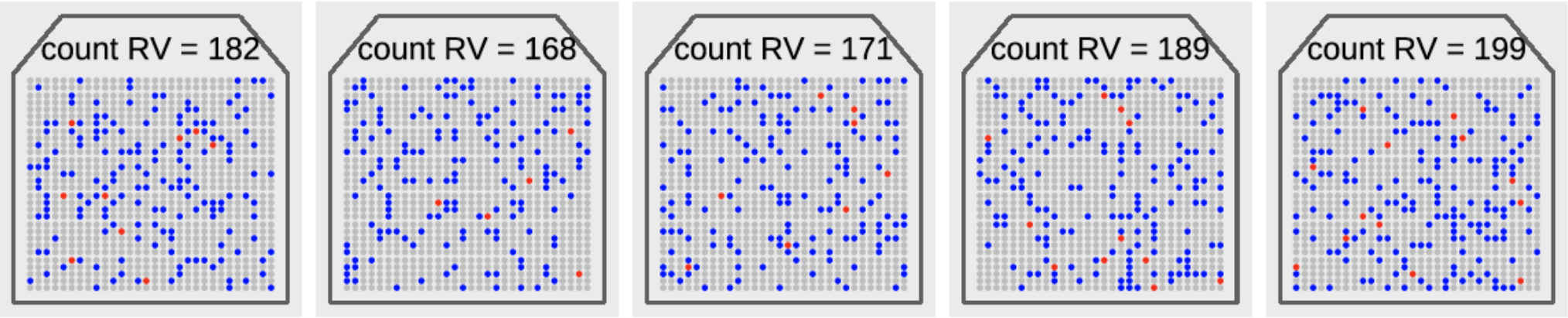
SNP: Single nucleotide polymorphism
SNV: Single nucleotide variant

Polygenic disease for individuals

Affected over lifetime



Not affected over lifetime



900 sites

RV =risk variant

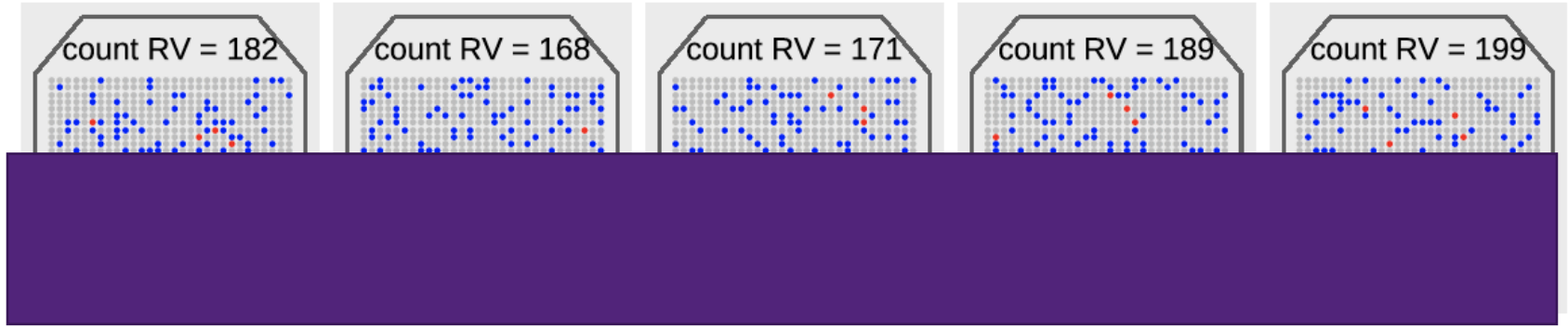
Frequency of risk variant at each site: 0.1

Heritability 0.7
Lifetime risk 0.01

Average person has 900*2*0.1 = 180 risk variant

Mean +/- 3SD: 142 to 218

Polygenic score



→ "True" polygenic score

Not all variants captured on genotyping arrays

Factors contributing to variation between people

All "factors"

All genetic factors

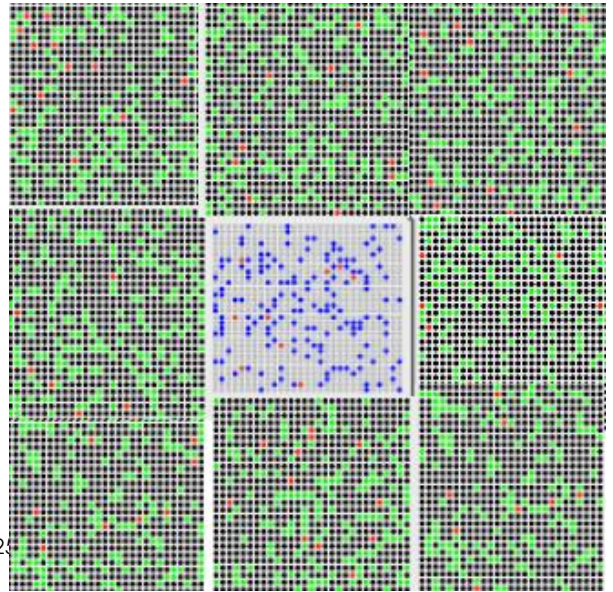
All genetic factors associated with common DNA variants

Genetic factors associated with common DNA variants that contribute to risk that we measure well

$heritability$

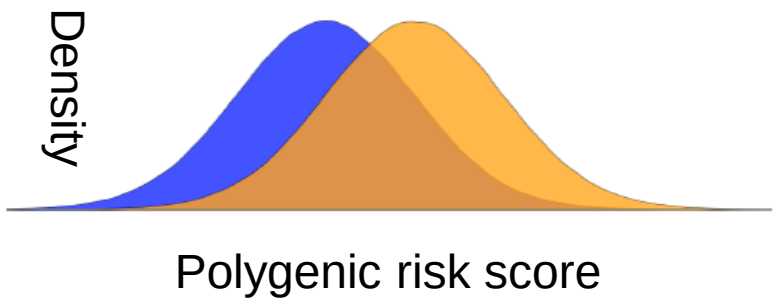
$SNP-based\ heritability$

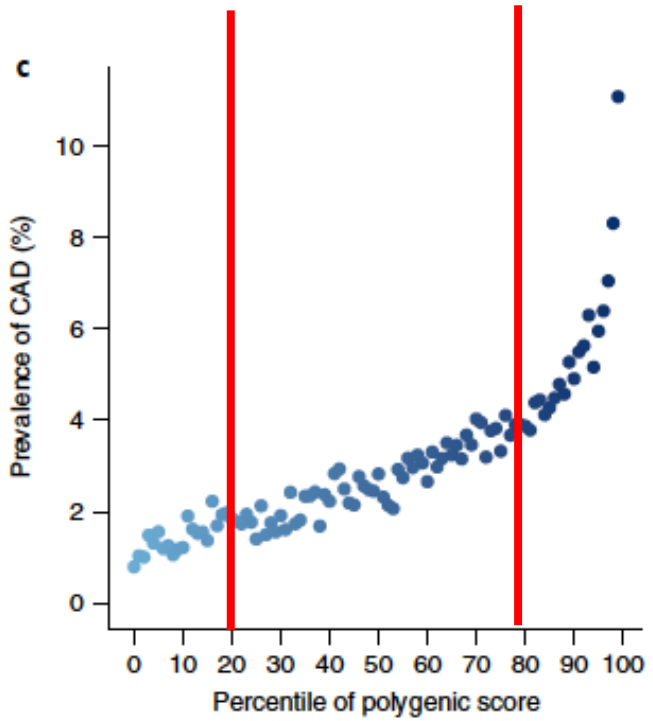
R^2 Discovery GWAS sample size

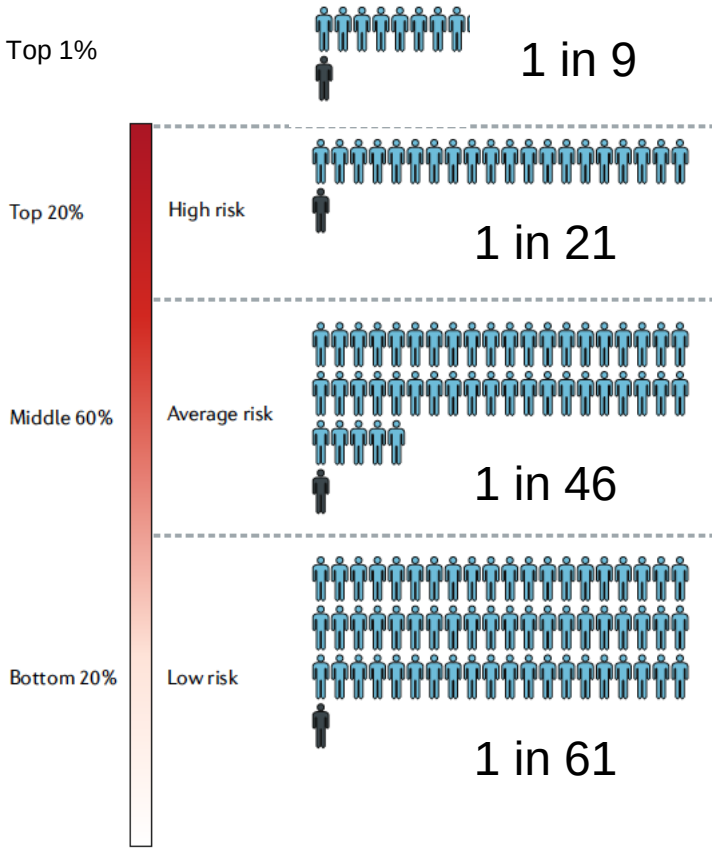


Polygenic scores cannot be highly accurate predictors of phenotypes

Different views of the same data







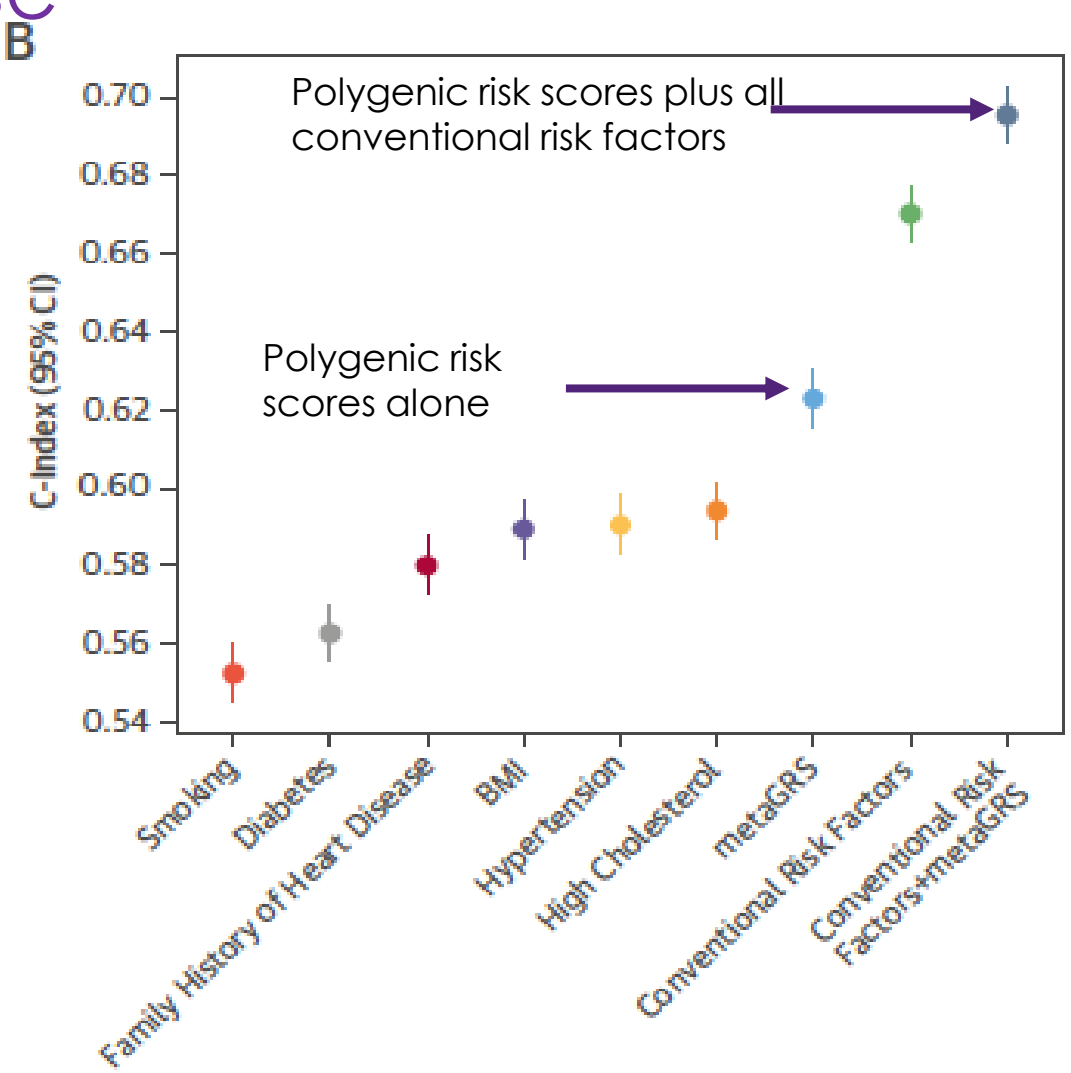
Risk stratification

Khera et al (2018) Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nature Genetics

Torkamani et al, Nat Rev Genetics, 2018

Combine PRS with conventional risk predictors Coronary Artery Disease

Within sex probability of ranking case higher than control (like AUC)



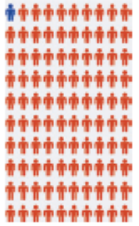
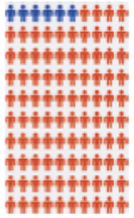
Inouye et al (2018) Genomic risk prediction of CAD in 480K adults. JACC

Polygenic risk score applications

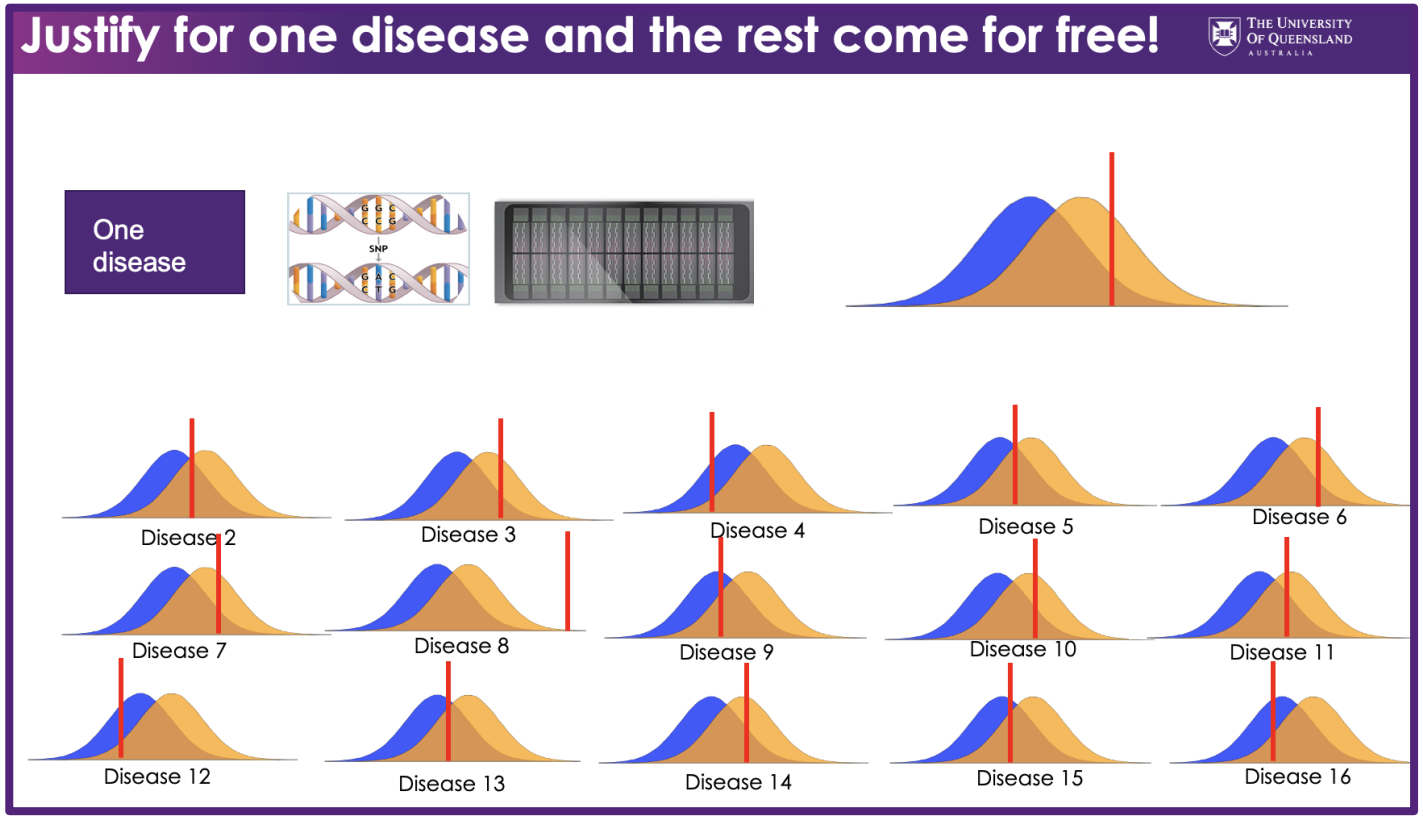
JAMA Psychiatry | Review

From Basic Science to Clinical Application of Polygenic Risk Scores
A Primer

Naomi R. Wray, PhD; Tian Lin, PhD; Jehannine Austin, PhD; John J. McGrath, MD, PhD; Ian B. Hickie, MD; Graham K. Murray, MD, PhD; Peter M. Visscher, PhD

Cohort where PRS applied:	Community
	 Of 100 people in the population, 1 will get "the disease" in lifetime, assuming a disease of lifetime risk of 1%
Utility of PRS:	PRS contribute to risk stratification
	 Of 100 people in the top PRS stratum, a higher proportion will get "the disease" in their lifetime and hence are particularly encouraged to enter established disease screening
Likely applications:	Common diseases/ disorders for which there is already population screening
Likely first applications:	Cancers: breast and colorectal; common eye disorders: glaucoma, macular degeneration; heart disease

Justify for one disease and the rest come for free!



Around the world:UK

+ Our Future Health

Our Future Health will recruit 5 million people into a prospective cohort, representative of the UK population

Diversity, scale and long term engagement opportunities

- Deep links to NHS clinical data
- Significant scale, diversity and breadth of participation
- Fast and cost effective recontact of participants
- Genetic info related to common disease areas

- Adults who represent the full diversity of the UK population
- Biological samples and health data on enrolment
- Consent to link with NHS records and additional data sources
- Stored samples that enable the application of newly available diagnostic tests
- Polygenic risk scores (PRS) on everyone
- Consent for health related feedback to participants
- Consent to invite to additional data collection, samples, or take part in new clinical studies
- Repeat sampling to observe the transitions from health to diagnosable disease

https://www.closer.ac.uk/wp-content/uploads/Andrew-Roddam.pdf

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Polygenic risk score: other applications

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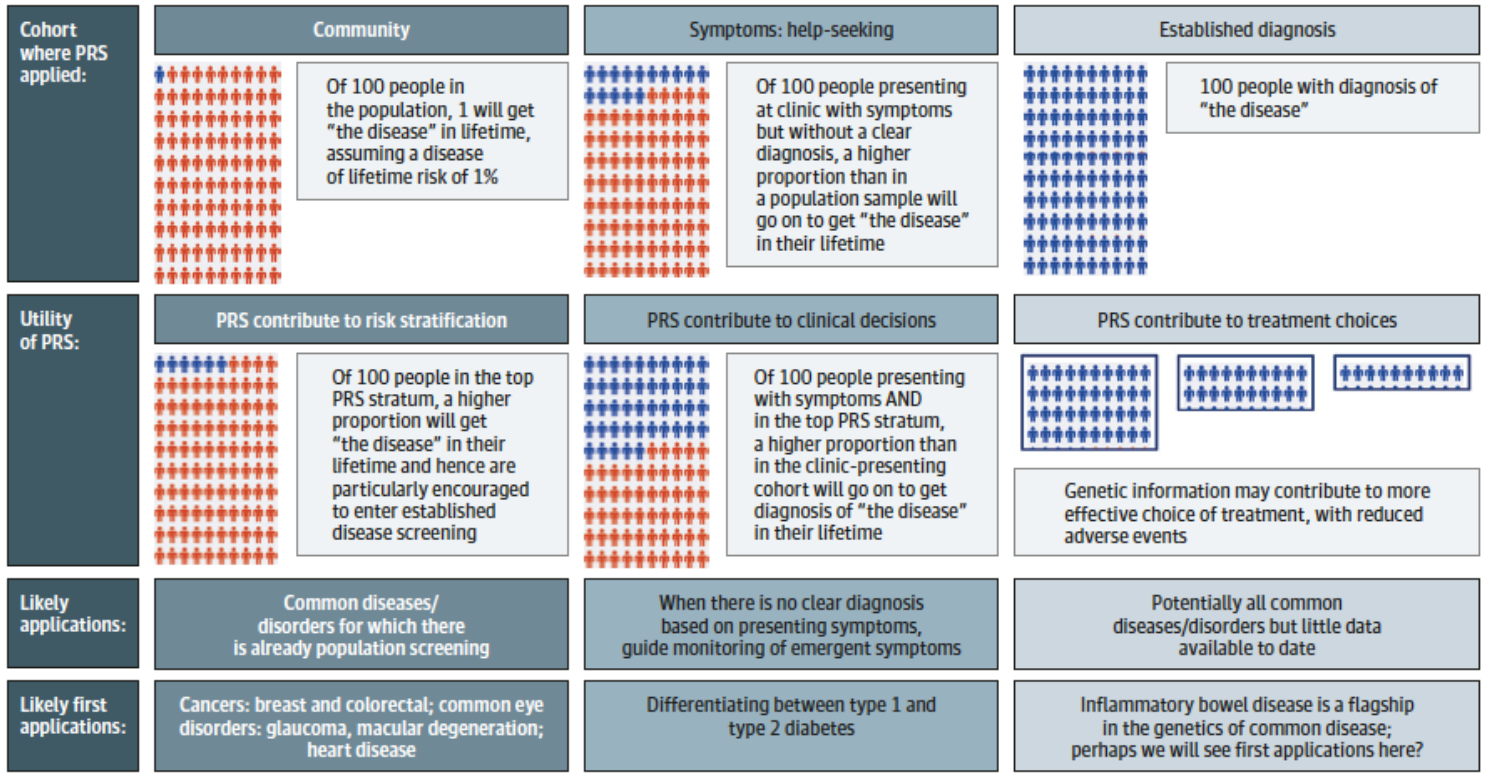
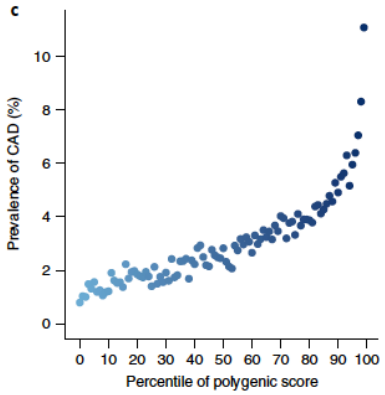


Schizophrenia polygenic risk prediction

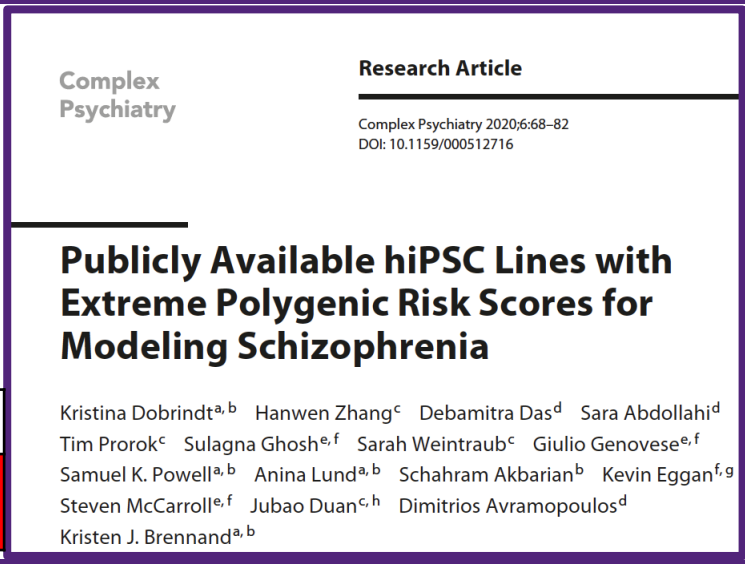
~10% variation in liability
AUC 0.73

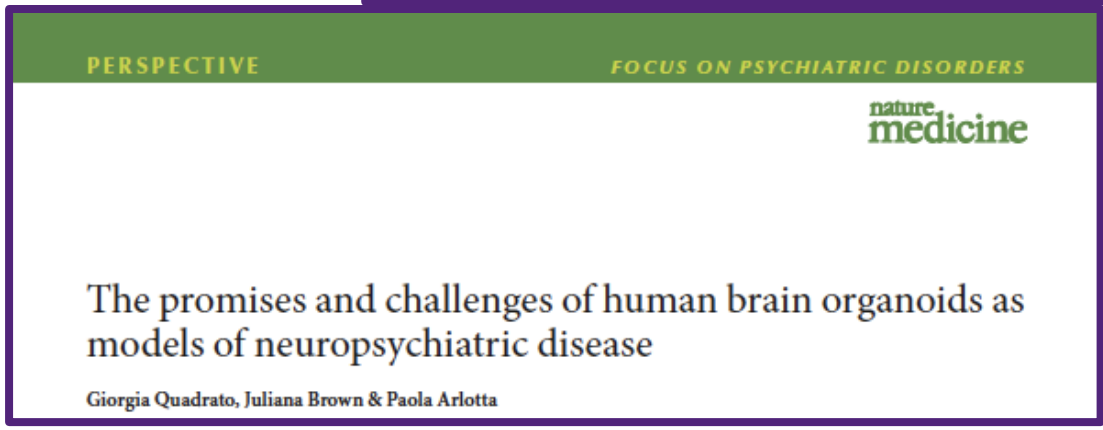
	Low PRS	HighPRS
No Disease		



Coronary artery disease
14-fold difference

Top percentile vs bottom percentile:
40-fold difference





	Low PRS	HighPRS
No Disease		
Disease		

Polygenic risk score applications in psychiatry

JAMA Psychiatry | Review

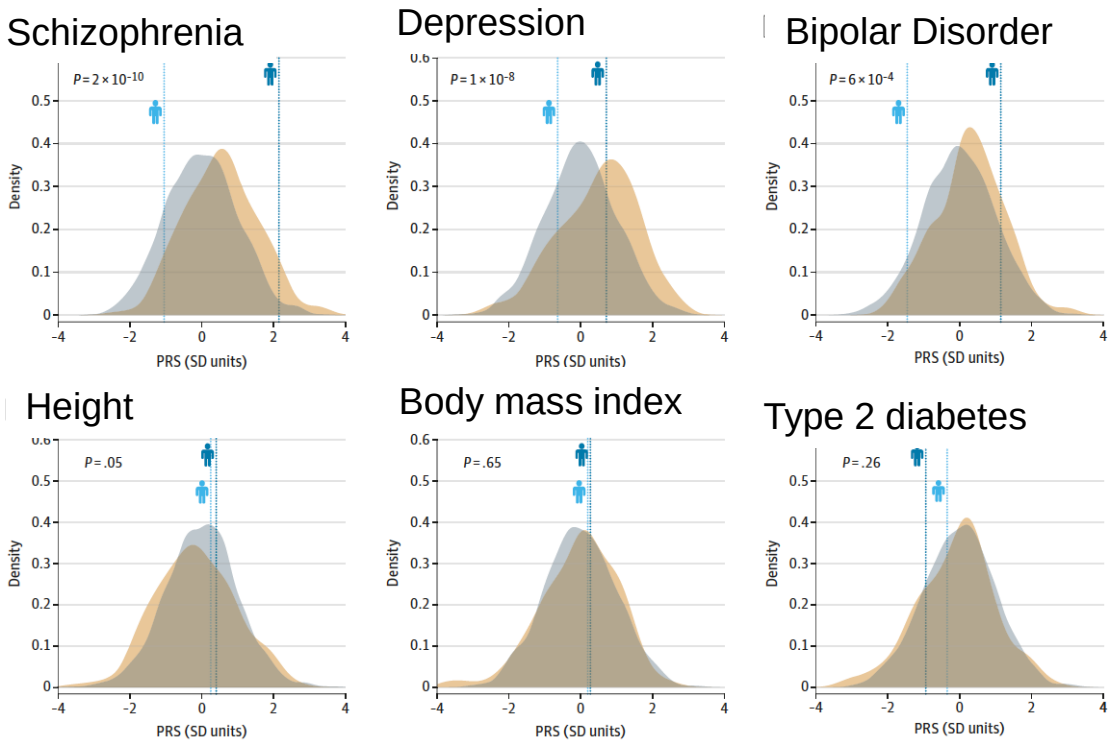
Could Polygenic Risk Scores Be Useful in Psychiatry? A Review

Graham K. Murray, MD, PhD; Tian Lin, PhD; Jehannine Austin, PhD; John J. McGrath, MD, PhD; Ian B. Hickie, MD; Naomi R. Wray, PhD

158 young adults presenting with symptoms at a youth mental health clinic

1528 community samples random ascertainment

	Community	Symptoms: help seeking
Cohort where PRS applied	Of 100 people in the population, 1 will get the disease in lifetime, assuming a disease of lifetime risk of 1%.	Of 100 people presenting at clinic with symptoms but without a clear diagnosis, a higher proportion than in a population sample will go on to get the disease in their lifetime.
Utility of PRS	PRS contribute to risk stratification	PRS contribute to clinical decisions
	Of 100 people in the top PRS stratum, a higher proportion will get the disease in their lifetime and hence are particularly encouraged to enter established disease screening, if relevant, or consider lifestyle risk factors.	Of 100 people presenting with symptoms and in the top PRS stratum, a higher proportion than in the clinic-presenting cohort will go on to get diagnosis of the disease in their lifetime.
Likely relevance to mental health disorders	This application of PRS is unlikely to be relevant in the short term. Possible applications in the long term • Contribute to risk screening for ASD or ADHD, where stratification for intensive evaluation could lead to earlier diagnosis and earlier behavioral interventions • High PRS for schizophrenia could lead to lifestyle guidelines on recreational drug use.	This application of PRS is likely to be relevant, and testing in clinical settings is justified. Young people presenting at youth mental health clinics have very general symptoms. Clinicians already try to identify those most likely to transition to severe disorders. High PRS could contribute to clinical decision-making.



Graham Murray, UoCambridge

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Family history

Will people withOUT known family history have high PRS?

Maybe, and that's important!

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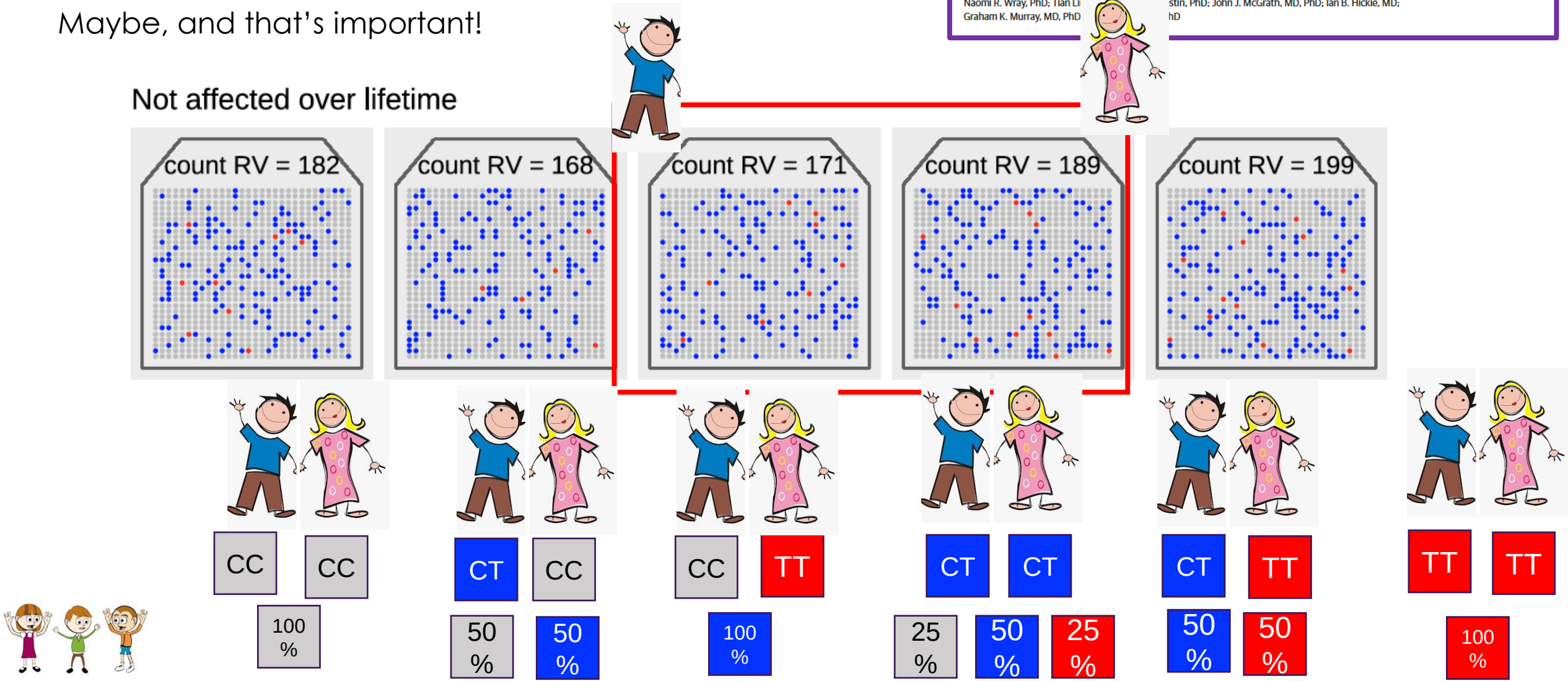
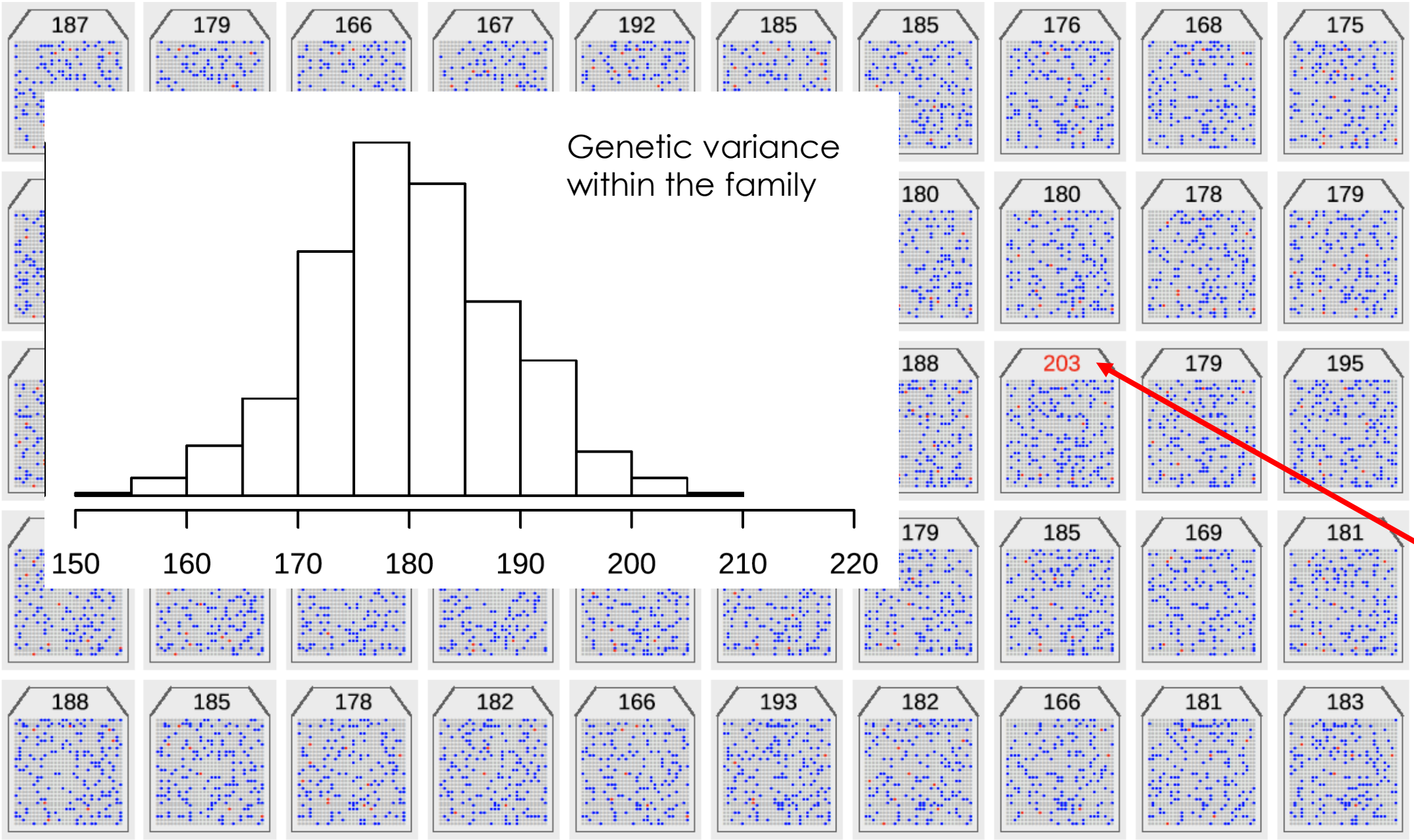


Children (Parents: 171 & 189)



Children of these parents
Mean: 180
+/-3SD: 153-207

Population
Mean: 180
+/-3SD: 142-218

No family history, but by chance segregation of alleles has high genetic risk

PRS in the clinically high risk

Polygenic Risk Score Contribution to Psychosis Prediction in a Target Population of Persons at Clinical High Risk

2019

Diana O. Perkins, M.D., M.P.H., Loes Olde Loohuis, Ph.D., Jenna Barbee, B.S., John Ford, M.S., Clark D. Jeffries, Ph.D., Jean Addington, Ph.D., Carrie E. Bearden, Ph.D., Kristin S. Cadenhead, M.D., Tyrone D. Cannon, Ph.D., Barbara A. Cornblatt, Ph.D., Daniel H. Mathalon, M.D., Ph.D., Thomas H. McGlashan, M.D., Larry J. Seidman, Ph.D., Ming Tsuang, M.D., Ph.D., Elaine F. Walker, Ph.D., Scott W. Woods, M.D.

- 764 people with psychosis high risk at baseline
  - 595 with follow-up
  - 238 EUR, 357 non-EUR
  - 84 converted to psychosis diagnosis (33 & 51)
- 279 unaffected

Conclusions: The PRS discriminates psychosis converters from nonconverters and modestly improves individualized psychosis risk prediction when added to a psychosis risk calculator. The schizophrenia PRS shows promise in enhancing risk prediction in persons at high risk for psychosis, although its potential utility is limited by poor performance in persons of non-European ancestry.

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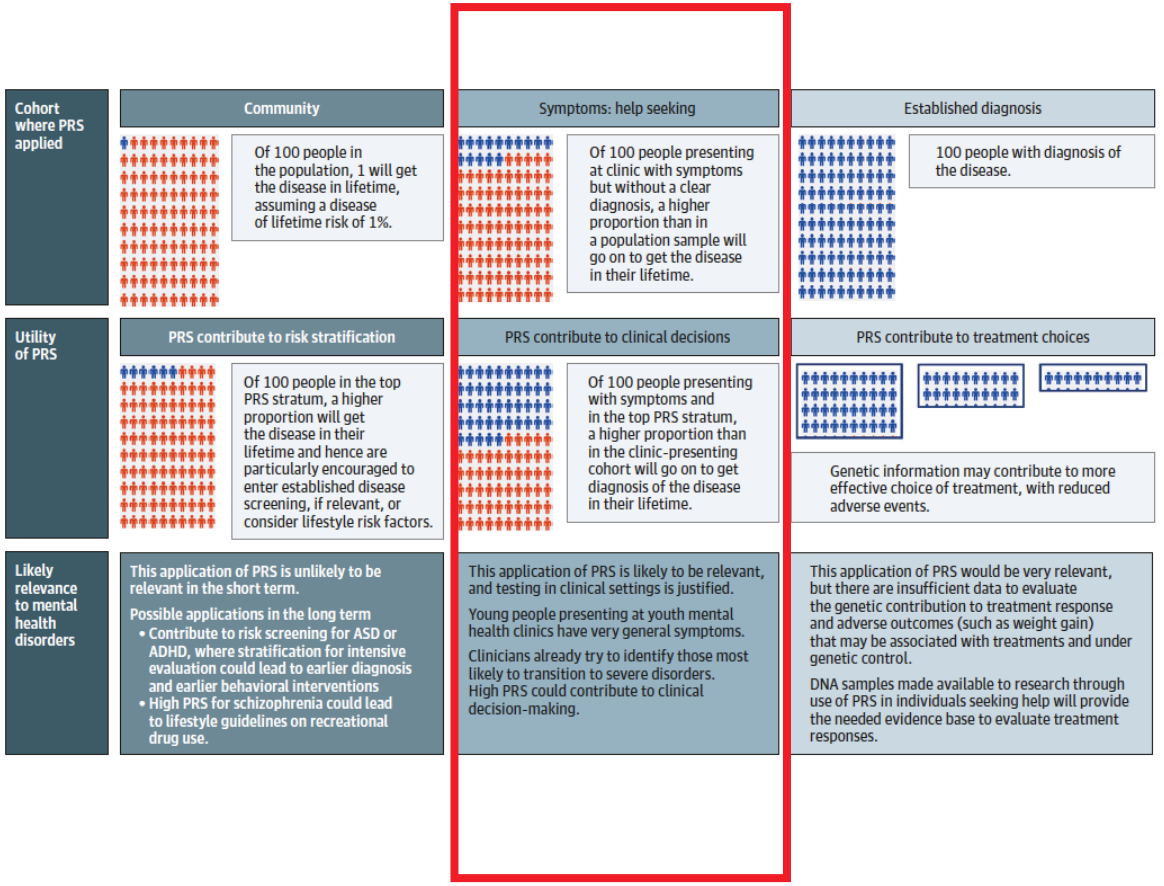


Summary

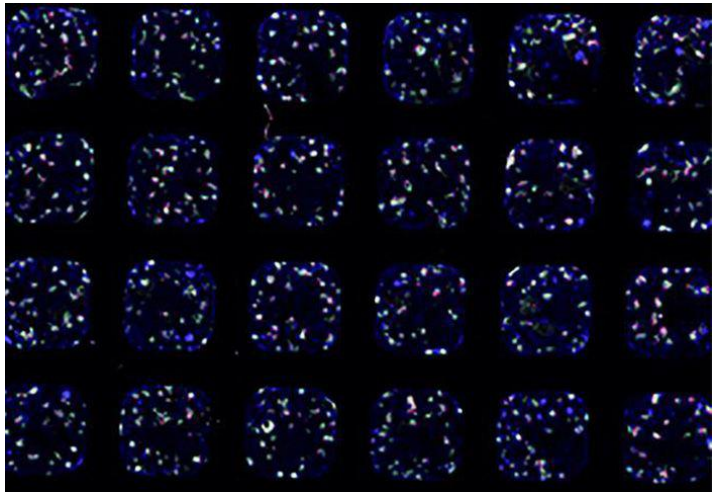
- Polygenic scores are biomarkers not diagnostic tests

- Polygenic risk scores will be evaluated in many common diseases and disorders in next 5-10 years
  - Context of population screening
  - Combined with non-genetic risk factors

- In psychiatry
  - Need to evaluate use of polygenic risk scores in the context of young people presenting with symptoms

  - 40-fold difference between top and bottom percentile can provide very powerful experimental design

  - Collect the samples today to allow the experimental designs of tomorrow



Robotic cellular phenotyping

Acknowledgements

Australian Government
National Health and Medical Research Council
NHMRC

PGC

NIH National Institutes of Health

FIGHT MND. IT TAKES PEOPLE

AutismCRC

JPND research

SALSA Systems Genomics Consortium

MINDALIS PARTNERSHIP

mnd Research Institute of Australia

BRAIN MEND

biobank uk
Enabling scientific discoveries that improve human health

Program in Complex Trait Genomics

The University Of Queensland AUSTRALIA | Institute for Molecular Bioscience | The University Of Queensland AUSTRALIA | Queensland Brain Institute