Australian Polygenic Risk Symposium

18 & 19 November 2019
Garvan Institute of Medical Research
Abstract booklet

Date: Monday 18 November
Session Title: **Theory to practice in Australia**
Session Chair: Prof Georgia Chenevix-Trench

Improved polygenic risk score accuracy for 50 traits in biobank scale data by exploiting phenotypes on inferred relatives	**Associate Professor S. Hong Lee,** University of South Australia

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To avoid bias and type I error, close relatives are usually excluded in conventional genome-wide association studies or in estimating single nucleotide polymorphism-based heritability for human complex traits. Because of this convention, polygenic risk score approaches to predict future phenotypes of target individuals have typically used information on unrelated individuals, thereby excluding or devaluating information from relatives. In this study, we show for 50 traits from the UK Biobank data that a design of 5,000 individuals with first-degree relatives can achieve a similar prediction accuracy, compared to that of ~ 220,000 unrelated individuals, although strikingly the difference in sample size is 44-fold. For lifestyle traits, the prediction accuracy with the first-degree relatives is even significantly higher than that with the unrelated individuals (1.36-fold increase). Key factors causing the difference between the predictabilities of unrelated and related individuals are the effective number of chromosome segments shared (also known as the number of independent SNPs) and common family effects shared beyond the additive genetic covariance. Finally, we show that ungenotyped relatives of the target individual can be included in the reference dataset, which results in a higher prediction accuracy than that without the ungenotyped relatives (1.29-fold increase). Our findings demonstrate that polygenic prediction integrating family information will accelerate precision health and clinical intervention.

Date: Tuesday 19 November
Session Title: **Polygenic risk and common complex disorders**
Session Chair: Prof Naomi Wray

Genomic risk score offers predictive performance comparable to clinical risk factors for ischaemic stroke	Presenting Author: **Dr Gad Abraham,** Baker Heart and DIabetes Institute; University of Cambridge; University of Melbourne

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Aims: Recent genome-wide association studies in stroke have enabled the generation of genomic risk scores (GRS) but the predictive power of these GRS has been modest in comparison to established stroke risk factors.
Methods: Here, using a meta-scoring approach, we developed a metaGRS for ischaemic stroke (IS) and analysed this score in the UK Biobank (n=395,393; 3075 IS events by age 75). *Results:* The metaGRS hazard ratio for IS (1.26, 95% CI 1.22-1.31 per standard deviation increase of the score) doubled that of previous GRS, enabling the identification of a subset of individuals at monogenic levels of risk: individuals in the top 0.25% of metaGRS had a three-fold increased risk of IS. The metaGRS was similarly or more predictive when compared to established risk factors, such as family history, blood pressure, body mass index, and smoking status. For participants within accepted guideline levels for established stroke risk factors, we found substantial variation in incident stroke rates across genomic risk backgrounds. We further estimated combinations of reductions needed in modifiable risk factors for individuals with different levels of genomic risk.
Conclusions: We have developed the strongest GRS for ischaemic stroke so far, with predictive performance rivalling that of established risk factors. Further, our analysis suggests that for individuals with high metaGRS, achieving currently recommended risk factor levels may be insufficient to mitigate risk.

Predicting the future of predicting the future	Presenting Author: **Associate Professor Stuart Macgregor,** QIMR Berghofer Medical Research Institute

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Polygenic risk scores (PRS) have been computed for many diseases and traits. However, their translational utility can be limited due to poor predictive power or because of a lack of clinical or treatment consequences. I will discuss progress to date and prospects for the future for PRS in two areas, eye disease and cancer.

Eye Disease: Glaucoma is a highly heritable disease of progressive optic nerve degeneration. I will show a glaucoma PRS based on a relatively limited number (<10,000) of cases (bolstered by data from correlated traits) enables effective risk stratification. With this sample size, the glaucoma PRS confers an odds ratio of >4 for the top 10% of individuals vs the remainder, a larger degree of PRS-based stratification than for any other complex human disease. This degree of PRS-based stratification is clinically relevant as glaucoma can be prevented via timely diagnosis and treatment.

Cancer: Although cancers typically have only moderate heritability, there are scenarios where PRS are useful because population wide screening may be impacted. Alternatively, there may be population subgroups at unusually high risk - e.g. I will show that a skin cancer PRS derived in the wider population provides risk stratification in organ transplant recipients, a group with very high absolute risks for certain skin cancers.

I will present modelling for the changes in prediction performance with anticipated increases in GWAS sample size and discuss the consequences for the use of PRS in the future.

Date: Tuesday 19 November
Session Title: **Abstracts in polygenic risk**
Session Chair: Prof Lyn Griffiths

Polygenic risk scores and breast and epithelial ovarian cancer risks for BRCA1 and BRCA2 carriers	Presenting Author: **Professor Georgia Chenevix-Trench,** QIMR Berghofer Medical Research Institute

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BRCA1 and BRCA2 mutation carriers are at elevated risk of developing breast (BC) and ovarian cancer (OC). Many BC and OC susceptibility SNPs identified in the general population are also risk modifiers for mutation carriers. Retrospective cohort data on ~31,000 BRCA1/BRCA2 carriers CIMBA were used to evaluate five PRS -overall BC (PRSBC), ER-negative BC (PRSER-), ER-positive BC (PRSER+), overall OC (PRSOC) and high-grade serous OC (PRSHGS) - derived from estimates from population-based studies. We assessed associations between these PRS with BC and OC risk, estimating per SD hazard ratios (HRs) by weighted Cox regression. The strongest BC associations in the retrospective cohort were with PRSER- for BRCA1 (HR=1.29, P=3.03x10-72) and PRSBC for BRCA2 (HR=1.31, P=7.11x10-50) carriers. PRSHGS yielded stronger associations with OC risk for BRCA1 (HR=1.32, P=3.01x10-22) and BRCA2 (HR=1.44, P=4.34x10-12) carriers. Very similar effect sizes were found in the prospective cohort analysis. Absolute risks of BC by age 80-years between the 5th and 95th percentiles of the PRS distributions differed by 24% for BRCA1 and 24% for BRCA2 carriers. Corresponding OC risk differences were 29% for BRCA1 and 18% for BRCA2 carriers. In conclusion, population-based derived PRS are strongly associated with BC and OC risk in independent samples of BRCA1 and BRCA2 carriers and can lead to substantial differences in absolute risks for women at PRS distribution extremes. These PRS should be incorporated into comprehensive risk prediction tools for carriers, such as BOADICEA.

Testing rare disease polygenic risk with trios	Presenting Author: **Dr Mark Pinese,** Children's Cancer Institute

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Polygenic scores promise to transform genetic risk stratification by dramatically expanding the number of patients for whom a genetic diagnosis can be reached. This is especially exciting in childhood cancer, where fewer than 15% of patients are currently diagnosed with a monogenic cancer syndrome. However, clinical application of polygenic scores requires their validation, and conventional case-control validation using large well-matched cohorts is challenging in a rare disease like childhood cancer. Motivated by the need to test polygenic risk scores in the rare disease setting, we have explored an alternative method for score validation that does not require genetically matched cohorts. This method, termed the polygenic transmission disequilibrium test (pTDT), employs parent-child trios and uses unaffected parental genotypes to internally control for the affected child's genetic background. Here we demonstrate that the pTDT is highly resistant to confounding from population background, and well-suited to the validation of polygenic scores in mixed cohorts. We compare the performance of the pTDT versus a case-control design under a range of scenarios, and show conditions under which the pTDT is superior. The pTDT is a valuable method for polygenic score validation that should be considered, particularly in the case of rare early-onset disease where the collection of trios is practical, and the identification of de-novo rare variants is also of interest. We plan to apply the pTDT to the Paediatrio PPM3 cancer risk module, to evaluate the contribution of polygenic risk to paediatric cancer incidence.

Genomic Risk Scores for Predicting Juvenile Idiopathic Arthritis	Presenting Author: **Dr Rodrigo Canovas,** Cambridge Baker Systems Genomics Initiative, The Baker Heart and Diabetes Institute

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Aims: Juvenile idiopathic arthritis (JIA) is an autoimmune disease and a common cause of chronic disability in children, with a prevalence of 1 in 1000 children of European ancestries. There is no definitive diagnostic test for JIA, and diagnosis is based on clinical symptoms, leading to treatment delays. JIA has substantial heritability, but the potential of using genomic risk scores (GRS) to aid diagnosis is not known. We sought to generate a GRS for JIA and evaluate its predictive power.
Methods: We examined three case/control cohorts (UK, USA, and Australia) with genome-wide SNP genotypes. We trained a GRS using a lasso-penalised linear model in cross-validation on the UK cohort and externally tested it on the Australian and USA cohorts. We also explored alternative approaches to enhance the GRS and assessed the impact of the JIA heterogeneity on predictive power.
Results: Our GRS achieved cross-validated AUC=0.67 in the UK cohort and externally validated AUCs of 0.67 and 0.66 in the Australian and USA cohorts, respectively. Subtype-specific models achieved AUCs between 0.5 and 0.8.
Conclusions: We have developed a JIA GRS which had consistent performance across three cohorts of European ancestry. This GRS has the potential to augment current JIA diagnosis protocols, prioritising higher-risk individuals for follow-up and treatment. Subtype-specific analyses further highlight the potential for genetic studies to better understand heterogeneous disease such as JIA.

Polygenic risk and monogenic risk in glaucoma	Presenting Author: **Dr Owen Siggs,** Flinders University

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Glaucoma is the leading cause of irreversible blindness. Early diagnosis and treatment are critical to prevent vision loss, particularly since glaucoma is asymptomatic in its early phase, and approximately half of all individuals with glaucoma are undiagnosed. Here we used a multi-trait PRS to compare the relative influence of polygenic and monogenic risk in glaucoma. Among individuals with glaucoma (N=3,922), those with a defined monogenic diagnosis had a younger median age at diagnosis than those without (CYP1B1, 4 years [95% CI: 0-20]; MYOC, 49 years [45-54]; no monogenic diagnosis, 61 years [60-62], P<0.0001). Those in the top decile of polygenic risk had a similar median age at diagnosis (58 years [56-60]) as those carrying the most common monogenic glaucoma risk variant (MYOC Gln368Ter, 54 years [52-60], P=0.33). When considering carriers of the MYOC Gln368Ter variant in UK Biobank, carriers in the top PRS tertile had a 6-fold higher absolute risk of glaucoma by age 60 than carriers in the bottom PRS tertile. In summary, polygenic risk variants predict age at glaucoma diagnosis to a similar degree as a single monogenic risk variant, and can also influence the penetrance of an otherwise 'monogenic' risk variant. This supports the clinical application of a glaucoma PRS in both common and rare forms of the disease.

Clinical phenotype of glaucoma patients stratified by an intraocular pressure polygenic risk score	Presenting Author: **Dr Ayub Qassim,** Flinders University

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Purpose To characterise the clinical phenotype of primary open angle glaucoma (POAG) in individuals stratified by their genetic risk burden of raised intraocular pressure (IOP), a major risk factor of POAG.
Method Using the summary statistics of an IOP genome-wide association study (GWAS) of the UK Biobank cohort (N = 103,914), meta-analysed with IGGC cohort's IOP (N = 29,578), we developed an IOP polygenic risk score (PRS) comprising 146 single-nucleotide polymorphisms (SNPs). 2,386 study participants with POAG were sampled from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) and stratified into three tiers based upon their IOP PRS. The highest quintile of the PRS was defined as high-risk, the middle three quintiles as intermediate-risk, and the lowest quintile as low-risk. Clinical data were compared between the three IOP PRS risk strata.
Results There was a dose-response relationship between the IOP PRS and the maximum recorded IOP, with the high genetic risk group having a higher maximum IOP by 1.7 (SD 0.62) mmHg than the low genetic risk group ($P = 0.006$). Compared to the low genetic risk group, the high genetic risk group had a younger age of diagnosis by 3.7 (1.0) years ($P < 0.001$), more family members affected by 0.46 (0.11) members ($P < 0.001$), and higher rates of incisional surgery (odds ratio 1.5; 95% confidence interval 1.1 - 2.0; $P = 0.007$). There was no statistically significant difference in mean deviation. We further replicated the maximum IOP, number of family members affected by glaucoma and treatment intensity (number of medications) results in the early POAG cohort ($P \leq 0.01$).
Conclusion Genes acting via IOP mediated pathways, when considered in aggregate have clinically important and reproducible implications for glaucoma patients and their close family members.

Pharmacological enrichment of polygenic risk for precision medicine in complex disorders	Presenting Author: **William Reay,** School of Biomedical Sciences and Pharmacy, The University of Newcastle and Centre for Brain and Mental Health Research, Hunter Medical Research Institute

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Individuals with complex disorders typically have a heritable burden of common variation that can be expressed as a polygenic risk score (PRS). While PRS has some predictive utility, it lacks the molecular specificity to be directly informative for pharmacotherapy. We therefore sought to develop a framework to quantify an individual's common variant enrichment in clinically actionable systems responsive to existing drugs. We designed a metric to achieve this designated the pharmagenic enrichment score (PES). The PES framework identifies clinically actionable pathways enriched with common variation using genome-wide association study data. Polygenic risk specifically for variation affecting these systems (PES) can then be profiled in individual patients for precision drug repositioning. We exemplified this approach for schizophrenia using SNP genotypes and gene expression data in a cohort of diagnosed cases. A large proportion of these cases had elevated PES in one or more of eight clinically actionable gene-sets enriched with schizophrenia associated common variation. Notable candidates targeting these pathways included vitamins, antioxidants, and insulin modulating agents. Interestingly, elevated PES was also observed in individuals with otherwise low common variant burden. The biological saliency of PES profiles were consolidated through their impact on gene expression in a subset of the cohort with matched transcriptomic data. Our data suggest that the PES framework could integrate an individual's common variant risk to inform personalised interventions, including drug repositioning, for complex disorders such as schizophrenia.

Date: Tuesday 19 November
Session Title: **Implementation**
Session Chair: A/Prof Anne Cust

New Zealand Health Practitioner's Perspectives Towards the Utility and Implementation of Polygenic Risk Scores	Presenting Author: **Brittany Jones,** University of Otago, Department of Mathematics and Statistics

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Professor Stephen Robertson, University of Otago, Department of Women's and Children's Health (DSM)
Dr. Phil Wilcox, University of Otago, Department of Mathematics and Statistics

Introduction: Polygenic risk scores (PRS) have the potential to influence clinical and personal decision-making. Identifying risk of disease on an individual- and population- based level may allow us to introduce pre-emptive therapies, lifestyle changes, or screening, for those at higher risk. The utility of PRS for different diseases and preparedness of healthcare professionals must be addressed before they can be implemented.

Objectives: the primary objective of this study was to test the perspectives and preparedness of health care professionals towards polygenic risk prediction both for general and scenario-specific use.

Methods: NZ-based General Practitioners (GPs) and Genetic Counsellors (GCs) were recruited to the study and participated in a face-to-face semi-structured interview consisting of questions addressing the general use of PRS, as well as scenario-specific uses. The scenarios were chosen to illustrate three key uses of PRS: PRS-informed interventions, life-planning, and population-level screening.

Results:

- There was strong support for population-level screening from both GPs and GCs
- GPs were more confident discussing PRS-informed interventions and identified patient adherence as a barrier to utility.
- GPs and GCs agreed that PRS utilisation required condition-specific consideration, particularly for life-planning.
- Participants would like more information about clinical validity, and resources for both them and patients
- NZ cultural contexts have unique challenges
- Perceived insurance discrimination is a barrier to implementation

Conclusions: Generally, there was support for PRS implementation, however it was condition and scenario specific, and heavily influenced by intervention availability, perceived PRS efficacy, and prior clinical success.