Proposed By: Amanda E. Toland

Proposed Moderator(s): Amanda E. Toland and Alison H. Trainer

Session Topic Area: 2. Complex Traits and Polygenic Disorders

Session Content: Scientific

Session Title: Realizing the promise of common genomic variation in rare and common disease: Clinical Implementation of Polygenic Risk Scores

Session Description:
Whilst the contribution of common genomic variation to both rare and common disorders has informed both human physiology, and disease etiology, its translation into the clinical setting is only now emerging. Individually each variant is of poor predictive or diagnostic value due to its low effect size, but evidence is emerging that an individualized combinatorial polygenic risk score (PRS) may have utility in both population-based and clinic-based medicine. Clinical trials are currently investigating the use of PRS-based assessments to aid in individual diagnosis or as a means of stratifying, and thereby appropriately targeting, disease risk at a population-level in order to increase diagnosis rate and cost-efficiency. In this session, we will highlight the clinical uses of PRS using results from current studies from a variety of medical specialties including cancer, cardiovascular disease, Alzheimer's disease and autism, and spanning different aspects of care from disease prevention to diagnosis and treatment. The session will also demonstrate the interplay between PRS, and additional monogenic variants and environmental factors in determining clinical phenotypes.

Session Rationale:
The goal of this clinical translational session is to highlight the significant contribution of common genomic variation to different disease types, and demonstrate how an individualized summary metric, the polygenic risk score, can be ascribed and used in clinical practice. The speakers will highlight results from clinical trials focused on the implementation of polygenic risk score assessments into clinical care in both a diverse range of clinical specialties, from cancer to Alzheimer disease, and at different times in the care pathway from primary disease prevention to disease diagnosis and treatment.

Learning Objectives
1. To consolidate the contribution of common genomic variation to a wide spectrum of common disease.
2. To demonstrate the clinical utility of polygenic risk score assessments in various clinical settings
3. To illustrate the interaction between polygenic risk scores, and other genetic and modifiable factors
4. To illustrate how polygenic risk assessments may target current primary disease prevention strategies to increase cost effectiveness

Attendee Benefits:
Attendees may identify methods to calculate polygenic risk scores, the ways in which they may interact with other genetic and environmental factors and how this test may impact their own future clinical practice. They will learn about ongoing clinical trials exploring the role of PRS assessments at a population as well as individual level. Individuals familiar with specific uses of PRS within their own clinical specialty may learn of new approaches and uses in the wider medical community.

Target Audience:
The session will be of interest to clinicians, population health specialists, economists, statistical geneticists, epidemiologists as well as genetic professionals and researchers interested in implementation of polygenic risk scores and genome wide association study findings into the clinic.

The competencies and attributes the session will address:
Patient Care
Medical Knowledge
Practice-Based Learning

Speaker 1: Elad Ziv
Presentation Title: Use of the Polygenic Risk Score as Part of Breast Cancer Risk Assessment in the WISDOM Risk Thresholds Trial
Presentation Content: The Women Informed to Screen Depending On Measures of Risk (WISDOM) trial is a randomized trial of breast cancer screening comparing annual mammography with a risk based screening approach. The risk-based screening arm receives breast cancer risk which includes a polygenic risk profile. The outcome of the trial is the number of late stage (Stage IIb and above) breast cancers. We will discuss the approach to generating breast cancer polygenic risk scores including challenges such as risk profiling in women of non-European ancestry and incorporating newly discovered SNPs. We will also describe the integrated risk model including genetic and non-genetic risk factors. Finally we will review the risk thresholds used to determine the initiation and intensity of screening.
Presentation Time Interval: 30 min

Speaker 2: Valentina Escott-Price
Presentation Title: Polygenic risk score analysis in the pre-symptomatic prediction and diagnosis of Alzheimer's disease.
Presentation Content: Based on work with Professor Valentina Escott-Price, we have found that polygenic risk scores using genetic variants with association p-value up to 0.5, are highly predictive of Alzheimer's disease risk with estimated area under the curve estimates of 75% in a clinical cohort and up to 84% in a pathologically confirmed cohort. The use of the PRS has much higher predictive accuracy than variants as the APOE locus alone. Furthermore, polygenic risk scores have higher prediction accuracy (79%) in sporadic early-onset Alzheimer's disease (EOAD) which fits with the higher estimated heritability of EOAD relative to late onset AD (72%). In this talk, we will review these findings and potential uses of PRS score for AD including design of clinical trials for prevention and treatment.
Presentation Time Interval: 30 min

Speaker 3: Elise Robinson
Presentation Title: Polygenic risk scores as a determinant of autism spectrum disorder heterogeneity
Presentation Content: Common risk alleles as well as de novo variants and inherited rare variants all contribute to the risk of Autism spectrum disorders (ASDs). Using polygenic transmission disequilibrium tests, we found that polygenic risk for Autism Spectrum Disorders (ASD) as well as schizophrenia and great educational attainment is over transmitted to offspring with ASD. In this talk, we will highlight results of our polygenic transmission disequilibrium tests (pTDT) and the association between the multiple types of genetic risk for AD that influence a range of behavioural and developmental traits. We will also detail how some of the elements of polygenic risk are independent and impact different phenotypes which has implications for the understanding of the genetic influences on pathways important for ASD.
Presentation Time Interval: 30 min

Speaker 4: Sekar Kathiresan
Presentation Title: Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations
Presentation Content: Identification of individuals at increased genetic risk for a complex disorder such as coronary disease can facilitate treatments or enhanced screening strategies. In this talk, we will describe data from a new, genome-wide polygenic score that aggregates information from 6.6 million common polymorphisms and show that this score can identify individuals with a 4-fold increased risk for coronary disease. In >400,000 participants from UK Biobank those in the top 2.5% of the distribution are at 4-fold increased risk compared to the remaining 97.5%. In a primary prevention randomized controlled trial, we showed that a polygenic risk score derived from 57 common variants associated with coronary artery disease was able to predict which participants had the highest relative risk reduction from statins. Individuals with the top quintile of genetic risk had a relative risk reduction of 44% whereas risk reduction in the other groups was only 24% despite similar effects of statin on cholesterol levels. Collectively these studies indicate that PRS can be used to identify individuals at elevated risk of coronary artery disease and those that derived greater relative and absolute benefit from statin therapy. Inclusion of PRS for coronary artery disease into clinical practice and disease prevention could have impact in prevention of coronary heart disease events.
Presentation Time Interval: 30 min