AB001. The path to genomic medicine

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Abstract: There are numerous obstacles to genomic medicine. These include the large number of rare and novel genomic variants per individual. The American College of Medical Genetics and Genomics (ACMG) has recommended that all pathogenic variants in 56 gene-disease pairs are identified incidentally in a genomic test be offered to the patient (Green et al., 2013, PMID: 23788249). We considered an expanded list of 112 actionable gene-disease pairs, ones where medical intervention is possible to prevent or detect disease early. We estimate the rate of these incidental findings (IFs) in European and African Ancestry groups. However, we found high discordance between classifications of expert reviewers. We have reported both inconsistency across labs in variant classification and a bias towards overcalling pathogenicity (Amendola et al., 2015, PMID: 25637381). Thus, there is a need to standardize classification of genomic variants in medical sequencing. To date genomics laboratories have used non-standard classification systems. The ACMG published guidelines for variant classification for Mendelian disorders designed to increase consistency among labs (Richards et al., 2015, PMID: 25741868). The Clinical Sequencing Exploratory Research (CSER) Consortium evaluated the use of these rules by nine of the CLIA laboratories supporting CSER projects, considering 99 germline variants. The results were examined to evaluate intralaboratory differences between variant classifications using the labs own criteria vs. adopting ACMG criteria and inter-laboratory differences using either the lab’s own system or the ACMG guidelines. Agreement among labs did not differ whether using the laboratory specific vs. ACMG criteria (P=0.9); i.e., the ACMG criteria did not yield more consistent variant classification in this exercise. We further analyzed sources of disagreement in the use of the ACMG criteria and identified causes of variance in classifications. In addition to providing useful analyses of how variant classifications approaches vary among laboratories, these data should allow clarification and refinement of the ACMG criteria that may increase consistency in variant classification.

Keywords: Genomic medicine; genomic variants; variant classifications

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AB002. The rare and undiagnosed diseases diagnostic service

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Abstract: The Rare and Undiagnosed Diseases Diagnostic Service (RUDDS) is a Clinical Genomic Diagnostic Pipeline operating within the clinical service at Genetic Services of Western Australia (GSWA). GSWA has provided a state-wide service for clinical genetic care for more than 25 years and it serves a population of 2.5 million people. It includes paediatric, adult, prenatal and familial cancer services in metropolitan and regional WA. Within this framework, and in partnership with the Office of Population Health Genomics, Diagnostic Genomics at PathWest and others, it is delivering a clinically integrated pipeline. This service is aligned to the WA Rare Diseases
Strategic Framework 2015-2018 to address the unmet need of the diagnostic odyssey of those living with rare and undiagnosed diseases. It is: (I) delivered in a patient-centric manner that is resonant with the patient journey; (II) offers multiple options including non-genetic testing; monogenic and genomic (targeted and whole exome) analysis, and matchmaking; (III) is synchronous with precision phenotyping methods, including 3D facial analysis, and phenotype-enabled decision support; (IV) captures new knowledge, including multiple expert review; (V) has multiple points for entry, exit and re-entry to allow people access to information they can use, when they want to receive it; (VI) draws on the clarity gained from the extremity of rare diseases to provide insights for more common diseases; (VII) is integrated with current translational genomic research activities; and (VIII) is designed for flexibility for integrative generation of, and integration with, further clinical research including for diagnostics, community engagement, policy and models of care.

Keywords: Genomics; genetic care; diagnosis; disease


AB003. The path towards translational medicine for common reproductive diseases

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Abstract: Genetic factors contribute to risk for many common traits and diseases affecting reproduction and fertility. We have used genome-wide association (GWA) studies to understand the genetic architecture and discover genomic regions associated with risk for endometriosis, dizygotic twinning, age at menarche and age at menopause. The next steps are to determine how DNA sequence variation alters regulation and/or function of specific genes and pathways to increase disease risk. Multiple approaches are required to interpret the genetic association results, identify the specific genes likely to be responsible, and obtain the necessary genomic evidence connecting the genetic results to the target genes. Strategies include fine mapping, functional annotation, genomics, and cell-based studies to define direct interactions between causal single nucleotide polymorphisms (SNPs) and target genes. GWA and replication studies have identified seven genomic regions with strong evidence for association with endometriosis risk. The target tissue for functional effects is not known, but current theories suggest changes in the endometrium. We are conducting studies of gene expression and epigenetic regulation in samples of endometrium in carriers of the risk alleles. Development of applications to use GWA data for risk prediction and studies of comorbidity also provide valuable insights into the genetic architecture of endometriosis and overlap in risk with other conditions such as ovarian cancer. Multidisciplinary studies combining genetics, genomics, functional biology, and clinical research will be essential better understand disease biology and translate the new knowledge into better outcomes for patients.

Keywords: Genome-wide association (GWA); genetic architecture; reproduction; fertility; endometriosis

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