The future of genomics in England’s NHS

Evident throughout the conference was the shared commitment of researchers and healthcare practitioners to move genomics directly into the personalised clinical care of patients. At the centre of this is the NHS Genomic Medicine Service which will be rolling out in England from 1 April 2020. In the opening keynote address, Dame Sue Hill, Chief Scientific Officer for NHS England, outlined the infrastructure that will support this. She emphasized that it is an evidence-based strategy, moving from single gene tests to gene panels, with the aim of standardizing the use of genomics within the healthcare system. New industry partnerships with Illumina will see whole genome sequencing (WGS) tested in routine clinical services, and charitable partnerships with Macmillan will see genomic specialist nurses available to support patients. The challenge going forward will be how best to use this new wealth of information – some inspiring examples of which were highlighted by researchers at the Festival.

Integrating genomic assays into routine clinical cancer care

In a session on ‘The Clinical Genome’, Dr Susie Cooke described the work she leads as Head of Medical Genomics at the Glasgow Precision Oncology Laboratory (GPOL). She began by explaining that the best time to integrate genomic test results into clinical cancer care is right at the beginning, when first planning patient care. To achieve this, there needs to be a single, comprehensive assay that covers different genomic features while also being useable across different cancer types and within the routine workflows of hospitals. The aim of the GPOL test is to make it easier to integrate medically actionable genomics into early phase trials, providing molecular profile matching with available clinical trials. The team at GPOL has reviewed 2000 genes, stratifying them into the clinically actionable (Tier 1); not yet actionable but high confidence for drug development (Tier 2) and genes that may be used for biomarker discovery applications (Tier 3). Importantly, the genomic features included are not just base substitutions but also encompass copy number variations and structural rearrangements. The test currently focuses on solid cancers. They are currently validating the GPOL test in their own trials, including the UK-wide PrecisionPanc trial for pancreatic cancer and the IMAGINE trial (Integrating Medically Actionable Genomics Into Early-phase Trials) which will support matching patients in the West of Scotland with available phase 1 trials through their genomic profile. The assay is also being tested outside of the UK in collaboration with Professor Aldo Scarpa of the University of Verona, Italy.

Population screening for cancer susceptibility

Professor Clare Turnbull, from The Institute of Cancer Research (London, UK), discussed the opportunities to use genetics to stratify population-level screening for cancer. Currently in the UK, there are 3 national screening programmes for cancer (breast, cervical and colorectal) and these are offered based on age. While there are a range of interventions that can be provided to those found to be at high-risk, these are clinically and economically unjustifyable at a population level. To refine screening, a polygenic risk score (PRS) can be applied to stratify the population. Although multiple studies have shown a reliable predictive ability of a PRS, particularly in breast cancer, they have not yet been implemented into the screening strategy of the UK NHS. For some cancers, it is simply not worth implementing. Testicular cancer, for example, is a very treatable, rare cancer with a good prognosis. In such a case, there is no benefit to risking stratified screening based on PRS. For other cancers, altering the screening approach requires careful consideration of over diagnosis vs lives saved, the danger of withdrawing screening from some individuals and how best to deliver the results of the test. Professor Turnbull is a program lead for CanGene-CanVar, a collaboration of multiple centres across the UK, that aims to provide research and resources to improve the delivery of NHS tests. With funding support from charity Cancer Research UK, they will be testing a digital delivery system to support the leveraging of PRS in early detection and prevention of cancer. They anticipate that a proportion of individuals may need to follow up with a genetic counsellor using a telephone hotline.

An additional challenge in implementing a PRS-screening strategy is that our current knowledge of PRS largely comes from genomic studies of Western cohorts. Applying it to other populations is less...
accurate. Professor Segun Fatumo, who also spoke at the Festival, has written a separate commentary for *EBioMedicine* discussing the opportunities for precision medicine of sequencing African populations (https://doi.org/10.1016/j.ebiom.2020.102721).

**Implementing rapid diagnostic sequencing in a hospital setting**

Demonstrating the ability of diagnostic sequencing to inform patient management in the clinic, Dr Lamia Mestek-Boukhibar of Great Ormond Street Institute of Child Health UCL and GOSH (London, UK) described efforts to implement a Rapid Paediatric Sequencing (RaPS) workflow. Critically ill children in intensive care at GOSH often have a genetic syndrome, which may be undiagnosed at the time of admission. Delivering a diagnosis for these children - who have variable phenotypes and may display incomplete penetrance - is already challenging, and the need to deliver these results in a clinically meaningful timeframe adds additional pressure. The RaPS workflow relies on a multi-disciplinary team, with priority access to sequencing resources, to analyse trio-WGS data and deliver their diagnostic reports. A tiered data interpretation strategy is used, beginning with analysis of established phenotype-specific gene panels (Phase 1). If no likely causative variant is identified, interpretation moves to the analysis of genes previously associated with disease in the literature (e.g. OMIM Morbid genes) (Phase 2). Finally, for patients still without a diagnosis, analysis moves to a research phase with data sharing through GeneMatcher and collaborations to build functional evidence. Dr Mestek-Boukhibar reported that they have been able to deliver a typical turnaround time of two weeks, with the fastest time to a diagnosis report of just four days. She gave an example of a child diagnosed with Ehlers-Danlos syndrome whose clinical management was directly changed as a result of their diagnosis, alleviating previous welfare concerns that had been raised. So far, the team have provided a full diagnosis for 18 patients, partial diagnosis for 4 and continue functional investigations for 3 cases. The diagnostic rate continues to improve, with the team being successful in identifying new disease genes. Her talk highlighted the need for considered and sustainable workflow practices. Rapid paediatric sequencing is now being offered by the NHS.