Project title: Validation of multiplex assays of variant effect (MAVES) in cancer susceptibility genes

Project Summary: Interpretation of variants in cancer susceptibility genes involves complex integration of multiple data types despite which, unless previously reported in multiple cases, can produce inconclusive classification as VUS (variant of uncertain significance). This is an unsatisfactory outcome, in particular for a patient and their family. Historically, assays of gene function were of low throughput and results were frequently not reproducible.

Concurrent technology advancement of next generation sequencing (NGS) and CRISPR gene editing have enabled saturation genome editing (SGE), whereby ever possible variant of interest can be assayed for its impact on survival in an informative cell line. As such, comprehensive variant-level functional maps can be generated by these multiplex assays of variant effect (MAVES), providing opportunity to transform clinical variant classification. In 2018 Findlay et al demonstrated proof of principle with functional data for ~4000 BRCA1 variants showing near perfect correlation against clinical classifications of pathogenicity.

However, many challenges need to be addressed before we can leverage data from MAVES to enable robust clinical classifications for newly identified variants in cancer susceptibility genes. Ensuring the assays correctly predict functions correlating with clinical pathogenicity. Ensuring consistent results across different MAVEs and different cell lines. Ensuring methodologies for quantitative validation against accurate truthsets. Ensuring the evidence scores generated are well calibrated.

In our recently awarded CRUK Program award, CG MAVE, Adams (Sanger), Findlay (Crick) and Turnbull (ICR) will be exploring these issues whilst developing new MAVEs for at least 15 cancer susceptibility genes. We are looking for a clinical fellow to undertake a PhD with Turnbull focused on development and application of methodology for validation of MAVE data against phenotypic and other data sources. The fellow will develop the relevant skill set in programming, data analysis, epidemiology and statistics. The fellow will be closely involved in CanVIG-UK (Cancer Variant Interpretation UK), the national network of clinical laboratory scientists and clinical geneticists led by Turnbull, through which we shall be procuring clinical data and also ratifying new guidance for use of MAVE data in NHS diagnostics.

The fellow will sit within the Turnbull team comprising bioinformaticians, software engineers, PhDs, Clinical Fellows, GC, project managers and administrators with opportunity for involvement in a range of discovery, translational and implementation projects in different areas of cancer susceptibility genomics. Ehsan Ghorani , Clinician-Scientist fellow and Team Leader at Imperial, will act as associate

supervisor and is a collaborator of Turnbull in a range of projects around diagnostic validity.

Supervisory Team: Prof Clare Turnbull, Dr Ehsan Ghorani

Clinical Specialities: Clinical Genetics, Public Health, Oncology, Pathology