Project Details	
Project Code	MRCPHS24Ex Jackson
Title	Investigating the penetrance of cancer susceptibility genes in a population cohort and the influences of family history and rare and common genetic modifiers
Research Theme	Population Health Sciences
Summary	Offering genetic testing only to those with a family history of cancer has led to current evidence on disease risk in carriers of cancer-causing variants being artificially inflated. This project will use large genetic datasets to compare effects of rare cancer-causing variants across groups based on variables such as age, sex, screening and family history in a general population setting. This work will help to inform clinicians how to counsel patients.
Description	Background One in two people born after 1960 will be diagnosed with cancer. UK cancer outcomes fall behind other European countries. Disease-causing genetic variants in some genes lead to an increased risk of cancer. The chances of an individual with a genetic variant developing cancer are influenced by a number of factors such as environmental influences, other genetic variants and family history. Existing risk estimates are derived from clinical research and are biased in how they were collected, overestimating the risk of these genetic variants in the wider population. Individuals are now receiving this type of genetic information as a result of taking part in research studies, direct-to-consumer genetic testing or after being investigated for unrelated conditions (additional or secondary findings). We have recently shown in a population cohort, that individuals without a family history of cancer have a lower risk of developing cancer themselves, despite having disease-causing variants for breast or bowel cancer. This could lead to patients being incorrectly advised of their risk status and potentially making injudicious decisions about screening or prophylaxis. We aim to develop more accurate risk predictions for other cancer susceptibility syndrome variants and refine them by family history (where available), genetic risk score (a collection of other genetic variants which contribute to cancer risk) and other relevant risk factors in a healthy population dataset. Key Research Question This project will primarily use the UK Biobank resource (~500,000 individuals, however throughout the course of the PhD we plan to include additional diverse datasets such as AllofUs, 100,000 Genomes Project, Biobank Japan and TopMed). While previous work has focused on breast and colorectal cancer with a focus on penetrance with and without a family history, this project will expand this work to other cancer sites and a wider range of clinical characteristics (such as age, sex, screening history, socio-economic status and some environmental factors). This will allow the student to steer the project towards cancer sites / clinical variables of interest. The student will also be responsible for deciding which variables end up in the final risk model and whether grouped or individual analyses or rare modifiers would be more relevant to their research question. Specific Objectives The aim of this project is for the first time to characterise the risk of cancer conferred by rare pathogenic genetic variants in cancer susceptibility genes and how this is influenced by family history and other genetic variants, both common and rare modifiers in a population

	cohort. Specific objectives include: ·Generate GRS for all cancers with a monogenic susceptibility gene where a suitable published GWAS exists. Where multiple exist, evaluate which performs best in our cohort ·Analyse whether cancer family history positive individuals are enriched for rare modifying variants. A panel of known oncogene and tumour suppressor genes as well as previously reported modifiers of penetrance will be tested across groups to see if there is an increased burden or rare variants in the family history positive group or whether cancer-type specific variants can be found ·Generate cancer-specific penetrance estimates for all monogenic cancer susceptibility syndrome genes where relevant cancer registry data exists in UK biobank. These estimates will additionally be refined by family history (where already available or as additionally generated during the project), GRS and enrichment of other rare modifying variants
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