Project Details	
Project Code	MRC22PHSBr Haycock
Title	Identifying opportunities for repurposing of approved drugs to new cancer indications using genetic and observational approaches
Research Theme	Population Health Sciences
Summary	Using regions of the genome that influence proteins as drug proxies, the student will test if selected drugs are associated with cancer survival (a Mendelian randomization approach). Findings from the latter analyses will be replicated in a "target trial" observational study of the Clinical Practice Research Datalink, a primary care database of anonymised records in up to 16 million patients. Overall findings will be used to prioritise treatments for cancer.
Description	Background Genetic approaches play an important role in prioritising therapeutic targets for disease treatment. Mendelian randomization (MR) is an epidemiological technique that exploits the random distribution and fixed nature of germline genotypes to identify causal relationships between intervention targets and disease. An exciting area of application is "drug repurposing Mendelian randomization" - where new indications are found for existing drugs using only the results from genome-wide association studies (GWAS) of disease. In the context of cancer, this could be applied to existing oncological medications (i.e. drugs approved to treat one type of cancer that are repurposed for the treatment of a different cancer) or non-oncological medications (e.g. drugs approved to treat cardiovascular disease that are repurposed for treatment of cancer). Along with MR, observational studies can be used to estimate the effects of medication use on cancer survival by employing a "target trial" framework. This approach involves applying design principles from randomised trials to observational research to minimise key sources of bias and confounding. Replication of findings from MR in target trial analyses can provide further support for the repurposing of existing drugs for cancer treatment. In this project, the student will apply MR and "target trial" approaches to investigate opportunities for repurposing of drugs to new cancer indications. Methods Drug proxies We have identified 241 cancer drugs (either approved or under evaluation) that could be proxied by genetic polymorphisms in MR analyses. For example, rs1411262, a genetic polymorphism associated with the PD-1 protein, will be used to proxy PD-1 inhibitors, which have been approved for treatment of 9 cancer types. Variants in genes encoding targets for (non-cancer) medications that lower cholesterol (e.g. 5 SNPs in the HMGCR gene for statins), blood pressure (e.g. 14 SNPs in the ACE gene for ACE inhibitors), and blood glucose levels (e.g. 1 SNP in SLC5A2 for SGLT2 inhibitors) will be used to proxy inhibition of these targets. GWAS summary data for cancer survival The student will obtain results from GWAS of cancer survival using the Open GWAS platform and other data sources. GWAS summary data for cancer survival is available for breast, prostate, ovarian and lung cancer (2,901-96,661 cancer cases across sites). For colorectal cancer, the student will submit an application to the International Survival Analysis in Colorectal cancer Consortium (6,077 cases). Conduct MR analyses The student will conduct MR analyses to assess whether the selected drug targets are associated with cancer survival (power varies

	by target but, for PD1 inhibition, should be >80% to detect hazard ratios ≤0.90 for most cancer sites [alpha=0.05]). The student will also conduct sensitivity analyses for key sources of bias, such as genetic confounding and selection bias. Perform target trial analysis Using the Clinical Practice Research Datalink (CPRD), a primary care database of medical records in ~16 million patients, the student will perform observational analyses using a "target trial" framework to triangulate findings for select medications from MR work. This approach involves explicitly emulating the design of a hypothetical intervention trial of a particular medication to minimise selection and time-related biases in observational analyses. Specifically, the student will develop a protocol for a hypothetical target trial to be emulated (e.g. specifying eligibility criteria, treatment strategy and assignment, and statistical analyses) and then perform this analysis in CPRD (power varies by target but for statin treatment, we expect power >80% to detect hazard ratios ≤0.76 across cancer sites [in intention to treat or per protocol analysis]).
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