Project Title: Liquid biopsy to improve the diagnosis and treatment of Cancers of Unknown Primary (CUP)

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Cancer of unknown primary (CUP) is a heterogeneous group of metastatic tumours for which a standardised diagnostic work-up fails to identify the site of origin at the time of diagnosis. There is a lack of research into CUP and the only approved treatment option is chemotherapy. It remains the 5th leading cause of cancer death in the UK.

Large-scale molecular profiling studies in CUP suggests up to 30% of patients harbour potentially actionable genomic alterations that could be amenable to targeted therapies. However, the absence of a tissue of origin (TOO) designation significantly limits the available treatment options for patients with CUP and the majority are currently treated with a 'one-size-fits-all' chemotherapy approach with limited therapeutic effect.

Our goal is to make a swift primary tumour diagnosis for patients with CUP via molecular profiling of their blood and identify actionable molecular alterations. As access to good quality tissue for molecular profiling remains a significant challenge in CUP, we are focussed on a liquid biopsy approach. We developed a robust, sensitive and reproducible whole genome circulating-free DNA (cfDNA) methylation profiling approach (T7-MBD-seq) (e.g., Chemi et al. 2022) and further developed our workflow to generate highly specific machine learning Tissue of Origin (TOO) classifiers for primary tumour determination. We applied this liquid biopsy to a pilot cohort of patients with CUP in a proof-of-concept study. Our preliminary work revealed commonly predicted tumour types within the CUP cohort which now warrant further characterisation.

In this PhD project, the student will optimise and deploy our TOO liquid biopsy to extend and validate the potential clinical utility of cfDNA molecular profiling from a single blood draw in patients with CUP. They will combine gene mutation and copy number analysis with the TOO prediction in a larger cohort of patients with CUP. Improvement of our prototype ctDNA methylation TOO classifier and development of a multi-modal approach will improve our ability to identify patients that could be re-classified and potentially stratified to alternative therapies in this hard-to-treat cancer group as well as further characterise potentially 'favourable' subtypes of CUP that could be stratified to better therapies. This project provides an opportunity to work in an area of clinical unmet need, with novel liquid biopsy technologies and develop core bioinformatic skills alongside an expert bioinformatics team.