**University of Leicester**

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| **Project Reference** | BRC Studentships |

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| **Additional Supervisor** | Dr David Guttery​ |

**Section 2 – *Project Information***

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| **Project Title** | ​Use of Oxford Nanopore Technology liquid biopsy workflows for early cancer detection, tissue-of-origin prediction and personalising cancer treatment. |
| **Project Highlights:** | 1. | Explore the use of third-generation sequencing technology to detect cancer early using liquid biopsies. |
| 2. | Expand the repertoire of approaches for profiling ctDNA using Oxford Nanopore Technology workflows to analyse genomic and epigenomic profiles for improved breast cancer detection and treatment response. |
| 3. | Application of machine learning approaches to enhance diagnosis, evolution and therapy outcome prediction through blood-based tests. |
| **Project Summary**  |
| **Background**: ​​Genomic profiling studies have illustrated the potential of circulating tumour DNA (ctDNA) as a liquid biopsy for detecting cancer, monitoring disease recurrence and selecting targeted therapies. However, some cancers only release limited amounts of ctDNA even in advanced disease stages, and can be undetectable in early-stage disease, necessitating development of alternative, more sensitive biomarkers. Recently, we have piloted Oxford Nanopore Technologies (ONT) sequencing for simultaneous analysis of copy number, mutations, DNA fragments and DNA methylation changes including 5-hydroxymethylcytosine (5hmC) modification, which provide useful information on cell of origin and gene expression respectively. As such, they provide for longitudinal assessment of altered gene expression patterns that accompany emergence of resistance to therapies. Thus far, the potential of these newer ctDNA approaches have not been fully explored.**Aim**: ​To improve the patient-level sensitivity of current ctDNA based methods for clinical application. The student shall evaluate multi-analyte profiles of ctDNA to determine the optimum circulating biomarkers for early cancer detection guiding precision treatment. ​ **Research Plan**: ​The student will analyze data generated using the ONT Promethion platform to generate full-length transcript data and plasma ctDNA data, from patients recruited through the Leicester Cancer Biobank in comparison with healthy age matched controls.  Raw reads will be processed using standard algorithms available at the ONT github repository (<https://github.com/nanoporetech>). Dr R Joshi will lead supervision of informatics analyses on our High-Performance Computing Facilities that will house data generated and enable efficient processing of genome-wide data. Results will be used to compare the sensitivity and specificity of ctDNA detection in the same patients. Machine learning (ML) will be applied to improve cancer detection with a range of supervised learning algorithms. The resulting models are expected to predict which patients have cancer with greater sensitivity and specificity than current ctDNA-based univariate mutational markers by identifying optimal combinations of patient features.  The supervisory team will support wet lab aspects in the Shaw lab, informatics in the Joshi group and patient recruitment with samples collected to the local cancer biobank.​**Expected outcomes and impact**: ​Community engagement and involvement, publication in high-impact journals and potential for transferability through the Oncology TRC. The potential clinical significance is that a more comprehensive blood-based multi-analyte workflow could aid with stratification and targeting therapy at an early stage. There is potential to generate data to lead to a grant application to the NIHR or breast cancer now for a ctDNA guided interventional clinical trial.  |
| **References** |