Title: Exploring the potential of pathomics in aiding risk stratification and therapeutic selection for patients with endometrioid ovarian cancer

Supervisors: Dr Robb Hollis, CRUK Scotland Centre, IGC. Dr Pete Bankhead, Centre for Genomics and Experimental Medicine, IGC.

Key collaborators: Prof Simon Herrington, CRUK Scotland Centre, IGC.

Project description (300w)

Endometrioid ovarian carcinoma (EnOC) is the second most common form of ovarian cancer, but remains critically understudied. EnOC is highly clinically heterogeneous; some patients experience excellent long-term survival, while others present with highly aggressive disease that is resistant to current treatment modalities. EnOC also demonstrates substantial histopathological heterogeneity (Figure 1).

In recent years, we have curated a large EnOC tissue resource in Edinburgh (n=176) with rich clinical annotation, whole exome sequencing data and histopathological images available for all cases[1-3]. We have used this unique resource to identify[1, 2] and refine[3] the molecular taxonomy for classifying EnOC based upon a combination of genomic and immunophenotypic data. This approach identifies both high-risk patients in need of novel therapeutics, as well as low-risk cases who represent potential candidates for de-escalation of adjuvant chemotherapy to less toxic regimens. Genomic data highlight several potential therapeutic vulnerabilities in high-risk cases (*BRCA1/2* mutations, PARP inhibitors; mismatch repair deficiency [MMRd], immune checkpoint inhibitors)[2]. Transcriptomic characterisation is currently underway to expand the available molecular annotation.

The present project proposes to investigate whether pathomics (analysis and interpretation of digital histopathological images using machine learning and artificial intelligence) can be used to classify EnOC into its molecular subtypes using routine H&E images, and explore the potential to identify tumours that harbour therapeutically-relevant molecular defects (*BRCA1/2* mutation, MMRd). Detecting the key prognostically and therapeutically-relevant molecular defects in EnOC currently requires both tumour sequencing and immunohistochemistry; this is not routinely performed in clinical settings. Moreover, these analyses are not feasible across many clinical contexts worldwide, including within low- and middle-income countries. Requirements for additional molecular testing also add to the growing burden on national health services. A reliable pathomic approach for tumour subclassification has the potential to facilitate high-resolution patient stratification using routine histopathological images without the need for resource-intensive ancillary molecular testing.

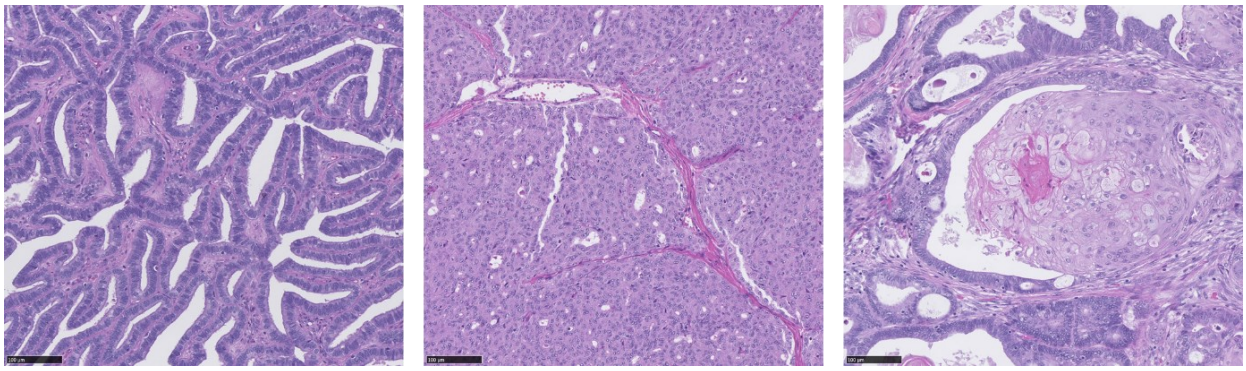

Figure 1. Histopathological heterogeneity in endometrioid ovarian carcinoma (EnOC). Left, classical low grade EnOC. Middle, high grade EnOC with extensive solid architecture. Right, EnOC demonstrating squamous differentiation. Scale bars represent 100µm.

Key references

1. Hollis RL, Stanley B, Iida Y, et al. Hormone receptor expression patterns define clinically meaningful subgroups of endometrioid ovarian carcinoma. *Gynecologic oncology*. Nov 2019;155(2):318-323. doi:10.1016/j.ygyno.2019.09.001

2. Hollis RL, Thomson JP, Stanley B, et al. Molecular stratification of endometrioid ovarian carcinoma predicts clinical outcome. *Nature communications*. Oct 5 2020;11(1):4995. doi:10.1038/s41467-020-18819-5

3. Hollis RL, Stanley B, Thomson JP, et al. Integrated molecular characterisation of endometrioid ovarian carcinoma identifies opportunities for stratification. *NPJ Precis Oncol*. Jun 2 2021;5(1):47. doi:10.1038/s41698-021-00187-y