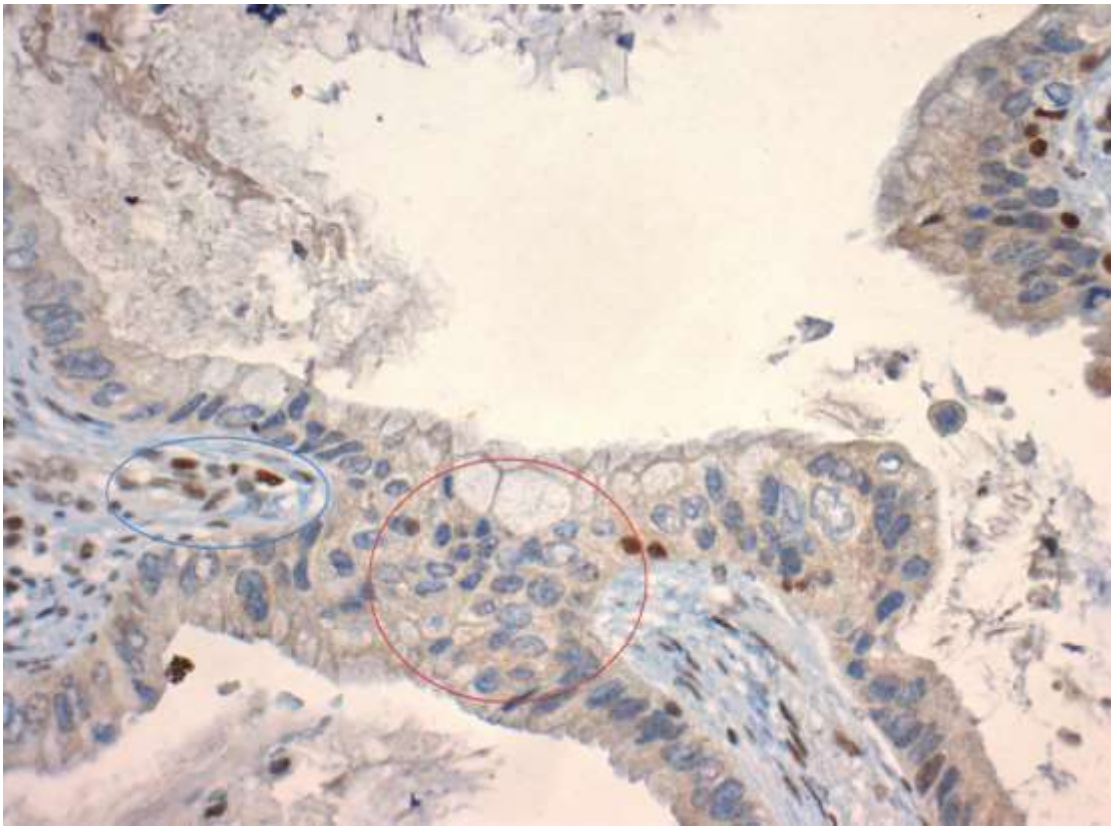
1. Clinical and Pathological Features of Familial Pancreatic Cancer
   I have completed a manuscript with the title above. It is currently under review (since 16th February 2014) at the journal *Cancer.* The important findings in this paper are summarized below.
   BACKGROUND: Inherited predisposition to pancreatic cancer (PC) contributes significantly to its incidence, and presents an opportunity for the development of early detection strategies. The genetic basis of predisposition remains unexplained in a high proportion of familial PC (FPC).
   METHODS: Clinico-pathologic features were assessed in a cohort of 766 patients with a diagnosis of PC. Patients were defined as FPC if they had ≥1 affected first-degree relatives (FDR), or otherwise classified as sporadic PC (SPC).
   RESULTS: The prevalence of FPC in this cohort was 8.9%. In FPC families with an affected parent-child pair, 71% were diagnosed 12.3 years younger in the subsequent generation. FPC patients had more FDRs with an extra-pancreatic malignancy (EPM) (42.6% vs 21.2, *P* <0.0001), in particular melanoma and endometrial cancer, but not a personal history of EPM. SPC patients were more likely to be active smokers, have higher cumulative tobacco exposure and have fewer multi-focal precursor lesions, but these were not associated with differences in survival. Long-standing diabetes mellitus (> 2 years) was associated with poor survival in both groups.
   CONCLUSION: FPC represents 9% of PC and the risk of malignancy in kindred does not appear to be confined to the pancreas. FPC patients have more precursor lesions and fewer active smokers but other clinico-pathologic factors and outcome are similar to SPC patients. Furthermore some FPC kindreds may show anticipation. A better understanding of the clinical features of PC will facilitate efforts to uncover novel susceptibility genes and the development of early detection strategies.

2. Mismatch repair (MMR) defects in PC
   The mismatch repair system is a DNA repair pathway which when mutated predisposes to development of colo-rectal and endometrial cancer and a number of other malignancies including pancreatic cancer. We have a cohort of 296 patients which we have sequenced the MMR genes in both normal and tumour DNA. Within this cohort approximately 9% have a family history of pancreatic cancer and 15% either a personal or family history of colo-rectal cancer. We are establishing the prevalence of loss of function mutations in MMR genes in PC. Furthermore we are assessing the pattern of mutations in the tumours and absence of protein expression (using immunohistochemistry –see picture below) for evidence of a defective MMR pathway in the progression of the cancer.

   Figure 1: MSH6 IHC – the tumour cells are negative (red circle) for MSH6 (one of the MMR proteins) while the surrounding stroma (blue circle) is positive.



I am preparing a manuscript for publication with estimated deadline by end of May 2014.

3. Other PC predisposition genes
   I have assembled a list of other candidate PC risk genes which include genes known to predispose to breast and ovarian cancer eg BRCA1, BRCA2 and PALB2 along with others which predispose to a wide range of cancers eg ATM. We are examining the prevalence of mutations in these genes in our cohort. We also aim to try and uncover potentially novel germline variants which may increase risk of developing PC. Already in this cohort we have found BRCA2 mutations in 5 patients, PALB2 in 2 and ATM in 2. This study is in concordance with the APGI ethics approval and if results are returned they are done so as part of the ethically defensible plan outlined in this. The estimated dat of completion of this is end of August 2014.