****

**Protein biomarkers and alternatively methylated cell-free DNA detect early-stage pancreatic cancer**

Ben-Ami R, Wang Q, Zhang J, et al. [Protein biomarkers and alternatively methylated cell-free DNA detect early-stage pancreatic cancer.](https://gut.bmj.com/content/73/4/639) Gut 2024; 73: 639-648. doi: 10.1136/gutjnl-2023-331074

Early detection of pancreatic ductal adenocarcinoma (PDAC) is a challenge. The current approach relies on radiological surveillance of cystic pancreatic lesions alongside serial measurements of serum CA19-9 (Carbohydrate antigen 19-9). Ben-Ami et al., investigate the role of protein and cell-free DNA (cfDNA, i.e. circulating DNA in plasma) as sources of biomarkers.

The performance of three panels were assessed in case-control sets: (1) CA19-9, TIMP1 (TIMP Metallopeptidase Inhibitor 1), LRG1 (Leucine-rich alpha-2-glycoprotein 1) (protein-based markers for early-stage PDAC identified in earlier studies); (2) the KRAS (Kirsten rat sarcoma virus) genetic mutation in cfDNA (Circulating free DNA) (mutations are implicated in 90% of patients with PDAC) and (3) methylated exocrine pancreas-specific markers in cfDNA.

For the training dataset, 50 patients diagnosed with localised or metastatic PDAC were recruited alongside controls with and without colorectal cancer. For the testing dataset, 86 patients with localised PDAC were matched with healthy controls and patients with chronic pancreatitis. Blood samples were obtained at time of diagnosis and prior to treatment.

Receiver-operating curves (ROC) were generated to measure the performance of these panels. KRAS cfDNA-based markers were insufficiently sensitive and not subsequently validated. Notably, the detection of early PDAC increased from 67% using CA19-9 alone to 80% with the use of the TIMP1 protein biomarker (at >90% specificity).

Ben-Ami et al., propose that CA19-9 could be used as an anchor marker and that the adjunctive use of biomarkers including TIMP1 and exocrine pancreas-specific cfDNA could increase the yield of detection of early cancers, particularly in cases where CA19-9 falls below the threshold. Further translational work is needed, however, before we see these markers in clinical practice.