Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report [1]

DNA methylation-based biomarkers from circulating tumour DNA for the diagnosis of pancreatic cancer

What is a Topic Exploration Report?

Topic Exploration Reports are not health technology assessments. These reports provide a high-level briefing on new topics submitted to Health Technology Wales and are not based on exhaustive or systematic literature searches. Instead, they rely on a focussed scan of key resources.

What evidence is used in a Topic Exploration Report?

Priority is given to summarising the most relevant or useful evidence, rather than covering all possible evidence. Information reported is typically based on abstracts and study authors' own conclusions, rather than detailed scrutiny of full texts.

What are the aims of a Topic Exploration Report?

Topic Exploration Reports offer an overview of the available evidence on a topic and aim to highlight any uncertainties or gaps in the evidence. These reports outline the quantity and type of evidence found, but no critical appraisal or formal evidence synthesis is conducted.

How should a Topic Exploration Report be used?

Topic Exploration Reports can be used to indicate what evidence may be available for a topic, and do not provide definitive guidance on how a technology should be used. The evidence presented within the reports should be interpreted with caution.

[1] Cyfieithu dogfennau HTW wedi'u cyhoeddi o'r Saesneg i'r Gymraeg
Translation of published technical HTW documents from English into Welsh

Topic exploration report number	TER637
Topic	DNA methylation-based biomarkers from circulating tumour DNA for the diagnosis of pancreatic cancer
Summary of findings	Pancreatic cancer has very low survival rates, primarily due to early-stage disease being asymptomatic and a lack of effective early diagnosis methods. A variety of novel biomarkers with the potential to detect early pancreatic cancer have been identified. DNA methylation signatures are a promising biomarker of pancreatic cancer, which can be detected in circulating tumour DNA (ctDNA), which is obtainable through liquid biopsies (such as blood draws). Next-generation sequencing can be used to determine whether any pancreatic cancer biomarkers are present in the liquid biopsy sample, potentially detecting the cancer at early or pre-lesion stages. Health Technology Wales (HTW) researchers searched for evidence on the clinical and cost effectiveness of DNA methylation biomarkers from ctDNA to diagnose pancreatic cancer. HTW identified one recent systematic review on the diagnostic accuracy of various biomarkers from liquid biopsies to detect pancreatic cancer, including six studies of DNA methylation markers in ctDNA. The sensitivities and specificities ranged from 0.40 to 0.97 and 0.83 to 0.94, respectively. One prospective cohort study for blood-based early detection of gastrointestinal cancers, including pancreatic, using targeted DNA methylation and fragmentomics sequencing was identified. The test showed good performance for pancreatic cancer detection in the validation and independent test cohorts, with sensitivities above 85% and specificities above 94%. Areas of uncertainty include there being a variety of potential biomarkers available, but it is unclear how many tests are available with regulatory approval. It is also unclear in studies what reference test has been used for determining diagnostic accuracy. No economic evidence was identified and there is a lack of reporting of longer-term outcomes.

Introduction and aims

Pancreatic cancer has very low survival rates, primarily due to early-stage disease being asymptomatic and most diagnoses being made with late-stage disease when curative treatments may no longer be feasible. Techniques such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound-guided fine needle aspiration, and testing for the non-invasive biomarker serum carbohydrate antigen 19–9 (CA19-9) are used to diagnose pancreatic cancer, but there is a lack of effective early diagnosis methods.

Next-generation sequencing (NGS) is the collective term for technologies that allow quick, low cost, high throughput DNA or RNA sequencing, including massively parallel sequencing that can be used to analyse many strands of DNA at the same time. A variety of novel biomarkers with the potential to detect early pancreatic cancer have been identified, which are obtainable through liquid biopsies (such as blood draws). DNA methylation signatures are a promising biomarker of pancreatic cancer, which can be detected in circulating tumour DNA (ctDNA) that can be derived from a standard blood draw. Next-generation sequencing can be used to determine whether any pancreatic cancer biomarkers are present in the liquid biopsy sample, potentially detecting the cancer at early or pre-lesion stages. These tests could potentially be deployed in primary and community care settings, as well as specialist care.

BT-Reveal is an example of an NGS blood test for pancreatic ductal adenocarcinoma (PDAC) that analyses DNA methylation in ctDNA from a standard blood draw and has CE marking as a general in vitro diagnostic (IVD) device under EU IVDD. The EU has extended the timeline that IVDs will be accepted with IVDD certificates under newer EU IVD Regulation (2017/746) (IVDR) transitional arrangements (MHRA 2025a). It is likely BT-Reveal will be 'upclassified' to a Class C device under EU IVDR, meaning that its EU IVDD certificate may be valid for the GB market until 31 December 2028, but will need approval by a notified body after this. However, current UK Medical Devices Regulation matches EU IVDD and it is unclear whether this will be changed (MHRA 2025b). BT-Reveal can be used for early diagnosis as well as at other points in the care pathway. The US Food and Drug Administration (FDA) granted BT-Reveal 'breakthrough device' designation due to its potential to fulfil an unmet medical need.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of DNA methylation biomarkers from ctDNA derived from blood draws to diagnose pancreatic cancer.

Evidence overview

Guidance

A NICE guideline on the diagnosis and management of pancreatic cancer in adults (NG85) was identified (NICE 2018). However, this guideline does not mention NGS, DNA methylation, or biomarkers for diagnosing pancreatic cancer, potentially due to the age of the guideline.

Secondary evidence

A systematic review and meta-analysis was identified, which looked at studies of various biomarkers detectable through liquid biopsy, including ctDNA, microRNAs, metabolites, and protein markers (Zheng et al. 2025). The review included seven studies that investigated ctDNA derived from blood, plasma or serum, with a total sample size of 1,065. Six of the seven studies used DNA methylation markers and sensitivities and specificities from these six studies ranged from 0.40 to 0.97 and 0.83 to 0.94, respectively. The pooled sensitivity and specificity of all seven studies were 0.65 (95% confidence interval [CI] 0.48 to 0.81) and 0.94 (95% CI 0.88 to 0.97), respectively.

Evidence overview

Primary evidence

One relevant study published after the search dates of the above systematic review was identified. Huang et al. (2025) conducted a prospective cohort study for blood-based early detection of gastrointestinal cancers, including pancreatic, using targeted DNA methylation and fragmentomics sequencing. GutSeer, the developed assay, was trained and validated on plasma samples from 1,057 cancer patients (87 with pancreatic cancer) and 1,415 healthy controls; it was then tested on an independent cohort of 846 participants (46 with pancreatic cancer). The test showed good performance for pancreatic cancer detection in the validation cohort, with sensitivity of 88.6% (95% CI 79.3 to 98.0%) and specificity of 95.8% (95% CI 94.3 to 97.2%). Within the independent test cohort, the sensitivity to detect pancreatic cancer was 87.0% (95% CI 77.2 to 96.7%) and specificity was 94.4% (95% CI 92.4 to 96.5%).

Areas of uncertainty

- It is not clear whether tests with appropriate regulatory approval, other than BT-Reveal, are available and were used in identified studies.
- It is not clear from the identified review what reference test was used in studies or what the most appropriate reference test would be.
- There is a lack of longer-term outcome reporting, such as cancer and survival outcomes. It is unclear whether this data is available yet.
- No economic evidence was identified.

Literature search results

Health technology assessments and guidance
NICE. (2018). Pancreatic cancer in adults: diagnosis and management. NICE Guideline NG85. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng85 [Accessed 31 December 2025].
Evidence reviews and economic evaluations
Zheng Z, Lu Z, Yan F, et al. (2025). The role of novel biomarkers in the early diagnosis of pancreatic cancer: a systematic review and meta-analysis. PLoS One. 20(5): e0322720. doi: https://doi.org/10.1371/journal.pone.0322720
Individual studies
Huang A, Guo DZ, Su ZX, et al. (2025). GUIDE: a prospective cohort study for blood-based early detection of gastrointestinal cancers using targeted DNA methylation and fragmentomics sequencing. Mol Cancer. 24(1): 163. doi: https://doi.org/10.1186/s12943-025-02367-x
Background information
MHRA. (2025a). Registration of certain in vitro diagnostic devices. Guidance. Medicines & Healthcare products Regulatory Agency. Available at: https://www.gov.uk/government/publications/registration-of-in-vitro-diagnostic-devices-with-expiring-ce-certificates/registration-of-certain-in-vitro-diagnostic-devices#annex-a-extended-validity-dates- [Accessed 28 January 2026]. MHRA. (2025b). Guidance on the regulation of In Vitro Diagnostic medical devices in Great Britain Guidance on legislation. Medicines & Healthcare products Regulatory Agency. Available at: https://assets.publishing.service.gov.uk/media/67863a313ef063b15dca0f47/Guidance_on_the_regulation_of_IVD_medical_devices_in_GB.pdf [Accessed 28 January 2026].

Date of search	28 January 2026
Concepts used	Next-generation sequencing, NGS, BT-Reveal, blood test, liquid biopsy, DNA methylation, circulating tumour DNA, ctDNA, pancreatic cancer, pancreatic ductal adenocarcinoma, PDAC

Proposed research question and evidence selection criteria (if selected)

Proposed Research question	**What is the clinical and cost effectiveness of DNA methylation biomarkers from ctDNA to diagnose pancreatic cancer?**

	Inclusion criteria	Exclusion criteria
Population	People under investigation for pancreatic cancer	
Intervention	Next-generation sequencing of DNA methylation biomarkers of pancreatic cancer from ctDNA derived from blood draws	
Comparison/ Comparators	Reference test: Imaging-based diagnosis, biopsy	
Outcome measures	Diagnostic accuracy outcomes: sensitivity, specificity, positive predictive value, negative predictive value Cancer stage at diagnosis Time to treatment Mortality/survival Patient acceptability Health related QoL Resource use Economic outcomes	

Proposed specialities	**Cancer; endocrine, nutritional and metabolic**