Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Blood-based liquid biopsy for the diagnostic triaging of symptomatic males suspected of prostate cancer
Topic exploration report number:	TER249

Introduction and aims

Health Technology Wales researchers searched for evidence on blood-based liquid biopsies for the diagnostic triaging of symptomatic males suspected of prostate cancer. The Manufacturer highlighted the trublood-prostate test, and other similar products will also be considered.

Typically, men undergo a biopsy of their prostate if they experience symptoms of prostate cancer or have a prostate specific antigen (PSA) test showing high levels of the PSA protein in their blood. However, the PSA test is not always accurate, which means that many men undergo unnecessary biopsies. Invasive biopsies not only cause pain and anxiety to patients but are also associated with procedural risks and costs.

Circulating tumour cells (CTCs) are malignant cells shed by tumours into the vasculature or lymphatics either as single cells or in clusters (circulating ensembles of tumour-associated cells [C-ETACs]). Because they are derived from the tumour mass itself, CTCs and their clusters are analytically equivalent to the tumour tissue without stromal content.

Trublood-prostate detects prostate cancer-specific CTCs in venous blood samples of symptomatic individuals with suspected prostate cancer. A specialised method is used to isolate the maximum number of CTCs for further testing. Following this, the CTCs are stained with specific immunocytochemistry based antibodies to identify the histopathological subtype. Trublood-prostate cannot however detect the grade of the tumour and does not detect haematolymphoid malignancies. Individuals positive for prostate cancer-specific CTCs can be prioritised for further clinical procedures while negative individuals can be considered for alternate diagnoses. The manufacturer proposes that the test results could be used to classify patients as either 'high risk' (prostate biopsy recommended) or 'Low Risk' (prostate biopsy not recommended).

The Manufacturer of trublood-prostate states that it is the first of its kind since, unlike the CellSearch test validated by the U.S. Food and Drug Administration, it does not provide CTC enumeration and hence is not intended for the future monitoring of a cancer patient. As of the

time of writing this report, trublood-prostate is validated for detection of prostate adenocarcinoma, and is not currently launched in the UK.

Summary of evidence

We did not identify any international or UK guidance, or systematic reviews, for the use of CTCs in the diagnosis of suspected prostate cancer.

In July 2021, the National Institute for Health and Care Excellence (NICE) produced a medtech innovation briefing (MIB268) for trublood-prostate for triaging and diagnosing people with prostate cancer symptoms.

Primary evidence

Diagnostic accuracy
Health Technology Wales researchers identified three primary studies regarding the diagnostic accuracy of CPCs in prostate cancer. Two of the primary studies reported using trublood–prostate to detect CTCs.

One observational study of 1,223 men with an elevated PSA (4 to 10 nanograms per millilitre [ng/ml]) compared the accuracy of neutrophil/lymphocyte ratio, free percent PSA, PSA density and the presence of CTCs for detecting prostate cancer at first biopsy. Sensitivity values of 0.388, 0.419, 0.598 and 0.966 and specificity values of 0.685, 0.897, 0.624 and 0.786 were reported for neutrophil/lymphocyte ratio, free percent PSA, PSA density and the presence of CTCs, respectively (Murray et al, 2019).

Two of the primary studies were funded by the Manufacturer. Akolkar et al (2019) screened 5,509 cancer patients from the ongoing TrueBlood study and 10,625 asymptomatic patients from the ongoing RESOLUTE study. Of the 153 confirmed prostate cancer cases, C-ETACs were detected in 90.2% of cases. An observational study of 558 people with a confirmed diagnosis of either malignant prostate cancer or benign hyperplasia or prostatitis, and people with suspected prostate cancer in India, found that CTC detection rate was 93.7% prospectively (111 samples) and 97.9% retrospectively (140 samples). The immunocytochemistry-based characterisation showed a 91.3% prospective sensitivity (154 samples) and 96.3% retrospective sensitivity (54 samples) when detecting malignant prostate cancer from benign conditions (Gaya et al, 2020).

Other outcomes
Health Technology Wales researchers did not identify any studies demonstrating the impact that liquid biopsy tests have on the management of patients with suspected prostate cancer (e.g. waiting times, drug treatment rates, surgical intervention and biopsy rates, mortality).

Economic evidence
No economic evidence was identified. According to NICE MIB268, the cost of the trublood-prostate test is £750 (excluding VAT), and this will be in addition to standard care.

Ongoing studies
The Manufacturer identified two primary ongoing studies, with unknown publication dates, and Health Technology Wales researchers identified another four ongoing clinical trials. Details of these can be found in the ‘Brief literature search results’ section.

Areas of uncertainty

Most of the evidence we identified investigated the prognostic/monitoring ability of liquid biopsies and not the diagnostic accuracy. The majority of the evidence we did identify for diagnostic accuracy comes from observational studies, some of which include data from ongoing studies where the full details are not yet published. In addition, the studies tended to report sensitivity but not specificity. We were not able to ascertain the 'downstream' treatment pathway benefits of using liquid biopsies to diagnose prostate cancer. None of the studies we identified were conducted in the UK, and so the relevance to the NHS setting is unclear. There is currently no evidence assessing the effect of the test on clinical decision making and long-term clinical outcomes in the NHS.

Conclusions

The evidence identified suggests that non-invasive blood-based liquid biopsies using CTCs/C-ETACs have high a sensitivity as a diagnostic biomarker for people with suspected prostate cancer, and could therefore potentially reduce the number of inappropriate invasive biopsies. However, the majority of data come from analyses of a small number of cohorts in observational studies, some of which are currently reported as ongoing.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant information or guidance from this source.
Health Technology Assessment Group	We did not identify any relevant information or guidance from this source.
Health Information and Quality Authority	We did not identify any relevant information or guidance from this source.
EUnetHTA	We did not identify any relevant information or guidance from this source.
International HTA Database	Adelaide Health Technology Assessment (2010) CellSearch: detection of circulating tumour cells for the prognosis and improved management of cancer patients: https://database.inahta.org/article/10987
U.S. Food and Drug Administration	https://www.accessdata.fda.gov/cdrh_docs/pdf7/k073338.pdf
UK guidelines and guidance	
SIGN	We did not identify any relevant information or guidance from this source.
NICE	MIB268: trublood-prostate for triaging and diagnosing people with prostate cancer symptoms. July 2021: https://www.nice.org.uk/advice/mib268
Secondary literature and economic evaluations	
Cochrane library	We did not identify any relevant secondary literature or economic evaluations from this source.
Medline	We did not identify any relevant secondary literature or economic evaluations from this source.
Primary studies	
https://www.epistemonikos.org/en/	We did not identify any relevant information or guidance from this source.
https://www.tripdatabase.com/	did not identify any relevant information or guidance from this source
Cochrane library	We did not identify any relevant information or guidance from this source.
Medline	Murray NP, Fuentealbla C, Reyes E, López MA, Anibal A, Minzer S, Munoz L, Orrego S, Guzman E, Arzeno L (2019). Predictive Value of Neutrophil to Lymphocyte Ratio in the Diagnosis of Significant Prostate Cancer at Initial Biopsy: A Comparison with Free Percent Prostate Specific Antigen, Prostate Specific Antigen Density and Primary Circulating Prostate Cells. Asian Pacific Journal of Cancer Prevention, 20 (11): 3385-3389: doi: 10.31557/APJCP.2019.20.11.3385
Ongoing primary or secondary research	
PROSPERO database	We did not identify any ongoing systematic reviews or meta-analyses from this source.
Clinicaltrials.gov	Early Detection of Prostate Cancer (PROLIPSY) (NCT04556916): 320 participants. Evaluate Liquid biopsy markers (CTCs, cfDNA, exosome) between the patients with histologically proven prostate cancer and age-matched non-cancer controls. Estimated completion date: 2033 https://clinicaltrials.gov/ct2/show/NCT04556916?term=liquid+biopsy&cond=prostate+cancer&draw=2&rank=2 Predicting Prostate Cancer in Elderly Men

	We aim to analyze whether the "liquid biopsy" model could increase the specificity of detecting 700 men with an aggressive (defined as Gleason score ≥ 7) prostate cancer and thereby reduce the proportion of men who undergo prostate biopsy, while at the same time maintaining the same sensitivity to detect aggressive prostate cancer as the PSA test alone Estimated completion date: 2039 https://clinicaltrials.gov/ct2/show/NCT04079699?term=liquid+biopsy&cond=prostate+cancer&draw=2&rank=3 Detection of Viable CTCs Using the EPIDROP Technology in Metastatic Prostate Cancer (EPIDROP) Sensitivity and specificity of a device called EPIDROP compared to CellSearch in 100 participants Estimated completion date: October 2023 https://clinicaltrials.gov/ct2/show/NCT04581109?term=liquid+biopsy&cond=prostate+cancer&draw=2&rank=7 Immuno-molecular Approaches for Non-invasive Diagnosis of Prostate Cancer (PROSTA-PAP) To determine the presence and number of prostate tumour cells in biological samples in 200 participants. Estimated completion date: 2024 https://clinicaltrials.gov/ct2/show/NCT04702633?term=liquid+biopsy&cond=prostate+cancer&draw=3&rank=11
Cochrane library	Isolation of circulating tumor cells from the blood of prostate cancer patients using an antibody-coated nanodetector (2012) ISRCTN10403616 https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01813573/full
Provided by the topic proposer through HealthTech Connect	RESOLUTE study: an Indian observational cohort study of 61,200 people, investigating the sensitivity and specificity of CTCs for many different types of cancer, including prostate cancer: http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=30733&EncHid=&userName=CTRI/2019/01/017219 Trueblood study: an Indian observational study of 40,000 patients with suspected or newly diagnosed cancer, or in cases of recurrence, irrespective of stage of the disease. The sensitivity and specificity of Trublood will be assessed, but not just for prostate cancer: http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=31879&EncHid=&userName=CTRI/2019/03/017918
Other	
Provided by the topic proposer through HealthTech Connect	Akolkar D, Patil D, Crook T, Limaye S, Page R, Datta V, Patil R, Sims C, Ranade A, Fulmali P, Fulmali P, Srivastava N, Devhare P, Apurwa S, Patel S, Patil S, Adhav A, Pawar S, Ainwale A, Chougule R, Apastamb M, Srinivasan A, Datar R. (2019). Circulating ensembles of tumor-associated cells: A redoubtable new systemic hallmark of cancer. International Journal of Cancer, 146, 3485–3494: https://doi.org/10.1002/ijc.32815 Gaya A, Crook T, Plowman N, Ranade A, Limaye S, Bhatt A, Page R, Patil R, Fulmali P, Datta V, Kumar P, Patil D, Akolkar D (2020). Evaluation of Circulating Tumor Cell Clusters for Pan-Cancer Noninvasive Diagnostic Triaging. Cancer Cryopathy: https://doi.org/10.1002/cncy.22366

Date of search:	April 2021
Concepts used:	circulating ensembles of tumour/tumor-associated cells (C-ETACs); circulating tumour/tumor cells (CTCs); diagnostic triaging; liquid biopsy, Immunocytochemistry, Trublood