NICE advice

trublood-prostate for triaging and diagnosing people with prostate cancer symptoms

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is trublood-prostate. It is for triaging and helping with the diagnosis of people with symptoms of prostate cancer.
- The **innovative aspects** are that trublood-prostate uses immunocytochemistry (ICC) profiling to characterise prostate adenocarcinoma-specific circulating tumour cells (CTCs) that have been isolated from patients' blood.
- The intended **place in therapy** would be either to triage people with suspected prostate cancer before having a conventional invasive prostate biopsy, or to make a diagnosis in people with suspected prostate cancer who are not well enough to have a prostate biopsy. The test would be used in secondary care after multi-parametric MRI to guide subsequent care.

- The **main points from the evidence** summarised in this briefing are from 2 observational studies including 1,208 people with suspected prostate cancer in India. They show that trublood-prostate has over 90% CTCs detection rate and over 90% sensitivity for detecting malignant prostate cancer.
- **Key uncertainties** around the evidence or technology are that the evidence is limited in quantity and quality. There is currently no evidence assessing the effect of the test on clinical decision making and long-term clinical outcomes in the NHS.
- The **cost** of trublood-prostate is £750 per test (excluding VAT). This will be in addition to standard care.

The technology

trublood-prostate (Datar Cancer Genetics) is a diagnostic test that uses immunocytochemistry to diagnose prostate cancer from blood samples of people with suspected symptoms of cancer. It uses circulating tumour cells (CTCs) or circulating ensembles of tumour-associated cells (C-ETACS) that are isolated from blood samples and treated through a negative enrichment technique. Harvested CTCs are then characterised by immunocytochemistry profiling specific to primary prostate adenocarcinoma (positive to alpha-methylacyl-CoA-racemase [AMACR] and prostate-specific membrane antigen [PSMA] antibodies and negative to p63 antibodies). Studies have shown that these immunohistochemical antibodies can be used by urological pathologists in cases when light microscopic findings of a biopsy are unclear (Ross et al. 2020; Magi-Galluzzi 2018). AMACR-positive cytoplasmic staining is expressed by about 80% of limited prostatic adenocarcinoma on needle biopsy (Magi-Galluzzi 2018). PSMA positive staining is seen in over 90% of prostatic adenocarcinomas on needle biopsy (Tsourlakis et al. 2015). Test results take 8 days. Depending on the test result people will be classed as either low risk with prostate biopsy not recommended or high risk with prostate biopsy recommended.

Innovations

trublood-prostate is the first in vitro diagnostic test based on C-ETACS and CTCs isolated from blood samples. It is a non-invasive test. Currently, people with symptoms of prostate cancer and a high prostate-specific antigen (PSA) test result for their age are referred for a multi-parametric MRI (mpMRI). Depending on the result of the mpMRI, people are referred for an invasive procedure such as prostate biopsy to get a definitive diagnosis. trublood-prostate aims to avoid a biopsy, or flag it up, in addition to mpMRI test. The company

claims that the potential test benefits would be reducing unnecessary invasive procedures and hospital visits. It claims its technology has an accuracy to detect prostate adenocarcinoma of 99.50%, a sensitivity of 100% and a specificity of 99.33%. These accuracy data are from unpublished company evidence for validation of the trublood-prostate diagnostic test.

Current care pathway

People with suspected prostate cancer are offered a blood test that looks for raised PSA levels. If these are raised, NICE's guideline on prostate cancer recommends offering mpMRI as the first-line investigation and reporting the results using a 5-point Likert scale. Different biopsies are offered depending on the results of mpMRI Likert scale. People whose mpMRI Likert score is 1 or 2 could opt out or opt in for a systematic prostate biopsy after discussing the risk-benefit ratio of the procedure with a healthcare professional. People whose Likert score is 3 or more will be offered a mpMRI-influenced prostate biopsy. The method used for the biopsy can be either transperineal, when the needle goes through the skin between the testicles and the back passage, or transrectal ultrasound-guided biopsy (TRUS), when the needle goes through the wall of the back passage.

A TRUS biopsy is done using local anaesthetic. Usually, 10 to 12 small pieces of tissue from different areas of the prostate are sampled and it takes 5 to 10 minutes. A template transperineal biopsy is normally done under general anaesthetic. In this, 2 to 3 small pieces of tissue from 8 sites are sampled and it takes about 20 to 40 minutes. A mapping transperineal biopsy is not offered as part of an initial assessment, unless as part of a clinical trial.

The NHS rapid diagnostic and research pathways handbook for implementing a timed prostate cancer diagnostic pathway set out that, if appropriate, a prostate biopsy should be done within 9 days from GP referral and a target of 5 days turnaround for reported pathology should be agreed as a minimum standard. This is a 14-day turnaround from GP referral to prostate biopsy result.

The following publications have been identified as relevant to this care pathway:

- NICE's guideline on prostate cancer: diagnosis and management
- NICE's guideline on suspected cancer: recognition and referral

- NHS England's handbook on implementing a timed prostate cancer diagnostic pathway.

Population, setting and intended user

trublood-prostate is intended for use either in triaging people with suspected prostate cancer before having a conventional invasive prostate biopsy, or for diagnosing suspected prostate cancer in people who are not well enough to have a prostate biopsy.

trublood-prostate is for use in primary, secondary and tertiary care settings. The test can be done at the same time as a PSA test and is requested by a GP, urologist or oncologist by completing a trublood-prostate test request and consent form and then sending it to Datar Cancer Genetics in the UK.

Pre-specified quantity of pre-barcoded trublood-prostate collection kits can be stocked at the primary, secondary or tertiary care centre or provided on advance request (with at least 48 hours notice) from the company. The trublood-prostate collection kit contains vacutainer tubes, test requests and patient consent forms, sample collection instructions, sample packing and shipping instructions. Other materials needed but not provided are blood collection needles, single-use alcohol swabs and medicated dressings.

The blood samples (16 ml) collected are sent to the Datar Cancer Genetics laboratory in the pre-paid shipping package provided by the company. No additional specialist training on sample preparation is needed for staff in the blood test centre. The test result is sent back to the referring clinician by secure email and a hard copy sent by post. Test results take 8 days.

The company recommends that trublood-prostate results be used in addition to mpMRI to identify people with a high risk of cancer and to achieve diagnostic triaging for people in whom the diagnosis still needs confirmation by tissue biopsy.

Costs

Technology costs

trublood-prostate costs £750 per person (excluding VAT), including trublood-prostate collection kit and shipment.

Costs of standard care

According to the national schedule of NHS reference cost 2018/2019 a transrectal ultrasound-guided biopsy of prostate (LB76Z) costs £504 and a transperineal template biopsy of prostate (LB77Z) costs £1,413. mpMRI for prostate costs £215 (RD03Z). Cost of staff time and equipment needed to collect a blood sample is £4 (DAPS08, phlebotomy).

Resource consequences

The company states that the technology is currently not used in the NHS.

The company states that the adoption of trublood-prostate for diagnosing prostate cancer could avoid unnecessary biopsies and reduce travel time. There is no published evidence to support these claims.

No charge is made for samples that are not tested (for example, haemolysed or coagulated samples, samples damaged in transit, insufficient samples, delayed samples and samples with significant deviations in shipping conditions). The requesting hospital or GP clinic will receive an invoice for the test after the Datar Cancer Genetics laboratory has generated a result. No additional equipment needs to be purchased and therefore no maintenance or training is needed.

Regulatory information

trublood-prostate is a CE-marked class general in vitro diagnostic regulated under the directive 98/79/EC. Renewal is due in July 2021.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

People with cancer are protected under the Equality Act 2010 from the point of diagnosis. Older people and people with an African-Caribbean and African family background are at higher risk of developing prostate cancer. A person can have a prostate but not identify as a man. Age, race, sex and gender reassignment are all protected characteristics under the

Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 2 observational studies of 1,208 people with suspected prostate cancer summarised in this briefing.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

Overall, the quantity of evidence for the accuracy of trublood-prostate is limited and of low methodological quality. The studies were done in India, not in the NHS setting. The description of prospective, independent, blind comparison with a reference (gold) standard of diagnosis was described only in a subset of the blood samples. The company stated that they have unpublished data on method development, analytical validation and blinded prospective validation of the technology using clinical samples. The published evidence came from 1 conference abstract and 1 paper that reported on multiple cancers but only data for prostate cancer was considered relevant for this briefing. More prospective comparative studies are needed to evaluate the accuracy of trublood-prostate. These should compare trublood-prostate with biopsy in the NHS setting. Those assessing the results of trublood-prostate should be blind to the results of biopsy.

Patil et al. (2020)

Study size, design and location

Observational study of 650 people with confirmed malignant and benign prostate enlargement to test the accuracy of immunocytochemistry (ICC)-based characterisation of circulating tumour cells (CTCs) in malignant prostate cancer in India.

Intervention and comparator

ICC-based characterisation of CTCs in prostate cancer. Gold standard was histopathological examination of biopsied tumour tissues (confirmed by the company because it was not described in the abstract).

Key outcomes

Viable CTCs could be obtained from 58 samples (89.2%) out of 65 confirmed prostate cancer cases. Among the 40 samples that were characterised by deep ICC profiling, all samples (100%) were positive for prostate-specific membrane antigen (PSMA) and AMACR. Among the benign cases, CTCs were seen in 10 samples (1.7%), of which all 10 were positive for PSMA but negative for AMACR. These people are having follow up. The possibility of other cancers is not ruled out in these people.

Strengths and limitations

This study is reported in conference abstract form only so is limited in detail. The reference gold standard and blinding of the test are not mentioned and the study was done retrospectively.

Gaya et al. (2020)

Study size, design and location

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.

Intervention and comparator

CTC detection rates and ICC-based characterisation of CTCs in prostate cancer (confirmed as trublood-prostate test by the company) compared with histological examination of biopsy samples.

Key outcomes

Overall, CTC detection rate was 93.7% prospectively (111 samples) and 97.9% retrospectively (140 samples). The ICC-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.

Strengths and limitations

One of the limitations is that this study reports on multiple cancers and data on prostate cancer for this briefing is a small proportion of the paper results section. The description of independent, blind comparison with a reference (gold) standard of diagnosis was only done in a subset of data.

Sustainability

The company claims that the trublood-prostate test may help reduce the environmental impact by decreasing energy use and travel. There is no published evidence to support these claims.

Recent and ongoing studies

- PROSTATE prospective observational open label trial: utility of ProState in distinguishing prostate malignancies from benign prostatic hyperplasia. WHO identifier: CTRI/2019/02/017863. Status: ongoing, interim results published (Patil et al. 2020; Gaya et al. 2020). Indication: prostate malignancy. Device: ProState (liquid biopsy platform). Date: 1 March 2019. Country: India.

- TRUEBLOOD prospective observational open-label trial: tissue biopsy replacement with unique evaluation of circulating bio-markers for morphological evaluation and clinically relevant molecular typing of malignancies from blood sample. WHO identifier: CTRI/2019/02/017918. Status: ongoing, interim results published for feasibility of harvesting CTC from cancer malignancies (Akolkar et al. 2019). Indication: cancer malignancies. Device: trublood test for different cancers including trublood-prostate. Date: 1 March 2019. Country: India.

Expert comments

Comments on this technology were invited from clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

Three experts contributed to the development of this briefing. Two experts were familiar with the technology, and 1 had used this technology before. All experts noted that the technology is not currently used in the NHS.

Level of innovation

All experts agreed that trublood-prostate could become an innovative minimally invasive diagnostic test for detecting prostate cancer. Experts also said that a blood test that could identify people who do need to have a biopsy or could make a diagnosis without biopsy would be a game changer in the current care of prostate cancer. However, 2 experts said that the evidence submitted so far for this technology is not sufficient to justify its routine use in the NHS. One expert said that they have no concerns about its use in the NHS because of the validation of the test in 2 observational studies of 1,208 people with suspected prostate cancer. One expert said that the innovative aspect is the circulating tumour cells (CTCs) enrichment technique and that the 8 days turnaround is a useful feature. All experts are aware of other CTCs biomarkers in development.

Potential patient impact

All experts recognised that having a blood test to avoid a prostate biopsy would be the main advantage for people. Experts felt the test would also be very useful for a small number of people who may not be well enough for a biopsy. One expert said that trublood-prostate could increase the diagnostic precision for people with serum prostate-specific antigen (PSA) values in the intermediate range (that is, between 4 and 10). One

expert felt that the test could be used to target all men over 50 years for mass screening. However, 3 experts said that these potential benefits need to be supported by robust validation data. One expert said that there is little evidence that early diagnosis of prostate cancer leads to improved mortality rates, unlike cervical, breast and colorectal cancer.

Potential system impact

One expert said that trublood-prostate is likely to be cost effective in the long term by allowing diagnosis of prostate cancer with high sensitivity and specificity from a blood test. One expert said that there would be a small increase in blood sample collection costs. Another expert reported that further data is needed to show that a test that could avoid a biopsy, like trublood-prostate, reduces the need of hospital visits or surveillance. It might be possible that hospital visits may increase to maintain reassurance that a significant cancer has not been missed.

General comments

All experts agreed that the trublood-prostate could be used in addition to standard care. One expert added that in the future the diagnostic test could be used together with PSA as a precision screening tool for prostate cancer. However, 3 experts agreed that the technology needs further clinical development first. One expert said that the technology would be currently used only in clinical trial settings because CTCs tend to be detected more readily in advanced cancer than at early stage, regardless of enrichment approaches. Another expert suggested using complete genomic sequencing on isolated CTCs to robustly identify the nature of CTCs. Two experts said that the use of this diagnostic test in the NHS is premature. One expert felt that this technology should be encouraged to help develop further validating trials. Research should include well powered prostate-specific controlled prospective trials with cross-site validation of the diagnostic device to address uncertainty about the evidence.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Simon Crabb, associate professor in medical oncology, University of Southampton. Did not declare any interests.

- Dr Timothy Crook, consultant in medical oncology. Locum. Has co-authored and published research on the trublood platform, including trublood-prostate.
- Professor Jonathan Waxham, professor of oncology, Imperial college London. Did not declare any interests.

  Professor Caroline Dive, interim director, Cancer Research UK Manchester Institute also contributed to this briefing.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement for medtech innovation briefings sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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