NICE advice

Stockholm3 for prostate cancer screening

Medtech innovation briefing
Published: 9 August 2022

www.nice.org.uk/guidance/mib303

Summary

- The **technology** described in this briefing is Stockholm3. It is used to help predict risk of prostate cancer in people aged 45 to 74 years with prostate-specific antigen (PSA) of at least 1.5 nanograms per ml and no previous diagnosis of prostate cancer.
- The **innovative aspects** are that Stockholm3 combines protein biomarkers, genetic markers and clinical data with an algorithm to help identify prostate cancer.
- The intended **place in therapy** would be as an addition to standard care for people with a PSA level of at least 1.5 nanograms per ml. The technology could be used in primary care or secondary care settings to test for prostate cancer.
- The **main points from the evidence** summarised in this briefing are from 7 diagnostic accuracy studies, using mixed methods, including a total of 460,503 people for prostate cancer screening in primary care and secondary care. The evidence suggests that Stockholm3 is more effective at predicting risk of prostate cancer than PSA testing alone for people aged 45 to 74.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

- **Key uncertainties** around the evidence or technology are that there is currently no evidence assessing the effect of the test on clinical decision making and long-term clinical outcomes in the NHS. Data about Black, Asian, and minority ethnic populations is currently limited.
- **Experts** agreed that the technology has the potential to improve diagnostic accuracy leading to a reduction in unnecessary MRI and biopsies. The technology is not yet used in the NHS and the main barrier to adoption is the lack of current initiatives or programmes for prostate cancer screening in primary care, and the additional financial cost to the NHS. Experts had mixed views on the most appropriate care setting and treatment pathway, with several options possible in both primary and secondary care. A patient organisation commented its concerns with adopting the device are that there is no defined place in the pathway for it to be rolled out and it questioned whether there is sufficient infrastructure and workforce in place within pathology for nationwide adoption.
- The **cost** of Stockholm3 is £350 per unit (excluding VAT) less applicable volume discounts. This includes the analysis of the blood test. There are additional costs such as for phlebotomy, and collection and transport of the samples to the reference laboratory. Some costs may already be captured in standard care costs depending on the care setting and proposed pathway.

The technology

Stockholm3 (A3P Biomedical AB) is a blood-based diagnostic test that is to be used alongside prostate-specific antigen (PSA) testing to predict risk of prostate cancer in people aged 45 to 74 years with no previous prostate cancer diagnosis. The technology uses an algorithm that combines plasma protein biomarkers, genetic markers, and clinical data and would be used in people with a PSA of at least 1.5 nanograms per ml. It uses 5 plasma protein markers (human glandular kallikrein 2 [hK2], microseminoprotein beta [MSMB], microphage inhibitory cytokine-1 [MIC1], total PSA and free PSA). The genetic markers include 101 single nucleotide polymorphisms. The clinical data captured in the algorithm includes age, family history and previous prostate biopsy. Stockholm3 gives a score that indicates the risk of prostate cancer. A Stockholm3 risk score of at least 11% is considered an indicator of prostate cancer risk, and if it is used in primary care, these people would be referred to a hospital for an MRI.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Innovations

The company claims that using Stockholm3 may improve diagnostic accuracy and reduce unnecessary MRIs and biopsies. The technology can predict the risk of prostate cancer in people with low PSA levels (at least 1.5 nanograms per ml) and increase the sensitivity to identify prostate cancer compared with age-specific PSA levels.

Current care pathway

The UK National Screening Committee does not currently recommend screening for prostate cancer. This is because the PSA test is not accurate enough to detect prostate cancer that needs treatment, there is a lack of treatment that is definitely better for people with early-stage prostate cancer, and the potential harm from PSA-based screening programmes.

PSA testing in the UK is only recommended in people suspected of having prostate cancer. Possible symptoms of prostate cancer include any lower urinary tract symptoms (nocturia, urinary frequency, hesitancy, urgency or retention) or erectile dysfunction. People with suspected prostate cancer based on the above symptoms are offered a blood test to check PSA levels and digital rectal exam (DRE). This is 1 of the points in the pathway where Stockholm3 is proposed by the company to be used, alongside the PSA test.

After the PSA tests and DRE (if done), some people may be referred to a urologist in secondary care where NICE's guideline on prostate cancer: diagnosis and management recommends offering multi-parametric MRI, with results reported using 1 of the 5-point scales (Prostate Imaging Reporting and Data System [PI-RADS] or the Likert scale). The company say Stockholm3 could be used as the first stage of testing in secondary care instead of MRI, meaning some people could avoid the need for MRI or biopsy. Urologists will currently consider if a biopsy is appropriate depending on the results of the MRI. People whose MRI score is 1 or 2 may opt in or out for a systematic prostate biopsy after discussing the risk-benefit ratio of the procedure with a healthcare professional. Individuals with a score of 3 or more should be offered a prostate biopsy. The prostate biopsy is done by a urologist. The tissue specimen from the biopsy is evaluated by a pathologist and scored according to the Gleason grading system. If it is Gleason grade 2 or more, the person is said to have clinically significant prostate cancer.

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

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

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. Many services adhere to The Royal College of Pathology's (RCP) key assurance indicators for laboratories. According to Prostate Cancer UK's best practice pathway, the diagnostic pathway can take up to 28 days before a definitive diagnosis is made. There is an acknowledged capacity challenge in the area with an increasing complexity and volume of pathology requests but with a lack of pathologists (see The Royal College of Pathologists report, Meeting pathology demand – Histopathology workforce census 2017/18).

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

According to the company, the technology is intended to help diagnose prostate cancer in people aged 45 to 74 years with no previous prostate cancer diagnosis and PSA of at least 1.5 nanograms per ml. Stockholm3 is intended to be used in addition to current methods of assessing PSA levels when testing for prostate cancer in primary care, where the same blood sample would be used if the PSA level is at least 1.5 nanograms per ml. It could alternatively be done by a urologist in a secondary care setting for people who would otherwise have an MRI. A clinical report is generated and sent to the doctor. The report includes a risk score that provides a recommendation on managing the condition for example, 'low risk of prostate cancer, new test recommended in 6 years' or 'increased risk for prostate cancer, referral to urologist is recommended'. A biopsy is recommended if prostate volume is less than 56 cubic centimetres or prostate DRE is abnormal. Otherwise, follow-up testing is recommended within 2 years.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Costs

Technology costs

The company states that the list price of Stockholm3 is £350 and that volume discounts are applicable. The company notes that their technology is more expensive than the PSA test alone, but claims it saves costs by reducing unnecessary MRIs and biopsies. The cost of £350 includes the analysis of the blood test. The total costs of delivering and implementing Stockholm3 will vary depending on the care setting and treatment pathway. Some additional costs such as for phlebotomy (£4; DAPS08), and collection and transport of the samples to the reference laboratory may already be captured in standard care costs.

Costs of standard care

Based on the Personal Social Services Research Unit (PSSRU) 2021, the cost of a DRE is £40 (GP appointment), and PSA testing in primary care is £27.75 (PSA test kit £8.75 plus nurse appointment £19). According to the national schedule of NHS reference costs 2019/20, a transrectal ultrasound-guided biopsy of prostate (LB76Z) costs £489 and a transperineal template biopsy of prostate (LB77Z) costs £1,477. A prostate multi-parametric MRI costs £273 (RD03Z). Cost of staff time and equipment needed to collect a blood sample is £4 (DAPS08, phlebotomy).

Resource consequences

The technology is currently not used in the NHS. It would be an addition to standard of care in the primary and secondary care setting. It would typically cost more than standard care but may result in improved outcomes because of improved sensitivity and specificity. This may result in earlier or more accurate diagnosis. The company claims that more accurate diagnosis may reduce overall patient mortality and would improve disease management or coordination of care and improve efficiencies within the NHS. The company states that adopting Stockholm3 for diagnosing prostate cancer could avoid unnecessary biopsies and reduce travel time. Summarised cost-utility evidence reports cost reductions of 17% and 23% to 28% because of reduced unnecessary MRIs, sepsis, and biopsies.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Regulatory information

Stockholm3 is CE-marked. The company intends to file for UKCA marking in July 2022.

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.

The technology is not suitable for people younger than 45 years or older than 74 years, or for people with a previous diagnosis of prostate cancer. The technology is suitable for transgender people.

People with an African family background have a high risk of prostate cancer (lifetime risk of approximately 1 in 4). The technology has been evaluated in Scandinavian populations (predominantly Caucasian). The summarised evidence showed limited data for Black, Asian and minority ethnic groups. The company submitted that this will be addressed by an ongoing clinical trial (ClinicalTrial.gov Identifier: NCT04583072).

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 7 studies summarised in this briefing including 460,503 people having prostate cancer screening in primary care.

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

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Overall assessment of the evidence

Overall, the quantity of evidence for the performance of Stockholm3 in prostate cancer screening is adequate and of good methodological quality. All studies summarised here were peer-reviewed. None of the studies are based in the UK and performance may vary across different populations owing to diverse clinical practice. More prospective comparative studies are needed to evaluate the performance of Stockholm3 within the NHS setting.

Nordström et al. (2021)

Study size, design and location

Prospective randomised open-label non-inferiority trial of Stockholm3 plus MRI targeted biopsy versus PSA testing plus systemic biopsy in 12,750 men aged 50 to 74 years for a population-based prostate cancer screening strategy in Stockholm.

Intervention and comparator(s)

Stockholm3 plus MRI-targeted biopsy was the main intervention compared with prostate-specific antigen (PSA) test and systematic prostate biopsy. Two analyses were used in the study:

- Stockholm3 (using scores of 0.11 and 0.15 as cut-offs) versus PSA in the experimental group to enable assessment of performance when an MRI-based strategy is used for cancer detection (paired analyses)
- PSA plus standard biopsy versus Stockholm3 plus MRI-targeted and systematic biopsy (unpaired, randomised analyses).

Key outcomes

The area under the receiver-operating characteristic curve for detection of clinically significant prostate cancer was higher for Stockholm3 (0.76; 95% confidence interval [CI] 0.72 to 0.80) compared with PSA (0.60; 95% CI 0.54 to 0.65). In the experimental group, a Stockholm3 of 0.11 or higher was non-inferior to a PSA level of 3 nanograms per ml or higher for detection of clinically significant prostate cancer (227 versus 192; relative proportion [RP] 1.18 [95% CI 1.09 to 1.28], p<0.0001 for non-inferiority), detected a similar

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

number of low-grade prostate cancers (50 versus 41; 1.22 [95% CI: 0.96 to 1.55], p=0.053 for superiority), and was associated with more MRIs and biopsies.

Compared with a PSA level of 3 nanograms per ml or higher, a Stockholm3 of 0.15 or higher provided identical sensitivity to detect clinically significant cancer and led to fewer MRI procedures (545 versus 846; 0.64 [95% CI: 0.55 to 0.82]) and fewer biopsy procedures (311 versus 338; 0.92 [95% CI: 0.86 to 1.03]). Compared with screening using PSA and systematic biopsies, a Stockholm3 of 0.11 or higher combined with MRI-targeted and systematic biopsies was associated with higher detection of clinically significant cancers (227 [3.0%] people tested versus 106 [2.1%] people tested; RP 1.44 [95% CI 1.15 to 1.81]), lower detection of low-grade cancers (50 [0.7%] versus 73 [1.4%]; 0.46 [95% CI: 0.32 to 0.66]), and led to fewer biopsy procedures. People randomly assigned to the experimental group had a lower incidence of being prescribed antibiotics for infection (25 [1.8%] of 1,372 versus 41 [4.4%] of 921; p=0.0002) and a lower incidence of admission to hospital (16 [1.2%] versus 31 [3.4%]; p=0.0003) than those in the standard group.

This study concluded that the Stockholm3 with MRI-targeted biopsy approach for prostate cancer screening decreases over-detection without losing the ability to detect clinically significant cancer.

Strengths and limitations

Randomisation and appropriate choice of the comparator accounted for some of the strengths of this study. Another strength was the large number of people enrolled in the study. One of the limitations was non-blinding of the urologists, clinicians and urologists who do biopsies. However, the block randomisation of people included minimised allocation bias. The study was done outside the NHS. This limits the applicability of these findings in the NHS.

Karlsson et al. (2021)

Study size, design and location

A model-based cost-effectiveness analysis of prostate cancer screening in 10,000 men using Stockholm3 in Sweden taking a societal perspective.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Intervention and comparator(s)

Stockholm3 was the primary intervention. Stockholm3 together with 3 PSA level cut-offs was compared with no screening, and with Quadrennial screening with PSA test alone. The 3 Stockholm3/PSA combinations were:

- PSA test and reflex Stockholm3 test for PSA levels of between 1 and 1.5 nanograms per ml
- PSA test and reflex Stockholm3 test for PSA levels of between 1.5 and 2 nanograms per ml
- PSA test and reflex Stockholm3 test for PSA levels of at least 2 nanograms per ml.

Key outcomes

At a PSA level threshold of 2 nanograms per ml, Stockholm3 was more effective than PSA test alone, reduced lifetime biopsies by 30%, and increased societal costs by 0.4%. Relative to the PSA test alone, the Stockholm3 with reflex thresholds of 1, 1.5 and 2 nanograms per ml, PSA levels had incremental cost-effectiveness ratio of 170,000, 60,000 and 6,000 € per quality-adjusted life year, respectively. The technology was cost effective.

Strengths and limitations

Using a lifetime horizon was 1 of the strengths of the study. The study is based on the Swedish healthcare system which limits translation of findings to the NHS setting.

Viste et al. (2020)

Study size, design and location

A longitudinal observation study (n=4784) comparing prostate cancer screening outcomes before and after introduction of Stockholm3 in Stavanger, Norway.

Intervention and comparator

Stockholm3 compared with PSA testing

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Key outcomes

After 12 months of introducing Stockholm3 in Stavanger, 97% (94 out of 97) of GP clinics did prostate cancer screening using Stockholm3. Out of the 4,787 people tested, 995 (20.8%) had a positive Stockholm3 risk score (Stockholm3 risk score=11% or more), while 1,387 (29.0%) had a positive PSA test result (PSA of 3 nanograms per ml or more). There was a 28% relative decrease in the number of tested people referred for further workup. Up to 520 out of 4,784 (11%) people who tested had a positive PSA but negative Stockholm3, and 128 out of 4,784 (3%) had negative PSA but positive Stockholm3 test. The proportion of biopsies positive for cancer that showed clinically significant prostate cancer increased from 42.1% (98/223) before implementation to 64.9% (185/285) after implementation of Stockholm3 in the Stavanger region. Correspondingly, both the number and the rate of clinically non-significant cancer decreased from 135 (57.9%) before implementation to 100 (35.1%) after implementation of Stockholm3. The cost saving of implementing Stockholm3 was estimated to be between 23% and 28% because of reduced number of unnecessary MRIs, sepsis and biopsies.

Strengths and limitations

One of the strengths of this study is the choice of outcomes which are relevant to the UK. This study showed a high acceptability among GPs in Norway. There is potential for differences in clinical practice between Norway and the UK. This potentially limits generalisation of these findings to the NHS.

Grönberg et al. (2018)

Study size, design and location

Prospective multicentre, paired diagnostic study assessing the performance of Stockholm3 and MRI in 532 men aged 45 to 74 years referred for prostate cancer workout in Stockholm (Sweden) and Oslo (Norway).

Intervention and comparator(s)

Combined Stockholm3 and MRI compared with MRI alone and systematic biopsy.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Key outcomes

The study showed that Stockholm3 reduced biopsies, decreased detection of Gleason grade 1 tumours, and maintained the detection of Gleason grade 2 or more tumours. Stockholm3 combined with MRI and systematic biopsy had an acceptable sensitivity (0.94; 95% CI 0.90 to 0.97) in detecting clinically significant prostate cancer with a Gleason grade score of 2 or more when compared with systematic biopsy in all people. Stockholm3 also reduced detection of Gleason grade 1 tumours by 30% and saved 38% of biopsies from being done. When Stockholm3 was combined with MRI or targeted biopsy and systematic biopsy, it improved detection of clinically significant prostate cancer by 10% compared with systematic biopsy alone. The combined strategy of only doing MRI or targeted biopsy in people with positive Stockholm3 showed similar sensitivity to detecting clinically significant prostate cancer compared with systematic biopsy alone, but decreased detection of clinically non-significant prostate with Gleason grade 1 score. Negative predictive value for Stockholm3 was 99% when both systematic and targeted biopsy were negative.

Strengths and limitations

This study explored different clinical scenarios of using Stockholm3 and the appropriate choice of outcomes which are also relevant to the UK. One limitation is that the study was not from the UK.

Bergman et al. (2018)

Study size, design and location

A study assessing the diagnostic precision of Stockholm3 compared to PSA testing in 547 men in Sweden.

Intervention and comparator(s)

Stockholm3 and PSA

Key outcomes

Biopsy was recommended in 62% of people who were referred for MRI after a positive Stockholm3 test. Of those having a biopsy, 58% had high grade cancer while only 6% had

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

low-grade cancer. A health economic analysis reported Stockholm3 with MRI followed by targeted and systematic biopsies had the lowest costs when compared with 1) PSA then systemic biopsy if PSA level is elevated (PSA level of more than 3 nanograms per ml), 2) PSA then MRI if PSA level is raised, then systemic biopsy if positive MRI results. The study showed the effectiveness of using a reflex testing model. Using nurses in the screening reduces visits to the urologists for patients that do not need a biopsy. The cost savings of implementing Stockholm3 was estimated to 17% because of reduced number of unnecessary MRIs, biopsies, and treatments.

Strengths and limitations

Some of the strengths for the study included study design, comparison of 3 strategies and including up to 10 primary care sites. One of the limitations is that the study was done outside the NHS. The study did not provide study design details.

Ström et al. (2017)

Study size, design and location

Prospective population-based diagnostic trial comparing Stockholm3 to PSA 3 nanograms per ml or more as indications for prostate biopsy in Stockholm, Sweden.

Intervention and comparator

Stockholm3 compared with PSA testing.

Key outcomes

The study looked at updating the Stockholm3 algorithm to improve its performance in prostate cancer diagnosis. When used as a reflex test for people with PSA levels of at least 3 nanograms per ml, Stockholm3 reduced the number of biopsies needed by 34% compared with using PSA levels alone, with equal sensitivity.

Strengths and limitations

One limitation was that the population was ethnically homogenous. This limits generalisation of the performance in other ethnic groups.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Grönberg et al. (2015)

Study size, design and location

Prospective, population-based, paired diagnostic trial of men aged 50 to 69 years for prostate cancer screening in Stockholm, Sweden.

Intervention and comparator

Stockholm3 compared with PSA testing.

Key outcomes

The Stockholm3 model performed better than PSA testing alone in detecting high grade cancers with a Gleason score of at least 7. Stockholm3 was also reported to reduce the number of biopsies by 32% and avoided up to 44% of benign biopsies.

Strengths and limitations

One limitation was that the population was ethnically homogenous. This limits generalisation of the performance in other ethnic groups.

Sustainability

The company claims the Stockholm3 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

- From PSA to Stockholm3, a Naturalistic Effectiveness Multipart Research Program: Study Part 1. ClinicalTrials.gov Identifier: NCT03381105. Status: recruiting. Indication: prostate cancer. Devices: PSA and Stockholm3. Estimated completion date: 31 December 2030. Country: Norway.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

- Validation of the Prostate Cancer Biomarker Stockholm3 for Improved Disease Detection and Classification in the Swiss Population. ClinicalTrials.gov Identifier: NCT05294627. Status: recruiting. Indication: prostate cancer. Devices: Stockholm3. Estimated completion date: 1 October 2022. Country: Switzerland.
- SEPTA Trial: Stockholm3 Validation Study in a Multi-Ethnic Cohort for ProsTAte Cancer. ClinicalTrials.gov Identifier: NCT04583072. Status: recruiting. Indication: prostate cancer. Devices: Stockholm3. Estimated completion date: 15 December 2022. Country: US.
- STHLM3 AS NorDCaP - a Follow-up Study of Men on Active Surveillance of Prostate Cancer. ClinicalTrials.gov Identifier: NCT04627948. Status: recruiting. Indication: prostate cancer. Devices: Stockholm3. Estimated completion date: 1 May 2023. Country: Sweden.

Expert comments

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

Four experts contributed to the development of this briefing. None of the experts had used the technology and only 2 were familiar with the technology. All experts noted that the technology is not currently used in the NHS. Two of the experts have done bibliographic research on the technology.

Intended setting

Views from experts varied around the most appropriate setting for Stockholm3. One expert stated that, considering the tests will be done in a reference laboratory, the test is best done by a urologist in a secondary care setting after the referral. In this case, they noted that about 50% of people who have a prostate-specific antigen (PSA) test would likely have a significantly raised PSA level and would go on to need the Stockholm3 blood test. Other experts stated the most appropriate point of introducing the technology would be at primary care at the outset of referral, recognising that it could be a useful screening tool but this would depend on initiative towards prostate cancer screening in the UK. One expert stated in addition to being used upfront in primary care, it could equally or perhaps more beneficially be used to follow up of people having investigations for suspected

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

prostate cancer and being discharged back to primary care with normal MRI or negative biopsies. The expert stated that the technology can then help to find an optimal point for people to be re-referred to secondary care for further investigations. Another expert stated they did not think it would gain use in primary care, but it would be used in secondary care in helping decision making for whether to biopsy after MRI for risk scores of 3 or below. This expert considered it unlikely to replace MRI as the primary screening tool.

Level of innovation

Two experts noted that there are a couple of blood-test tumour markers that have been published which include: the 4Kscore test; a prebiopsy test that incorporates 4 prostate proteins along with clinical information and the Prostate Health Index (PHI); a formula that combines all 3 forms of PSA. Prostate cancer antigen 3 (PCA3) is another urinary test that measures the concentration of PCA3 molecules in urine. Another expert noted that the PCA3, free or total PSA has been tried before but not routinely used.

Potential patient impact

Three experts said that the main patient benefit would be a possible reduction in unnecessary MRIs and biopsies in people with suspected prostate cancer. Avoiding the unnecessary invasive tests subsequently avoids the accompanying complications. One expert highlighted that the technology would mainly benefit all those aged above 50, particularly people over 70 and people with a family history of prostate cancer. Another expert said the technology is likely to benefit 2 groups of people who are normally disadvantaged by PSA testing alone. One of the groups in the 15% that present with normal PSA levels but may have prostate cancer, and a second group in the 2% that present with normal PSA levels but may have a fast-growing cancer. The other expert mentioned that younger people with smaller prostates who have harder to interpret MRIs were likely to benefit from the technology.

Potential system impact

One expert said the technology would lead to a small reduction in biopsies but would be unlikely to replace the use of MRIs. Another expert said the cost of the new technology would likely balance out against reduced diagnostic and treatment interventions, hospital visits, capacity and staffing in the NHS. Furthermore, the expert said the technology would

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

likely be cheaper and beneficial in the long run. Another expert suggested the resource impact of adopting the technology would likely be less or the same as the current standard of care. Several experts commented that there will be additional financial costs to providing equipment, staff and potential training for doing the Stockholm3 blood test which will be borne by the reference laboratory. One expert said that there would need to be a reference laboratory (United Kingdom Accreditation Service [UKAS] and International Organisation for Standardisation [ISO] accredited) with all the appropriate CE accredited tests both plasma proteins and molecular testing. Another expert said there would be no change in facilities except for additional logistics to get test and results communicated.

Safety

One expert said there was no potential harm of using the technology while another expert said that potential harms of the technology are similar to the harms of using PSA testing which would be underdiagnosis or overdiagnosis of prostate cancer.

Evidence

All experts recommended some additional research. One expert felt that there was a need for long term (over 15 years) longitudinal follow-up data in people who had testing with the technology and who did not have an MRI or biopsy. Another expert noted the need for research to see how the technology works in Black, Asian and minority ethnic populations. The expert also acknowledged there is an ongoing study in the US which might address this issue. One other expert recommended that additional research in the UK setting was needed and stated that the issue which would prevent adoption of the technology would be the additional expense and unclear benefits in the NHS setting. One expert mentioned the need for more clarity on cut-off levels.

Patient organisation comments

A representative from 1 patient organisation, Prostate Cancer UK, gave the following comments on Stockholm3.

The benefits of Stockholm3 are that it is convenient and results in quick or accurate care provision. Stockholm3 prevents harm from unnecessary biopsies. For people who are concerned about their prostate cancer risk, this technology could rule out any unnecessary worry of being referred into secondary care for an exploratory MRI scan or

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

biopsy. Stockholm3 test should be used in monitoring for those people who have a raised prostate-specific antigen (PSA) level but have had a negative biopsy.

Three subgroups who would benefit from the technology included people at higher risk but who have a lower PSA level than is currently needed for secondary care referral, those currently on active surveillance or those who have had a negative MRI or biopsy and who are referred back to primary care, and those referred for a biopsy with low risk and low-grade cancer.

The potential disadvantages of the technology might include possible side effects and practical difficulties, for users or carers. Patients getting a high-risk percentage score might experience a degree of stress with this outcome before moving into secondary care for an MRI. We would favour a strong education and support system being in place alongside Stockholm3 testing for those people who end up with a higher score and therefore are referred to secondary care. People with communication difficulties, learning difficulties and mental health problems using Stockholm3 need special consideration compared with the general patient population.

Regular use of this technology within the NHS could create delays within pathology which could delay a person's diagnosis.

NICE guidance on Stockholm3 would improve equal access to the technology for all people who might benefit from its use, throughout England.

At £350 per test cost price the health economics surrounding the test would not hold up for mass use within the NHS. The concerns with adopting the device are that there is no defined place in the pathway for this diagnostic to be rolled out and whether there is the infrastructure and workforce in place within pathology for a new test to be rolled out nationwide.

Expert commentators

The following clinicians contributed to this briefing:

- Dr John Bolodeoku, consultant chemical pathologist, JB consulting MDP Limited. Declared no conflicts of interest.

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

- Mr Aniruddha Chakravarti, consultant urological surgeon, The Royal Wolverhampton Hospitals NHS Trust. Declared no conflicts of interest.
- Mr Freddie Banks, consultant urologist, West Herts Teaching Hospitals Trust. Declared no conflicts of interest.
- Prof Sanjeev Madaan, consultant urological surgeon, Dartford and Gravesham NHS Trust. Declared no conflicts of interest.

Representatives from the following patient organisations contributed to this briefing:

- Prostate Cancer UK.

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.

ISBN: 978-1-4731-4689-1

© NICE 2023. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).