

MSAC Application 1781

**Risk assessment in prostate cancer
using the Stockholm3 multiparametric
blood test**

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

Stockholm3 is intended for males aged 45 to 74 years without a prior prostate cancer diagnosis with PSA levels of at least 1.5 ng/mL and above.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

The relevant patient group for Stockholm3 is men with no previous prostate cancer diagnosis, aged 45-74 that wish to assess risk of prostate cancer.

The patient journey begins with a request by the patient or a recommendation by the doctor to perform a check for prostate cancer providing the patient meets the initial screening criteria – between 45 and 74 years of age and no prior prostate cancer diagnosis. Two tubes of blood will be collected. If elevated PSA is detected, the Stockholm3 test is performed.

Provide a rationale for the specifics of the eligible population:

The National Health and Medical Research Council (NHMRC) has approved clinical practice guidelines developed by the Prostate Cancer Foundation of Australia (PCFA) and the Cancer Council Australia (CCA)¹. These are summarised below:

1. Men at average risk of prostate cancer who decide to undergo regular testing should be offered PSA testing every 2 years from age 50 to 69.
2. Men with a family history of prostate cancer who decide to be tested should be offered PSA testing every 2 years from age 40/45 to 69, with the starting age depending on the strength of their family history.
3. Men should be offered the opportunity to consider and discuss the benefits and harms of PSA testing before making the decision whether or not to be tested.

The more recent European Association of Urology² recommends the following:

- Ensure prostate cancer awareness among men.
- Counsel men on the benefits and harms of prostate-specific antigen (PSA) testing.
- Offer an individualised risk-adapted strategy for early detection to men aged >50 years with a life expectancy of 10+ years.

¹ Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel. Draft clinical practice guidelines for PSA testing and early management of test-detected prostate cancer. Prostate Cancer Foundation of Australia and Cancer Council Australia, Sydney (2016).

- Offer early PSA testing to men with an elevated risk of having prostate cancer such as men aged:
 - >45 years with a family history of prostate cancer
 - >45 years from high-risk ethnicities
 - >40 years carrying BRCA2 gene mutations.
- Limit testing when life expectancy suggests unlikely benefit.

The proposed population for Stockholm3 aligns with current clinical guidelines for PSA testing.

Stockholm3 is only performed if the PSA is ≥ 1.5 ng/ml.³ That is, intended place for the proposed technology 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 risk of having prostate cancer.

Stockholm3 is designed to identify the high-risk patients at PSA levels as low as 1.5 ng/ml while also identifying the low-risk men at PSA levels above 3 ng/ml.

Are there any prerequisite tests?

Yes

Are the prerequisite tests MBS funded?

Yes

Please provide details to fund the prerequisite tests:

Provide a response if you answered 'No' to the question above

Intervention

Name of the proposed health technology:

Stockholm3

Describe the key components and clinical steps involved in delivering the proposed health technology:

Stockholm3 is a multiparametric blood test that uses protein analyses, genetic analyses, clinical data and an algorithm to provide the Stockholm3 Risk Score estimating the risk of having clinically significant prostate cancer (csPC) (defined by a Gleason score ≥ 7 or an ISUP grade ≥ 2).

³ Nordström, T., Adolfsson, J., Grönberg, H. *et al.* Effects of increasing the PSA cutoff to perform additional biomarker tests before prostate biopsy. *BMC Urol* **17**, 92 (2017). <https://doi.org/10.1186/s12894-017-0281-8>

The Stockholm3 Risk Score uses the following inputs:

- clinical variables:
 - o age,
 - o first-degree family history of prostate cancer,
 - o previous prostate biopsy,
 - o use of 5 alpha reductase inhibitor.
- protein biomarkers:
 - o total PSA,
 - o free PSA,
 - o KLK2 (kallikrein-2),
 - o GDF15 (growth differentiation factor-15),
 - o PSP94 (prostatic secretory protein);
- and a genetic risk score based on a combination of several single nucleotide polymorphisms (SNPs)

The Stockholm3 test is carried out according to the following steps:

- 1) When a patient aged from 45 to 74 with no prior diagnosis of prostate cancer needs to be tested for prostate cancer, the doctor submits a request to perform PSA and the Stockholm3 test (applicable for patients who exhibit high PSA levels of 1.5 ng/mL or higher). The requesting physician provides essential patient information, including age, family history of prostate cancer, history of negative biopsy, and any use of 5-alpha reductase inhibitors, that will be used for Stockholm3 Risk Score calculation where relevant.
- 2) Two tubes of EDTA blood are collected. One of these tubes is centrifuged to separate the plasma, which is then transferred to a tube without additives. The other tube contains whole blood.
- 3) PSA (total PSA and free PSA) is measured in EDTA plasma... If PSA is ≥ 1.5 ng/mL, proceed to steps 4-9, otherwise PSA results are reported out.
- 4) DNA is extracted from the whole blood sample.
- 5) Genetic analysis is performed on the extracted DNA to identify single nucleotide polymorphisms (SNPs) using the ThermoFisher QuantStudio 12 K Flex instrument and a custom SNP chip from ThermoFisher.
- 6) The plasma is analyzed for PSP94 (prostatic secretory protein-94: marker of prostate cancer), GDF15 (growth differentiation factors: cancer marker) and KLK2 (kallikrein-2: protein associated with prostate tissue, marker of cancer aggressiveness) using a standard ELISA instrument. Reagents are provided by Biovendor.
- 7) Data from laboratory tests and clinical information are input into Stockholm3's proprietary algorithm, resulting in the Stockholm3 Risk Score.
- 8) The Stockholm3 Risk Score, presented as a rounded whole number, along with a recommendation, is communicated to the prescribing doctor.
- 9) The doctor interprets the Stockholm3 results, and based on these findings, may refer the patient to a specialist urologist.
 - a) If the Stockholm3 Risk Score is greater than 11, the patient is recommended to be referred to a urologist who will assess the need for follow-up diagnostics (e.g., MRI or prostate biopsy).

- b) For Stockholm3 Risk Score between 4 and 10, a follow-up within 2 years is recommended.
- c) If the Stockholm3 risk score is less than 4, the patient is classified as low risk, and a follow-up within 6 years is recommended.

Identify how the proposed technology achieves the intended patient outcomes:

The Stockholm3 test enhances prostate cancer diagnosis by complementing the traditional use of PSA testing in men without a prior prostate cancer diagnosis. Stockholm3 offers several advantages:

- **Reducing overdiagnosis:** Stockholm3 lowers the detection of low-grade, clinically insignificant prostate cancers, which shall help reduce unnecessary treatments and biopsies. In a diagnostic system with MRI, it reduces the need for MRI and biopsies. In a system without MRI, it reduces the need for biopsies.
- **Increased specificity of early cancer testing:** Stockholm3 helps identify those who truly need further evaluation and/or intervention.
- **Enhanced sensitivity of early cancer testing:** Stockholm3 can detect more cases of clinically significant prostate cancers and earlier. As a result of these improvements, the proportion of metastatic cancers at diagnosis is expected to decrease significantly.

Several studies support these claims:

- In an observational study (N=547), Bergman et al. (2018), the use of Stockholm3 (in reflex to elevated PSA ≥ 1.5 ng/mL) in conjunction with MRI reduced the need for biopsies by 32% and increased sensitivity by over 100% compared to PSA (with threshold for PSA ≥ 3 ng/mL) alone.
- Viste et al. (2020) conducted a clinically useful cross-sectional study (N=4784), that found using Stockholm3 with a PSA threshold of ≥ 1.5 ng/mL as a selection tool for MRI reduced MRI usage by 28%, biopsies by 34%, and clinically insignificant prostate cancers by 26%, while identifying 89% more clinically significant cases compared to a PSA threshold of ≥ 3 ng/mL for MRI selection.
- In a study (N=532) by Grönberg et al. (2018), Stockholm3 + MRI was compared to the combination of PSA and MRI and discovered a 62% reduction in unnecessary biopsies and MRIs, along with a 29% reduction in non-significant prostate cancers while maintaining a 92% sensitivity for clinically significant cases. In a population screening trial (N=12,750), Nordström et al. (2021), using Stockholm3 (in reflex to PSA ≥ 1.5 ng/mL) with a Stockholm3 Risk Score threshold of ≥ 15 as a selection tool for MRI reduced MRI usage by 36% without missing any clinically significant cancers compared to PSA with a threshold of ≥ 3 ng/mL as a selection tool for MRI.
- In a clinical utility study (N=12,406), Palsdottir et al. (2023, submitted manuscript), using Stockholm3 in reflex to PSA ≥ 1.5 ng/mL with a Stockholm3 Risk Score threshold of ≥ 11 as a selection for MRI, the rate of metastatic prostate cancer was reduced by 22%.

These findings show that Stockholm3 significantly improves the efficiency and accuracy of prostate cancer diagnosis and management.

Traditionally, prostate-specific antigen (PSA) has been employed to identify men with an elevated risk of developing prostate cancer. While PSA remains a valuable tool for monitoring patients' post-treatment, its sensitivity and specificity are insufficient for the early detection of prostate cancer. The responsibility for offering PSA testing falls on primary care physicians, who often grapple with uncertainty when determining whether to offer this blood test to asymptomatic men, as accurately highlighted in an article published in the Australian Journal of General Practice on March 3, 2023⁴. This underscores the need for novel approaches to early prostate cancer detection.

In this context, Stockholm3 emerges as a robust, non-invasive diagnostic solution. It estimates the risk of having a clinically significant prostate cancer in asymptomatic patients.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

Provide a response if you answered 'Yes' to the question above

The name Stockholm3 is registered with the Registered/Protected trademarks.

New Zealand:

Number of the international registration: 1607014

Number of the New Zealand trademark: 1186482

UK:

Trademark number: UK00918286899

US:

Trademark number: 1607014

Registration number: 6854609

Switzerland, Brazil and Turkey:

Trademark number: 1607014

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

⁴ <https://www1.racgp.org.au/ajgp/2023/march/prostate-specific-antigen-psa-testing-for-prostate#:~:text=Prostate%20cancer%20is%20the%20most,from%20prostate%20cancer%20in%202022>

Provide details and explain:

Stockholm3 is not intended for detection of prostate cancer relapse or as a follow-up test after active treatment or in active surveillance of men with a prostate cancer diagnosis, for patients younger than 45 or older than 74 years, nor for patients with PSA below 1.5 ng/ml.

For patients with unidentified primary prostate cancer this would be a *once off* diagnostic test. For patients with low risk of developing prostate cancer as defined by this test, repeat testing would be recommended after 6 years. For patients with normal risk, repeat testing would be recommended after 2 years. For elevated risk, repeat of Stockholm3 test is not required.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Stockholm3 is intended to be performed in a primary or secondary care setting. The following engagement is expected from medical personnel:

- a physician to recommend the test and interpret the results,
- a technician from a medical laboratory to perform DNA extraction, PCR and ELISA analyses, and the PSA analyses as well as for quality control and validation of the test and results,
- The laboratory should be under the supervision of a registered pathologist.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

The service can only be delivered by a National Association of Testing Authorities (NATA) accredited laboratory under the supervision of a pathologist.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

The proposed service should be restricted to a certified doctor (any specialty).

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

No

Provide details and explain:

The laboratory performing the analyses requires the standard ISO15189 accreditation. The test report comes with an easy to act-upon recommendation, no further training required.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:
(select all relevant settings)

- Consulting rooms
- Day surgery centre
- Emergency Department
- Inpatient private hospital
- Inpatient public hospital
- Laboratory
- Outpatient clinic
- Patient's home
- Point of care testing
- Residential aged care facility
- Other (please specify)

Specify further details here

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:

Provide a response if you answered 'No' to the question above

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

The relevant comparator for use of Stockholm3 as a reflex to PSA ≥ 1.5 ng/ml is the use of PSA testing alone.

Investigative: PSA ≥ 1.5 ng/ml + Stockholm3

Comparator: PSA ≥ 3 ng/ml

In Australia, current practice regarding prostate cancer testing involves offering PSA testing to eligible men aged 45 and older, following a recommended discussion on the benefits and risks of the PSA test. Although PSA testing is not mandatory, it is endorsed by various medical organizations, including the National Health and Medical Research Council (NHMRC), The Royal Australian College of General Practitioners (RACGP), and the Urological Society of Australia and New Zealand (USANZ).

List any existing MBS item numbers that are relevant for the nominated comparators:

66654 – Prostate specific antigen – quantitation in the monitoring of high-risk patients. For any particular patient, applicable not more than once in 11 months.

66655 - Prostate specific antigen—quantitation. For any particular patient, applicable not more than once in 23 months

Please provide a rationale for why this is a comparator:

Prostate specific antigen (PSA) is currently the only laboratory test that is used for non-invasive early detection of prostate cancer.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

- None – used with the comparator
- Displaced – comparator will likely be used following the proposed technology in some patients
- Partial – in some cases, the proposed technology will replace the use of the comparator, but not in all cases
- Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:

The current comparator will not be substituted. The Stockholm3 will be performed following PSA testing if PSA \geq 1.5 ng/ml.

Outcomes

(Please copy the below questions and complete for each outcome)

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator): (please select your response)

- Health benefits
- Health harms
- Resources
- Value of knowing

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Stockholm3 does not disrupt established patient management pathways but can offer significant benefits to specific patient groups.

For patients identified as low risk for clinically significant prostate cancer, the Stockholm3 risk score can be employed to safely extend the time between follow-up visits. This not only enhances the

quality of life for these individuals but also helps reduce anxiety associated with unnecessary medical interventions.

The utilization of Stockholm3 has a positive impact on the prognosis of newly diagnosed prostate cancers by enabling early detection of clinically significant cases and thus improving the prognosis.

Current guidelines from The Royal Australian College of General Practitioners recommend a prostate biopsy if an elevated PSA is detected. However, PSA testing alone has limitations in differentiating between clinically significant cancers and indolent ones. This often leads to a significant number of patients being over-diagnosed and unnecessary medical interventions for patients who may not benefit from immediate treatment. On the other hand, patients who are commonly diagnosed too late, when the cancer has already spread, stand to benefit from the early detection following Stockholm3.

By accurately identifying high-risk cases and distinguishing them from low-risk ones, Stockholm3 ensures that patients receive the appropriate level of care and intervention, ultimately leading to improved patient outcomes and a higher quality of life.

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator): (please select your response)

- Health benefits
- Health harms
- Resources
- Value of knowing

Stockholm3 is a blood test. As with most blood tests, there is a risk of false negatives or false positives, leading to unnecessary MRIs and biopsies and undetected potential cancers. However, the rate of false negatives and false positives is significantly lower than that of current diagnostics with PSA alone.

Conversely, the Stockholm3 test mitigates the health risks linked to the overdiagnosis of prostate cancers, a frequent issue in the diagnostic process based solely on PSA levels. This concern is a key reason why the PSA test alone is not universally recommended.

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator): (please select your response)

- Health benefits
- Health harms
- Resources
- Value of knowing

The Stockholm3 test is an additional cost in the prostate cancer testing phase, however this is offset by the anticipated reduction in MRI's and biopsies and the early detection and treatment of

cancers. This claim is supported by the significant body of evidence cited above involving over 90,000 men.

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):

Stockholm3 is not yet available in Australia.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention: (please copy the below questions and complete for each proposed item)

Proposed item details

MBS item number (where used as a template for the proposed item)	XXXX
Category number	6
Category description	Pathology services
Proposed item descriptor	Quantification of prostate cancer risk using Stockholm3, in patients aged 45 to 74 years of age and when the level of prostate specific antigen (PSA) quantitation is equal to or greater than 1.5 ng/ml. For any particular patient, applicable not more than once in 11 months
Proposed MBS fee	750 AUD Fee: \$750.00 Benefit: 75% = \$562.50 85% = \$637.50
Indicate the overall cost per patient of providing the proposed health technology	750 AUD
Please specify any anticipated out of pocket expenses	The difference between the proposed benefit and the scheduled fee may be an out-of-pocket expense if the service is not bulk-billed. This will be \$187.50 for a 75% benefit and \$112.50 for an 85% benefit.
Provide any further details and explain	

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

The Stockholm3 administration requires the following steps:

- Symptomatic or asymptomatic men aged 45 to 74 years who are eligible considered for PSA testing are informed about the risks and available tests – PSA and Stockholm3
- If the patient is considered for testing, blood sample is collected in 2 tubes – one is centrifuged to separate the plasma, which is then transferred to a tube without additives. The other tube contains whole blood. PSA analysis is performed, and if elevated (1.5 ng/mL or above), Stockholm3 is performed.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

As stipulated in the current edition of Australian PSA testing guidelines, in asymptomatic men without a diagnosis of prostate cancer, repeat PSA testing should be offered every 2-4 years from age 50 to 69 and in men over 45 with a family history of prostate cancer. Patients at high risk may now have a PSA test once a year. Repeat testing would be associated with a visit to a nurse for blood sample collection and/or a visit to the primary care physician.

Stockholm3, if implemented, will not affect the clinical management algorithm prior to initial testing with PSA.

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Use of Stockholm3 will not require additional healthcare resources compared to the use of comparator and/or current practice.

Explain what other healthcare resources are used in conjunction with the comparator health technology:

Use of PSA alone and PSA + Stockholm3 will require the same healthcare resources, time, number of visits. There is no difference here between Stockholm3 and the comparator.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Use of PSA alone and PSA + Stockholm3 will require the same healthcare resources, time, number of visits. There is no difference here between Stockholm3 and the comparator other than the additional cost of Stockholm3.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

This algorithm helps guide the management of patients with elevated PSA levels ($\text{PSA} \geq 1.5 \text{ ng/ml}$) and provides tailored recommendations based on their risk assessment:

- If PSA is elevated (threshold of $\text{PSA} \geq 1.5 \text{ ng/mL}$), Stockholm3 is performed. The outcome from the test is the Stockholm3 Risk Score, an integer (no decimals) between 1 and 99 and an accompanying recommendation.
 - o If Stockholm3 Risk Score is 1-3, a new test is recommended in 6 years.
 - o If Stockholm3 Risk Score is 4-10, a new test is recommended in 2 years.
 - o If Stockholm3 Risk Score ≥ 11 , referral to urologist and further diagnostic work-up (in accordance with clinical practice) is recommended.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:

As stipulated in the clinical guidelines from the Royal Australian College of General Practitioners and in the current edition of Australian PSA testing guidelines, clinical management after using the comparator health technology (PSA testing) is as follows:

PSA $\geq 3.0 \text{ ng/mL}$:

- The PSA test may be repeated if it is mildly elevated.
- The clinical guidelines from the Royal Australian College of General Practitioners stipulate that a specialist urological referral is indicated in case of elevated PSA, or a rapid rise of PSA and a prostate biopsy may be recommended.
- Multiparametric MRI (mpMRI) can be considered for risk assessment, which can increase the detection of clinically significant prostate cancers and reduce unnecessary biopsies but is not yet a standard practice. MRI can guide the decision for a biopsy but should be made in consultation with the patient.

PSA $< 3.0 \text{ ng/mL}$: the result is considered negative, no further action or follow up is required.

As stipulated in the guidelines from the Prostate Cancer Foundation of Australia, for PSA 2.0-2.9 ng/mL, there is still a measurable probability of missing clinically significant cancers. This is especially true for men with increased genetic risk of prostate cancer. However, current clinical recommendations neither necessitate, nor justify the need of further diagnostic investigation for these men, precisely due to insufficient specificity of the PSA.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

The implementation of Stockholm3 is expected to change use of healthcare resources:

- Fewer patients diagnosed with low-grade prostate cancer, resulting in lower resource utilization for visits, consultations, and active surveillance (Grönberg et al., 2015; Eklund et al., 2016; Bergman et al, 2018; Viste et al, 2020; Nordström et al., 2021; Palsdottir et al., 2023).
- More patients identified at clinically manageable stages of significant prostate cancer, leading to reduced resources needed for treatment, follow-up, and multidisciplinary conferences (Bergman et al, 2018; Viste et al, 2020).
- No need for repeat PSA testing at initial diagnosis, which saves time for medical personnel.
- Fewer prostate biopsies required in both settings with MRI before biopsy and compared to biopsies performed based on elevated PSA above 3 ng/mL alone, contributing to resource conservation (Grönberg et al., 2015; Eklund et al., 2016; Viste et al, 2020; Nordström et al., 2021; Söderbäck et al., 2023; Palsdottir et al., 2023; Vigneswaran HT et al., 2023).
- The need for risk assessment in patients with the controversial level of PSA at 1.5-2.9 ng/mL is addressed, reducing underdiagnosis and future cancer development.
- Patients at low risk of clinically significant cancer, based on Stockholm3 Risk Scores, require less frequent follow-up visits.
- The laboratory personnel will need to perform Stockholm3 test upon detection of PSA of 1.5 ng/ml or higher in the sample with associated time and sample management required.

Stockholm3 addresses the need for more accurate risk stratification in identifying patients who would benefit from treatment.

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Note: Please ensure that the diagrams provided do not contain information under copyright.

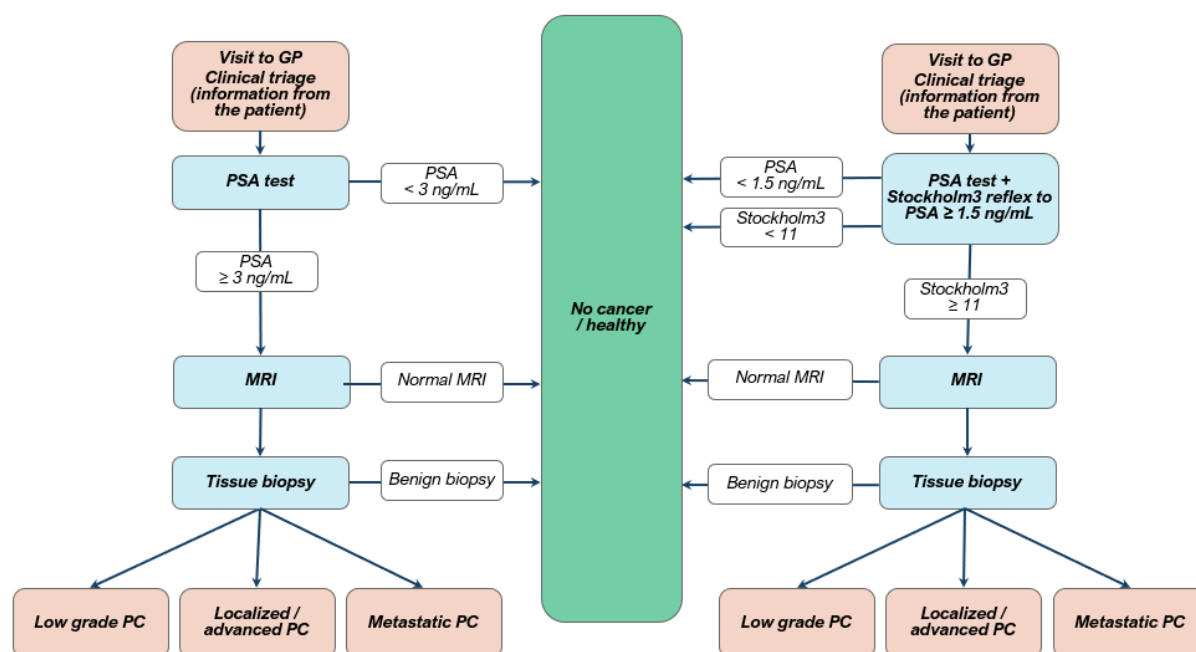


Figure 1. Clinical management algorithm without (on the left) and with (on the right) the proposed health technology. Stockholm3 is performed by the laboratory technician as reflex to PSA 1.5 ng/mL or higher with no intermediate visit or consultation with the requesting GP.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)? (please select your response)

- Superior
 Non-inferior
 Inferior

Please state what the overall claim is, and provide a rationale:

The overall claim is that PSA testing plus Stockholm 3 is superior to PSA testing alone in men without prostate cancer aged 45-74 years.

Stockholm3 as a reflex test to PSA ≥ 1.5 ng/ml presents an advanced risk assessment tool that can be employed to focus diagnostic procedures on clinically significant prostate cancer (csPC), reducing the overdiagnosis of low-grade cancers and allowing more efficient use of healthcare resources, compared to current PSA test alone with cutoff 3 ng/ml. These improvements can be achieved without disrupting the current care pathway, altering patient management, causing delays in diagnosis and referral, or necessitating additional medical visits.

The benefits of implementing Stockholm3 in the early diagnosis pathway include:

- Enhanced detection of clinically significant localized prostate cancer, which can result in a better prognosis for affected individuals.

- A reduction in the overdiagnosis of low-grade cancers, preventing unnecessary treatment and emotional stress for patients.
- Fewer cases of metastatic disease diagnosed at advanced stages, increasing the chances of successful treatment.
- Fewer follow-up visits for low-risk individuals, reducing the burden on both patients and the healthcare system.
- Lower resource requirements for follow-up visits and diagnostic procedures, such as MRI scans and prostate biopsies, for low-grade cancers. This leads to reduced healthcare costs and avoids overtreatment.
- Improved precision in the diagnostic workup, resulting in a lower level of stress and anxiety for men aged over 45 years who are concerned about prostate cancer.
- Addressing the need for the diagnosis and care of aggressive prostate cancer in patients with PSA levels between 1.5 to 2.9 ng/mL, who are currently at risk of underdiagnosis due to the accepted PSA alone with cutoff of 3 ng/ml.
- Overall cost savings in prostate cancer care, benefiting the healthcare system and patients.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

The choice to use Stockholm3 as a reflex test to PSA \geq 1.5 ng/mL aims to improve patient risk assessment, address access disparities, and enhance early detection of prostate cancer. Stockholm3 doesn't replace shared decision-making but complements PSA testing for selected individuals. It detects prostate cancer early, reducing the risk of metastasis and related harm, especially in patients with longer life expectancy. This comprehensive approach contributes to better screening and prevention, ultimately reducing the morbidity rate from this disease and preventing avoidable harm.

Identify how the proposed technology achieves the intended patient outcomes:

Stockholm3, used as a reflex test to PSA \geq 1.5 ng/mL, exhibits higher sensitivity and specificity for clinically significant prostate cancer compared to PSA alone (the comparator).

The sensitivity of PSA cutoff at 3 ng/mL is estimated to be in the range at 30-60% (Thompson et al., 2006⁵; Leal et al., 2018⁶). These results underline that using a PSA threshold \geq 3 ng/mL inevitably leads to a proportion of clinically significant prostate cancers (ISUP \geq 2) being missed. This issue has been recognized and emphasized in international recommendations, consensus papers, and highlighted in the guidelines from the Prostate Cancer Foundation of Australia. However, due to the lack of more sensitive non-invasive technology to complement PSA, lowering of the PSA cutoff

⁵ Ian M. Thompson, Chen Chi, Donna Pauler Ankerst, Phyllis J. Goodman, Catherine M. Tangen, Scott M. Lippman, M. Scott Lucia, Howard L. Parnes, Charles A. Coltman, Effect of Finasteride on the Sensitivity of PSA for Detecting Prostate Cancer, *JNCI: Journal of the National Cancer Institute*, Volume 98, Issue 16, 16 August 2006, Pages 1128–1133, <https://doi.org/10.1093/jnci/djj307>

⁶ Leal J, Welton NJ, Martin RM, Donovan J, Hamdy F, Neal D, Noble S, Lane A, Wolstenholme J. Estimating the sensitivity of a prostate cancer screening programme for different PSA cut-off levels: A UK case study. *Cancer Epidemiol.* 2018 Feb;52:99-105. doi: 10.1016/j.canep.2017.12.002. Epub 2018 Jan 4. PMID: 29278842.

has not been justified. With use of Stockholm3, the initial threshold for PSA to 1.5 ng/mL may be lowered to address the need for better identification of these cancers.

Stockholm3 is used as a reflex test after PSA \geq 1.5 ng/mL to allow for higher sensitivity compared to the PSA \geq 3 ng/mL threshold. The initial PSA analysis acts as a selection step, with Stockholm3 amplifying the sensitivity of early detection by incorporating information from total and free PSA as well as other protein and genetic markers, age and clinical data.

For some people, compared with the comparator(s), does the test information result in:

(please highlight your response)

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? Yes

Please provide a rationale, and information on other benefits if relevant:

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator? (please select your response)

- More costly
- Same cost
- Less costly

Provide a brief rationale for the claim:

The proposed reimbursement for Stockholm3 is 750 AUD. The cost of the comparator (PSA) is 37.30 AUD (MBS items 6660). Stockholm3 will be an additional cost to the MBS applicable for an estimated 40-60% of the population tested with PSA.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary (repeat columns as required).

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary (repeat columns as required).

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1	Primary care setting, a prospective population-based diagnostic study	Grönberg et al. Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study. The Lancet Oncology. 2015 The study was registered with ISCRTN.com, number ISRCTN84445406.	This publication from The Lancet Oncology focused on a prospective study of 58,815 healthy men aged 50 to 65 years. The results of this study concluded that the Stockholm3 test reduced benign biopsies by 44% and reduce low grade cancer by 17%, while maintaining a relative sensitivity of 100%.	http://dx.doi.org/10.1016/S1470-2045(15)00361-7	2015
2	Observational, registry study	Eklund et al. The Stockholm-3 (STHLM3) Model can Improve Prostate Cancer Diagnostics in Men Aged 50–69 yr Compared with Current Prostate Cancer Testing. European Urology Focus. 2016.	In European Urology Focus, a prospective study with 103,970 men (aged 50-69) showed Stockholm3 test's comparable sensitivity. Use of Stockholm3 could reduce biopsies by 53% (CI: 41-65%), sparing 76% negative biopsies and decreasing Gleason 6 cancers by 23% (CI: 6-40%), offering a substantial biopsy reduction while maintaining sensitivity.	https://www.eurofocus.europeanurology.com/article/S2405-4569(16)30156-0/fulltext	2016

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3	Observational study	Bergman M. et al, Structured care for men who want to get tested for prostate cancer, findings from Capio S:t Görän prostate cancer center. Lakartidningen. 2018.	Capio S:t Görän Prostate Cancer Center's structured model shortened the time from suspicion to treatment from 200 to 60 days, outperforming traditional care. Over 50% of biopsied men have treatment-requiring cancer, reducing overdiagnosis. The most cost-effective approach combines the Stockholm3 test with MRI and targeted biopsies.	https://pubmed.ncbi.nlm.nih.gov/30351440/	2018
4	A prospective, multicenter, paired diagnostic study	Grönberg H, et al. Prostate Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric Magnetic Resonance Imaging. European Urology. 2018 NCT02788825 (ClinicalTrials.gov)	First paper in literature evaluating biomarker with MRI (Primary analysis of N = 532), Strategies combining the blood-based Stockholm3 test and MRI-targeted biopsies can be used to inform biopsy decision making	https://www.sciencedirect.com/science/article/pii/S0302283818304470?via%3Dihub	2018
5	Observational clinical utility study	Viste et al. Effects of replacing PSA with Stockholm3 for diagnosis of clinically significant prostate cancer in a healthcare system - the Stavanger experience. SJPHC. 2020.	This observational clinical utility study (N=4,784) was used to compare outcome measures before and after the implementation of Stockholm3. Key conclusions: implementation of Stockholm3 i) increased the detection of clinically significant prostate cancer in biopsy by 89%, while at the same time ii) reduced overdiagnosis of non-significant (Gleason grade group 1) prostate cancer by 26% ii) decrease in MRI by 28%, decrease in biopsies by 34% and iii) led to a reduction in direct costs of 28%.	https://www.tandfonline.com/doi/full/10.1080/02813432.2020.1802139	2020

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6	Population-based diagnostic trial (STHLM3, N = 58,588)	Nordström T, et al. Identifying Prostate Cancer Among Men with Lower Urinary Tract Symptoms. Eur Urol Open Sci. 2021 NCT03377881 (ClinicalTrials.gov)	(Secondary analysis of N = 1,554) In men with lower urinary tract symptoms often related to enlarged prostate and benign prostatic hyperplasia, Stockholm3 is more predictive than PSA density in choosing men for further workup. In men with elevated International Prostate Symptom Score (IPSS) score (≥ 8), Stockholm3 can reduce biopsies by 53% with 95% sensitivity.	https://www.sciencedirect.com/science/article/pii/S2666168320363825?via%3Dihub	2021
7	Primary care setting, prospective, randomized, population-based, paired, clinical utility study (N=12,750)	Nordström et al. Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. The Lancet Oncology. 2021.	The Stockholm3 test, in combination with MRI, outperformed PSA in detecting clinically significant prostate cancer by 18%. Additionally, it reduced the need for MRI procedures by 36% and lowered unnecessary biopsies by 76% with a 22% higher sensitivity for detecting clinically significant prostate cancer than PSA 3 ng/mL and systematic biopsies.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00348-X/fulltext	2021
8	The cost-effectiveness study	Hao et al. Cost-effectiveness of Stockholm3 test and magnetic resonance imaging in prostate cancer screening: a microsimulation study. European Urology. 2022	Stockholm3 test as a reflex PSA ≥ 2 ng/mL: <ul style="list-style-type: none"> - was predicted to be cost effective and reduced unnecessary biopsies and MRIs; - is more cost effective than using a PSA threshold of ≥ 3 ng/mL for MRI without Stockholm3; - resulted in a 60% reduction in MRI compared with screening using PSA only. 	https://www.sciencedirect.com/science/article/pii/S0302283821022697	2022
9	Observational clinical utility study	Söderbäck et al. Improved prostate cancer diagnostics with a structured pathway including Stockholm 3 test, MRI and targeted perineal biopsies. Lakartidningen. 2023	A clinical utility study (N=5,439) at Capio S:t Görans Hospital in 2017 explored a nurse-led prostate cancer diagnostic pathway using Stockholm3 and MRI. Key findings: Stockholm3 lowered care costs by 28%, reduced MRI by 46%, doctor visits by 89%, and biopsies by 41%, surpassing other Swedish regions.	https://lakartidningen.se/wp-content/uploads/2023/08/23077.pdf	2023

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10	Observational clinical utility study	Palsdottir T. et al. (submitted manuscript)	The Capio PCC Model reduces MRI referrals by 43% compared to the conventional PSA threshold. It effectively detects clinically significant prostate cancer in individuals with PSA levels between 1.5 and 2.9 ng/ml. The streamlined diagnostic process leads to reduced lead times and cost savings of approximately 25%.	NA (Manuscript)	2023
11	SEPTA - prospective, multi-centered trial	Vigneswaran HT. et al. (Manuscript) NCT04583072 (ClinicalTrials.gov)	The SEPTA trial demonstrated Stockholm3's effectiveness in a racially diverse cohort, including Black, Hispanic/Latino, and Asian men. Results showed that Stockholm3 reduced unnecessary prostate biopsies by 45% compared to the standard PSA test without missing clinically significant cancer, with similar benefits across ethnicities.	NA (Manuscript)	2023

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).