REPORT

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SINGLE TECHNOLOGY ASSESSMENT

Stockholm3 test to estimate the risk of prostate cancer

NIPH
Norwegian Institute of Public Health

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Executive summary

Introduction

Prostate cancer is the most common form of cancer in men in Norway. In recent years, over 5,000 new cases of prostate cancer have been diagnosed each year. The Division of Health Services at the Norwegian Institute of Public Health was commissioned in May 2021 to conduct a single technology assessment (STA) of the Stockholm3 test to estimate the risk of prostate cancer. Stockholm3 is a multi-parametric blood test utilizing protein analyses, genetic analyses, clinical data, and an algorithm, to estimate the risk of having a clinically significant prostate cancer (defined as Gleason Score ≥ 7) in biopsy.

Objective

The objective of this STA was to appraise the evidence provided in the submission file from A3P Biomedical (submitter) concerning the use of the Stockholm3 test for estimating the risk of prostate cancer compared with using only prostate-specific antigen (PSA). We also appraised the cost-minimisation analysis and budget impact analysis provided by the submitter.

Method

The appraisal included assessment of the quality of the literature search, the submitter's summary of the prognostic accuracy of the Stockholm3 test, and the cost-minimization and budget impact analyses provided by the submitter. This implies that NIPH has not performed additional literature searches, any compilations of effects and safety, nor conducted any supplementary health economic analyses.

Results

Clinical effectiveness

The submitter included eight studies in their literature review. However, these eight studies do not represent eight independent samples. All studies compared Stockholm3 with PSA and were conducted in Sweden and/or Norway. None of the studies has been conducted by an independent research group.

All studies excluded patients with previous prostate cancer diagnosis. One of the studies was a randomized controlled trial. The others were prospective paired diagnostic studies or observational studies. The largest study (Grönberg 2015) which was a prospective, population-based, paired, screen-positive, diagnostic study with more than

58,000 participants reported that use of the Stockholm3 model could reduce the number of biopsies by 32% (95% CI 24–39), could avoid 44% (35–54) of benign biopsies, and reduce unnecessary biopsies by 37%. It was not feasible to pool the results from the studies presented in the submission, due to variations in designs and research questions.

Health economics

Testing with Stockholm3 entails an additional direct costs of [redacted] NOK per test. However, the submitted analysis indicates that it could be a cost-saving strategy compared to PSA testing alone. The analysis shows cost-savings of 1,400 NOK per man. The submitted budget impact analysis also indicates cost savings each year after implementation of Stockholm3.

Discussion

The documentation of the diagnostic accuracy provided by the use of Stockholm3 is considered to be uncertain. This is partly due to variability in the design and outcomes of the relevant studies which implied that it was not feasible to pool studies for overall assessments. Furthermore, none of the studies were conducted solely by independent researchers.

There are several substantial uncertainties in the health economic analyses. The major driver of the results are differences in the proportions of positive test results with the Stockholm3 test compared to those with PSA tests alone. Only non-published data are used in the analysis for estimating these differences. Assumptions in the analysis on the further diagnostic work-up, surveillance and treatment of patients after referral to urologists are also uncertain and mainly based on input from the clinical experts consulted by the submitter. Furthermore, the current practice in terms of diagnosis and treatment of prostate cancer varies and is under continous development. This makes it difficult to assess whether the analysis provides a relevant basis for clinical practice in the next coming years.

Based on the one-way deterministic sensitivity analyses that the provider has chosen to perform, the analyses indicate that Stockholm3 will still be a cost-saving alternative compared to the PSA strategy. However, if two or more of the parameters associated with substantial uncertainty in the model are changed simultaneously, Stockholm3 is no longer cost saving compared to PSA testing. The budget impact analysis is also associated with substantial uncertainty.

Conclusion

The clinical documentation submitted does not allow clear conclusions on to which extent a work-up which includes the Stockholm3 test will provide improved detection of clinically significant prostate cancer and avoiding unnecessary biopsies and cancer treatment compared to current clinical practice with PSA as the initial test.

The submitted cost-minimisation analysis indicates that Stockholm3 could be a cost-saving strategy compared to standard practice with PSA-testing. However, there are

substantial uncertainties in the structure and assumptions applied in the model, and the results of the analysis should therefore be interpreted in light of these caveats.

Sammendrag (Norwegian summary)

Innledning

Prostatakreft er den vanligste kreftformen hos menn i Norge. De siste årene har over 5000 nye tilfeller av prostatakreft blitt diagnostisert hvert år. Område for helsetjenester ved Folkehelseinstituttet fikk i mai 2021 i oppdrag å gjennomføre en hurtig metodevurdering av Stockholm3-testen for å estimere risikoen for prostatakreft. Stockholm3 er en multiparametrisk blodanalyse som bruker proteinanalyser, genetiske analyser, kliniske data og en algoritme for å estimere risikoen for å ha en klinisk signifikant prostatakreft (definert som Gleason Score ≥ 7) i biopsi.

Hensikt

Målet med denne metodevurderingen var å vurdere dokumentasjonen fra A3P Biomedical (innsender) angående bruken av Stockholm3-testen for å estimere risikoen for prostatakreft sammenlignet med bruk av kun prostataspesifikt antigen (PSA). Vi vurderte også den innsendte kostnadsminimeringsanalysen og budsjettkonsekvensanalysen.

Metode

Denne rapporten om Stockholm3-testen var en hurtig metodevurdering der vi vurderte dokumentasjonen mottatt fra innsenderen. Dette inkluderte vurdering av kvaliteten på litteratursøket, innsenderens sammendrag av den prognostiske nøyaktigheten til Stockholm3-testen, samt innsendt kostnadsminimerings- og budsjettkonsekvensanalysene. Dette innebærer at Folkehelseinstituttet ikke har utført ytterligere litteratursøk, sammenstillinger av effekter og sikkerhet eller utført supplerende helseøkonomiske analyser.

Resultater

Klinisk effekt

Innsenderen inkluderte åtte studier i sin litteraturgjennomgang, men disse åtte studiene representerer ikke åtte uavhengige utvalg. Alle studiene sammenlignet Stockholm3 med PSA og ble utført i Sverige og/eller Norge. Ingen av studiene er utført av en uavhengig forskningsgruppe.

Alle studiene ekskluderte pasienter med tidligere prostatakreftdiagnose. En av studiene var en randomisert kontrollert studie. De andre var prospektive kontrollerte diagnostiske studier eller observasjonsstudier. Den største studien (Grönberg 2015), en prospektiv, populasjonsbasert, parret, screen-positiv, diagnostisk studie med mer enn

58 000 deltakere rapporterte at bruk av Stockholm3-modellen kunne redusere antall biopsier med 32 % (95 % KI 24–39), kunne unngå 44 % (35–54) av benigne biopsier, og redusere unødvendige biopsier med 37 %. Det var ikke mulig å slå sammen studiene som ble presentert i dokumentasjonen, på grunn av variasjoner i design og forskningsspørsmål.

Helseøkonomi

Testing med Stockholm3 innebærer en ekstra direkte kostnad på [redacted] kroner. Den innsendte analysen indikerer imidlertid at Stockholm3 kan være en kostnadsbesparende strategi sammenlignet med PSA-testing. Analysen viser kostnadsbesparelser på 1 400 kroner per mann. Den innsendte budsjettkonsekvensanalysen indikerer også kostnadsbesparelser hvert år etter implementering av Stockholm3.

Diskusjon

Dokumentasjonen av den diagnostiske nøyaktigheten ved bruk av Stockholm3 anses å være usikker. Dette skyldes delvis variasjon i design og resultater av de relevante studiene som tilsa at det ikke var mulig å slå sammen studier for helhetsvurderinger. Videre var ingen av studiene utført bare av uavhengige forskere.

Det er flere vesentlige usikkerhetsmomenter i de helseøkonomiske analysene. En viktig driver av resultatene er forskjeller i andelen positive testresultater med Stockholm3-testen sammenlignet med de med PSA-tester alene. Kun ikke-publiserte data er brukt som grunnlag i analysen for å estimere denne forskjellen. Forutsetninger i analysen om videre diagnostisk vurdering, overvåking og behandling av pasienter etter henvisning til urolog er også usikre, og er i hovedsak basert på innspill fra kliniske ekspertene som innsender har konsultert. Dagens praksis når det gjelder diagnostikk og behandling av prostatakreft varierer og er under kontinuerlig utvikling. Dette vanskeliggjør en vurdering av hvorvidt analysen gir et godt bilde av klinisk praksis i de nærmeste årene.

De enveis deterministiske sensitivitetsanalysene som innsender har valgt å gjennomføre indikerer at Stockholm3 fortsatt vil være et kostnadsbesparende alternativ sammenlignet med PSA-strategien. Men, hvis to eller flere av parameterne knyttet til betydelig usikkerhet i modellen endres samtidig, er Stockholm3 ikke lenger kostnadsbesparende sammenlignet med PSA-testing. Budsjettkonsekvensanalysen er også forbundet med betydelig usikkerhet.

Konklusjon

Den fremlagte dokumentasjonen gir en viss støtte for at Stockholm3 testen har fortrinn sammenlignet med PSA når det gjelder påvisning av klinisk signifikant prostatakreft og å unngå unødvendige biopsier og kreftbehandling. Dokumentasjonen av effekt og sikkerhet er imidlertid usikker.

Den innsendte kostnadsminimerings-analysen indikerer at Stockholm3 kan være en kostnadsbesparende strategi sammenlignet med standard praksis med PSA-testing. Det er imidlertid betydelige usikkerhetsmomenter i dokumentasjonsgrunnlaget, strukturen

og forutsetningene brukt i modellen, og resultatene av analysen bør derfor tolkes i lys av disse usikkerhetsmomentene.

Preface

The Division of Health Services at the Norwegian Institute of Public Health (NIPH) was commissioned in May 2021 to conduct a single technology assessment of the Stockholm3 test to estimate the risk of prostate cancer. The single technology assessment was commissioned within the National System for Managed Introduction of New Health Technologies. The commissioner is comprised by the executive directors from the four regional health authorities in Norway.

In a single technology assessment, the technology (a pharmaceutical or a device) is appraised by NIPH based on documentation submitted by the company owning the technology, or their representatives ("the submitter"). The submitter in this assessment is A3P Biomedical.

In August 2021, NIPH initiated discussions with the company regarding their intent to submit documentation for the STA. In October 2021, the company sought input on their documentation, especially the health economic analysis, with NIPH emphasizing alignment with Norwegian clinical practice. In December 2021, the company submitted a cost-minimisation analysis indicating potential cost savings from implementing the Stockholm3 test. However, in early 2022, after review and consultation with experts, NIPH identified issues regarding assumptions about Norwegian clinical practice. NIPH informed the company about this in March 2022, leading to their intention to revise the documentation without a specified timeline. NIPH updated the commissioner on the situation. In April 2022, NIPH addressed additional questions from the company. In June 2022, the company indicated plans to submit revised documentation in autumn 2022. Finally, NIPH received revised documentation in February 2023, and accepted this in March 2023.

A detailed progress log is provided in Appendix 5.

Contributors

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- Jan Marcus Sverre
- Gunn Eva Næss
- Kjetil Brurberg /Jan Marcus Sverre (management contact person)

External clinical experts:

- Karol Axcrona, Senior Consultant, Unit of Urology, Akershus University Hospital

- Sven Löffeler, Senior Consultant, Department of Surgery/Unit of Urology, Vestfold Hospital Trust

Patient representative:

- Daniel Ask, Chairman, Prostatakreftforeningen (the Norwegian prostate cancer association)

We thank colleague Anna Stoinska-Schneider for internal review and comments to the report.

Conflicts of interest

All authors, external group members and reviewers have completed a conflict of interest form, and no conflicts of interest have been reported.

The NIPH is solely responsible for the content of this report.

Kåre Birger Hagen *Specialist director of Reviews and Health Technology Assessments*	Kjetil Brurberg *Department Director*	Geir Smedslund *Project Manager*

Glossary/list of abbreviations

Term/abbreviation	Explanation
cnsPC	Clinically non-significant prostate cancer
csPC	Clinically significant prostate cancer
DRE	Digital Rectal Examination
Gleason score	Grading system used to evaluate the aggressiveness of the cancer based on the microscopic appearance of prostate tissue samples, with higher scores indicating more aggressive tumors.
MRI	Magnetic resonance imaging
Multiparametric magnetic resonance imaging	Imaging technique that combines several different types of MRI sequences to provide detailed information about the prostate gland, allowing for improved detection and characterization of prostate tumors.
NIPH	Norwegian Institute of Public Health
NOK	Norwegian kroner
NoMA	Norwegian Medicines Agency
PSA	Prostate-specific antigen
PIRAD-S	Prostate Imaging-Reporting and Data System
RCT	Randomized controlled trial
STA	Single technology assessment
STHLM3	Stockholm3
T-stage	Refers to the stage of cancer determined by evaluating how far the tumor has spread beyond the prostate gland, with higher T-scores indicating more extensive local or distant spread of the cancer.

Introduction

Background

Prostate cancer in Norway

Prostate cancer is the most common form of cancer in men in Norway. In recent years, over 5,000 new cases of prostate cancer have been diagnosed each year (1).

Table 1. *Incidence, mortality and prevalence of prostate cancer 2013–2022 (2)**

Year	Incidence / year	Mortality	Prevalence
2022	5,490	**	61,645
2021	5,263	895	59,307
2020	5,122	958	56,969
2019	5,029	960	54,658
2018	4,960	928	52,380
2017	5,123	936	50,033
2016	5,326	965	47,514
2015	5,196	1,047	44,780
2014	4,970	1,093	42,128
2013	4,893	1,012	39,687

*The table is a modified version of the table provided in the annual report by the Norwegian Cancer Registry for 2022 (2)

**Mortality not available from the source.

The prevalence of prostate cancer has been rising steadily during the latest decade. There has also been an increase in the yearly incidence since 2018. This development can be seen in relation to the increase in the number of elderly people in the population. However, the number of people dying from prostate cancer has decreased in the same period. This implies that in recent years there is a substantial increase in the number of men who live with prostate cancer, and who need some form of follow-up for their illness.

In 2022, 46% of those diagnosed were younger than 70 years at the time of diagnosis (median age was 71 years). 54% of those diagnosed had localized prostate cancer, 29%

had a regional spread and 9% had distant metastases at the time of diagnosis, while the stage was unknown for 8% of the patients (2).

According to the annual report by the Norwegian Cancer Registry for 2022 (2), much of the increase in this period is due to more active diagnostic practice and surveillance of the disease, particularly because of increased use of the blood test of prostate specific antigen (PSA).

Diagnostic practice in Norway

PSA is an enzyme that is formed in the prostate, and normally a small proportion is found in the bloodstream. In various conditions affecting the prostate the PSA concentration in the blood increases. The PSA test is not an exact or specific test for the detection of cancer but may be an indication that further investigation is warranted.

Elevated PSA (the reference values depend on age) can also occur with benign prostatic hyperplasia (enlarged prostate) and prostatitis (inflammation of the prostate) (3). One major challenge with the diagnosis of prostate cancer in general is that approximately one third of the persons tested have clinically insignificant cancer that neither affects the person's function nor life expectancy (3;4). Unnecessary examinations give rise to the risk of complications and overtreatment and may affect the person’s longevity and quality of life.

Guidelines from the Directorate of Health describe the diagnostic work-up of patients with potential prostate cancer (5). According to these guidelines the purpose of the investigation of patients with potential prostate cancer is to secure the diagnosis and map the spread of the disease. When alternative treatment options are assessed, age, comorbidity, life expectancy and the risk of complications are taken into account. Investigation and subsequent treatment should be carried out by a specialist team with a particular interest in, and knowledge of prostate cancer.

Essential elements for the investigation and diagnosis are clinical examination with rectal palpation of the prostate; PSA measurement; biopsy according to current national guidelines; and multiparametric MRI which should preferably be taken before biopsy.

If the diagnosis is confirmed histologically, based on PSA value, histology (Gleason score, i.e., the most common prostate cancer grading system) and assessment of T-stage, it must be supplemented with investigations for skeletal metastases and locoregional lymph node metastases for intermediate and high-risk patients. Diagnostic imaging in high-risk patients include MRI with metastasis protocol of the pelvis and skeleton and possibly skeletal scintigraphy.

Description of the Stockholm3 test and patient population

The text in *italic* is directly copied from sections of the documentation submitted by the company.

Descriptions of the Stockholm3 test

"Stockholm3 is a multi-parametric blood test utilizing protein analyses, genetic analyses, clinical data, and an algorithm, to estimate the risk of having a clinically significant prostate cancer (csPC) (defined as Gleason Score ≥ 7) in biopsy."

"Stockholm3 uses input from protein markers (total PSA, free PSA, PSP94, GDF15, KLK2) and genetic markers (101 single nucleotide polymorphisms) as well as clinical markers (age, previous biopsy, family history of prostate cancer, use of 5 alpha reductase inhibitors) and a proprietary algorithm to calculate a risk for clinically significant prostate cancer."

"The main outcome from the health technology is a risk score (Stockholm3 Risk Score) which is an estimate of the risk of having a csPC in biopsy. The risk score is between 0-100. From a practical point of view, the health technology is a simple blood test, i.e., the doctor orders a Stockholm3 (as a reflex to PSA) the same way she would order any other blood-based test, e.g., PSA".

Implications of introducing the Stockholm3 test

"Stockholm3 will not change the patient pathway regarding prostate cancer diagnostics. The health technology is intended to replace one blood test (PSA) with another (Stockholm3) in a clinical situation. Such a use of this new technology will not drive care and is not intended as a tool for population-based screening in Norway. There will be no change in the organization of the health service, spatial requirements, monitoring, follow-up, and administration. The referring doctor will however need to be informed to replace PSA with Stockholm3 when ordering a prostate cancer test for men not previously diagnosed with prostate cancer. Thanks to the clear recommendation given to the referring doctor, no extra training to evaluate the Stockholm3 test result is typically needed. The urologist will need to be informed about the Stockholm3 test outcomes and specifically that men with PSA < 3 ng/ml can be positive on Stockholm3. In addition, the total healthcare costs can be reduced, primarily by reducing unnecessary magnetic resonance imaging (MRIs) and biopsies. Introducing the new technology will not have any negative consequences for vulnerable patient groups."

Comments by NIPH

The scope, organizational aspects, and content of diagnostic approaches to potential prostate cancer in Norway is currently under discussion and development. The potential consequences of introducing Stockholm3 test in a clinical environment which is under development is therefore difficult to foresee. Please see the related comments on these issues from the consulted clinical experts in Appendix 1.

According to the submitter it should be noted that the Stockholm3 test will be introduced as an additional (reflex) test based on the results of the initial PSA test. This contrasts to the implications of introducing the Stockholm3 test described above "*The referring doctor will however need to be informed to replace PSA with Stockholm3 when ordering a prostate cancer test for men not previously diagnosed with prostate cancer."*

At the time of submission (February 2023) the company stated that the Stockholm3 test was in use in the Stavanger region with approximately 3,000 patients yearly at a cost of approximately NOK 7 million. However, during the early spring of 2023, Stavanger University Hospital decided that the Stockholm3 test should not be part of the routine investigations at the hospital for financial reasons. It is of interest to note that Stavanger is the region with the highest rate of MR exams of the prostate in Norway in 2022. In addition, there has been a clear increase in this rate during the period 2020–2022 (6). To what extent this development is related to the use of Stockholm3 in the region is unclear.

Description of patient population
"The relevant patient group for Stockholm3 is men with no previous prostate cancer diagnosis, aged 45-69 who want to assess risk of prostate cancer".

Comments by NIPH
Norwegian guidelines state that screening with PSA testing is recommended only for men with genetic predisposition (7). PSA should not be taken to detect early cancer in men who are not candidates for curative local treatment due to old age, depending on biological age, severe comorbidity or life expectancy below 10–15 years (7). The age cut off for testing with Stockholm3 (45–69 years) for men with no previous cancer diagnosis may be regarded as relevant.

PSA testing is still common in clinical practice. Current Norwegian guidelines (8) on PSA testing in men with no symptoms or known risk recommends that decisions on PSA testing should be made in consultation with a physician and be based on sober information about the potential pros and cons of such testing. The patient population described by the submitter as relevant for Stockholm3 testing are those in the age group 45-69, "who wants to assess the risk of prostate cancer" is broad and potentially without a clear clinical rationale or indication for testing (i.e., signs, symptoms, DRE findings, familial history, etc.)

The submitter's description of the patient population relevant for testing implies that Stockholm3 testing of patients 70 years and above with, or without clinical indications will not be candidates for the Stockholm3 test. This should be seen in context of the finding that the median age at the time of prostate cancer diagnosis in 2021 was 70 years. This implies that a substantial proportion of those diagnosed with disease (those above 70 years of age) would not have been candidates for initial testing with the Stockholm3-test had this been available.

Objective

In February 2023 A3P Biomedical provided documentation for an STA of the Stockholm3 test, and NIPH has assessed the submitted documentation.

The objective of the current report was to appraise the evidence provided in the submission file from A3P Biomedical (submitter) concerning the use of Stockholm3 test for estimating the risk of prostate cancer. We also appraised the cost-minimisation analysis and budget impact analysis provided by the submitter.

Process and input from clinical experts and patient representative

This report is based on the company's submission followed by NIPH's comments to the company's input when appropriate. As a part of the assessment, NIPH has consulted clinical experts appointed by the regional health authorities. This is related to the current Norwegian clinical practice, and the data input and assumptions which provide the basis for the health economic analyses.

The clinical experts had several comments to the commission itself, and input regarding the clinical practice in Norway. They have provided perspectives and opinions in a separate document attached in this report (see Appendix 1).

The patient representative provided input via a short questionnaire (see the patient perspective domain).

Assessment of clinical efficacy and safety

Methods

The submitter provided the following PICO for their systematic literature search:

- Population: men, aged 45–75 years with no previous prostate cancer diagnosis.
- Intervention: Stockholm3 for detection of clinically significant prostate cancer[1]
- Comparator: PSA alone for detection of clinically significant prostate cancer
- Outcomes: unnecessary biopsies (specificity), identification of clinically significant prostate cancers (sensitivity), mortality, quality of life, cost-effectiveness ratios and cost outcomes

Assessment of the search strategy

The search as it appears is potentially inadequate. This is because there is too much use of delineation in the overall search strategy in the form of the Boolean operator, AND. By ANDing both Stockholm3, the antigen and prostate cancer and telling the database that all three of these components must be in either the title or the abstract, there is a risk of missing studies that, for example, only mention one or two of these components in the title and abstract. When searching for a topic where we assume there will be few matches, it is always more appropriate to only search for one term. In this case it would be "Stockholm3". By doing so, we tell the database that we want to find all studies that contain "Stockholm3" in either the title or abstract. Thereby, we would get a slightly larger number of hits since we do not limit further. However, on such a small topic, this would be justifiable, since the amount of hits will presumably be small both with and without delineation. It is not likely that the submitter has missed studies in this search, since there are presumably few in the first place, but it is likely that there might be a few. This may be important because there are so few hits overall. The search, executed during August and September 2021, is also too old as it appears now.

[1] Defined as Gleason Score 7 or above

Description of the included studies

The submitter included eight studies in their literature review. All studies compared Stockholm3 with PSA and were conducted in Sweden and/or Norway. The number of study participants ranged from 500 to almost 60,000 in each study. Most participants were from Stockholm, but there were few participants from Oslo (n=236) and from Tønsberg n=1369 (Grönberg 2018). Only 272 participants were from the study in Värmland (Walden 2022). Some of the participants were "screening by invitation," and others requested cancer testing themselves. All studies excluded patients with previous prostate cancer diagnosis. One study was a randomized controlled trial. The others were prospective paired diagnostic studies or observational studies.

Comments by NIPH

The age span of the population in the included studies deviates somewhat from what the submitter has described as the target population for Stockholm3 testing, which is men with no previous prostate cancer diagnosis, aged 45-69 that want to assess risk of prostate cancer. Four of the studies included men older than 70 years, and two studies included men younger than 45 years.
Table 2 lists the eight included studies.

Table 2. *Included studies*

Study (acronym, ID no.) Type of design	Reference	Population	Intervention	Comparison
Study 1: STHLM3	Grönberg, The Lancet Oncology 2015 (Gronberg et al., 2015)	Men, aged 50-69 years	Stockholm3	PSA
Study 2: STHLM3 MRI Phase I	Grönberg, European Urology, 2018 (Gronberg et al., 2018)	Men, aged 45-75 years	Stockholm3	PSA
Study 3: Capio	Bergman, Läkartidningen, 2018 (9)	Men, aged 33-84	Stockholm3	PSA
Study 4: Stavanger	Viste, Scandinavian Journal of Primary Health Care, 2020 (10)	Men, aged > 40	Stockholm3	PSA
Study 5: STHLM3 MRI Phase II	Nordström, The Lancet Oncology, 2021 (Nordstrom et al., 2021a)	Men, aged 50-74	Stockholm3	PSA
Study 6: Värmland	Walden, manuscript, 2021 (Waldén, 2021)	Men, aged 49-70 years	Stockholm3	PSA
Study 7: STHLM3 vs Clinical Practice	Eklund, European Urology Focus, 2018 (Eklund et al., 2018)	Men, aged 50-69	Stockholm3	PSA
Study 8: STHLM3 and LUTS	Nordström, European Urology Open Science, 2021	Men, aged 50-69	Stockholm3	PSA

	(Nordstrom et al., 2021b)		

A study by Walden et. al. (2021) was listed as an unpublished manuscript. We located the published study (Walden et. al. 2022). When we contacted the submitter, they stated that we should use the published article. The submitter stated that "In most of the studies, specificity was used as the primary outcome and sensitivity as the secondary." But this does not accord with their Table 10 in the submitted report. The table lists primary outcomes in most studies as both number of performed prostate biopsies (specificity) and number of detected clinically significant prostate cancers (sensitivity).

As shown in Table 3, results from several ongoing studies are expected during 2023. One of them (STHLM3 Mortality study) will provide data on mortality, which has so far been lacking. There is also one ongoing study: The SEPTA trial (NCT04583072) with expected end date June 15th, 2023. Another ongoing study from Aarhus, Denmark (NCT03431753) had expected end date December 31st, 2001.

Table 3. *Expected publications*

Study	Description	Expected availability
STHLM3 MRI clinical study	Randomized study with 12,750 men aged 45-74 years invited for screening comparing PSA followed by MRI with Stockholm3 followed by MRI. Main results from the study have been published in the New England Journal of Medicine (Eklund et al., 2021) and The Lancet Oncology (Nordstrom et al., 2021a).	Additional results from this major study are expected during 2023
STHLM3 Mortality study	Follow-up study from STHLM3 with comparison of prostate specific mortality in men taking one Stockholm3 test versus men not participating. 60,000 men invited for STHLM3 study followed up for mortality 6-8 years later. Unpublished initial results indicate that testing with Stockholm3 significantly reduces prostate cancer specific mortality.	Expected publication 2023
Norwegian studies	Follow-up studies from Stavanger University Hospital on the implementation of Stockholm3 in clinical practice including studies on: From PSA to Stockholm3; The impact of the change of diagnostic tool on the diagnosis of clinically significant prostate cancer in regular general practice o Comparison of the diagnosis of prostate cancer among men between 40 and 70 years of age in 2015/2016 (based on PSA) versus 2019/2020 (based on Stockholm3) o Comparison of the diagnosis of prostate cancer among men of 70	Expected publication 2023 Expected publication 2023

	years of age and older in 2015/2016 (based on PSA) versus 2019/2020 (based on Stockholm3)	Expected publication 2023
	The effect of replacing PSA with Stockholm3 on GPs' compliance with test results. A comparison of the GP's follow-up of patients with positive PSA test in 2015/2016 versus positive Stockholm3 test in 2019/2020.	Expected publication 2023
	The risk of clinically significant prostate cancer in patients with positive Stockholm3 test and negative MRI.	Expected publication 2023
	Improved follow up routine of men on active surveillance for low-risk prostate cancer using Stockholm3 (Multi-center study)	
STHLM3 MRI Health economic study	Pre-print manuscript shows that screening with Stockholm3 followed by pre-biopsy MRI improves the precision and is health economy viable compared to PSA + MRI.	Expected publication early 2022

Risk of bias and applicability concerns

The QUADAS-2 assessments showed that no study had low risk of bias in all domains, as several of the studies had risk of bias related to patient selection. There was risk of bias for patient selection in four studies (Grönberg 2018, Bergman 2018, Viste 2020, Walden 2022) because of lack of randomization. Also, there were risk of bias for applicability concerns in three studies (Grönberg 2015, Nordström 2021, Walden 2022).

The eight included studies do not represent eight independent samples. The STHLM3 studies involve the same cohort. Among the 39 unique authors of the eight included studies, one (Tobias Nordström) has authorship of seven, Henrik Grönberg is among the authors of six. Markus Aly and Martin Eklund are listed as authors of five of the articles. The samples from Värmland (Walden) and from Stavanger (Viste) are independent from the STHLM cohort, but no study has been conducted solely by independent researchers.

In the article by Walden et al (2022) the authors stated: "The Karolinska Institutet collaborates with A3P Biomedical in developing the technology for the Stockholm3 test. Henrik Grönberg, Martin Eklund, and Tobias Nordström report owning shares in A3P Biomedical. The upcoming SEPTA trial conducted in the USA, is also sponsored by Karolinska Institutet with Henrik Grönberg listed as responsible party (ClinicalTrials.org). Also, the ongoing trial from Aarhus lists Karolinska Institutet as collaborator at ClinicalTrials.org.

Results

Comments by NIPH

It was not feasible to pool the studies presented in the submission due to variations in designs and research questions. Some studies included participants who were screened by invitation, while other studies included participants who requested cancer testing. Some of the studies were based on the same participant samples. The studies report results in different ways (e.g., area under curve, percent reduction in unnecessary biopsies, percent increase in detected cancers, sensitivity) which prohibits overall summaries of results based on these studies. We therefore present the main results from each of the studies separately based on the submitted documentation).

Study 1: Grönberg et al., 2015 (STHLM3) N=58 818
Detection of cancer Gleason>=7: AUC was 0.56 (0.55-0.60) for PSA alone and 0.74 (0.72-0.75) for Stockholm3.
At the same level of sensitivity as the PSA test using a cut-off of ≥3 ng/mL to diagnose high risk prostate cancer, use of the Stockholm3 model could reduce the number of biopsies by 32% (95% CI 24–39), could avoid 44% (35–54) of benign biopsies, and reduce unnecessary biopsies by 37%.

Study 2: Grönberg et al., 2018 (STHLM3 MRI Phase I) N=532
Compared with PSA + MRI, Stockholm3 + MRI reduced the number of unnecessary biopsies with 56% with a relative sensitivity of 92%.

Study 3: Bergman et al., 2018 (Capio S:t Göran Real-life) N=547
Compared to PSA≥3, Stockholm3 reduced biopsies with 32% (from 34% of tested to 23% of tested) and increased sensitivity by more than 100% (8% positive cases versus 3%).

Study 4: Viste et al., 2020 (Stavanger Real-Life) N=4784
The number of csPC increased from 98 before to 185 after the implementation of the Stockholm3 test. In the same time period, the number of cnsPC decreased from 135 to 100. These changes are statistically significant. The proportion of biopsies positive for cancer that showed csPC increased from 42.1% (98/233) before implementation to 64.9% (185/285) after implementation of Stockholm. Correspondingly, the proportion of cnsCP decreased from 58% (135/233) before implementation to 35% (100/285) after implementation of Stockholm3.

Study 5: Nordström et al., 2021 Lancet (STHLM3 MRI Phase II) N=12 750
AUC for csPC was 0.76 for Stockholm3 and 0.60 for PSA. Compared to PSA + MRI, Stockholm3 (0.15) + MRI provided identical sensitivity to detect csPC and led to a reduction of MRI with 36% and unnecessary biopsies with 18%. Compared with screening using PSA and systematic biopsies, Stockholm3 (0.15) + MRI provided identical sensitivity to detect csPC and led to a reduction of unnecessary biopsies of 76%.

Study 6: Walden et al., 2021 – (Värmland Real-life) N=272

Compared with using PSA + MRI (MRI strategy) Stockholm3 (without MRI) found more (32 versus 30) clinically significant prostate cancers while reducing the number of clinically non-significant prostate cancers from 35 to 27 (23% reduction) and the total number of biopsies from 123 to 89 (28% reduction).

Study 7: Eklund et al., 2016 (STHLM3 vs Clinical Practice) N=47 688 + 56 282

With the same sensitivity for Gleason Score ≥7 prostate cancers as in CPT, Stockholm3 was estimated to reduce the number of biopsies by 53% (95% confidence interval [CI]: 41–65%). Moreover, Stockholm3 would have reduced the number of benign biopsies by 76% (95% CI: 67–81%) and Gleason Score 6 cancers by 23% (95% CI: 6–40%). The overall proportion of biopsies detecting Gleason Score ≥7 cancers with CPT was 19% compared with an estimated 41% with Stockholm3.

Study 8: Nordström et al., 2021 European Urology Open Science (STHLM3 and LUTS) N=4588

This is a post hoc analysis of a population-based diagnostic trial (Grönberg et al 2015, STHLM3, n = 58,588). The use of Stockholm3 with a cut-off of 0.11 would result in decreasing the detection of ISUP 1 tumours by 42% (n = 123 undetected ISUP grade 1 tumours). The AUC of the Stockholm3 test was 0.77 for the detection of significant prostate cancer.

Health economic assessment

Methods

Introduction and presentation of the chosen analysis method

The main aim of any health economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration. When the evidence of effectiveness suggests that the new intervention has a better effectiveness while also being more costly than current practice, one should consider whether the potential incremental costs of implementing the intervention are reasonable in relation to the health benefits gained. This is usually assessed by conducting an incremental analysis in which the differences in costs between an intervention and its comparator are compared with differences in benefits. The recommended unit for measuring health benefits in Norway is quality-adjusted life-years (11).

In cases where it can be shown that the intervention is not less effective than the comparator, a cost-minimisation analysis can be used (12). The submitter has chosen a cost-minimisation analysis method based on the argument that this condition is fulfilled.

Comments by NIPH to the health economic method chosen by the submitter: cost-minimisation analysis

The submitted clinical documentation provides some support that the Stockholm3 test may be at least as effective as PSA regarding the detection of clinically significant prostate cancer and avoiding unnecessary biopsies and cancer treatment. As such, there is to some degree a rationale for performing a cost-minimisation analysis.

However, the external validity, for example to what extent it can be claimed that the comparator arms in the clinical trials, and the work-up and treatment of patients in these trials are adequate presentations of current Norwegian clinical practice is questionable. Furthermore, it should be noted that none of the clinical trials presented in the submitter's documentation have been used as basis for the clinical input in the submitted cost-minimisation analysis.

Structure of the submitted cost-minimisation analysis and patient pathway

According to the submitter, men at risk with an initial threshold PSA value of 1,5 ng/ml or above will get Stockholm3 as a reflex test (test performed subsequent to initial test results) in the Stockholm3 strategy. The prescriber of Stockholm3 is typically a general practitioner, who also prescribes the initial blood test for PSA analysis. If the age adjusted Stockholm3 test is found to be positive, the man will be referred to a urologist for further assessment. According to the submitter, in the standard practice pathway, the men at risk will have a PSA test. If the PSA is positive in line with the age-adjusted PSA thresholds, the man will be referred to a urologist. After this selection, the health care pathway is the same in the intervention and the comparator path, i.e., that a proportion of men will go through MRI, a portion of these will have a biopsy, and then a proportion of these will go through cancer treatment. See the care pathway in Figure 1.

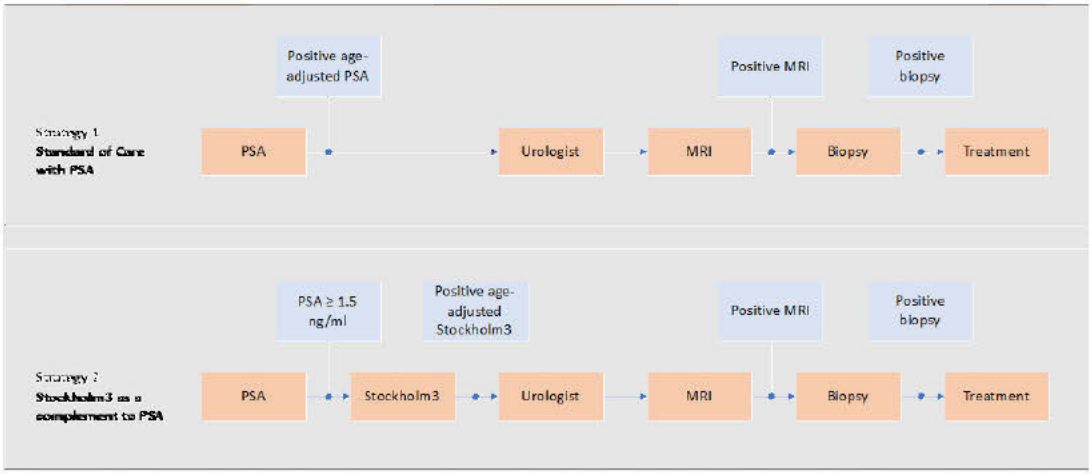

Figure 1. *The submitted patient pathway for Stockholm3 and standard practice with PSA*

Comments by NIPH on the structure of the cost-minimisation analysis and patient pathway

As presented above, it is assumed that the health care pathway is the same for the intervention and the comparator path after the patient has been referred to a urologist. However, based on feedback from the clinical experts, it is likely that steps in the pathways presented in Figure 1 does not fully reflect current clinical practice. This implies that the consequences of e.g., PSA density, and/or velocity measurements on decisions for further investigations has not been considered.

Population in the submitted analysis

The population in the analysis is men between 45 and 69 years without any previous prostate cancer diagnosis who are at risk of having prostate cancer.

Comments by NIPH on the population

According to the consulted clinical experts this age range is in line with general recommendations that healthy men above 70 years of age should not be tested with PSA.

Clinical effectiveness in the submitted analysis

The clinical effectiveness in the analysis is based on the real-life study conducted in the Stavanger region of Norway (10), as well as non-published real-life data from the Stavanger region. This data include analysis of 16,417 consecutive measurements from Stavanger from 2017 to 2022.

According to the submitter the difference in effectiveness in analysis is that Stockholm3 more correctly identifies those who are not at risk of clinically significant prostate cancer, thus a smaller proportion of men will have a positive Stockholm3 test than with PSA test only. Thus, fewer patients will go through subsequent examinations and cancer treatment.

In the analysis the submitter has age-adjusted values for what is considered positive Stockholm3 test for various age-levels. The age-adjusted threshold for positive PSA is taken from the clinical guidelines (13). See the age adjusted thresholds of positive tests and proportions of positive tests in Table 4.

Table 4. *Age adjusted thresholds of positive tests and proportions positive tests*

Direct health care resource utilization and clinical input	Proportion (%) (used in model)	Source (default value)
Proportion PSA ≥ 1.5	44%	Internal A3P analyses of 16,417 consecutive measurements from Stavanger from 2017 to 2022
Proportion positive PSA		
Age 45-49, PSA ≥ 2.5	6%	
Age 50-59, PSA ≥ 3.5	13%	
Age 60-69, PSA ≥ 4.5	18%	
Proportion positive Stockholm3		
Age 45-49, Stockholm3 ≥ 11	22%	
Age 50-59, Stockholm3 ≥ 15	25%	
Age 60-69, Stockholm3 ≥ 23*	16%	

*In the submission file it is stated ≥ 20 and in the analysis in Microsoft Excel it is ≥ 23.

Men with positive tests, either based on PSA or Stockholm3 test will all be referred to urologists. It is assumed that the further care pathway and the distribution of prostate cancer risk groups are the same regardless of the initial test that was used.
All assumptions on proportions on further work-up and treatment are based on clinical expert opinion. See
Table 5.

Table 5. *Proportions of positive tests and examinations in the further care pathway*

Direct health care resource utilization and clinical input	Proportion (%) (used in model)	Source (default value)
Proportion of patients referred to MRI by urologist	80%	NIPH expert input*
Proportion of positive MRIs	40%	Expert input
Proportion of positive biopsies	50%	Expert input
Proportion of biopsies leading to sepsis	0.25%	NIPH expert input*
Proportion of biopsies leading to re-biopsy	3%	NIPH expert input*

Comments by NIPH on clinical effectiveness and assumptions on subsequent examinations

The clinical input in the analysis is based on a real life study conducted in the Stavanger region of Norway (14), as well as non-published real-life data from Stavanger region.

It is a major limitation that the relevant data from this Stavanger registry has not been published elsewhere. As such, the submitted health economic analysis is based on unpublished clinical data. To which extent the population in the registry is representative for the population in question in current clinical practice is uncertain. The proportion (44%) of patients with PSA ≥ 1.5 ng/ml derived from the registry may not be representative for the proportion of patients with PSA > 1.5 ml in the general population who are candidates for further investigation. However, according to the clinical experts, 44% seems like a reasonable assumption.

Furthermore, the submitter states that the clinical input is also based on the real-life study of Viste et al. (10). The patient population in this study was included in the period 2017–2018 and is therefore likely included in the registry data described above. In this study, general practitioners were advised to continue their diagnostic practice as before, but to use Stockholm3 instead of PSA when they decided to test patients without known prostate cancer. Furthermore, there is no mentioning of a cut-off value for PSA for when a Stockholm3 test should be used as a reflex test in this study. In the study, a cut-off for PSA of ≥ 3 ng/ml was chosen as a positive PSA test. However, this cut-off is not in line with current clinical recommendations and has not been applied in the health economic analysis.

In the analysis, the presented age-specific cut-off values for positive PSA and Stockholm3 tests have been applied, come from unpublished data. Based on this it is estimated that out of 10,000 men tested, 1,459 will have a positive PSA test compared to 885 men with a positive Stockholm3 test. However, potential differences in numbers of men with false negative or false positive test results and the potential clinical and economic consequences of this have not been accounted for.

Work-up by urologists includes information on the person's medical history, clinical examination with DRE and PSA density, and/or velocity measurements as basis for decision about further referral to MRI. In the analyses it is assumed that 80 % of patients referred to urologist are referred to MRI of the prostate. According to the clinical experts, this percentage is likely to be an overestimation, and a percentage between 50% and 75% is considered more realistic.

In the analysis it assumed that the percentage of men having a positive MRI and referred to biopsy, is 40%. However, the assessment of MRI scans of the prostate is based on various methods which may impact decisions of what is defined as positive MRI scans. According to the clinical experts, a positive MRI would usually entail a biopsy as well. Thus 40% seems to be an underestimation and an assumption of around 80% would be more reasonable.

In the analysis it is assumed that 50% of biopsies are considered positive. A definition of what is considered a positive biopsy has not been presented. If those biopsies with a PI-RADS (Prostate Imaging-Reporting and Data System) score of 4 or above or a Gleason score of 6 (3+3) or above, are all considered to be positive, then, the estimate of 50% positive biopsies are likely to be an underestimate according to the clinical experts. Then, 80% would be more reasonable.

The assumptions about proportions having sepsis after biopsy and those requiring re-biopsies seem reasonable according to the clinical experts.

Resource use and costs in the submitted analysis

The submitter has included costs for blood sampling, Stockholm3 analysis, urology visit, MRI, biopsy and pathology workup, sepsis treatment, and costs for cancer treatment. The unit costs are presented in Table 6.

Table 6. *Unit costs used in the analysis*

Direct health care unit costs	NOK/unit (used in model)	Source (default value)
Blood sampling	126*	Blood test. Unit cost database V1.3 from the Norwegian Medicines Agency (NoMA). (15)
PSA analysis	126	Blood test. Unit cost database V1.3 from NoMA. (15)
Stockholm3 analysis (excl. value added tax)	[redacted]	Company price information (retail price without value added tax)
Stockholm3 analysis (incl. value added tax)	[redacted]	Company price information (retail price with 0% value added tax) (for budget impact)*
Urology visit	975	Physician (specialist). Unit cost database V1.3 from NoMA. (15)

MRI	4,990	MR Prostata. Prices from Unilabs. (16)
Biopsy and pathology workup	17,567	DRG financing system in Norway 2023 (17). DRG code 216O Biopsies from the musculoskeletal system and connective tissue, outpatient surgical treatment. Weight 0.355 x DRG unit price 45,808 = 16,262 NOK.
Sepsis treatment	133,508	DRG financing system 2023 (17). DRG code 416N "Sepsis with diseases in main diagnostic group 18 >17 years". Weight 2.698 x DRG unit price 45,808 = 123,590 NOK.
Cancer treatment (average, discounted)	126,434	Calculated. See Table 7 and Appendix 2.
Cancer treatment (average, undiscounted)	126,998	Calculated. See Table 7 and Appendix 2.

*Stated by the submitter

The costs for cancer treatment are based on the DRG reimbursement system and tariffs and was weighted according to the distribution of prostate cancer risk groups as presented in Table 7. Details on the calculations for cancer treatment costs can be found in Appendix 2.

Table 7. *Proportions used in weighing cost of cancer treatment*

Direct health care resource utilization and clinical input	**Proportion (%) (used in model)**	**Source (default value)**
Proportion of prostate cancer stratified as:		Norsk kvalitetsregister for prostatakreft – Årsrapport 2021, Table 3.2 in the report (1)
Low risk	19%	
Intermediate and high risk localized	69%	
Metastatic	11%	

Extended costs

In accordance with the extended health care service perspective, the submitter has also included extended health care costs. These are costs of patients' time spent during examinations, sepsis treatment and cancer treatment. These costs and units are presented in Table 8.

Table 8. *Submitted costs and units used to calculate extended costs*

Extended health service unit costs	**NOK/unit (used in model)**	**Source (default value)**
Average wage in NOK per hour	514	Unit cost database from NoMA (15)
Extended health service resource utilization	**Unit (used in model)**	**Source (default value)**
Time blood sampling (hours)	1.0	Clinical expert input
Time Doctors visit (hours)	1.0	Clinical expert input**
Time MRI (hours)	2.5	Clinical expert input**
Time Biopsy* (hours)	3.5	Clinical expert input** (including pathology work-up)
Time sepsis*(hours)	72	Clinical expert input** (3 days = 72 hours for in-hospital treatment)
Time prostate cancer treatment (hours, average)	96	Clinical expert input*** (4 days = 96 hours for in-hospital)

* Rehabilitation time included

**Clinical expert which the submitter has consulted

Comments by NIPH on the resource use and costs

Some costs seem to be missing in the "cost for blood sampling", but this is of no importance since all patients will go through this, thus no difference in these total costs.

The price of the Stockholm3 test in Norway is presented by the submitter. In other European countries, the price is higher than what is used in the submitted analyses. Therefore, it must be considered that the price for the Stockholm3 test may potentially be raised in the future. It is unclear whether the cost of Stockholm3-test covers costs related to taking a new blood sample, e.g. reagens, materials, and personnel costs.

The cost of MRI is taken from a private provider's price list. Normally, tariffs for reimbursement are used since we rarely have micro costing analyses available. The highest tariff for reimbursement of MRIs is NOK 2,516 (18). This amount is usually multiplied by two to represent the full cost (12). With that in mind, the MRI cost seems reasonable.

The cost of biopsy and pathology in the submitted analysis is NOK 17,600. This is one of the main cost drivers. In a recent HTA by NIPH (19), the cost of transrectal biopsy was calculated to be NOK 1,700 and 2,573 for transperineally performed biopsy (currently the recommended procedure). These costs are without the cost of pathology workup. We have not investigated further how much this would mean, but it is likely that the cost of biopsy and pathology workup is overestimated in the analysis.

Cancer treatment (including active surveillance) is highly resource demanding and a key cost driver. The cost of cancer treatment was calculated as a weighted average of proportions in each risk group multiplied by unit costs of treatment or active surveillance. It is assumed that follow-up and treatments are performed according to the stratification of cancer at the time of diagnosis as presented in Table 7. All patients with low-risk cancers are followed with active surveillance, patients with intermediate and localized high-risk cancer are treated with radical prostatectomy or radiotherapy, while all patients with metastatic cancer are treated with chemotherapy plus hormone therapy.

According to the clinical experts, the assumptions on active surveillance and treatments provided groups are oversimplifications of clinical practice. This is mainly related to heterogeneity in treatments provided for patients in the intermediate and localized high risk cancer groups and the assumption that chemotherapy plus hormone therapy is provided to all patients with metastatic cancer. The submitter has grouped together intermediate risk and high-risk localized cancer for calculating treatment costs and then this group divided into 70% radical prostatectomy and 30% radiotherapy). According to the experts one could rather split these up or, have grouped together low risk and intermediate risk. NIPH split up the groups, so we had low risk, intermediate, high risk localized cancer, and high-risk local advances cancer and metastatic cancer according to the distribution of annual report by the national quality registry for prostate cancer (1), and calculated a cost with the new weights. This new estimated cost was close to the one applied in the analysis, but somewhat higher.

The costs used to calculate cancer treatment cost was mostly based on the reimbursements in the system for activity-based financing of hospitals in Norway. This is a reasonable method to calculate costs. For calculating costs of the cancer drugs, the submitter has used publicly available list prices and dosing regimens. See Appendix 2 for more details.

The submitter has included extended healthcare costs in the form of the costs of patients' time spent during diagnosis and treatment. This is in line with the STA guidelines and the estimations seem reasonable.

The other costs in the analysis seem in general reasonable and/or have little impact on the result of the analysis.

The submitted budget impact analysis

Budget impact is defined as additional costs, i.e., the total expenditure of implementing the technology minus the total expenditure of current practice. In general, the budget impact analysis covers the financial, rather than the economic, costs of the intervention versus its comparator over a five-year period at the national level.

Number of tests calculations

The submitter has calculated the number of patients expected to be tested with Stockholm3 and PSA based on extrapolated data from the Stavanger region. In Stavanger region there are about 370,000 inhabitants. The average number of PSA tests in the period 2014–2016, before Stockholm3 was implemented, was 26,387. This corresponds to 0.0713 tests per capita. This ratio has then been extrapolated to the Norwegian population of 5.4 million inhabitants, resulting in approximately 385,000 PSA tests nationwide.

The submitter used data from the tests done by A3P Lab (the manufacturer's lab) for Stavanger region in the period 2017–2022 to calculate number of tested in the population 45- to 69-year-old men. The data showed that 77% were men between 45 and 69 years and 23% were men above 70 years. The submitter then assumes that total addressable market size for men aged 45–69 years is to be about 296,450 (= 385,000 × 77%).

Market share

The submitter used the number of Stockholm3 tests for the analysis on estimated market share between Stockholm3 and PSA, if Stockholm3 is implemented. Year 1 to 3 are based on statistics from Stavanger and year 4 to 5 on assumptions based on extrapolation on the historic pattern. The expected market shares are presented in Table 9 below.

Table 9. *Expected market share over the next five-year period if the intervention is implemented*

	Year 1	Year 2	Year 3	Year 4	Year 5
Stockholm3	5%	15%	20%	25%	30%
PSA	95%	85%	80%	75%	70%

Decreased number of tests

The submitter assumed a reduction in overall testing if Stockholm3 is implemented. They use data from the Stavanger region from 2017 to 2019 and show a decrease of around 10 %. In the five-year analysis they have applied a yearly decrease of two percent. See details on this and the Stavanger data in Appendix 3.

Number of tests in the budget impact analysis

The number of tests in the budget impact analysis is depicted in Table 10.

Table 10. Number of tests in the scenarios in the budget impact analysis

Scenario and strategy	Year 1	Year 2	Year 3	Year 4	Year 5
If the intervention is implemented					
Stockholm3	14 729	43 304	56 584	69 315	81 515
PSA (standard practice)	279 855	245 389	226 335	207 945	190 201
	294 584	288 693	282 919	277 260	271 715
If the intervention is not implemented					
Stockholm3	0	0	0	0	0
PSA (standard practice)	300 596	300 596	300 596	300 596	300 596

Expenditure per patient

The expenditure per patient is according to the submitter based on the results from the direct health care costs from the health economic analysis including value added tax and is [redacted] for Stockholm3 and NOK 4,891 for the PSA strategy.

Comments by NIPH on the budget impact analysis

The submitter has assumed that the PSA testing practice and demographics of Stavanger region which was obtained from 2014 to 2016 are relevant for the current PSA testing practice and can be generalized to the whole Norwegian population. Furthermore, the estimated ratio of PSA tests per capita (0,0713) is based the population in the Stavanger registry and is assumed applicable for estimating the expected number of PSA tests in Norway for 2022. There are several reasons for why these assumptions may be questionable. This is partly due to the development of recommendations on PSA testing over the last years (13), and partly related to the question of whether the population in the Stavanger registry is representative for the general population who are candidates for PSA testing.

The submitter assumed a two percent decrease in total number of tests each year if Stockholm3 is implemented. They argue that reduction is expected since Stockholm3 gives a clear recommendation for when the next test should be taken. They also refer to the 10% decrease in Stockholm3 testing from 2017 to 2019 as shown in the Stavanger data. We question the assumption of reduced overall testing (both Stockholm3 and standard practice with PSA) if Stockholm3 is implemented. The 2% yearly decrease also implies a reduction in the standard practice with PSA testing due to that market share of Stockholm3 is 5% in year 1 and increases yearly to 30% in year 5.

The submitter claims to have included value added tax in the cost per patient in the Stockholm3 approach and the standard practice with PSA strategy. However, they did not provide a price for the Stockholm3 analysis with value added tax. In the calculation of the weighted cancer treatment cost, it seems that the drugs are also without value added tax. These costs were used in the budget impact analysis but should have been

with value added tax. These issues seem to have little impact on the result of the budget impact analysis.

Results from the submitted analyses

Base case health economic analysis

The submitted base-case analysis show cost-savings of 1,400 NOK per man. See Table 11.

Table 11. *Submitted base case results of Stockholm3 compared to standard practice with PSA*

Strategy	Total direct costs (NOK)	Total extended health service costs (NOK)	Total costs (NOK)	Total costs per patient (NOK)
PSA (standard practice)	48,775,368	20,163,814	68,939,182	**4,878**
Stockholm3	40,692,502	14,251,495	54,943,997	**4,069**
Difference total	-8,082,867	-5,912,319	-13,995,185	
Difference per patient	-808	-591	**-1,400**	

One-way sensitivity analysis

The submitter conducted a one-way sensitivity analysis to assess the impact of varying input parameters one by one. Each parameter was varied with 20% increase and decrease. The results from the one-way sensitivity analysis are presented in Appendix 4. This analysis showed that the result is most sensitive to the proportion of patients referred to MRI by the urologist, the proportion of positive MRIs, the proportion of positive biopsies, and the cost of prostate cancer treatment. The results were cost saving in all parameter variations.

Budget impact analysis

The submitted budget impacts of implementing Stockholm3 is presented in Table 12. The numbers are in million NOK.

Table 12. *Expected budget impacts of implementing Stockholm3 (in MNOK)*

	Year 1	Year 2	Year 3	Year 4	Year 5
STH is implemented	1,429	1,377	1,338	1,300	1,263
Stockholm3 is not implemented	1,470	1,470	1,470	1,470	1,470
Budget impact	**- 41**	**- 93**	**- 132**	**-171**	**- 208**

The submitter has also performed a sensitivity analysis of the budget impacts. This can be found in Appendix 3.

Comments by NIPH on the results

Based on the given assumptions the submitted base case health economic analysis shows that Stockholm3 would be a cost-saving strategy compared to standard practice with PSA. It shows cost-savings based on direct medical costs, and even more so if extended costs are included in the analysis.

The main driver of this result is the difference in estimated proportions of men with a positive test with Stockholm3 compared to PSA who is referred to urologist. However, these estimates are based on unpublished data from the Stavanger registry and not on results from any of the clinical trials that provide the basis for the clinical documentation of the Stockholm3 test. NIPH considers that the results of the health economic analyses are subject to considerable uncertainty. Although clinical pathways after referral to urologist are assumed equal between the alternatives, assumptions on the proportion of patients referred for further assessments and treatment, as well as assumptions on resource use and costs for each of these following steps will also drive the results of the analysis.

In general, increasing the costs and the proportions of men going through examinations and treatment in the analysis will be in favour of the Stockholm3 strategy. This is because the increased costs of testing with Stockholm3 compared to PSA are lower than the potentially avoided costs for further work-up and cancer treatment. However, the clinical and economic consequences of potential differences in false negative results from the initial testing have not been assessed or accounted for.

As pointed to in the sections "Comments by NIPH on clinical effectiveness and assumptions on subsequent examinations" and "Comments by NIPH on the resource use and costs" NIPH considers there is a high degree of uncertainty associated several of the central elements in the health economic analysis.

The one-way sensitivity analyses performed by the submitter shows that the results of these analyses are robust to parameter changes one by one. However, if more than one of the parameters that are considered to be uncertain and therefore changed simultaneously, Stockholm3 may not be a cost-saving alternative. An example is if the proportion of men with a PSA test > 1,5 ng/ml in the general population is 20% higher than in the Stavanger registry, and the referral from urologist to MRI are 20% lower than assumed in the model, the Stockholm3 strategy would incur higher direct medical costs than the PSA testing strategy.

The yearly total direct medical costs per person for either initial PSA testing or Stockholm3 testing in the budget impact analysis are based on the costs estimated in the cost-minimisation analysis. As such the uncertainties related to the costs estimates in the cost-minimisation analysis also apply for the budget impact analysis.

In the analysis, the number of PSA tests are based on the yearly PSA tests per man (age group 45–69) in the Stavanger region in the period 2014–2016 and has been applied to the general population of Norway. There are no published data on the current number of PSA tests performed per year in Norway. However, given the guidelines on PSA testing from 2021(13), it is difficult to assess the appropriateness of applying data from 2014–2016 from a selected region on the national level.

In the analysis it is assumed that there will be a 2% decrease in total number of tests per year over the five-year period if Stockholm3 is implemented. This is based on the argument that Stockholm3, in contrast to PSA, gives a clear recommendation for when the next test should be taken. If Stockholm3 is not implemented, it is assumed that the total number of PSA tests will be unchanged over the five-year period. As above, given the recent guidelines this assumption can be questioned.

The development of the market share of Stockholm3 is based on findings from the Stavanger region where Stockholm 3 testing was implemented as an alternative to PSA testing in 2017. The GPs in the region were informed that referrals to the hospital based on PSA could be rejected because the hospital wanted to use Stockholm3 for prioritization of patients. The development of market share of the Stockholm 3 test versus PSA testing based as presented in the budget impact model is not likely to be representative for the market share development in general Norwegian practice should it be decided to implement the Stockholm3 test.

Patient perspective

A patient representative was recruited from the Norwegian Prostate Cancer Association (Prostatakreftforeningen). The patient representative was given information about Stockholm3 and was then asked to complete a questionnaire consisting of three questions. The following response was provided (partly summarized, and translated into English):

1. If you have experience or knowledge of Stockholm3: what could be the most important advantages / disadvantages of initial testing with Stockholm3, compared to using PSA measurements like today?

The patient believes that Stockholm3 is precise on aggressive prostate cancer. A disadvantage mentioned was that it is costly relative to the benefit gained. The patient representative also stated that when it was piloted in Norway in 2017, it was beneficial because it decreased number of biopsies. Furthermore, the patient representative meant that this has, however, been evened out since the standard practice with PSA is also algorithm-based (many factors already go into the assessment of risk), and new research is considered in this process. He also argued that the benefits Stockholm3 gave, i.e., fewer biopsies, and reduction of sepsis and antibiotics (for treating these infections), is not that relevant benefits anymore since the new method of performing the biopsy, by going transperineally, has become standard practice and is used in Norway (this method has lower risk of infection).

2. What are important aspects for patients in the initial testing for possible prostate cancer?

The patient representative commented that it is important that general practitioners refer patients to the specialist health care or urologist if they are not certain. In addition, he noted that the specialist medical doctor's modern examination and testing methods with PSA already result in reduced unnecessary MRIs.

3. If you have inputs or opinions that has not come through in the previous questions, please add.

The patient representative stated that Stockholm3 is mainly meant for aggressive prostate cancer types, i.e., Gleason 4+3 and up, and, therefore, the algorithm causes some

underdiagnosis. He also highlighted that Stockholm3 is costly, complicated, and bothersome to use as a "screening marker". Further, the patient representative states that in Sweden, which has implemented organized prostate testing, they use PSA and not Stockholm3, and only one county has partly used Stockholm3.

Other remarks made by the patient representative after review of the report draft

The patient representative underlined that all eight studies come from a commercial sponsor, with no new independent literature searches, and that this does not provide confidence in the results. And, that most of the eight studies were conducted between 2015 and 2018, and much has changed in the diagnosis of prostate cancer since 2018. He also added that in 2018, MRI before biopsy was implemented as the standard practice in Norway and that together with the modern organised use of PSA, this provides a very good selection, rendering the previous benefits of Stockholm3 obsolete.

Further he stated that Stockholm3 does not include Gleason 3+4 and that this is also a weakness, since it excludes many cases, and that after all, the latest annual report from the Norwegian Cancer Registry shows that 22% of those who died from prostate cancer had a diagnosis of localized cancer with intermediate aggressiveness.

He further raised questions about the cost-effectiveness, and noted that on the private market, the producer recently stated a price of NOK 4,600 for a Stockholm3 test. He also noted that there is uncertainty about the cost-effectiveness due to lower costs resulting from the new biopsy method.

Discussion

Discussion – clinical efficacy and safety

The submitter has provided eight studies that suggest that use of Stockholm3 can increase the detection of significant cancer and reduce unnecessary MRIs and biopsies. Although there are eight studies comparing Stockholm3 with PSA, the patient samples are overlapping, and the studies are conducted by the same group of Swedish researchers. It is not possible to perform meta-analyses, and the estimates of effect and safety are uncertain.

Because the documentation was so heterogenous regarding samples, research designs, and outcome reporting, it was not feasible to assess the confidence in the results using e.g., the Grading of Recommendations Assessment Development and Evaluation (GRADE) tool. The estimates and confidence intervals are uncertain, and the external validity is unclear.

Discussion – health economics

With the assumptions applied in the health economic analysis, the results indicate that Stockholm3 could be a cost-saving strategy compared to PSA testing.

However, there are several substantial uncertainties in the health economic analyses.

A major driver of the results of the health economic analysis are differences in the proportions of positive test results with the Stockholm3 test compared to those with PSA tests alone. Only non-published data are used in the analysis for estimating this difference. It has not been possible for NIPH to assess the generalisabilty of these data.

Assumptions in the analysis on the further diagnostic work-up, surveillance and treatment of patients after referral to urologists are mainly based on input from the clinical experts consulted by the submitter. However, current practice in terms of diagnosis and treatment of prostate cancer is various and under continous development. The clinical experts consulted by NIPH has elaborated these issues in Appendix 1.

One-way deterministic sensitivity analyses on selected parameters have been performed. The results of these analyses indicate that by varying the chosen parameters one by one with +/- 20%, Stockholm3 will still be a cost-saving alternative compared to the PSA strategy. However, the rationale for selecting the specific parameters included in the sensitivity analyses have not been presented. Furthermore, if two or more of the parameters associated with substantial uncertainty in the model are changed simultaneously, the results indicate that Stockholm3 is no longer cost-saving compared to PSA testing. This occurs, for example, if you simultaneously increase the proportion of PSA tests that are above 1,5 ng/ml, reduce the proportion of postive test results with PSA and Stocholm3 and reduce proportion referrals from urologists to MRI exams (with 20% increase or reduction).

As presented above, the budget impact analysis is associated with substantial uncertainty both in terms of costing, the total number of tests performed and the market shares of Stockholm 3 tests versus the PSA tests. The estimated cost savings if the Stockholm3 test should be implemented is therefore fraught with substantial uncertainty.

Implications for practice

The clinical practice in terms of diagnostic approaches in potential prostate cancer in Norway is currently under discussion and development, see Appendix I. We have not presented potential implications for clinical practice of implementing the Stockholm3 test.

Need for further research

To gain more robust evidence for decision making concerning possible introduction of the Stockholm3 test, it could be desirable to:

- Await the results from a number of ongoing studies, among which one is from the USA, and one is from Denmark.
- Have future studies reporting results in a standardized and consistent manner (i.e., always report true positive, false positive, false negative and true negative). This presupposes that the clinical and research communities agree on a definition of significant prostate cancer.

Conclusion

The clinical documentation submitted does not allow clear conclusions on to which extent a work-up which includes the Stockholm3 test will provide improved detection of clinically significant prostate cancer and avoiding unnecessary biopsies and cancer treatment compared to current clinical practice with PSA as the initial test.

The submitted cost-minimisation analysis indicates that Stockholm3 could be a cost-saving strategy compared to standard practice with PSA-testing. However, there are substantial uncertainties in the structure and assumptions applied in the model, and the results of the analysis should therefore be interpreted in light of these caveats.

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Appendix 1: Statement by the clinical experts

Statement written by the clinical experts in the project:

Utredningen rundt STHLM-3 testen har pågått i to år. Det har vært utvikling innen det faglige feltet under tiden som ikke er hensyntatt av premissene som leverandøren har lagt til grunn.

- Det er kommet rekommandasjoner fra EU des -22 om at screeningstudier for prostatakreft bør utredes som baserer seg på PSA prøvetaking i kombinasjon med MR prostata (https://ec.europa.eu/commission/presscorner/detail/en/ip_22_7548 og https://pubmed.ncbi.nlm.nih.gov/37704541/).

- Det er kommet rekommandasjoner fra EAU (den Europeiske Urolog foreningen) i 2021 om å bruke PSA test/MR prostata algoritme (https://pubmed.ncbi.nlm.nih.gov/34407909/). Denne algoritmen holder på å bli implementert i klinisk praksis rundt om i Norge (ved en del helseforetak er den implementert) og er den som STHLM-3 «konkurrerer» med.

- STHLM-3 testen er en test tiltenkt å erstatte PSA testing i Norge. I store deler av Sverige er det implementert et OPT (Organisert Prostata Test program) som baserer seg på PSA testing som del av en utredningsalgoritme inkluderende MR prostata (https://cancercentrum.se/globalassets/vara-uppdrag/prevention-tidig-upptackt/prostatacancertestning/nationell-rekommendation-opt-rcc-2023-final-r1.pdf). I Norge har Norsk Urologisk Forening (NUF), forankret i hele det urologiske fagmiljøet), fremmet et ønske om utredning for implementering av et OPT program (https://www.legeforeningen.no/foreningsledd/fagmed/Norsk-urologisk-forening/aktuelt/otp/#Vedlegg). Introduksjon av STHLM-3 ville derfor gå på tvers av det faglig ønske fra fagmiljøene.

Appendix 2: Inputs in the health economic analysis

Table 1. *Inputs stated by the submitter and used for calculation of weighted average cost for cancer treatment (some Norwegian text has been translated to English by NIPH)*

Unit	Proportion / unit cost	Source
Proportion prostatectomy	70 %	*Not stated by submitter*
Proportion radiotherapy	30 %	*Not stated by submitter*
Active surveillance (undiscounted)	40 038	Active surveillance at outpatient care: with MRI+Targeted biopsies/systematic biopsies 648 EURO (€, 2019) and 7035,93 NOK. Consumer price index converted from 2019 to 2023 = 8007,50 NOK (annual cost). Source: Hao pre-print cost-effectiveness study. Table 1B. 5 years cost = 40,038 NOK = 5 x 8,007.5 NOK.
Active surveillance (discounted)	37 074	Calculated including discount 4% rate. Source above.
Radical prostatectomy	110 399	DRG financing system 2023. DRG code 335 [larger operations in male pelvis without comorbidity with hospitalization], with a DRG weight of 2.231 x DRG unit cost of 49,484 = 110,399 NOK.
Radiotherapy	60 024	DRG financing system 2023. DRG code 850A [outpatient consultation for planning of radiation therapy] + 25 times of DRG code 851N [outpatient radiation therapy in tumour in male reproductive organs], with DRG weight of 0.363 and 25 x 0.034 respectively x DRG unit cost of 49,484.
Chemo + hormone therapy	487 660	Based on: A) Drug cost for Abiraterone and B) Cost of outpatient consultation with chemotherapy. A) The list price for Abiraterone per package, 500mg, pack of 56 pieces is 26,949.46 NOK in pharmacy maximum sale price excl. value added tax (VAT) (for model calculation). The recommended dose is 1.0 mg per day for 8–24 months (Summary of Product Characteristics for Zytiga). For an average of 16 months, this results in a cost of 479,198.24 NOK pharmacy maximum sale price excl. VAT ((((26,949.46/56 tablets) x 2 tablets per day) * 28 days a month) x 16 months) *. The list price for Abiraterone per package is 33,686.83 NOK AUP incl. VAT (for budget impact calculation). This results in a cost of 538,989.28 NOK AUP incl. VAT. B) Cost of outpatient consultation with chemotherapy (drug cost excluded) with a DRG code of 856N [outpatient drug therapy of tumour in male reproductive organs], with DRG weight 0.171 x DRG unit cost of 49,484 NOK = 8,461.76 NOK.

		Total: Drug cost of 479,198.24 NOK + outpatient consultation with chemotherapy of 8,461.76 NOK, gives in total 487,660 NOK for chemo and hormone therapy treatment.
Weighted total costs (undiscounted)	126 998	Calculated based on proportion cancer risk group and cancer treatment cost parameters
Weighted total costs (discounted)	126 434	Calculated based on proportion cancer risk group and cancer treatment cost parameters

*Comment by NIPH: The submitter has not shown where they found or how they calculated the price of abiraterone excl. VAT. Calculation by NIPH would indicate 33,868.83 * (1-0,25) = 25,401.62 NOK (the submitter has used 26,949 NOK). Also, the calculation stated by the submitter of 26,949.46/56 tablets x 2 tablets per day * 28 days a month x 16 months equals to 431,919.36 NOK, not 479,198 NOK as stated by them.

Appendix 3: Budget impact analysis details

Decreased number of tests in the budget impact analysis (text directly copied from the submission file)

Unpublished data from the Stavanger region shows that both the number of tests as well as the number of men tested decreases after implementation of Stockholm3 (Figure 1 below). The 3 years before the implementation of Stockholm3 (2014-2016) there were approximately 26,000 prostate cancer tests taken on approximately 20,000 men. Two years after the implementation in 2019, 23,454 prostate cancer tests were taken on 17,532 men, i.e., a reduction of approximately 10%. The reduction is expected given that Stockholm3, in contrast to PSA, gives a clear recommendation for when the next test should be taken. For example, 49.3% of the men taking a Stockholm3 test in Stavanger are recommended a new test in 6-10 years.

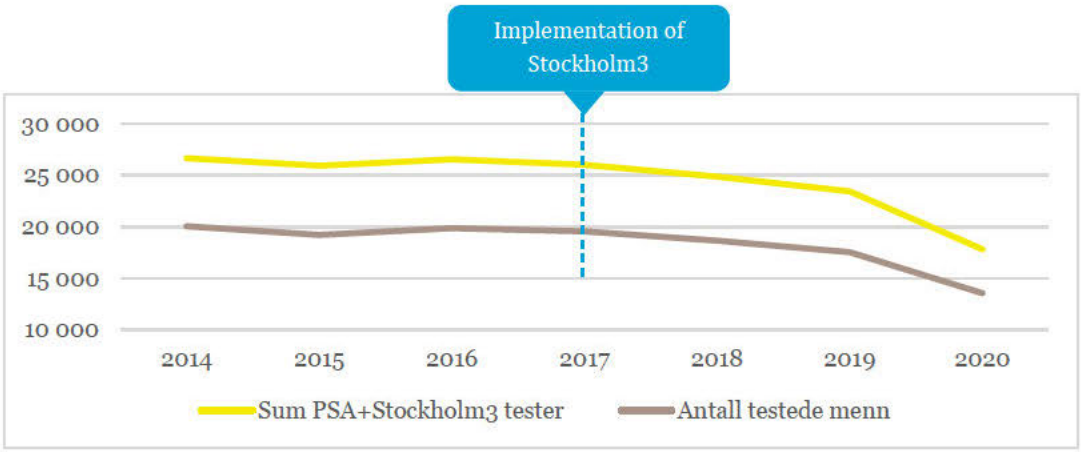

Figure 1. *Number of prostate cancer test and number of tested men in the Stavanger Region (only men without previous prostate cancer diagnosis). Unpublished data.*

Table 1. *Registry data from Stavanger University Hospital (unpublished) on number of tests*

Tests of men without known PCa	2014	2015	2016	2017	2018	2019	2020
No of PSA tests	26 666	25 941	26 558	24 633	20 825	19 514	14 683
No of men tested with PSA	20 047	19 216	19 865	18 682	16 039	15 021	11 329
No of Stockholm3 tests	-	-	-	1 409	4 039	3 940	3 133
No of men tested with Stockholm3	-	-	-	1 394	3 958	3 896	3 101
Sum PSA+Stockholm3 tests	26 666	25 941	26 558	26 042	24 864	23 454	17 816
No of tested men	20 047	19 216	19 865	19 539	18 634	17 532	13 547

Source: Register data from Stavanger University Hospital (unpublished)

Sensitivity analysis of the budget impact analysis (text directly copied from the submission file)

Sensitivity analyses have been performed from the base case budget impact analysis with +/- 20% difference in market share and +/- 20% difference in tests per capita nationwide. The results have been presented in Table e 2.

Table 2. *Sensitivity analysis on expected budget impact of adopting the intervention for the relevant indication, from base case scenario*

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
+ 20% market share for Stockholm3	-43 785 477	-100 500 713	-141 706 700	-181 812 344	-220 845 175
- 20% market share for Stockholm3	-38 991 912	-86 407 631	-123 291 741	-159 254 018	-194 316 584
+ 20% tests	-49 666 434	-112 145 007	-158 999 065	-204 639 817	-249 097 055
- 20% tests	-33 110 956	-74 763 338	-105 999 377	-136 426 545	-166 064 703

Market share (text directly copied from the submission file)

The number of patients expected to be treated with Stockholm3 and PSA respectively, are based on extrapolated data from Stavanger region. In Stavanger region there are approximately 370,000 inhabitants. The average number of PSA tests during 2014-2016, before Stockholm3 was implemented, was 26,387 tests. This corresponds to 0.0713 tests per capita. This ratio has then been extrapolated to the Norwegian population of 5.4 million inhabitants, resulting in approximately 385,000 PSA tests nationwide. This figure is also in line with the approximately 160,000 PSA tests taken yearly in the Stockholm region with 2.3 million inhabitants (Karolinska Institutet database of all prostate cancer diagnostics in Stockholm Region).

Assumption								
Population Stavanger [number]	370 000							
Number of Prostate Cancer tests in Stavanger [*]	**2014**	**2015**	**2016**	**2017** [1]	**2018** [2]	**2019** [3]	**2020** [4]	**Source**
PSA [number]	26 666	25 941	26 558	24 633	20 825	19 514	14 683	Stavanger data
Stockholm3 [number]				1 394	3 958	3 896	3 101	Stavanger data
Total	26 666	25 941	26 558	26 027	24 783	23 410	17 784	Calculated
Market share Stockholm3	NA	NA	NA	5 %	16 %	17 %	17 %	Calculated
Market share Stockholm3 excluding double PSA [3]				6 %	19 %	20 %	21 %	Calculated
Reduction of tests compared to average 2014-2016 [4]	NA	NA	NA	1 %	6 %	11 %	33 %	Calculated
Calculations								
Average number of PSA pre Stockholm3	26 388	Average PSA-tests 2014-2016, pre Stockholm3 implementation						
Yearly PSA test per capita	0,07131982							

Figure 2. *Data from the Stavanger region from the submitted budget impact analysis on number of tests and general population size*

Appendix 4: One-way sensitivity analysis

Table 1. *Parameter variation in one-way sensitivity analysis*

Parameter	Value base case	Change to value	Ra-tionale
Proportion of patients referred to MRI by urologist	80%	64%; 96%	± 20%
Proportion of positive MRIs	40%	32%; 48%	± 20%
Proportion of positive biopsies	50%	40%; 60%	± 20%
Proportion of biopsies leading to sepsis	0.25%	0.2%; 0.3%	± 20%
Proportion of biopsies leading to re-biopsy	3%	2%; 4%	± 20%
Cost PSA analysis	126	101; 151	± 20%
Cost Stockholm3 analysis	[redacted]	[redacted]	± 20%
Cost urology visit	975	780; 1,170	± 20%
Cost MRI	4,990	3,992; 5,988	± 20%
Cost biopsy and pathology workup	17,567	14,054; 21,080	± 20%
Cost sepsis treatment	133,508	106,806; 160,210	± 20%
Cost prostate cancer treatment	126,434	101,147; 151,721	± 20%

Table 2. *Results of the one-way sensitivity analysis*

Parameter	Value base case	Change to value	Strategy 1 (PSA)	Strategy 2 (Stockholm3)	Strategy 2 vs 1
Proportion of patients referred to MRI by urologist	80 %	64 %	5 712	4 777	-934
		96 %	8 076	6 211	-1 865
Proportion of positive MRIs	40 %	32 %	5 858	4 866	-992
		48 %	7 930	6 122	-1 807
Proportion of positive biopsies	50 %	40 %	6 049	4 982	-1 067
		60 %	7 739	6 007	-1 732
Proportion of biopsies leading to sepsis	0,25 %	0,20 %	6 890	5 492	-1 398
		0,30 %	6 898	5 497	-1 401
Proportion of biopsies leading to re-biopsy	3 %	2 %	6 864	5 476	-1 388
		4 %	6 924	5 513	-1 411
Cost PSA analysis	126	101	6 869	5 469	-1 400
		151	6 919	5 520	-1 400
Cost Stockholm3 analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
Cost urology visit	975	780	6 865	5 477	-1 388
		1 170	6 922	5 512	-1 411
Cost MRI	4 990	3 992	6 777	5 424	-1 354
		5 988	7 010	5 565	-1 445
Cost biopsy and pathology workup	17 567	14 054	6 725	5 392	-1 333
		21 080	7 063	5 597	-1 466
Cost sepsis treatment	133 508	106 806	6 891	5 492	-1 398
		160 210	6 897	5 496	-1 401
Cost prostate cancer treatment	126 434	101 147	6 286	5 126	-1 160
		151 721	7 502	5 863	-1 639

Appendix 5: Progress log

Date	Correspondence
31 May 2021	NIPH got the STA commissioned
17 June 2021	NIPH contacted the company to check interest to submit
24 June 2021	The company responded positively
25 August 2021	Pre-submission meeting was held between NIPH and the company. the company confirmed their intent to submit the documentation required for the STA.
31 August 2021	Clinical experts were first contacted
1 September 2021	Experts recruited
October 2021	The company requested input on the documentation they planned to submit, in particular on the planned health economic analysis. NIPH clarified the criteria for carrying out a cost-minimisation analysis and emphasized that the assumptions underlying the analysis must be in line with Norwegian clinical practice.
17 December 2021	NIPH received the first submission
21 December 2021	NIPH contacted umbrella patient organisation for patient representative
17 January 2022	NIPH sent a reminder to patient organisation
17 January 2022	NIPH were contacted by the prostate cancer association
9 February 2022	NIPH received contact details for a patient representative. NIPH contacted the representative.
11 February 2022	NIPH held meeting with the clinical experts about assumptions in the health economic analysis.
8 March 2022	NIPH gave feedback to the company about the need for revised analysis. NIPH had concluded that the submitted cost-minimisation analysis was based on assumptions that were inconsistent with Norwegian clinical practice.
14 March 2022	The company informed that they would submit revised documentation. They did not provide a timeline.
March 2022	NIPH informed the commissioner of the ongoing process with the company
21 April 2022	NIPH received questions from the company about the planned revised analyses

26 April 2022	NIPH informed the patient representative about the status and process for patient involvement
28 April 2022	NIPH responded to the company's questions
5 June 2022	The company informed that they sought to submit revised documentation during the autumn
21 June 2022	NIPH informed the patient representative about the status and delay
26 February 2023	NIPH received revised documentation
1 March 2023	NIPH accepted the documentation for conducting an STA
12 June 2023	NIPH held a meeting with the clinical experts about their views and input to the STA, and NIPH's question about assumptions in the health economic analysis. It was agreed that the experts would prepare a document about their perspective and comments on the STA.
21 June 2023	NIPH contacted a new patient representative and got a positive reply.
11 October 2023	Draft report draft sent to clinical experts
18 October 2023	Draft report draft sent to patient representative
20 October 2023	Feedback received from patient representative
13 November 2023	Feedback and a separate note received from clinical experts
22 November 2023	Draft report sent to the submitter
24 November 2023	Draft report sent to the internal reviewer
18 December 2023	Feedback received from the submitter
22 January 2023	Final report submitted

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