



York Health Economics Consortium

# PROSTATE CANCER RESEARCH

## Review of the Economic Model Used to Inform National Decisions on Prostate Cancer Screening in the UK

### Final Report

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# Executive Summary

## 1. INTRODUCTION

Prostate cancer is the most common cancer in men in the UK [4, 5]. Recent research has indicated that it has also now become the most common cancer in the UK across men and women, overtaking diagnoses of breast cancer [7]. The most common age for diagnosis in England for prostate cancer is between 70 and 79 years old [6]. There is currently no national screening programme. Instead, prostate-specific antigen (PSA) tests are used for anyone with symptomatic concerns or all males above the age of 50 that request a test. A positive PSA test results in a referral for further diagnostic testing. There is ongoing debate surrounding the utility of PSA testing as a screening tool, with some evidence suggesting it results in overdiagnosis. The UK National Screening Committee (NSC) recently commissioned Sheffield Centre for Health and Related Research (SCHARR) to develop a prostate cancer screening model. The results of this model and recommendations made by SCHARR form a large component of the evidence used by the NSC to inform their decision on whether to implement prostate cancer screening in the UK. It is therefore very important that the modelling choices and evidence used to inform the model are robust, to suitably inform reliable and accurate decision making. Prostate Cancer Research (PCR) commissioned York Health Economics Consortium (YHEC) to provide a critique of the economic model used to inform the NSC recommendations. The points raised within this critique are specific to YHEC, and do not necessarily represent the views of consulted stakeholders.

## 2. METHODS

The critique of the model had three components.

**Component One:** We conducted a detailed review of the technical report, including understanding the methods selected, the overarching structure of the model, and the data underpinning the analysis.

**Component Two:** We facilitated a series of clinical validation workshops that served as a platform for expert elicitation.

**Component Three:** We approached SCHARR with questions based on our initial review to ensure there was no misinterpretation. We also provided suggestions for scenarios to run in the model, which were provided by SCHARR.

## 3. RESULTS

The results of the critique highlight concerns relating to the economic model report used for the NSC's prostate cancer screening recommendations. Specifically:

1. The screening policy that was evaluated in the model is to implement additional 'structured' PSA testing for all men in addition to current practice, where men ask their GP for a test (opportunistic testing). It is unlikely that current practice will continue unaffected with the implementation of a structured screening strategy.
2. There are several concerns with how the model deals with clinical parameters, including:

- Calculated overdiagnosis between treatment arms. Currently, it is unclear how overdiagnosis is defined, and only the harms of organised screening on overdiagnosis are considered, not the potential reduction in overdiagnosis as well.
  - Treatment and diagnostic costs. Treatment costs are underestimated for those with late-stage cancers, while there are concerns that some of the diagnostic costs do not match the diagnostic pathway. Both of these factors are likely to bias against screening.
  - The relationship between cancer stage and grade. The mapping between these two aspects means that treatment costs may be overestimated, due to people ending up in higher grades than reality at earlier stages of cancer. This would likely impact the screening arm more, due to the treatment effect of earlier diagnosis.
3. The model and report do not discuss, acknowledge or evaluate the impact on health equity.
  4. Changing some of the underlying data and assumptions within the model, based on the concerns raised, changed the direction of some of the economic results within the scenario analysis we requested. Although these were crude scenarios, it highlights the importance that assumptions made, and data selected have on the modelling outcomes, particularly for Black Men and those with family history of prostate cancer.

#### **4. CONCLUSIONS**

Modelling the impact of a national screening programme for prostate cancer is complex and will require various assumptions. However, we recommend that adjustments be made to the economic model to ensure that valid and robust results are used to inform NSC recommendations. It is important for the assumptions and biases of the model to be reflected on and reported appropriately. The concerns highlighted in our critique are all important considerations, particularly for at-risk subgroups, where the cost-effectiveness estimates are relatively close to the threshold.

## Acknowledgements

We would like to thank The Sheffield Centre for Health and Related Research (SCHARR) for assisting us in running model scenarios and their time answering clarification questions. We would also like to thank the 15 clinicians and expert advisors, as well as Prostate Cancer Research (PCR) for their time and advice supporting the validation of the model.

The points raised in this critique reflect the opinions of the York Health Economics Consortium (YHEC) project team only. These represent our interpretation of the SCHARR technical report, advice provided by expert advisors, our own knowledge on the topic area, and knowledge identified through targeted literature searches.

## Abbreviations

AE	Adverse event
AQuA	Analytical Quality Assurance
ATM	Ataxia telangiectasia mutated
bpMRI	Bi-parametric magnetic resonance imaging
CAP	Cluster randomised trial of PSA testing for prostate cancer
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
ERSPC	European Randomised Study of Screening for Prostate Cancer
FIT	Faecal immunochemical testing
GGG	Gleason Grade Group
GP	General Practitioner
HRG	Healthcare Resource Groups
HRQoL	Health-related quality of life
LATP	Local anaesthetic transperineal
LUTS	Lower urinary tract symptoms
mpMRI	Multi-parametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSC	National Screening Committee
PCR	Prostate Cancer Research
PROMIS	Prostate MRI Imaging Study
ProtecT	Prostate testing for cancer and Treatment
PSA	Prostate-specific antigen
PSS	Personal Social Services
QALY	Quality-adjusted life year
SACT	Systemic anti-cancer therapy
SCHARR	Sheffield Centre for Health and Related Research
TRANSFORM	Trial of Randomised Approaches for National Screening FOR Men
UK	United Kingdom
YHEC	York Health Economics Consortium

## About YHEC

York Health Economics Consortium (YHEC) is a health economics consulting company owned by the University of York. It provides a range of services, including economic modelling, literature searching, systematic reviews, network meta-analyses, patient-reported outcomes, service review and applied research and training to the National Health Service (NHS) and the pharmaceutical and healthcare industries. YHEC also carries out work for a range of clients outside the health sector, including Local Authorities and the voluntary sector. Current clients include: NHS England, the National Institute for Health and Care Excellence (NICE), a range of local NHS trusts and several large multi-national pharmaceutical, device and nutrition companies.

YHEC is one of a group of Health Economics departments at York, which is the largest and most active group in the United Kingdom. It is the main consultancy provider of Health Economics expertise at York, combining rigorous research standards with efficient project delivery. As well as its own multidisciplinary staff, YHEC often draws on the specific expertise of staff in related academic departments.

# 1 Introduction

In the United Kingdom (UK), prostate cancer is the most common cancer in men. Recent research has indicated that it is also now the most common cancer in the UK across men and women, overtaking diagnoses of breast cancer [7], with an estimated 64,000 diagnoses in 2022 and approximately 12,000 deaths each year [10]. The most common age for diagnosis of prostate cancer is between the ages of 70 and 79 years in England [6].

There is currently no national screening programme for prostate cancer [11]. Instead, all males above the age of 50 (with or without concerns) can request a prostate-specific antigen (PSA) test from their GP. As part of the national guidelines on recognition of possible prostate cancer, a PSA test is recommended for men with lower urinary tract symptoms (LUTS), erectile dysfunction, or haematuria [12]. A PSA test is a blood test that measures the PSA protein, which is produced in the prostate gland and can assist with the detection of prostate problems, like cancer. Those with elevated PSA levels will then be referred for further diagnostic testing. Consulted clinical experts and the wider academic literature suggest the current opportunistic approach is suboptimal and requires optimising to target those at highest risk [13].

However, there is ongoing global debate surrounding the utility of PSA testing as a screening tool for prostate cancer [14]. PSA is present at some level for all men, and increases with prostate size, and sometimes age, as well as being elevated by active inflammation in the prostate. PSA testing is therefore an imperfect choice for screening due to the high potential for overdiagnosis or false positives, leading to increased harm and unnecessary further testing such as biopsies [15]. It also may lead to the detection of low-risk prostate cancers, which are clinically insignificant and is associated with lead-time bias.

Nonetheless, screening with PSA tests may still provide benefits to the national population. The use of MRI and risk stratification plays a role in the reduction of false positive cases and overdiagnosis. Screening can be beneficial to people by helping to detect the disease early, allowing earlier treatment and potentially improving morbidity and mortality. This is reflected in the European Union's recommendation in 2022, that organised screening programmes should be undertaken for prostate cancer [16]. This should also be balanced with consideration of the costs of implementing the screening programme, and any harms screening may cause.

The UK National Screening Committee (NSC) recently commissioned Sheffield Centre for Health and Related Research (SCHARR) to develop an economic analysis to evaluate the cost-effectiveness of prostate cancer screening [17]. This involved an economic evaluation to determine the cost-effectiveness of introducing a nationwide screening programme. The model captured the impact on the general male population over the age of 50, as well as targeted screening for higher risk subpopulations.

Higher risk populations include those with:

- A familial history of prostate cancer.
- The BRCA gene mutation (BRCA1 and BRCA2).
- Black ethnicity.

The modelling approach adapted the previous MIMIC-Bowel model used to inform the impact of bowel cancer screening. The draft recommendations advise against routine population screening and targeted screening for at-risk populations such as Black men or men with a familial history of prostate cancer. Screening was only recommended for those with a known BRCA gene mutation. The decision by the NSC was informed by the cost-effectiveness model. These recommendations are currently open for public consultation.

## 1.1 Objectives

Prostate Cancer Research (PCR) approached York Health Economics Consortium (YHEC) to critique the economic model used to inform the NSC's recommendations. This critique involved:

- An assessment of the methodological, structural, and parameter choices made in development of the model, with respect to the current clinical pathway and published literature.
- A review of the model findings, technical report, and the consequent recommendations made to the NSC.
- Engagement with SCHARR, clarifying structural and parameter choices in the model, as well as requesting additional scenarios.
- Engagement with clinical experts and expert advisors for prostate cancer, to support the evaluation of the model's validity.

This report summarises the methods and findings from the critique, including recommendations to improve the robustness of the model.

## 2 Methods

The first stage of the project included a detailed review of the technical report describing the model used to inform the NSC's decision on prostate cancer screening. YHEC requested the executable model for this critique; however, SCHARR did not provide this. Therefore, this critique is based on the technical report alone and is unable to consider programming errors.

The review of the technical report focused on understanding the methods selected by SCHARR, including the overarching structure of the model, and data underpinning the analysis. Internal validation involved a thorough review of the inputs used to ensure they matched the source materials. This was extended further by conducting targeted literature searches for key inputs, to consider if alternative options were more suitable. The model structure was then compared with national guidelines surrounding prostate cancer diagnosis and treatment, to understand if it appropriately captured diagnostic and treatment pathways. This stage also assessed if the report aligned with established health economic standards for reporting [18-20].

To assess the model's clinical relevance and face validity, we facilitated a series of clinical validation workshops involving 15 clinical experts and advisors from a range of specialities based both in and outside of the UK, including oncologists, urologists, radiologists, and biostatisticians (see Appendix D). These workshops served as a platform for expert elicitation, where clinicians were asked a range of questions on the core assumptions made in the model and supporting data, pathways, and outcomes. The feedback gathered was from a range of experts to construct a comprehensive understanding of the decision problem to support the findings outlined in this report.

Finally, we were able to provide questions to SCHARR based on our initial review of the model, to ensure the approach taken by SCHARR was not misinterpreted. These clarification questions helped shape our understanding of the approach, the rationale for SCHARR's decisions, and the findings of the critique. Further to this, we also provided SCHARR with some suggestions of scenarios which would be useful to run through the model. Given the time available before consultation to the recommendations closed, the scenarios were limited to simpler changes, rather than structural changes or modifications to the scope of the analysis. The scenarios requested are presented in Appendix B. The results of these scenarios are provided in Appendix C and discussed in Section 4.

## 3 Summary of Key Concerns

This section will address the key concerns identified throughout our review process. Additional, less critical, concerns are provided in Appendix A. Therefore, Sections 3.1 to 3.6 cover the key considerations for any updates to the cost-effectiveness model, or to NSC guidance.

### 3.1 Reporting Quality and the Principles of Robust Analysis

Transparency, objectivity and a reflection of uncertainty are fundamental concepts of all robust analyses. For example, The Analytical Quality Assurance (AQuA) Book was published in 2015 [21], in response to recommendations from the 2013 Quality Assurance of Government Models Review [22]. Although it is not specific to health, the book outlines principles required for robust economic analysis. The following statement from The AQuA Book outlines the key pillars of any analysis:

**“Quality analysis needs to be repeatable, independent, grounded in reality, objective, have understood and managed uncertainty, and the results should address the initial question robustly.”**

We recognise that accurately reflecting the patient pathway and complexities of screening is a challenge and that some elements will, by necessity, be subjective or require the use of assumptions. However, it is important to consider whether the analysis meets the standards required to inform policy decisions. Our initial overview of the report identified concerns surrounding the quality and transparency of the reporting. The model was not made available to us for this review when requested, so any insights made in this critique were based solely on the technical report.

In health economics, a common tool used to establish reporting quality is the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [19]. Another commonly used tool to critically appraise economic evaluation is the Drummond checklist, which focuses on ten key areas for the reporting of economic analysis [23]. As part of our external validation, the model reporting quality was assessed against economic evaluation reporting standards including the Drummond checklist, CHEERS checklist, and The AQuA Book.

We identified several areas where the reporting lacked clarity and transparency to allow for a clear deliberation on the impact of screening.

For example, using the CHEERS checklist, a common tool for assessing health economic analysis reporting, we identified the following concerns, which highlight the wider concerns on reporting quality:

- Lack of clarity on the model decision problem (**Item 5-7**). The report fails to clearly define the comparator or the intervention, making it hard to determine the appropriate allocation of costs and consequences to each model arm. For example, it was only upon further clarification from SCHARR that it was confirmed that there are no differences associated with opportunistic screening modelled between treatment arms. This is not explained or stated with sufficient detail in the report. This lack of context and transparency makes it difficult to critique model outcomes and may produce a misleading interpretation of the results.

- Another key point that is not explicitly mentioned is the model perspective (**Item 8**). It is important to clearly outline the viewpoint from which costs and benefits are being considered to adequately determine the relevant parameters and scope of the model. We understand this to be from a National Health Service (NHS) and Personal Social Services (PSS) perspective.
- The authors also do not state and justify the discount rate used (**Item 10**). The discount rate is only referenced in the scenario analysis, but does not confirm the base case discount rate, and is only shown in the results during scenario analysis.
- There are many assumptions surrounding data, inputs or extrapolated evidence that are not adequately explained (**Item 17**). For example, on page 69 it is stated in the report “*The base case screening uptake was used from the CAP trial: 36% for the PSA test and 85% for the follow up biopsy [28]. It was assumed that mpMRI will have the same uptake as the biopsy.*” However, the rationale for this assumption is not explained any further. Further examples include what year the utility multipliers were calculated from (page 71), what period the palliative care costs cover (page 79), and why cumulative hazards with respect to risk factors were unrealistic (page 36).
- The report does not include any discussion of the distributional effects (**Item 19**), or any equity considerations (**Item 26**). The SCHARR model accounts for certain high-risk populations including those with family history or Black ethnicity. However, this is done with high uncertainty due to the lack of evidence available. Whilst we acknowledge the lack of data, particularly in the Black ethnicity population, there is no discussion of the impact of health inequalities concerning both education and access to current care pathways on this population. The variation in impact, correlated with socioeconomic status within these populations, is not explored qualitatively or quantitatively with respect to an organised screening programme. It is recognised that a complex quantitative equity analysis would not have been possible within the scope and timeframes of this project. However, we recommend that the report be amended to include at least a qualitative discussion of the impact of the model findings with respect to health equity and recommendations for further research surrounding the distributional effects.
- The report does not adequately describe the methods used to identify uncertainty (**Item 20**) or provide an estimate of the impact of various uncertainties on the model outcomes (**Item 24**). Parameter uncertainty is often identified through probabilistic sensitivity analysis. The report includes details of sensitivity analyses run for each subgroup; however, it does not provide sufficient detail to identify the key drivers. For example, on page 98 of the report, it is stated that for the general population “*uncertainty in the natural history parameters, specifically those correlated with age (see Supplementary C) was the most influential factor in determining cost-effectiveness*”. However, there is no further discussion on the cause or impact of this uncertainty, and no other influential factors are identified. Structural uncertainty is validated against the CAP and ERSPC clinical trials to minimise structural flaws. Unfortunately, these trials are outdated and do not reflect modern updates to the diagnostic pathway. The authors fail to sufficiently identify or explore the impact of this uncertainty. Trials such as the PROMIS [24], and GÖTEBORG-2 [25] trials could have been used to validate a more modern diagnostic pathway. We recommend that early results of the TRANSFORM trial [3] also be used to explore this uncertainty with a more modern diagnostic pathway for validation once available. Further sections in this report discuss alternative data that could have been considered.
- The report does not include the breakdown of the costs for the main results (**Item 23**). This makes it very difficult to determine the key drivers of the model outcomes and consequently assess the results appropriately. All health economic evaluations should

break down the core results to show the drivers of change and impact from the model between treatment arms.

- There is limited discussion provided of the study's weaknesses and constraints (**Item 26**). The model limitations are briefly discussed on pages 179-180 of the report. However, there are key limitations such as the model structure not reflecting a modern diagnostic pathway or the use of alternative biomarker tests. Further details on limitations are discussed throughout the rest of this report. All models are expected to have limitations, but these should be clearly identified and the potential impact of these explored and discussed. Some of the limitations discussed in the report were identified only after consultation with SCHARR, rather than directly from the technical report.

Overall, the points raised above with respect to the CHEERS checklist result in concerns around reporting quality. Similar guidance documents referenced suggest similar principles that should be adopted within the analysis. Beyond the reporting quality with respect to economic guidelines, the document is missing sections. For example, in the report it is stated that "*the decrement in utility due to age was detailed in the 'Modelling Changes in Phenotypic Characteristics by Age' on page 70 of the report*". However, this section does not exist in the report, so is difficult to interpret. The list above does not contain an exhaustive list of reporting concerns but highlights that further work should be conducted to make the report more transparent and robust for informing national policy.

#### **Recommendations for updates**

We recommend an update of the report to address the concerns outlined above in order to meet key economic reporting standards. The points raised reflect a lack of overall clarity, reducing the credibility and replicability of the work. We recommend that the authors consult key checklists for reporting, including the CHEERS checklist, discussed within this section.

## **3.2 Key Definitions and Opportunistic Screening**

The definitions of the comparator and intervention were not made clear in the report. However, clarification from SCHARR confirmed the following:

- The **comparator** is modelled as 'current care': opportunistic screening for anyone with concerns (i.e. LUTS, erectile dysfunction, haematuria) or any men over the age of 50 who request a PSA test from their GP.
- The **intervention** is modelled as the addition of organised screening to the current care pathway, without the cessation of any opportunistic screening currently occurring.

### 3.2.1 Definition of comparator

The definition of the comparator is not clearly defined in the report. However, the definition provided by SCHARR is likely not accurately reflected in the model. It is unclear whether the cost of opportunistic PSA testing for those who do not go on to receive a positive diagnosis is included within the model.

Feedback from clinical experts indicated that there are currently a large amount of opportunistic, asymptomatic screening tests happening, which will incur substantial costs to the NHS at a population level. For instance, Vickers and Brentnall (2026) [26] estimate a total incidence of 1.88 million PSA tests under current opportunistic screening practice. Additionally, a paper by Merriel et al (2025) [27] suggested that in 2018, one in five people with prostate cancer in England were diagnosed through asymptomatic screening tests. It is likely that this figure will fluctuate year-on-year due to various factors, such as media campaigns or other events raising awareness. However, considering the sensitivity and specificity of PSA testing, MRI scans, biopsies, and the available evidence on total population screening, approximately 300,000 opportunistic asymptomatic PSA tests were done in 2018 in order to detect this many cancers. Furthermore, previous literature and clinical experts raised how current opportunistic screening is more concentrated among wealthy individuals who are white [28]. This means current practice is likely to exacerbate health inequalities.

As discussed in Section 3.2.2, the intervention arm is likely to overestimate the number of opportunistic asymptomatic PSA tests. Therefore, it does not seem plausible to omit the cost of current opportunistic testing from the economic model.

### 3.2.2 Definition of intervention

The definition of the intervention provided by SCHARR suggests that the introduction of a screening programme is completely additive to any opportunistic screening occurring. This is unrealistic for several reasons.

Firstly, it does not reflect the process used to introduce other screening programmes such as bowel cancer screening. In this case, when the use of faecal immunochemical testing (FIT) to screen for bowel cancer was introduced, the NSC recommended the permanent discontinuation of bowel scope screening, the current standard of care [29]. Evidence also indicated that FIT testing became more appropriate after introduction of the screening guidelines, with more people tested who were eligible and recommended to be tested [30]. Models exploring the cost-effectiveness of screening for prostate cancer across Europe typically capture the comparator as no screening [31]. They consequently do not account for any opportunistic screening in the intervention arm, only capturing the impact of age- or risk-based screening for the indicated populations. It would, therefore, be feasible to assume that the introduction of prostate cancer screening would be implemented alongside the recommendation to adjust the requirements for opportunistic screening, which will then feed through to clinical practice. This view was supported by the clinicians and expert advisors consulted for this review.

Furthermore, clinical experts highlighted the over-testing currently occurring in older populations. It was agreed that the introduction of a screening programme would likely reduce opportunistic testing for these populations. Anecdotal evidence was provided from clinicians in

the US and Sweden of this being the case. However, there is evidence from Lithuania [32] which has shown that, upon implementation, the opportunistic testing of people not fitting within the criteria for testing reduced year on year by nearly 80%. We acknowledge that the generalisability of this to the UK is uncertain, given differences in health systems and populations. However, we would expect similar results to be achievable with the implementation of suitable changes to policy and standard procedure. There was consensus from experts that we would expect a downwards effect on opportunistic screening in the UK, even if the magnitude of that effect is uncertain [26]. This could be done through the implementation of policy decision for primary care, impacting the ability to order PSA tests for asymptomatic men who do not fit the screening criteria. It is also likely to occur naturally as it is expected that people who test negative through the screening programme are not likely to also attend their GP for additional testing outside of the programme, if asymptomatic.

These expected impacts would likely contribute towards a reduction in opportunistic screening once organised screening is introduced. It is then important to relate the impact of changes to opportunistic screening on the economic model results. Considering the impact on overdiagnosis, the current report highlights the harms of increased overdiagnosis from screening. However, what is not taken into account is the counteractive effect of screening: that a strict screening programme will also likely reduce screening in other lower-risk populations. If opportunistic screening is reduced, overdiagnosis will be reduced in populations that were not suitable for a PSA test, where there is little benefit of testing. Therefore, it is important to consider the overall impact of screening on overdiagnosis, not just focusing on new over diagnosed cases identified in screening.

The second consideration is with respect to cost differences. It is likely that the net number of PSA tests (and subsequent diagnostic tests) is overestimated, given that screening is assumed to be completely additive. It is likely some of the people currently receiving opportunistic tests will fall within categories considered for screening. In this case, the costs from introducing a screening programme are overestimated. Furthermore, if the introduction of a screening programme reduces PSA testing for populations that are not suitable for a PSA test, then this will also overestimate the true cost of rolling out the screening programme. One previous paper has suggested PSA testing would reduce by approximately 25%, of which a proportion would be from opportunistic screening [26].

Thirdly, the screening scenarios modelled for the intervention incorporate minimal risk stratification (See Appendix A for further explanation and supporting literature). Clinician opinion suggested that it would not make sense for those who attended screening with consistently low PSA levels to continue to attend screening every two years. In these scenarios it is more plausible that they would then be advised to reduce attendance. For example, they may then be recommended to only attend screening every 5 years. This contributes to the overestimation of the number of PSA tests occurring in the intervention arm.

### Recommendations for updates

We recommend that the comparator be adjusted to reflect the current levels of PSA testing occurring, if it does not already, and the report be amended to clearly define the comparator. This is so the expected impact between the intervention and comparator can be appropriately modelled.

We also recommend that the intervention arm be restructured to reflect organised screening for the indicated populations only, with a range of scenarios covering the cessation of current practice for those outside this population.

This uncertain limitation should then also be explored further in the discussion of the report, so that the uncertainty is fairly reflected in decision making. This discussion should cover the expected impact and bias on the overall results.

### 3.3 Overdiagnosis

The report initially defines overdiagnosis as “*the proportion of all screen-detected cancers that would not have caused harm during a patient’s lifetime*”. However, based on the calculation provided for the overdiagnosis model output (page 17), it is interpreted that *overdiagnosis within the model is estimated as all incremental cases identified through screening that would not have been identified in the comparator arm*. This modelling choice does not reflect the provided definition and suggests that all prostate cancer cases not diagnosed under current care practice would never have caused harm. There is also no clarification provided as to what constitutes ‘harm’ for the purposes of this definition. For example, for the proportion diagnosed who remain on active surveillance, they may never experience cancer progression which needs to be treated in their lifetime. This could be classed as the cancer not causing harm, but a form of management was still provided instead of discharge. Therefore, the lack of clarity on what constitutes harm in the definition results in ambiguity in the estimations of overdiagnosis. Furthermore, if all incremental cases identified through the screening arm are due to overdiagnosis, this assumes that none of these cases would have caused harm in the comparator arm. This would lead to an over-estimation of the consequences of overdiagnosis due to screening. Clinical feedback suggested a more suitable definition to identify diagnosis would be assuming those diagnosed and classified as Gleason Grade Group 1 (GGG1) are likely to be the over-diagnosed cases.

There is a further lack of clarity in the report surrounding the application of the provided definition of overdiagnosis to the comparator arm. The modelled definition of all incremental cases identified through screening implies that any cases detected in the comparator arm that would have caused ‘harm’ in a patient’s lifetime are not defined as over diagnosed. This inconsistency in the application of the definition would overestimate the incremental impact of overdiagnosis by failing to acknowledge the level of overdiagnosis already present in current care. This is an implicit assumption being applied based on how overdiagnosis is currently being captured in the evaluation. Clinical and expert advisors have confirmed that this is unrealistic given that current levels of PSA testing results in high levels of overdiagnosis,

particularly in older men. It is unrealistic to assume that there is no overdiagnosis within standard of care that could be avoided with the implementation of a formal screening pathway [26].

Additionally, the choice to model the intervention as the addition of organised screening to current opportunistic screening also contributes to the overestimation of the impact. This structural choice ignores any benefit of the potential for an organised screening programme to reduce current overdiagnosis occurring as a result of opportunistic screening. We acknowledge that there is uncertainty regarding the impact on opportunistic screening. However, this uncertainty should have been explored through a scenario analysis. The exclusion of this consideration reflects an inherently biased approach to modelling against screening and should be rectified to provide decision makers with a range of potential outcomes from a pessimistic scenario through to an optimistic scenario. The reality of screening impacts is likely to fall somewhere between these two scenarios. This will better capture the possible value, and risks, of a potential national screening strategy. This scenario analysis can be informed by clinical feedback, particularly from those who are involved in exploring screening opportunities in the UK [33], as well as data from European screening studies [32] to estimate the anticipated impact on opportunistic screening with the introduction of an organised screening programme.

It is unclear how the GGG cases were distributed in the over diagnosed cases within the model. If these were spread across the GGGs in the same distribution as diagnosed cases, the treatment costs and health-related quality of life (HRQoL) decrements will be overestimated because it is likely that any cases classified at GGG2 or higher would require treatment to prevent harm and are, therefore, not over diagnosed. Alternatively, if the incremental cases identified as over diagnosed are mostly classified as GGG1, then the method used to allocate treatment costs is flawed. The weighting of treatment costs is based on the current distribution of treatments which is in turn driven by the distribution of GGGs under current practice. Therefore, it would be necessary to reweight the treatment costs for the screening arm to reflect a higher proportion of GGG1 cases. For example, the source used for the weighted treatment costs [34] assumes 37.8% of people with stage 1 cancer still receive treatment compared with between 50.4% and 76.6% for later stages. An increase in the proportion of lower stage cases identified should, therefore, be reflected by an increased proportion of those on active surveillance instead of receiving treatment, and subsequent reduced cost. Further feedback from clinicians also suggested that with the introduction of a screening programme, they would expect behaviour changes, with a larger proportion of GGG1 cases assigned to active surveillance rather than treatment. This would further decrease treatment costs for the intervention arm and treatment-related adverse events (AEs). Lastly, the alternative assumption proposed above, that all GGG1 cases be defined as over diagnosed, would help prevent the overestimation of the negative consequences of screening. This is by avoiding defining any incremental cases identified at a higher GGG, which are likely to cause harm and would benefit from treatment, as over diagnosed.

The definition of overdiagnosis includes both true diagnosed and false positive cases. This definition does not align with clinical feedback and current medical literature stating false positives should not be defined as overdiagnosis [35-37]. Consultation with SCHARR confirmed that false positives were modelled to proceed through diagnostic testing (mpMRI and potential biopsy). Any that continued to have a false positive result were then treated as GGG1 and assigned the costs of active surveillance only. Clinical feedback suggests that this is not a

suitable assumption. We acknowledge that the sensitivity and specificity data may imply that a small number of people will have a false positive diagnosis. However, in clinical practice, following positive results of a PSA test, magnetic resonance imaging (MRI), and biopsy (for those who require it), a multidisciplinary team meeting would be held which would consider this, alongside other clinical factors, to determine a diagnosis. Expert opinion advises that at this stage, a negative diagnosis would likely be decided and no further treatment costs or surveillance would be applied. This population would likely be correctly identified as false positive following a few additional tests and be discharged. Therefore, applying the full active surveillance costs to this population is overestimating the cost impact. A scenario should be run testing this with the alternative approach mentioned above, to explore the total impact on costs.

### **Recommendations for updates**

We recommend that the definition of overdiagnosis is amended to exclude false positives in alignment with accepted modelling practice. We also recommend that overdiagnosis is identified in both the comparator and intervention arm or that this is further clarified within the report if it is already reflected in the model. Similarly, we recommend that false positives are identified separately in both model arms, and that only the diagnostic costs are applied, with no GGG, utility decrement, or active surveillance modelled.

As a point of key importance, we recommend that additional scenario analysis is performed to explore the potential changes to current overdiagnosis levels with the addition of organised screening.

Alongside this, we also recommend that the weighting of the treatment costs for the screening arm be adjusted to reflect the increased proportion of lower grade cases identified and scenario analysis be carried out to explore the impact of an increased proportion of GGG1 cases receiving active surveillance.

If the GGG distribution of the over diagnosed cases reflects the distribution of the known cases, then we would recommend both an optimistic scenario (all incremental cases anticipated to cause harm and require treatment) and a pessimistic scenario (all incremental cases are over diagnosed and do not require any management/treatment) be modelled, to test the impact of this uncertainty surrounding over diagnosed cases.

## **3.4 Policy Considerations**

### **3.4.1 Health equity concerns**

A key subgroup modelled within this analysis is men of Black ethnicity. Black men are known to have a higher risk of prostate cancer compared with the general population [38] and some evidence suggests that Black men are also more likely to experience more aggressive cancer which spreads at a faster rate, and experience worse care outcomes compared with the general population [39]. It is concluded within the report that the data used to model this population was too uncertain to determine whether this would be a cost-effective application of

screening. The recommendations from the report suggest that *“this group would benefit from having better data on how cancer develops, progresses, and what the expected participation rate in screening would be for this population group”* with screening not recommended due to this uncertainty.

However, the report does not include any quantitative analysis surrounding health equity, or a more qualitative discussion surrounding the impact of the recommendations on health equity. The NSC has previously outlined the important principles of health inequalities, and why they are important to be considered, and also aligns with wider government stakeholders [40]. However, the SCHARR report contains no mention of equity, despite this being a core principle of the NHS 10-year plan [41]. Therefore, we expect authors to discuss the implications for health equity and health inequalities, given that these are core values for the NHS. The current report does not make any acknowledgement of wider policy, including the Core20PLUS5 framework [42]. This framework outlines the need to actively target inequalities for minority ethnic groups, with one of the 5 key clinical focus areas being the earlier diagnosis of cancer. If considering wider implications for health inequalities, there is evidence that Black men are less likely to get tested for the BRCA gene, so are likely to be disproportionately affected by current recommendations [43]. Furthermore, there are strategies within the current model, where screening Black men is considered more likely to be cost-effective than not, based on the results presented in Figure 99 of the SCHARR report. It is, therefore, surprising that the balance between uncertainty and health inequalities is not discussed, given the competing factors of ‘value’ to the NHS.

Additionally, the report also does not acknowledge the impact on regional inequities surrounding access to care and current screening. The SCHARR report does not discuss the anticipated effect with respect to income related inequities and their impact on health literacy. Previous studies have shown that areas of higher socioeconomic deprivation in the North of England have lower incidence rates of prostate cancer but higher rates of metastatic cancers [8]. This reflects the lower rates of testing in more deprived areas of the UK resulting in later diagnosis and consequent poorer outcomes. Organised screening could impact this, by increasing testing in areas that are more deprived. However, the true impact on health equity would have to consider by how much testing also increases in less deprived areas.

Variation in health literacy has also been found to disproportionately impact those from lower socioeconomic backgrounds. Previous studies have found people from lower socioeconomic backgrounds are less likely to identify problematic symptoms or know that they are able to request a PSA test from their GP [27].

Finally, deprivation has also been linked to knowledge of BRCA status, with those in more deprived areas found to have lower uptake of BRCA gene testing [44]. The recommendation to continue opportunistic testing and only recommend screening for those with knowledge of BRCA gene mutation may further enhance inequities in more deprived backgrounds.

We acknowledge that limitations on the scope and timeframe of this project would not have allowed for a full quantitative equity analysis. However, this report is intended to inform national decision making and would benefit from a discussion of the impact on health equity from potential recommendations.

### 3.4.2 Cost-effectiveness threshold

A £20,000 per quality-adjusted life year (QALY) cost-effectiveness threshold was used based on the National Institute for Health and Care Excellence's (NICE's) cost-effectiveness threshold [45]. The justification provided for this was alignment with previous NICE evaluations of screening where the lower bound is used to reflect high uncertainty often found in screening programmes. Screening for the general population is shown to be highly uncertain in the results of the probabilistic sensitivity analysis. However, we can see from the cost-effectiveness planes that for some specific screening scenarios, such as screening men of Black ethnicity starting at age 45 once every 4 years (Figure 94), there is a much tighter cluster of points. This indicates much higher certainty in the results of these scenarios which would provide justification for the use of a higher cost-effectiveness threshold.

Although it is up to the NSC what threshold they choose to use for the economic analysis, we believe that more justification needs to be provided for the use of a lower threshold, other than "screening is uncertain" as stated in the SCHARR report, and a clear rationale should be provided for the selected threshold. We also acknowledge there are trade-offs to using different thresholds, given that opportunity cost estimates (health that will be otherwise forgone) are lower than the NICE threshold [46]. However, it is important to note that if the NSC has previously aligned with the NICE threshold for decision making, it would appear to be inconsistent if they did also not adopt the new NICE threshold. This is particularly the case given the screening committee have expressed an interest in continuing to update the model with more relevant evidence.

#### **Recommendations for updates**

We recommend that an additional discussion of the impact of the model results and uncertainty on wider health equity concerns be included in the updated report. This should contextualise the recommendations made based on the model uncertainty and discuss the impact on the NHS focus to reduce health inequities. It is important that factors of value are appropriately discussed, to allow for a transparent, clear and deliberative decision-making process.

We also recommend that the base case cost-effectiveness threshold either be updated from £20,000 to align with the new cost-effectiveness threshold of £25,000 to £35,000, or that the approach is revised to consider aligning with an opportunity cost informed threshold. This would increase the credibility of any recommended decisions made based on the threshold.

## 3.5 Parameter Suitability

### 3.5.1 Baseline utilities

The utility reflective of a 70-year-old man was used as a reference value for the general population without cancer, to which multipliers were applied to determine the utility of each stage of cancer. The report does not include a justification as to why this utility was utilised as a baseline value. This assumption is likely an inaccurate reflection of the true utility value for both older and younger ages. The use of this utility value would lead to under valuing utilities for those under 70 years old and over valuing those above 70 years old.

#### Recommendations for updates

We recommend that the age specific utilities are selected from UK population norms utility data [1]. Further, it is recommended that SCHARR provide justification for their rationale behind parameter choices.

### 3.5.2 Costs and Resource Use

We have reviewed the costs and resource use inputs within the model as part of this critique. This section of the critique is split into sub-sections where additional considerations are required, to improve the robustness and reliability of the model. Based on our review, there are concerns surrounding the treatment costs, diagnostic costs and palliative care costs.

#### 3.5.2.1 Treatment costs

The key concern with respect to treatment costs is the reliance on extrapolating clinical trial data and applying costs, which does not reflect modern practice. We acknowledge that the nature of research is constantly evolving, and up to date data may not have been available when the SCHARR model was being developed. However, SCHARR has utilised data and structural validation from clinical trials including the CAP [47], ERSPC [48] and ProtecT [49] trials, which may not be representative of current clinical practice. Specifically, SCHARR has used long-term treatment costs that are based on the ProtecT trial and are no longer representative of the costs associated with current practice, given this data was collected up to 2009.

Another key concern around treatment costs is the treatment intensification proportions, and wider costs associated with stage four metastatic prostate cancer. SCHARR has applied a proportion of 1.8% of people receiving treatment intensification to stage 3 prostate cancer, and 28% for stage 4 [34]. However, these proportions are not reflective of the number of people receiving systemic anti-cancer therapies (SACTs) in current practice. Recent National Prostate Cancer Audit data [6] has established that approximately 47% of people with metastatic prostate cancer were receiving SACTs in 2022. Furthermore, a study conducted by Dodkins et al. 2025 [5], identified that out of 45.1% of people with metastatic hormone sensitive prostate cancer, approximately 70% received treatment intensification with either enzalutamide or apalutamide, with approximately 30% receiving other SACTs including docetaxel or abiraterone within 12 months post-diagnosis. We appreciate that SCHARR has adjusted the SACT

treatment costs to reflect current practice. However, the extent of recent advancements and accurate proportions of those receiving high-cost medications are still not adequately reflected in the model. This results in the underestimation of value from detecting earlier stage cancers and preventing their progression to higher cost stage 4 treatments.

Discussions with SCHARR indicated they will try to capture this in future updates, with the NSC indicating that they are open to future iterations of the model. They suggested adjusting down those diagnosed at stage 4, to account for the fact some people will progress to stage 4, and that will make up the whole number of people on SACTs. However, this will weight down the true number of people receiving SACT. 47% of people diagnosed at stage 4 should be allocated to receive SACT based on the available evidence, and this number scaled down for earlier stages, to account for progression. Those diagnosed at stage 4 should not be scaled.

A further concern is that SCHARR has applied SACT costs for a maximum of three years. Realistically, a substantial proportion of people with metastatic prostate cancer will live much longer than three years. Clinicians suggested that life expectancy for metastatic disease has increased from three years to approximately seven years on average. Additionally, published NHS England data identified that people diagnosed with stage four prostate cancer have an overall survival of 60.4% after five years [9]. This increase in life expectancy could potentially double the costs of SACTs for late-stage cancers, which SCHARR has not accounted for in the model; therefore, underestimating the treatment costs. All clinical experts that attended the workshops advised that where possible SACTs would be continued for the duration of a person's lifetime, unless the treatment stopped responding.

Finally, the model does not capture people progressing onto SACT costs from earlier stages. For example, a person diagnosed at stage 4 who dies from other causes after 15 years of follow-up is assigned SACT costs for the period stated. In contrast, a person diagnosed at stage 2 who subsequently progresses to stage 4 is not assigned SACT costs at all, even though it is clear that they experienced advanced disease before death. This is because progression is not explicitly captured. This has two effects in the model. Firstly, because less people are diagnosed at stage 4 in the screening arm, SACTs will be underestimated for those, who are now diagnosed at stage 2 or 3. However, those who are diagnosed earlier due to screening that were not going to be diagnosed at stage 4 in current practice, the value of screening is underestimated, as screening is likely to see less people ever progress to stage 4. Without adjusting the modelling to account for progression, it is not possible to say which bias will have the bigger impact.

### **Recommendations for updates**

We recommend two options to consider for long-term treatment costs. The first is that they should be acknowledged as out of date, and further clarity should be provided on the limitations of using this source, and the potential impact this has on the results (including the direction of the impact). The second option is to review more recent reports of ongoing trials to inform treatment costs. This could include potentially considering alternative trials and observing the resource use, for example, the recently launched TRANSFORM trial [3]. The risk of this is overestimating costs, due to differences in healthcare systems across countries. However, it is worth exploring more recent trials further. At a minimum, a more reflective discussion within the wider report would be helpful to convey transparency about the potential impact of outdated sources such as the ProtecT trial.

We recommend reviewing and adjusting the model parameters and structure to accurately reflect more updated data that is now available such as the National Prostate Cancer Audit 2025 [6] and Dodkins et al. 2025 [8]. This would result in more accurate assessment of late-stage cancer costs. Alongside this, updated survival estimates should be provided for stage 4 [9]. This will further increase treatment costs due to SACTs but may also result in a reduced positive impact on mortality due to screening, if people with advanced stages of cancer are living for longer.

We also recommend that SCHARR applies the SACT costs continuously to those alive with metastatic disease beyond year three.

### **3.5.2.2 Additional resource use**

From the report and additional queries with SCHARR, it is confirmed that the cost of resource use associated with prostate cancer (other than that included in treatment costs) has not been accounted for in the model, potentially introducing bias into the results. We identified previous NICE assessments and published research highlighting that it is likely that people will use more healthcare resource use outside of treatment, and this will likely increase with more advanced stages of the disease [50-55]. This exclusion likely biases the results and disregards the downstream burden imposed on the healthcare system.

### **Recommendations for updates**

We recommend that SCHARR incorporates wider healthcare resource use, beyond just treatment, to reflect real-life healthcare consumption of people with prostate cancer at different stages of disease. Further, SCHARR should account for wider resource use to capture the burden on primary care.

### 3.5.2.3 Diagnostic costs

The key concern with respect to diagnostic costs is the choice of diagnostic strategy applied in the model. Whilst SCHARR used the NICE guidelines [56] to inform the inclusion of multi-parametric MRI (mpMRI) in the model, a consensus amongst clinicians identified that these guidelines are now outdated as they are not fully reflective of current practice. Additionally, clinician feedback established that bi-parametric MRI (bpMRI) is being routinely used in a substantial number of areas across the country and is typically the preferred imaging technique for asymptomatic people. It also highlighted the substantial difference in costs associated with each of the screening techniques, leading to cost savings when using bpMRI. Further clinician consensus suggested that for any Trusts still using mpMRI, the disruption to practice caused by switching to bpMRI would be minimal and likely to improve capacity.

A second concern identified when cross-checking parameters was the source of the local anaesthetic transperineal (LATP) biopsy cost. SCHARR reported the cost for a transperineal biopsy of £1,138. Initially, this value could not be sourced; however, following additional clarification from SCHARR, it was identified that this cost was correct but not accurately described in the report and instead reflects the overall Healthcare Resource Groups (HRG) cost rather than the outpatient specific cost.

Whilst the cost SCHARR has used is likely reflective of current practice with no organised screening, it is important to acknowledge the recent and ongoing shift in policy and general advice suggesting that LATPs can and should be conducted in an outpatient setting where possible, which may change during screening [57-59]. Therefore, we would recommend running a scenario with LATP costs from outpatient services, to see the impact it has on the results.

#### **Recommendations for updates**

We recommend that SCHARR runs a model scenario with bpMRI to capture the potential impact this could have on the model, in addition to reflecting current practice. Other parameters would have to be adjusted for this model scenario; recommendations for these additional parameters can be found in Appendix A.

We recommend that SCHARR update the report with the correct description for the cost used for LATP. It should be stated that this cost reflects that of an overall LATP rather than an outpatient specific cost as is currently reported.

We also recommend that SCHARR runs a model scenario with a cost reflecting an outpatient LATP (£479.04) using the NHS reference cost of a transperineal biopsy (code LB77Z, urology service). It would be interesting to see the potential impact this change in cost would have to align with the shift in policy and general advice.

### 3.5.2.4 Diagnostic resource use

A further observation of the SCHARR report is that diagnostic resource use has not been adequately accounted for, potentially omitting the pre-diagnosis resources; for example, people

that remain in a 'watchful waiting' period. Additional clarification was sought from SCHARR, and it was confirmed that the number of biopsies was included as a parameter in the model to account for additional resource use. However, including this does not capture the wider diagnostic healthcare use throughout the diagnostic pathway for prostate cancer.

#### **Recommendations for updates**

We recommend that SCHARR considers the addition of further resource use associated with the diagnosis of prostate cancer to adequately reflect clinical practice. We also recommend that the inclusion of any resource use within existing parameters is made clearer in the report.

#### **3.5.2.5 Palliative care costs**

A concern pertaining to the palliative care costs is the potential double-counting of costs around end-of-life treatments for those with prostate cancer. We were unable to ascertain which treatment costs are applied alongside palliative care costs within the timepoint of 12 months before death due to a lack of reporting clarity. However, in the instance that the palliative care costs are applied alongside treatment costs, the costs associated with active treatment may be accounted for two-fold since the palliative care costs include the cost of some cancer treatments such as opioids for pain-relief. This would subsequently result in the overestimation of costs associated with end-of-life care.

#### **Recommendations for updates**

We recommend that SCHARR addresses these concerns by enhancing the transparency in costing methods and reporting quality. Clinical experts have confirmed that the overall difference in costs between a prostate cancer death and non-prostate cancer death are reasonable, so the concern is mainly surrounding double counting.

#### **3.5.2.6 Diagnostic specificity**

Following discussions with clinicians, there is a concern with the diagnostic MRI specificity and whether the value used is representative of a screened population, when bpMRI is primarily used, not mpMRI. Please see section 3.6.4 for further details.

#### **Recommendations for updates**

We recommend that SCHARR updates the specificity of the MRI as the current value is not representative of a screened population and will therefore not accurately represent the patient flows through the system. We recommend using the specificity of 0.72, which is reported in Bass et al. (2021) [2]. Further, the same value representing a screened population from the STLK3-MRI screening trial (0.72) has been independently quoted by clinical experts.

## 3.6 Model Structure

The review highlighted some key areas of critique within the chosen model structure for the analysis.

### 3.6.1 Risk factors

The model included age, ethnicity, family history of breast, ovarian or prostate cancer, and BRCA gene mutation as risk factors for prostate cancer. While the possession of these risk factors is not treated as independent, the individual risk of prostate cancer for a person with multiple risk factors is treated as independent and non-cumulative. The model only applies the highest hazard ratio present when a person possesses multiple risk factors. This is likely to underestimate the risk of prostate cancer for those men who have multiple risk factors. Therefore, this is likely to undervalue the early detection of prostate cancer in certain risk groups. This also leads to overestimation of the harms of over diagnosing low-risk cancers.

It was stated in the report that the risk factors were initially modelled as cumulative. However, the report states that this led to unrealistic results. While it does not state in the report what is meant by 'unrealistic', clarification was provided by SCHARR that this resulted in little to no men within the lower GGGs throughout the model. It is accepted that this result is unrealistic. However, the concern remains, based on feedback from clinical experts, that having multiple risk factors would increase the risk of prostate cancer beyond the highest hazard ratio present. Clinical experts, including geneticists, agreed that the risks are not likely to be completely independent. However, they also stated that they are not perfectly cumulative. Generally, they agreed that having multiple risk factors is greater risk than just having one risk factor.

Published literature, such as Nyberg et al. (2021), highlight that the relative risk of prostate cancer varied by age, ethnicity, and BRCA mutation when multiple risks are present [60]. To explore the impact of the assumption in the model, a scenario could be run where a multiplier is applied to the hazard ratios when multiple risks are present. We recommend eliciting values with geneticists to explore reasonable ranges to consider for this parameter.

We acknowledge that, due to data limitations, assumptions have been applied in the model where these have been conservative estimates. However, lack of appropriate scenario analyses around these assumptions results in producing outcomes that are likely biased against screening. Appropriate testing of the assumption is required, guided by clinical opinion when current assumptions do not reflect the population and real-world practice appropriately, to show the impact of these assumptions on the model results. This allows more transparent and informed decision-making.

#### **Recommendations for updates**

We recommend that SCHARR considers conducting scenario analyses to explore the cumulative impact of a person having a multifactorial risk profile and to explore if BRCA1 and BRCA2 variant genes should be treated as independent populations.

### 3.6.1.1 Familial history subgroup

An additional concern on model subgroups, is that SCHARR has treated familial history as one subgroup and has defined familial history as broad as possible. The definition used is a person having one or more first-degree relatives previously diagnosed with prostate, ovarian or breast cancer. Clinical feedback suggests that this should be defined as a family member presenting with cancer prostate, ovarian or breast cancer before the age of 60. This is because those diagnosed at later ages may not necessarily increase the risk of a family relative also getting prostate, ovarian or breast cancer.

However, previously published evidence has also suggested that risks differ depending on the type of family history. A nationwide study conducted by Bratt et al, 2016 established that those with no family history of prostate cancer were associated with a 13% risk [61]. However, those with family history had an increased absolute risk of 26% for an affected father, 35% for two affected brothers, and for those two combined the risk rose to 48% [61]. Additionally, the study identified that family history cannot be used to determine cancer aggressiveness and that having relatives diagnosed at an earlier age is associated with a higher absolute risk of developing prostate cancer at an earlier age. According to the report, the current definition of family history represents approximately 1/3 of all men. It may not be cost-effective to provide a screening to this whole subpopulation, but it may be cost-effective to provide screening to a narrower subpopulation, based on higher risk.

#### Recommendations for updates

We recommend that SCHARR further defines the familial history subgroup. Clinician feedback suggests a definition of people presenting before the age of 60 years old.

We recommend that SCHARR further refines the familial history subgroup based on risk, exploring in scenario analysis, to determine the impact of more specific definitions of family history on the cost-effectiveness results.

### 3.6.2 Mapping to cancer stages and progression

The methods used to map GGG 1 to 5 to cancer stages in the model are ambiguous. The report states that the incidence rates of GGG by stage were taken from the Get Data Out dataset from the National Cancer Registration and Analysis Service 2020. Due to a different staging system being used (localised, locally advanced, and metastatic) compared with the model, they were loosely converted to stages 1 to 4. The report then goes on to state that weighted averages were applied to avoid conflict with NHS Digital data. However, there is a lack of detail regarding how these were calculated. This assumption has a substantial impact on the results of the model, due to the current approach of treatment distribution across the GGGs. A flawed mapping approach could lead to an increase in the number of men within higher GGGs, resulting in inflated treatment costs and health-related quality-of-life (HRQoL) decrements. It was also noted by clinicians that the treatment allocation within the GGGs is not reflective of current practice, which is especially evident for GGG 1. It is believed that almost all patients within this GGG should be receiving active surveillance. In turn, this would result in lower treatment costs.

The approach adopted in the model to mapping GGG to cancer stage appears to suggest the notion that priority was placed on fitting the decision problem into the model, rather than fitting the model to the decision problem. Previous economic models (e.g. NG131) do not use the staging system of 1 to 4 that is used in this current model. It is possible that altering the structure of the model to incorporate alternative cancer staging could have led to improvements in clarity of the modelling methods.

In addition, it is unclear how this differs between the intervention and comparator particularly for over diagnosed cases. As stated in Section 3.3, the distribution of over diagnosed cases across the GGGs is not explored. The mapping of an over diagnosed case should result in a lower cancer stage, due to the assumption that the cancer diagnosed would not cause harm over the person's lifetime. This evident lack of clarity impacts the assumption regarding the progression of GGG, as it is unknown how the link between GGG and cancer stage was made. Additional clarification is required regarding how GGG was mapped to the cancer stages. The difference in mapping between the comparator and intervention arm should be clearly outlined, with particular emphasis on the assignment of GGG scores to those classed as over diagnosed.

Furthermore, the progression time of undiagnosed cancer was sampled from a Weibull distribution, with the assumption of perfect correlation. In turn, meaning that those who progress rapidly through stages 1 and 2, would do the same for remaining cancer stages, and vice versa if initial progression was slow. Clinical opinion was mixed on this. Some experts considered this a fair assumption, and that progression was relatively linear. However, other experts suggested that progression may become faster, particularly as people move into more advanced stages. Further scenario analysis surrounding this is likely to be useful.

#### **Recommendations for updates**

We recommend that SCHARR provides clarification regarding how GGG was mapped to the cancer stages. We also recommend that SCHARR provides clarification on the difference in mapping between the comparator and intervention arm, with particular emphasis on the distribution of GGG scores for those classed as over diagnosed.

### **3.6.3 Application of discounting**

There is a lack of clarity within the report regarding the application of discounting in the model. The report states that discounting is applied from (a) *“the cycle of the youngest age across all interventions”*, and (b) *“the cycle in which each intervention began”*. It is unclear whether this means that discounting is applied at two different points in the model at the same time or if a combination of methods has been used. The report also states that discounting was applied *“from the first cycle of the intervention for both the intervention and comparator arms”*, which adds further uncertainty. At present we understand this to mean that discounting occurs at two separate time points in the intervention and comparator arms, which is incorrect. If modelled appropriately, people may be undergoing their first diagnostic tests at different time points in the intervention and comparator arms, for each simulated patient. This reflects the variation in practice that will be introduced from a formal screening strategy. Therefore, it is recommended that further clarity is provided, if the above is misinterpreted. Alternatively, if the above is true,

discounting must be applied from the same cycle equally in the comparator and intervention arms.

#### **Recommendations for updates**

We recommend that SCHARR provides clarification on the application of discounting in the model.

### **3.6.4 Diagnostic pathway**

The diagnostic pathway used in the model includes the use of mpMRI prior to biopsy. This was chosen based on the current NICE guidelines for prostate cancer diagnosis [51]. However, it was stated by numerous clinicians that there is an ongoing transition to the use of bpMRI within the healthcare system. Evidence suggests that bpMRI is as equally effective as mpMRI [62], as well as increasing efficiency [63].

This accelerated imaging time will reduce the diagnostic costs associated with prostate cancer screening but has also been shown to potentially have a higher specificity [2, 64]. Additionally, multiple clinicians noted that bpMRI would be easy to implement into the diagnostic pathway for prostate cancer. As a result, it is recommended that a scenario is run where a proportion of patients receive bpMRI prior to biopsy as well as a scenario where all patients receive a bpMRI. This will enable a better understanding of what the impact on the model results will be from switching the cohort to have a bpMRI.

Discussion with clinicians has outlined that the introduction with bpMRI is likely to substantially improve specificity. Previous evidence suggests that the use of strict PI-RADS 4/5 cutoffs with bpMRI enables much higher specificity, thereby preventing the diagnosis of indolent cancers. The specificity value of 0.45 used in the model currently is extrapolated from routine urological outpatient settings (PI-RADS 3-5), where diagnostic priorities differ from those in population screening. Therefore, this underlying specificity does not represent a screened population. As a result, the patient flow through screening is likely to be substantially different, with a much lower number of false negatives than currently estimated. Further, previous studies suggest that bpMRI is likely to have much higher specificity, but with minimal change to sensitivity [65].

#### **Recommendations for updates**

We recommend that SCHARR alters the base case so that men receive bpMRI rather than mpMRI.

## 4 Scenario Results

As part of this critique, we requested that scenarios were run by SCHARR (see Appendix B). The results of these scenarios have been provided (see Appendix C). There were 4 scenarios run for both the Black ethnicity and familial history subgroups in an additive manner (e.g. scenario 1; scenario 1 and 2; scenario 1,2, and 3; and finally, all 4 scenarios together).

One final scenario was run to see the impact of all 4 scenarios together on the general population to make a total of 9 scenarios. Following the discussion with SCHARR (see Appendix B for further details) the scenarios applied were as follows:

- **Scenario 1:** The cost of biopsy for the screening arm has been decreased to model a scenario where all biopsies are performed as outpatient procedures.
- **Scenario 2:** The cost, specificity and sensitivity of MRI in the screening arm have been updated to model the use of bpMRI rather than mpMRI.
- **Scenario 3:** The weighting of the SACT costs was altered across both arms to reflect a greater proportion of people receiving them, reflected in an increased weighted cost.
- **Scenario 4:** The SACT costs in both arms have been assumed to continue, remaining constant until death for those who were not discontinued by the end of the third year.

Before running these scenarios, additional changes were made by SCHARR to the model base case and any interpretation of the scenario results assumes these changes were also applied (see the “Summary of changes” document in Appendix C for an overview of the adaptations to the model base case).

It is important to note that the scenarios conducted were likely to be crude, given the time limitations associated with running scenarios. Therefore, the aim of the scenarios was to understand the sensitivity of the results to underlying assumptions and data points in the model. We acknowledge the uncertainty of these results because of the crude changes, and we do not advocate that these scenarios should represent the new base case. The scenarios also only cover a limited number of concerns raised in this report.

### 4.1 Black Ethnicity

All screening strategies with multiple screenings become more likely to be cost-effective when all recommended scenarios were applied, when compared with the new base case. Screening every 4 years, 3 years, and yearly between 55 and 60 years of age has an incremental cost-effectiveness ratio (ICER) substantially below the £20,000 per QALY threshold (all less than £9,000 per QALY). Additionally, all single age screening scenarios, except from screening at 45, 65, and 68, may be cost-effective at a £20,000 threshold, with screening at age 58 having an estimated ICER of £951 when all scenarios were applied.

### 4.2 Family History

All screening strategies with multiple screenings become more likely to be cost-effective when all recommended scenarios are run, when compared with the new base case. All screening strategies with multiple screenings become more likely to be cost-effective at a £20,000 per

QALY threshold. The greatest ICER reduction evident for annual screening between 55 and 62 years of age, with new ICERs ranging between £11,709 per QALY and £15,126 per QALY. Also, single age screening populations for ages 50, 55, 58, 60 and 62 were estimated to be cost effective at a £20,000 per QALY threshold.

### **4.3 General Population**

The incremental results from the new base case with the additional requested scenarios estimated that a single screening scenario for ages 55 or 60 would be cost effective under the £20,000 per QALY cost-effectiveness threshold with an ICER of £12,800 and £19,800 per QALY respectively. In addition, considering a £25,000 per QALY threshold, in line with the updated NICE cost-effectiveness threshold recommendations, the testing every 5 years between 50 and 60, testing every 3 years between 55 and 61, and single screening at age 58 are all cost-effective. The scenarios were not applied incrementally for the general population. However, the results of the combined scenarios indicate that further exploration would be useful to explore the cost-effectiveness of specific screening methods for all men.

### **4.4 Scenario Impact**

Overall, the scenario analysis results suggest that scenario 4 had the greatest impact on the results when compared to the other scenarios. Scenario 4 resulted in the largest ICER reductions, leading to more screening populations being more likely to be cost effective at a £20,000 threshold. It is important to note that this scenario is likely to overestimate SACTs costs, given it may not adequately reflect discontinuation after year 3. However, given that SACT costs were underestimated in the base model, understanding the potential impact, highlights the importance of accurately predicting these long-term treatment costs. This is because a substantial proportion of people with stage 4 disease will still be on SACT, as discussed in Section 3.5.2.1.

When considering the incremental impact of each scenario we see that for both the familial history and Black ethnicity subgroups, the most impactful incremental effect was between the base case and the introduction of scenario 1. The introduction of a screening programme alongside guidance to perform transperineal biopsies as outpatient procedures may change the picture of for both subgroups for specific screening methods, regardless of any other concerns raised with respect to the model.

We acknowledge the limitations of the scenarios discussed. For instance, scenarios 1 and 2 were based on clinical advice surrounding adaptations to the current testing process that could be plausibly implemented with the introduction of a screening programme. These do not necessarily reflect current practice, and it is likely that the adherence to this guidance would not be 100%. Additionally, due to structural constraints, the application of scenarios 3 and 4 is uncertain (see Appendix C). It is also important to note the results from the scenarios do not cover the uncertainty from a probabilistic sensitivity analysis. However, we believe the results suggests that further modelling should be conducted to address the concerns raised within this report, given it could change the direction of the economic results.

## 5 Discussion

Our review identified a range of concerns regarding both the modelling choices and reporting of the SCHARR model. This discussion focuses on the points raised and the recommended updates that are anticipated to have the greatest impact on the model outcomes and subsequent decision making. Additional concerns are detailed in Appendix A.

A key concern identified throughout the report is that the model does not capture a system where the introduction of organised screening for prostate cancer reduces opportunistic screening or negates the need for it entirely. It is unrealistic that the scale of opportunistic PSA testing would remain constant with the addition of organised testing, which has a knock-on effect on the model results. The current model structure fails to accurately capture the potential variability in changes to the clinical pathway when organised screening is implemented. Therefore, it is difficult to apply the results of the model to the real world. It is necessary to update the intervention and comparator definitions in the model to adequately reflect what would occur in practice to provide valid results.

Another concern is the direction of bias in the assumptions made. It is reported throughout that assumptions are mostly conservative with respect to screening and, as a result, are likely to be biased against the introduction of organised screening. This includes (but is not limited to) assumptions surrounding opportunistic screening, the definition of overdiagnosis, application of treatment costs and definitions of family history. These assumptions are particularly important for subgroup results for populations with family history and Black men, given the estimated results are close to the cost-effectiveness threshold. Adjustments in these assumptions could lead to the results changing direction, and organised screening within these subpopulations becoming cost-effective.

The conservative nature of the modelling approach is also reflected in the phrasing of discussion throughout the report, with a primary focus on the harms of overdiagnosis. We believe it is important to make sure that balance is given to the discussion, so that potential biases are appropriately described, including their direction. We acknowledge that assumptions are unavoidable in a modelling process and best practice, and often the more conservative assumption is taken in the base case. However, due to the large number of assumptions necessary in this model, the cumulative effect is likely to be underestimating the potential value of organised screening, and the impacts of relaxing these assumptions are not appropriately explored. As a result, we recommend further exploration of the impact of these assumptions, utilising clinical feedback to inform plausible parameter values in the absence of appropriate evidence. This will help provide a report which better acknowledges the uncertainties, to support NSC in making a more informed decision.

Furthermore, treatment and diagnostic costs are not reflective of current practice. For instance, recent innovation concerning the use of SACTs for late-stage cancers are anticipated to have a substantial effect on overall treatment costs. SACTs are associated with a high cost and are currently recommended for the remainder of the person's lifespan, which is not reflected in the current model. SACTs are also expected to increase life expectancy, essentially increasing the costs associated with stage 4 disease, but may also reflect lower than expected improvements in survival from screening. SACT costs are also not applied to earlier stages, which will bias the results in two ways. It will bias in favour of screening, for those diagnosed earlier than stage 4

because of organised screening but would otherwise be diagnosed at stage 4, given a stage 2 diagnosis in the model does not capture any future SACTs being used. However, it will also bias against screening, given some people will be diagnosed at stage 1 instead of 2 or 3 because of organised screening, and the earlier diagnosis means they are less likely to ever need SACTs.

Another key concern highlighted within our review is in relation to the way in which GGG was mapped to cancer stages. There is a lack of clarity provided for the calculation, how this differed for over-diagnosed cases, and how it differed between the intervention and comparator arms of the model. The current approach is likely to increase treatment costs due to the distribution across GGG between diagnosed and over diagnosed cases. We recommend that further clarity on the method used to map GGG to cancer stage be added to the report. It would also be beneficial to perform scenario analysis to explore the impact of structural uncertainty introduced here, concerning the treatment costs, by reweighting treatment distribution by GGG for cases identified through screening and the subsequent mapping and impact on cancer stages.

The definition and modelling of the family history high-risk subgroup is an area that will benefit from further exploration. Feedback from clinicians consistently emphasised the importance of additional exploration of this risk factor. The application of an equal hazard regardless of the number of relatives with cancer, type of cancer, age of diagnosis for the relative, and cancer stage for diagnosed relative was deemed to be insufficient and over-generalised. As stated in previous sections, previous published evidence has stratified this risk further, and it is likely that the current definition of family history is not fit for purpose. For example, the relative risk of prostate cancer for someone with multiple close family members diagnosed with aggressive prostate cancer at a young age is much higher than for someone with one family member diagnosed with low-grade ovarian or even prostate cancer at an older age. It is therefore important to consider if family history could be narrowed down, to understand if screening is cost-effective in specific populations with familial history, rather than considering family history as one collective group.

Finally, the methods used to identify and estimate the associated impact of over diagnosed cases are not made clear in the report. The provided definition does not appear to align with the application to the model. Additionally, the omission of a results breakdown increases the difficulty with determining whether this has been consistently applied to both arms and the extent of the impact this has on incremental results. The definition of the intervention including organised screening as completely additive to current practice also contributes to the overestimation of the incremental impact of overdiagnosis. Therefore, we recommend that the definition of overdiagnosis be clearly defined and the method of application be adjusted to reflect this. We also recommend scenario analysis to explore the uncertainty surrounding the distribution of GGG and the associated treatment costs, as well as the impact on the incremental effect if the intervention definition is altered to reflect an adjustment to current opportunistic screening with the introduction of an organised screening programme.

The scenario analysis to explore the potential impact of assumptions made as part of the modelling approach also highlighted the sensitivity of the results to these assumptions, particularly in sub populations where the risk of prostate cancer is higher. Therefore, it is

important to consider the potential concerns raised in this report, to reflect a more robust analysis of prostate cancer screening in the UK.

The concerns raised throughout this report are important to be considered by the NSC, as well as how they may impact the cost-effectiveness results. The concerns raised are also likely to have much more impact on the specific at-risk populations. This is because for those with family history and Black men, the cost-effectiveness results were uncertain, close to the cost-effectiveness threshold, and were sensitive to changing assumptions and data. We believe the recommendations throughout this report should be taken forward into future analysis, to provide the most robust evidence to inform evidence-based policy surrounding prostate cancer screening.

## 5.1 Limitations

This critique provides a comprehensive overview of the main concerns identified. However, there were also limitations to the critique.

A key limitation of this critique was the lack of access to SCHARR's executable model, on which the report and recommendations were formed. Not having access to the model hindered the validation process of key structural and parameter choices, which would have been easier to understand with access to the model. The lack of reporting clarity led to calculations, such as the mapping of GGGs to cancer stage, being unclear, and therefore difficult to interpret and validate. It was also difficult to determine the key drivers of the model with uncertainty surrounding the resources, costs, and utilities assigned to each model arm. Therefore, all recommendations in this critique are based solely on the technical report and may not be applicable in instances where the SCHARR report incorrectly reflects the methods used in the model. We assumed that there are no programming errors in the model calculations. We were unable to verify the calculations made so any suggested amendments assume that all methods outlined in the report were correctly applied.

Additionally, this critique did not include an exhaustive literature search. Instead, pragmatic literature searches were conducted, targeting areas where the report stated a paucity of available evidence. Therefore, we acknowledge that more suitable data may be available to inform certain parameters that we did not capture within our targeted searches. However, to mitigate this potential omission of evidence, we consulted an extensive range of clinical experts to assist with the process so that the most recent and appropriate known evidence was considered.

As discussed in Section 4.4, we also acknowledge the limitations of the crude scenarios conducted to explore the potential impact of certain assumptions on the model. We believe more comprehensive updates should be made to the model, to more accurately reflect the concerns in this report. As a result, we also believe the results presented in scenario analysis should not present the new base case for the economic analysis.

## 6 Conclusion

We acknowledge the important work that the NSC conducts on screening recommendations, and the work of SCHAAR in modelling a complex screening intervention. We also recognise the challenges faced by analysts in providing robust analysis to inform evidence-based policy.

Initiating screening involves a complex array of factors that must be quantified in the analysis and, as such, assumptions are necessary to estimate the impact. Whilst we do not expect the economic analysis to be able to capture every possible complexity, a transparent description of the analysis, including a thorough discussion of uncertainty and the challenges encountered is required.

We also believe that there are a range of concerns surrounding the economic analysis that can be updated, beyond a more detailed and thorough write up of the analysis. Some of these changes are simple amendments to make, while others are more complex and will be more time consuming. However, the concerns are all important considerations, particularly for at-risk subgroups, where the cost-effectiveness estimates are relatively close to the threshold. We recommend that the updates listed throughout this document are implemented, to provide a more robust economic analysis to inform the NSC's decision on prostate cancer screening.

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## Appendix A: Other Critique Considerations

Point of consideration	Page number	Interpretation of justification	YHEC evaluation of consideration	YHEC recommendation
The search strategy is not included in the report	23	No justification provided	<p>It is important to consider the breadth of evidence that was considered as part of the review. If certain evidence was missed as part of the searches being more pragmatic, then it is important to reflect how this may impact the results.</p> <p>It is best practice, even for pragmatic reviews, to provide the search strategy, where possible. Providing a search strategy is common for other large technical reports, including NICE submissions. This allows transparency over the scope of evidence considered.</p> <p>From the searches provided to us, it is clear that important papers were not picked up in the pragmatic review. These papers are referenced throughout Section 3.</p>	<p>Provide an appendix where the search strategy is detailed. It is worth discussing the likelihood of missed evidence in the discussion sections of the report.</p> <p>Papers referenced throughout our report are not identified using SCHARRs search strategy.</p>
The disutility scores for biopsies are applied for one week, but longest symptoms last for 5 days.	72	Generally applied conservatively to account for the fact that some people may have symptoms or impacts for longer.	<p>The disutility scores for biopsy (although low) are likely an overestimate. They are also applied to lots of people, so this could have an significant impact.</p> <p>SCHARR assumes that a disutility of -0.013 last for one week. However, they also state that (i) "the longest symptoms last for five days", (ii) people who received biopsies "more than recover", implying that their quality of life returns higher than before the biopsy. This might be a valid finding, in that the biopsy provides reassurance and relief from worry which is not reflected. They also state that many people do not have any symptoms.</p>	Adjust the application of disutilities so they only apply for 5 days. If data are available, then SCAHRR should consider the benefit from quality of life improving due to receiving a test.
The source cited for the palliative care costs is incorrect.	79	SCHARR cites Diernberger et al, (2023)[63] in the text but reference 63 is a Diernberger et al, (2021) paper.	<p>We believe the correct source is:</p> <p>Diernberger K, Luta X, Bowden J, Droney J, Lemmon E, Tramonti G, Shinkins B, Gray E, Marti J, Hall PS. Variation in hospital cost trajectories at the end of life by age, multimorbidity and cancer type. <i>Int J Popul Data Sci.</i> 2023 Jan 16;8(1):1768. doi: 10.23889/ijpds.v8i1.1768. PMID: 36721848; PMCID: PMC9871727.</p>	Amend the reference list to cite the correct paper.
Screening strategies with multiple screening tests consider scenarios for risk adjustment. However, this is only reinventing those with a PSA result of 2.5ng/mL or 3ng/mL. There is a range of evidence that suggests people with	N/A	SCHARR explored a range of screening strategies. However, it is not clear if they considered the impact of low PSA test results on future testing within these scenarios.	It is unclear why only those under 3 ng/mL or 2.5ng/mL were selected for scenarios where they are not screened further. Previous evidence still indicates that the risk in these groups of developing prostate cancer is quite high. Therefore, strategies could be considered for those at much lower risk. Clinicians indicated that it would still be useful to test these people every five years, rather than no longer screening them at all.	Adjust the scenarios to only consider reducing follow up testing based on those at lowest risk, not just under 2.5ng/mL or 3ng/mL.

Point of consideration	Page number	Interpretation of justification	YHEC evaluation of consideration	YHEC recommendation
an initially low PSA test results are less likely to go on to develop prostate cancer (less than 1ng/ML) [66-72]				
SCHAAR's modelling generally focuses on screening strategies between age 50 and 60. However, clinical feedback, and evidence from other countries suggest the most effective screening happens between ages of 55-69 [73, 74].	N/A	It is not clear why SCHARR focused screening on ages 50-60.	It is unclear the rationale for many of the screening strategies considered looking at age 50-60. Given evidence from other countries, screening strategies at ages beyond 60 should also have been explored, to understand the impact on the results. For instance, it could be that screening those close to 50 is likely not efficient, or it could be that screening close to 70 is not efficient. However, it is difficult to comment given this was not fully explored.	Consider changing the screening strategies that capture age groups to reflect those used in other countries, based on previous evidence.
Concerns were raised by clinicians that active surveillance methods have changed since 2016-2018. Clinicians raised concerns that the guidelines are out of date, and the costings likely do not reflect current practice.	N/A	SCHARR has based their modelling on the most recent guidelines, and available data they identified.	We acknowledge the challenge of modelling a disease area where the care pathway is changing relatively quickly. However, it is also important that a wide range of clinical experts is consulted to inform modelling parameters and structure, which does not appear to be the case. For example, in the SCHARR report (page 22), an oncologist was not consulted as part of validating the model.	Seek further clinical engagement to discuss current practices in surveillance. This will help shape what can be costed as part of active surveillance costs. It is likely the Wills et al (2024) costs can be adjusted to better reflect current practice, based on clinical advice.
The specific device used for LATP was not specified in the report.	N/A	N/A	NICE guidance outlines the four recommended freehand needle positioning devices for LATP including: <ul style="list-style-type: none"> <li>▪ PrecisionPoint</li> <li>▪ EZU-PA3U device</li> <li>▪ Trinity Perine Grid</li> <li>▪ UA1232 puncture attachment</li> </ul> Each of these devices is associated with a different cost. These costs can be sourced from the NICE Resource impact report (HTG680) [52].	Consider the specific device used in practice to accurately cost the diagnostic pathway. If this is already accounted for in the average cost, then this should be made clear in the text
The report does not discuss the inequalities associated with knowing BRCA status.	N/A	No justification provided	Knowledge of the BRCA gene mutation requires genetic testing. Genetic services are vulnerable to accessibility barriers that prevent equitable access to services. These difficulties in access disproportionately affect those who are more socially vulnerable due to factors such as socioeconomic status and ethnicity. This is also reflected in a lack of resources and physical access to services [75]. This analysis does not model BRCA gene testing as it falls outside of the project scope. However, it should	The impact of these inequalities should be discussed within the report

Point of consideration	Page number	Interpretation of justification	YHEC evaluation of consideration	YHEC recommendation
			consider the impact of recommending screening for those with known BRCA status on the health equity gap.	

## Appendix B: Model Scenario Requests

The document embedded below shows the model scenario requests made and the exchange between YHEC and SCHARR clarifying what would be run.



*Following discussion, the final responses for request 3 exchanged further via email were as follows:*

### **YHEC response**

We think this comes from trying to overcomplicate the scenario. We are not saying that people from earlier stages won't progress and require SACTs. However, it seems like you are weighing down those diagnosed directly at stage 4 (not a progression), to account for progression (we know you are not modelling this explicitly). This will then underestimate the SACT costs, because this is a one-year snapshot and we cannot entangle where exactly people come from in a snapshot. Specifically, from the data, given the definitions are not the clearest, you cannot necessarily untangle who was a progressed metastatic cancer, and who was a new metastatic cancer. The base assumption would be that it doesn't matter, and that 47% of people who progressed to stage 4 go on to get SACTs, and 47% who were diagnosed immediately at stage 4 get SACT, given there is no distinction between how you got to stage 4.

What we're saying is that 47% should be applied to those who are diagnosed at stage 4, and then those diagnosed at earlier stages the costs can be scaled to account for the fact that some people will progress to stage 4 from earlier stages. The complexity comes in because you are trying to line up progression on a 1-year snapshot of data. Stage 1,2,3 would be working out how many people we expect to progress to stage 4, and 47% of those people who progress will then receive SACT (47% multiplied by the proportion expected to progress to stage 4 in each stage) We know this second step is done implicitly rather than explicitly by weighting treatment costs.

We are not saying that it should be applied to only people diagnosed at stage 4. However, you developed the model around the datapoint that 28% of people received treatment in stage 4. We are saying this should be replaced with 47%, with 47% of people diagnosed at stage 4 receiving SACT, and if done before, working out roughly how many people would progress to stage 4 from earlier stages, and taking that 47% of those would receive SACT too. It was not clear in the original report that you adjusted earlier stages for SACT (based on the fact some people will progress), but it was clear you had used the datapoint of 28%. The assumption was

that the 28% was pivotal to weighting costs before, so we are suggesting replacing it with 47% and spreading this appropriately to capture metastatic disease

### **Reply from SCHARR**

Following several discussions with the UK NSC, I would be grateful if you could confirm whether you agree with this approach for Scenarios 3 and 4, as a summary of all email exchanges, or suggest an alternative approach which is feasible to implement easily within the model structure? SENSS does not have capacity to look for data and recalculate proportion of patients annually progressing across the stages to calculate average weighted costs now, so if this is YHEC suggestion, could you please provide these calculations and references.

SENSS suggestion:

Stage 4 at diagnosis: Allocate SACT treatment costs to 46.88% of men.

Stage 1–3 at diagnosis: Allocate one year of stage 4–related costs to those patients who were diagnosed at stages 1–3 and progressed to stage 4 in the year of their death, under the assumption that progression to stage 4 occurred prior to mortality.

### **YHEC response**

We're aware it is a difficult scenario to run quickly and will take longer to investigate more thoroughly. In that case we're happy to run the scenario suggested.

## Appendix C: Scenario Results



final.zip

This zip file contains the information relating to the scenario analysis and updated base case.

## Appendix D: Clinical and Expert Advisors

The below table details the 15 clinicians and expert advisors consulted for this critique.

Name	Occupation
Dr Simon Bott	Consultant Urologist, Frimley Park Hospital
Professor Ola Bratt	Professor of Clinical Cancer Epidemiology, University of Gothenburg and Chairman of the National Working Group for Organised Prostate Cancer Testing
Dr Kyle Bryan	Global Head, Oncology Center of Excellence & Chief Medical Officer, IQVIA Biotech
Professor Sigrid Carlsson	Division Head of the Clinical Epidemiology of Early Cancer Detection at DKFZ German Cancer Research Center
Mark Chapman	Former director of HealthTech, NICE
Professor Philip Cornford	Consultant Urologist Bon Secours Cork and Honorary Professor. Chair of EAU Prostate Cancer Guidelines
Professor Simon Crabb	Professor of Experimental Cancer Therapeutics, Southampton School of Cancer Sciences and Honorary Consultant in Medical Oncology, University Hospital Southampton
Professor Harry de Koning	Deputy Head and Professor of Public Health & Screening Evaluation, Department of Public Health, Erasmus MC University Medical Centre
Professor Ruth Etzioni	Program in Biostatistics, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center
Professor Nick James	Professor of Prostate and Bladder Research, Institute of Cancer Research and Royal Marsden Hospital
Professor Stephen Langley	Professor and Clinical Director of Urology at the Royal Surrey County Hospital
Professor Anwar Padhani	Oncological Radiologist, Mount Vernon Cancer Centre and Professor of Cancer Imaging at the Institute of Cancer Research
Professor Prasanna Sooriakumaran	Consultant Urological Surgeon, University College London Hospitals
Dr Andrew Vickers	Attending Research Methodologist, Memorial Sloan Kettering Cancer Center
Pieter Vynckier	Department of Public Health and Primary Care, Ghent University