UK National Screening Committee

Screening for Prostate Cancer

19 November 2015

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based upon the evidence presented in this document, whether or not screening for prostate cancer meets the NSC criteria to support the introduction of a population screening programme.

Current recommendation

2. The 2010 review of screening for prostate cancer in adults concluded that there is insufficient evidence to warrant a screening programme.

   This was due to the fact that:

   - The test for prostate cancer is not effective enough and does not identify a large proportion of men who in fact have prostate cancer.
   - A positive test will lead in most cases to a biopsy, which often does not give a definitive answer and leads to anxiety and to further investigations.

Review

3. This update review has been undertaken by Dr K Louie, to advise the UK NSC whether the evidence published between 2010 and 2014 suggests that a change to the current recommendation is required.

4. The updated review examined the UK NSC criteria focused on the epidemiology including risk factors, the natural history (how prostate cancer develops), the test, the treatment, and updating screening trials.

5. The review concluded that:

Prostate cancer is a major public health problem with significant health impacts. It is the second-leading cause of cancer-related deaths after lung cancer among UK men. In 2011, there were 41736 new diagnoses and 10793 deaths from prostate cancer. Incidence is 134 new prostate cancer diagnoses per 100,000 men in the UK population.

A major problem is the accuracy of the PSA test. The current evidence suggests that the major harms from prostate cancer screening using PSA still outweigh the benefits.

- PSA is still a poor test for prostate cancer and a more specific and sensitive test is needed
- PSA is unable to distinguish between clinically significant and non-significant cancers

Besides PSA, the current evidence does not support a population-based screening programme using any other test as a prostate screening test. Evaluations of new biomarkers and models are ongoing and have the potential to improve the specificity of PSA testing to discriminate men at greater risk for clinically significant prostate cancer.

Updates from the major ERSPC randomised trials show that prostate cancer deaths can be reduced by at least 21%. Despite this significant reduction the evidence is not yet sufficient to justify introducing a national screening programme using PSA as the harms still outweigh the benefits.

Research is underway that may help to shift the balance of harms and benefits of PSA testing. The CAP and ProtecT trials are expected to report in 2016. These studies will address the effectiveness of a population-based PSA screening policy to reduce mortality and the comparative effectiveness of active surveillance and radical treatment therapies for screen-detected localised prostate cancers. Results are also expected next year from the PROMIS trial in which the use of multiparametric MRI with targeted biopsies could further reduce overdiagnosis and unnecessary biopsies. Outcomes will guide diagnostic guidelines following a positive PSA screen.

Consultation

6. A three month consultation was hosted on the UK NSC website, and 22 organisations were contacted directly. Annex A

7. Eight responses were received from the following stakeholders: British Association of Urological Surgeons (BAUS), Prostate Cancer Support Federation (Tackle), Cancer Research UK, Prostate Scotland, Alexander Root, Royal College of Radiologists, Royal College of Physicians, National Clinical Director for Diagnostics, NHS England.

8. A range of views on the overall recommendation were submitted. No responses disagreed with the recommendation, five agreed with the recommendation and three response made no direct comment on the recommendation

Below are the 7 key stakeholder comments in bold, and the reviewer/NSC response:

- **New markers and models for prostate screening are being developed and produced frequently. New data have just been reported from the Stockholm 3 Study by Gronberg et al 2015 which suggests that their multivariable STHLM3 model of plasma protein biomarkers, genetic polymorphisms and clinical variables perform significantly better than PSA to detect clinically significant prostate cancer.** *While formally outside the dates for the literature review, these data was felt to be of significance. The review document has been altered to include an assessment of this research and its effect on the screening evidence. In general, the evidence is not yet clear how additional markers or clinical variables may improve a man's predictive risk of prostate cancer or of clinically significant prostate cancer. A review of prostate cancer risk models by Louie et al 2014 which considers these additional variables besides PSA was unable to demonstrate which model would be most informative to help a man make a decision about screening or weigh his lifetime risk of prostate cancer. These models have yet to demonstrate in a screening context whether it is effective in reducing morbidity and mortality*.

- **There is an awareness that a number of research studies (CAP, ProtecT, and PROMIS) are due to report in the next year or two.** *The UKNSC will keep the research under review and return to the assessment of screening for prostate cancer when significant new peer reviewed work is published.*

- **Men at high risk: African and Caribbean descent and those with a family history of prostate cancer. Such men should be encouraged to undergo PSA testing and DRE periodically after the age of 40 years.** *The UKNSC does not review or make evidence based recommendations on high risk groups. The review has been updated to better reflect the epidemiology of men at risk (section 1.1)*

- **An early PSA test between age 40 and 45 gives a good baseline risk before the confounding increase in BPH with age. This is supported by the Melbourne consensus statement.** *Reviews of screening at this age have not been found to be effective in reducing morbidity and mortality. In addition, data from Lilja et al 2011 suggests that a single PSA test at age 44-50 has the potential to predict a man's risk of advanced PCa 30 years later but it doesn't predict mortality. It's possible that an individual PSA test before age 50 could be a factor that could be considered but the practicalities of this approach in clinical practice have not yet been evaluated and only analysed within the context of a retrospective study. Additional research is needed prospectively and validated in other populations and ethnic groups besides Sweden.*

- **There is a continuing concern that there is RCT level evidence of a reduction in prostate cancer mortality from the ERSPC trial .** *Although, the trial does demonstrate a reduction in prostate cancer mortality of 21% at 13 years of follow-up, further research is still needed to identify appropriate strategies to reduce overdiagnosis preferably by avoiding unnecessary biopsy procedures, and reducing the very large number of men who must be screened, biopsied, and treated to help only a few patients. Anticipated results from ProtecT will address these unresolved issues.*

- **The historical risk of overtreatment is now greatly reduced by routine use of MDTs and informed decision making in the UK, and a high proportion of men with clinically insignificant prostate cancer are under active surveillance.** *Although reduced, the risk of overtreatment still exists and we await results from the ProtecT Trial to best inform management strategies for those diagnosed with prostate cancer.*

- **The Prostate Cancer Risk Management programme public and GP information should be updated.** *PHE is currently working on a redraft of the documents and it should be available in the new year. It is under development with primary health care professionals and user stakeholders.*

Recommendation

9. The committee is asked to approve the following recommendation:

   A systematic population screening programme for prostate cancer is not recommended.

Prostate cancer is a serious public health problem. Evidence suggests that PSA screening can reduce prostate cancer mortality by 21%. However, strategies to manage the harms of overdiagnosis and overtreatment are not yet known.

Based upon the UK NSC criteria to recommend a population screening programme, evidence was appraised against the following criteria:

	Criteria	Met / Not met
The Condition		
1	The condition should be an important health problem.	Met ✓
2	The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic phase.	Not met ✗
The Test		
5	There should be a simple, safe, precise and validated screening test.	Not met ✗
6	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	Not met ✗
8	There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.	Met ✓
The Intervention		
10	There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	Not met ✗

11	There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.	Not met ✗
12	Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to the participation in a screening programme	Not met ✗
The Screening Programme		
13	There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.	Met ✓
14	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	Not met ✗
16	The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against the criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resources.	Not met ✗
20	Evidence – based information, explaining the consequences of testing, investigation and treatment should be made available to potential participants to assist them in making an informed choice.	Met

Annex A

List of organisations contacted:

1. The British Association for Cancer Research;
2. British Association of Urological Nurses;
3. The British Association of Urological Surgeons;
4. Cancer Black Care;
5. Cancer Research UK;
6. Everyman;
7. Faculty of Public Health;
8. Macmillan;
9. Orchid;
10. Primary Care Urology Society;
11. The Prostate Cancer Charity;
12. Prostate Cancer Support Federation;
13. Prostate Scotland;
14. Prostate UK;
15. Radiology: National Clinical Director for Diagnostics NHSE;
16. Royal College of General Practitioners;
17. Royal College of Physicians;
18. Royal College of Physicians of Edinburgh;
19. Royal College of Radiologists;
20. Royal College of Surgeons;
21. Society and College of Radiographers;
22. Tenovus;

Name:	Professor Alan McNeill	**Email address:**	**xxxx xxxx**
Organisation (if appropriate):	British Association of Urological Surgeons (BAUS)		
Role:	**Chairman, BAUS Section of Oncology**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes X☐ No ☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
General comment		We would like to draw attention to what we believe is new evidence. From Monique Roobol: the updated ERSPC and specifically Gotenberg cohort clearly shows a prostate cancer specific survival benefit to PSA screening. **Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up.Lancet. 2014 Dec 6;384(9959):2027-35** This found: The absolute risk reduction of death from prostate cancer at 13 years was 0·11 per 1000 person-years or 1·28 per 1000 men randomised, which is equivalent to one prostate cancer death averted per 781 (95% CI 490-1929) men invited for screening or one per 27 (17-66) additional prostate cancer detected. After adjustment for non-participation, the rate ratio of prostate cancer mortality in men screened was 0·73 (95% CI 0·61-0·88).

1. BRITISH ASSOCIATION OF UROLOGICAL SURGEONS (BAUS)

General comment		Whilst we do not disagree that population screening is not currently justified, however we would like some recognition of the increased risk for those with a family history and those of African & Caribbean descent. Whilst not yet screening these men the statement about 'PSA testing being performed on request' might be amended to say 'particularly in those of African and Caribbean descent and those with a family history of prostate cancer'. Such men should be encouraged to undergo PSA testing and DRE periodically after the age of 40 years. An early PSA test between 40-45 gives a good baseline risk before the confounding increase in BPH. This is supported by the Melbourne consensus statement.
General comment	Melbourne consensus statement	We would like to recommend that prostate cancer diagnosis be uncoupled from prostate cancer treatment. We in the UK have one of the best Active Surveillance figures in the world with >40% of men with low risk disease offered AS. There is increasing evidence that PSA testing reduces prostate cancer specific mortality and the incidence of metastatic prostate cancer. PSA testing should not be considered on its own but as part of a multivariable approach to prostate cancer (PHI test, Volume, MRI etc).

1. BRITISH ASSOCIATION OF UROLOGICAL SURGEONS (BAUS)

		We do however accept that morbidity of treatment remains high precluding a national screening programme.
Web page bullet points	Current research indicates for every 100,000 men at age 50 offered screening, 748 would end up being treated. The men accepting screening would have their lives extended on average by a day – while 274 men would be made impotent, 25 incontinent and 17 would have rectal problems as a result of the treatment.	Could you please confirm the source of this statement?
General comment		Given that the PROTECT trial will be publishing next year we would suggest this topic should be scheduled for an early review.

2. PROSTATE CANCER SUPPORT FEDERATION

Name:	Frank Chinegwundoh MBE	**Email address:**	**xxxx xxxx**
Organisation (if appropriate):	Prostate Cancer Support Federation (Tackle)		
Role:	Trustee & Urologist		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ✓ **No ☐**

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Introduction Page 5	The debate (Summary response)	**Lead author of response - Chris Booth, Urologist** **Response on screening** Our summary response to this screening paper is based upon the consensus views of respected UK urologists. Published studies support the idea that men should be aware that prostate cancer can be diagnosed earlier by PSA testing and that this can save some lives but with the possibility of doing harm; either from complications relating to the biopsy (predominantly septicaemia) or from over treatment of low risk prostate cancer. Therefore PSA testing needs to be part of a shared decision making process with the concept of identifying those who are potentially at risk of developing the disease. A base-line PSA value at around 50 years of age may predict the risk of disease and suggest the interval for repeat testing. Men should be assessed on an individual basis but particular "at-risk" groups include men with one or more affected first-degree relatives or those of

		African or Caribbean descent; and targeting these men using public awareness campaigns should be considered. Men should be able to request and receive counselling, followed by prompt PSA testing if desired and further investigation when necessary. **Background to our response:** Prostate cancer is now the most commonly diagnosed non-skin cancer in men. The current estimated lifetime risk of diagnosis is 14.3%, whereas the lifetime risk of death from prostate cancer is 3.6%. Whilst there is level 1 evidence for men aged 50–69, demonstrating that PSA testing reduces prostate cancer-specific mortality and the incidence of metastatic prostate cancer, there is no evidence that it reduces all cause mortality. The United Kingdom National Screening Committee (UKNSC) provided a definition for screening as: *Screening is a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition.* The UKNSC reviews screening policies every 3 years and makes recommendations to ministers in the 4 UK countries about whether or not a screening programme should be set up. Although PSA screening meets some of the criteria for cancer screening it does not satisfy all the criteria and the UK policy is currently not to

		recommend PSA screening. However, the UK Prostate Cancer Risk Management Programme (PCRMP) recommends to GPs that *'any man over the age of 50 who asks for a PSA test, after careful consideration of the implications, should be given one'.* The PCRMP aims to help the GP give clear and balanced information to men who request details about testing for prostate cancer. The management of low volume, low-risk localised prostate cancer has moved away from radical treatment in the past five years. As a result of the 2008 and 2014 NICE guidelines on prostate cancer, an increasing number of men with low risk cancer are managed initially by active surveillance rather than radical therapy. Hence, the number of patients at risk of over-treatment and therefore potential side effects of their treatment is lower in 2014. **Evidence to support our response** Three randomised studies have been published which contribute to our understanding. • The PLCO trial (1) failed to show a benefit for additional screening in an already heavily-screened population. It is likely that this contamination of the control arm markedly reduced the power of the study, hence few conclusions can be drawn. (http://www.ncbi.nlm.nih.gov/pubmed/19297565) • The ERSPC study (2) demonstrated a 29% cancer-specific survival benefit (adjusting for non-compliance) with median 11 years follow-up. However, this is at the cost of over-treatment and presumably side-effects in a significant group of men, most of whom would not die from prostate cancer. The number needed to detect to save one life was 33. There was no difference in overall mortality between the two study

		groups. (http://www.ncbi.nlm.nih.gov/pubmed/19297566) • The Göteborg subgroup of the ERSPC (3), had longer follow-up of median 14 years, an earlier onset for screening and a slightly lower PSA threshold for biopsy. This study showed clearly that PSA testing reduced prostate cancer mortality by 40%. The number needed to treat was just 12 (to save a life) implying that the benefits of screening accrue with longer follow-up. Importantly, about a third of men with low-risk prostate cancer stayed on monitoring programmes, demonstrating that early diagnosis does not necessarily translate into "over–treatment". (http://www.ncbi.nlm.nih.gov/sites/entrez/20598634 • A landmark UK trial, ProTecT, has combined a randomised trial of PSA screening with randomised management of the detected localised cancers by surgery, radiation or surveillance. ProTecT is expected to report its first long-term survival results in summer 2015 (FC Hamdy, in conversation with Chris Booth). • PROBASE Trial 2013 – current – a Prospective Randomized Evaluation of Risk-adapted PSA Screening in Young Men (45 or 50) comparing 5yrly, 2 yrly or immediate intervention based on base-line PSA. 15-20 year German study. Arsov 2013 Eur Urol.
Introduction Page 5	Latest developments	This section should mention the percentage of normal PSA tests when there is underlying prostate cancer (20%) and should state that sequential PSAs will usually show an uprising trend eventually.
		A raised PSA is frequently a presentation of symptomatic BPH, which has been ignored in this section. This is clinically valuable, even in the absence of prostate cancer.

2. PROSTATE CANCER SUPPORT FEDERATION

		The historical risk of overtreatment is now greatly reduced by routine use of MDTs and informed decision making in the UK.
		Increasing numbers of patients now undergo MRI scans before having random biopsies.
		Template biopsies are now the preferred method of biopsy for UK urologists were they to need a biopsy themselves (BAUS conference, 2015).
		There is no mention here of European trials showing a clear benefit from screening.
1.1 Incidence and mortality Page 8	Incidence	The incidence of prostate cancer and its histological aggressiveness are both rising. PSA use (and TURP to a lesser degree) has resulted in far fewer men now presenting with metastatic disease (approximately 60% in 1980's falling to 20% now).
	Risk Factors	There are three universally accepted risk factors: age, ethnicity and family history. New risk factors appear to be obesity, possibly dairy products and height.
The Test Page 17	Risk prediction models Melbourne consensus statement	There is increasing evidence that risk assessment should play a key role alongside informed PSA testing. This will also help over diagnosis and over treatment.
	PSA Testing	The PPV (positive predictive value) of PSA at a normal upper cut off value of 4ug/ml is 30%. Though this potentially leads to overuse of biopsies and over-diagnosis, this section proceeds without mention of MRI or Template Biopsies.

2. PROSTATE CANCER SUPPORT FEDERATION

		The section correctly points out that repeat PSA testing reduces the need for biopsy because the repeated result is often lower than the initial result.
6.1 PSA Testing Page 27	Repeat Testing Melbourne consensus statement	Asymptomatic men over 40 should consider a single "baseline" PSA test to help predict their future prostate cancer risk. The higher their PSA level is above the age-specific median value, the more they should be encouraged to be re-tested at an earlier interval.
7. The Test should be acceptable Page 28	Source Reference 5 (Cochrane)	"To date, there is no conclusive evidence that PSA screening reduces mortality....." . This statement is factually incorrect and potentially invalidates this section. The Cochrane report is over three years out of date. The European Randomised Study of Screening for Prostate Cancer (ERSPC) results reported in August 2014 show a 27% reduction in men screened over 13 years (Schroder et al, The Lancet Vol 384 No. 9959 P2027-2035 December 2014)
		The Goteborg study reports a "nearly 50% reduction in mortality for men below the age of 60 who entered the screening arm (Hugosson/Neal, Lancet Oncology Vol 11 No 8 P702-703 August 2010)
8. Policy on further diagnostics Page 29	Policy	We fully agree there should be a policy to be recommended by urologists in the UK. Experience points to MRI scans reducing the biopsy rate by a third and improving the detection rate overall of clinically significant cancer.
	Further investigation	It is worth considering an investigation "roadmap" as developed by Dr E D Crawford at the University of Colorado. In summary, this helps urologists filter patients who will benefit from treatment, without unwarranted biopsies. His proposal, although based on USA diagnostic options, is a useful benchmark..... *On reaching the age of 50 a man should start routine PSA tests similar*

		to other annual blood tests such as lipids and blood sugar. If the PSA test result is below 1.5, he should be advised to return in 5 years. If it is above 1.5, he should be referred to the urologist for discussion and further monitoring. If the urologist finds the man's PSA and DRE are suspicious for prostate cancer, a test such as PHI, PCA3, or 4Kscore should be undertaken. If the results indicate low risk, the man should return to routine PSA screening. If a higher risk level is apparent, a TRUS biopsy should be undertaken. If the biopsy is negative, a ConfirmMDX test or PCA3 test should be carried out. . If those results are negative, the man is referred back to screening. However, if these tests return an unfavourable result, a 3T mpMRI should be offered. If there is a suspicious area then an MRI-guided targeted biopsy should be undertaken. If this is positive with a high proportion of Gleason 4, treatment options should be discussed. If it is Gleason 3+3, a genomics test should be undertaken (such as Prolaris or OncotypeDX in USA) to ascertain the genetic risk level. If the cell line is insignificant, the patient can embark on active surveillance subject to monitoring with 3T mpMRI. (Sperling Prostate Center May 4 2015 www.sperlingprostatecenter.com/food-for-urologic-thought-from-e-david-crawford-md/) Looking at what might be the equivalent in the UK, the Crawford "road map" provides more evidence for a risk based strategy, like PROBASE which starts with a PSA at 50 and promotes stratification into risk groups with clinical and cost benefits. The problems that remain include: • Getting more men screened using PSA; • Achieving a better appreciation by primary care clinicians of the benefit of risk based PSA testing; • Getting more men with normal PSA (1.5 to 4) but at risk (8% Crawford/PROBASE, etc) recognised as being at risk and referred from primary care to urologists;

		• Similarly for men with a PSA in the range 4 to 10; • Provide an adequate NHS shared care structure to cope with the inevitable increased work load.
10. The Treatment	Agreement on treatment	There is never any likelihood of absolute agreement on optimal treatment for early prostate cancer as science advances too quickly and new treatments constantly emerge. The cancer services audit confirmed that MRI scans, bone scans and MDT were available for virtually all UK patients. Therefore the tools for determining "optimum" treatment are already in place in the UK.
13. The Screening Programme Page 40	PCRMP	The UK's Prostate Cancer Risk Management Programme is too long and too complex for many men and 50% of GPs are unaware of it. (Journal of Clinical Urology. 2014, 7(1), 45-54). However, it is due to be updated by the end of 2015
	PLCO and ERSPC	The PLCO and ERSPC trials are quoted in the review but the former has been discredited due to contamination of the control arm. The latter has been updated, but the update showing a clear benefit in screening reducing prostate cancer mortality has not been quoted, particularly the "cleaned up" statistics that have removed the "contamination" of the screening arm. This has resulted in a quoted 50% drop in prostate cancer mortality. (Brockhorst et al, European Urology Vol 65 Issue 2 P329-336 February 2014)
	Mortality	The quote "The <u>modest</u> reduction of prostate cancer specific mortality" is a subjective term. A conservative 21% reduction in mortality due to screening would cut UK deaths by at least 2,000 per annum. This statistic and reference should be given, not a subjective quote. There is no modelling to show the likely effect of screening black men, who are at higher risk of getting the disease and dying from it. In the absence of a specific screening study in black men, it would not be unreasonable to suppose that the numbers needed to screen to detect prostate cancer and

		treat it would be even more favourable than the ERSPC and Goteborg studies, which were predominantly in white populations.
Table 15 Page 47	CAP, ERSPC and PLCO trials	These trials will provide robust estimates on screening and screening-detected prostate cancer when they report in 2016.
14. Evidence Page 48	Shared Decision Making	There is currently insufficient consultation time (typically 8 to 10 minutes per patient) or knowledge in primary carte for this to be implemented or for it to have a meaningful impact.
15 Benefits Page 50	Over diagnosis	The prostate cancer audit shows that historically about one-third of UK men with early prostate cancer have been over-treated. MDT intervention and shared decision making in Secondary Care should already be reducing this risk substantially in future.
23. Implications	Screening markers	There is no mention of hK2 which is an easy to use and simple blood test, and is relatively inexpensive as a second line marker for equivocal PSA of 4-10 ug/ml. It also provides risk percentages for the presence of low and high risk prostate cancer. This greatly assists in the choice of whether to proceed to MRI and/or biopsy, and in clinical practice reduces the unnecessary biopsy rate. (National Review Clinical Oncology, 2010, 7, 424).

3. CANCER RESEARCH UK

Name:	Sara Bainbridge	**Email address:**	**xxxx xxxx**
Organisation (if appropriate):	Cancer Research UK		
Role:	Policy Adviser		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes x☐ No ☐

Section and / or page #	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
23.	Implications for policy: …there is no updated evidence to justify a national screening programme for prostate cancer using PSA or any other test as a screening test.	Cancer Research UK welcomes this appraisal of screening for prostate cancer. We support the conclusion of the report that at this time the harms of prostate cancer screening using PSA outweigh the benefits, and that screening for prostate cancer should not be recommended. In the light of these findings, we would also welcome the view of the NSC on the implications for the current Prostate Cancer Risk Management Programme. As prostate cancer is one of the most common causes of cancer death in men, the ability to reliably detect prostate cancer, and distinguish between clinically significant and non-significant cancers within the general population is urgently needed. To date, no tests are suitable for a national screening programme however due to the rapid pace of developments, close monitoring of the evidence is vital.

3. CANCER RESEARCH UK

23.	The UKNSC evidence review on prostate cancer screening will evolve with the emerging evidence.	We look forward to results from upcoming prostate cancer trials which will significantly add to the existing evidence base and encourage the National Screening Committee to continue to monitor and evaluate emerging evidence in a timely fashion. We appreciate that the National Screening Committee is under review, but it is essential that the timetable for the next review should be clearly articulated, and that going forward that the National Screening Committee should operate in an agile manner to respond to emerging evidence.
5.6	Reflex testing with PSA isoforms and the Prostate Health Index of men in the grey zone, PSA 2-10 ng/ml	We would recommend the UKNSC incorporate the recent findings from the NICE report on Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index into their review.

5. PROSTATE SCOTLAND

Response and comments by Prostate Scotland to the UKNSC Screening for Prostate Cancer review 2014 update

1. Introduction

Prostate Scotland welcomes the opportunity to contribute comments on the evidence review by the UK National Screening Committee as part of its consultation on screening for Prostate Cancer.

Prostate cancer is a significant issue in Scotland and is the most common cancer in men in Scotland[i] representing a frequency of 21% of cancers in males in Scotland and recent projections by the Information Services Division of the NHS National Services Scotland [ii] suggest that incidence is set to increase by 35% by the years 2023-27 which would represent a numerical rise from just over 5000 cases between 1983-87 to a projected number of 20,000 cases between 2023 and 2027) It is against this backdrop that the review of screening is taking place and makes the review of particular importance .

There has been a welcome reduction in death rates from prostate cancer in Scotland over the past few years by some 11.3% but prostate cancer remains the second most common cause of death from cancer in men in Scotland[iii]. Of key importance, in view of this, is the need to encourage not only greater awareness of prostate issues, but for men with potential symptoms to seek medical advice if they have these and to do so as early as possible. In addition the issue of detection of disease and potential treatment for men who are asymptomatic is clearly important. In this context clearly the question arises as to whether screening may be relevant and beneficial both for detection of prostate cancer in asymptomatic and symptomatic men in Scotland.

2. Prostate Scotland

Prostate Scotland was set up in 2006 as a Scottish charity (registered charity no SC037494) to develop awareness of prostate disease, to support men and their families/ partners with the disease through providing advice and information and to advance treatment and research into prostate disease.

Our Board of trustees is made up of people with personal knowledge and experience of prostate disease, as well as some of the leading medical experts on prostate disease and on cancer in Scotland. We work with:

- Men and their families/partners to provide them with information about prostate disease and treatments;
- Doctors, medical staff and organisations to look at ways of providing the best information about treatment and developments;
- Other charities, government and health boards to progress prostate health issues developments and to advance prostate health care

5. PROSTATE SCOTLAND

We work closely with a range of partner organisations in the health and cancer field, as well as with government, parliamentarians, businesses and public sector organisations. We provide:

- A range of information for men and their families about prostate cancer and prostate disease, in booklet, and web formats including video interviews with men with prostate disease about their choice of treatment, as well as from leading clinicians about symptoms and treatments;
- We also undertake significant awareness activities including a Workplace Initiative with many businesses and organisations as well as hold events and conferences and develop awareness materials about prostate cancer and prostate disease;
- We are also taking forward a research project in partnership with the Cancer Care Research Centre at the University of Stirling into the future services and treatment needs of men with prostate cancer in Scotland.

Our comments are based on and informed by our experience of working with men with prostate cancer and disease and their families in Scotland, our research work and a strong belief in the importance of evidence based approaches.

3. **Prostate cancer screening**

We do not take a predetermined view in favour or against screening instead we feel that the starting point of looking at the question of prostate cancer screening must be to look at it within the overall context of information, awareness, diagnosis, testing, treatment and the development of the disease - and that as far as possible any decisions to introduce a screening system or not should be taken on the basis of evidence.

We are also believe that, supported by an evidence based approach, that the benefits of a screening programme would need to show that it could lead to positive health improvements for men with prostate cancer through early and earlier diagnosis and potential reduction in prostate cancer related death ratios and increased survival; as well as ensuring that benefits of increased detection, treatment and improved survival ratios justified any impact of any overtreatment. In addition any screening system would need to be:

- Relevant, straightforward, reliable and easy for both men undergoing screening and clinicians to operate the system;
- Based on the screening system and test being accurate, commanding both respect and support amongst both clinicians and the public;
- Based on the availability of treatment services to take forward the outcomes of a screening programme;
- Take into account the development of the disease and that some men have a higher risk of prostate cancer:
    - Men with a close relative (a brother or father) who have prostate cancer have a 2.5 times greater risk (rising to 4.3 fold risk if the relative is under 60 at time of diagnosis) [iv];
    - Black men have a 3 times greater risk of developing prostate cancer than White men[v];
    - Where there is a family history of genetic breast cancer, most likely arising as a consequence of the BRCA1 and BRCA2 genes[vi] .

5. PROSTATE SCOTLAND

We note the conclusion of the previous reviews by the UK Screening Committee in 1997 and 2010 which showed that 'no clear evidence that prostate cancer screening using the PSA test brings more benefits than harms and the Committee recommended against offering prostate cancer screening'[vii]. We note also the conclusion of the current review that (see page 56) that in order for it to be 'valuable it must be effective in reducing prostate cancer specific morbidity and /or mortality. This review shows that there is no updated evidence to justify introducing a national screening programme for prostate cancer using PSA or any other test as screening test. The harms from prostate cancer screening using PSA outweigh the benefits'.

To this end having considered the review study and its' results and conclusions we have doubts that a screening programme based on PSA Testing, given its limitations, would fully meet the criteria that we have set out above. Whilst we wish to see greater early detection and improved survival and these are likely to result from PSA testing we have concerns that a population PSA based screening scheme for men over the age of 50 could also result in levels of overtreatment that could reduce the benefits of screening.

However, we note also the conclusion in the current draft review[viii] page 5 that '*more careful selection of patients for screening to detect clinically significant prostate cancer is needed to reduce over treatment and harms of screening*' which we feel is an important and relevant observation and conclusion. ***We were disappointed that despite the review coming up with this conclusion that there did not appear to be discussion in it as to how this might be considered or taken forward, or any scenarios considered or developed as to how it could be achieved, despite the fact that the review itself considered key higher risk groups on grounds of age, ethnicity and family history.*** We feel that this is an unfortunate and disappointing omission and should be revisited by the Committee.

We also note that the conclusion of the review study on page 56 does not appear to take into account the points cited earlier in the review study on page 40 that the European Randomised Study of Screening for Prostate cancer (ERSPC) [ix] had *'found that PSA screening significantly reduced prostate-specific mortality as compared to controls'*. Whilst this does not necessarily overcome the issue of possible overtreatment arising from PSA based screening it is an extremely important finding from such a large randomised study that screening does and can reduce prostate specific mortality and ***we feel that this should be properly reflected in the conclusions and discussion of the review.***

We were also surprised that consideration of the evidence on pages 44-47 of the review study did not appear to consider the findings from the studies by Vickers et al[x] and Lijla et al[xi] from the Malmo Preventative Project which showed that a single PSA test measured at age 44- 50 could predict advanced prostate cancer up to 20 years earlier. The authors of the studies suggest 'that an early PSA value could be used to individualise later screening for prostate cancer' and that this information be used, based on a single screen, to significantly reduce the numbers of men needing to be called for later screening - enabling screening to focus on men with higher concentrations of PSA.

The authors advocate 'a change in the paradigm for prostate cancer screening and propose that screening frequency be determined by individual risk from an early PSA test. Early PSA testing could also serve as the foundation for a more comprehensive risk assessment that also includes genetic markers, family history, race and risk factors defined in the future'. ***We feel that the***

In regards to points above:

- "More careful selection of patients for screening to detect clinically significant……"

review for the UKNSC needs to fully take into account and consider this evidence as it could effectively change the nature of the discussion about screening.

4. Risk Factors and High Risk Groups

The evidence set out on higher risk groups on grounds of age, family history, and ethnicity and indeed on men with a family history of breast cancer from early onset BRCA and BRCA2 genes on pages 11-14 of the draft review is both significant and important. The evidence review found inter alia that:

- Studies dating back to the 1950s show family history is a strong risk factor for prostate cancer and that men were at an increased risk of death if their father or brother died from prostate cancer;
- 'About 5-10% of all prostate cancers diagnosed are associated with hereditary prostate cancer genes. Studies have identified a number of common heritable genetic mutations that may contribute to a man's risk of prostate cancer. There is some evidence that some men with these genetic mutations are particularly susceptible to early onset of disease.... 'a recent study has shown that testing men with a family history of prostate cancer could potentially help identify those at higher risk for advanced prostate cancer' (see page 14)
- Black men in the UK present with higher rates of prostate cancer than other races and they also appear to have a 30% higher mortality rate than white men

In view of this we were therefore surprised that there was not further discussion and consideration of this evidence and whether this evidence merited consideration of targeted screening for men who may fall into these groups. At present a key determining factor as to whether men who may fall into these groups receive or are offered PSA tests is reliant on the PCRMP and its effective application. Whilst the PCRMP has an important role, its effectiveness depends on awareness of it by primary health. Unfortunately we continue to come across and receive reports of men who fall into one of the higher risk group categories, who are not aware of their increased risk. In addition we have also received some reports of men who fall into these categories who have been turned down for PSA tests by their GPs.

Whilst we have produced specific information in Scotland for men in these categories about risk factors (and also about the benefits and drawbacks of the PSA test) – there remains a significant and important task to increase awareness amongst men and especially men most risk of prostate cancer. We believe that there urgently needs to be a proactive approach to reaching out to men with information who fall into the highest risk categories.

Whilst the awaited review of the PCRMP offers an opportunity alongside the recent circulation of updated information to GPs on suspected cancers we also believe that there is a need for the UKNSC to consider whether, in light of the evidence, as to whether a targeted screening system of men who are most at risk of prostate cancer. Given the higher risk factors involved the risk of overtreatment is likely to be considerably lower. In addition the number of men potentially needing to be called for screening would be considerably lower than a screening system for all men over the age of 50. (It should also be noted that the evidence in the Review (page 34) as regards the positive predictive value of PSA testing for men with BRCA mutations is considerably higher and also better at detecting high grade disease in BRCA 2 carriers.

5. PROSTATE SCOTLAND

We believe that looking into a targeted system of screening for the men at the highest risk of prostate cancer should be a priority for the UKNSC as part of its review.

5. Emerging evidence

We also note that the CAP and ProtecT trial conclusions are expected in 2016 which may provide further evidence about the effectiveness of a population based PSA screening policy and we were pleased to note that the UKNSC review on prostate cancer screening will evolve with the emerging evidence. We would ask that that the UKNSC, in view of the importance of this evidence, fully revisit the issue once this evidence is available, rather than waiting for a further five year review period to expire. The scale of prostate cancer as a significant health issue is such that it warrants early consideration.

6. Additional comments on detailed sections of the report

- P. 14 BRCA1 and BRCA2

  "In addition, there is a subset of men with breast cancer 1, early onset (BRCA1) or particularly breast cancer 2, early onset (BRCA2) mutation genes who have an increased risk of prostate cancer. There is evidence to suggest that men who carry these BRCA mutations have more aggressive disease poorer prognosis, and increased mortality rates, compared to non-carriers, particularly those with BRCA2. However, the burden of BRCA gene carriers represent <1% of all prostate cancer cases"

  From reading, the subset identified here is unclear as it is mainly close male relatives of *women* diagnosed with BRCA1 and BRCA 2 breast cancer who are at increased risk of prostate cancer. The review appears to insufficiently consider how to approach this subset on the grounds that it represents ≤1%, despite the fact it is stated that they may have more aggressive disease and a poorer prognosis. In addition to the comments we have made elsewhere on the potential for targeted screening of this group it is also likely to require an information/education programme for GPs, Practice Nurses and potentially activities such as the Keep Well checks/Deep End practices and Link Worker Programmes to inform men of the risks and to consider how this message could potentially be passed on by women diagnosed with BRCA1 and 2 breast cancer to help inform male relatives.

- P14/ Paragraph 2.2 Obesity

  "Besides being at higher risk for more aggressive tumours, obese men are more prone to treatment failure and complications, and prostate cancer-related deaths"

  Although the findings in the report state that *"Although obesity is a modifiable risk factor, few data exist on the effectiveness of weight loss and exercise interventions to reduce prostate cancer risk"*, it could be prudent to include these findings within the updated Prostate Cancer Risk Management Programme as weight loss could potentially have a role in tackling the treatment failure and complications associated with obese men.

- P20/ Paragraph 5.4 Risk Assessment Tools

  "A number of ... risk assessment tools are readily available online as a decision aid for an individual man to evaluate his own risk for prostate cancer such as the Prostate Cancer Prevention Trial (PCPT) Risk calculator and the European Randomized Study of Screening for Prostate Cancer (ERSPC) Risk Calculator

"Although risk prediction models have the potential to improve on the accuracy of PSA screening, further investigation is needed to evaluate the effect of these predictive risk models to detect clinically significant prostate cancers. Although these risk prediction models are readily available online, it's not clear whether these online risk models help a man make an informed decision about the need for a prostate biopsy or a repeat biopsy after PSA screening or not. Nor do the risk models help a man understand his risk of clinically significant prostate cancer vs. overall risk of prostate cancer"

We agree with the view expressed in the review about how far these various tools can help men with the clarity of making an informed choice. With most of these tools, it is necessary for the man to have results available to him e.g. DRE, biopsy findings, PSA etc. There are so many of these available and it can be confusing for men coming new to the topic. It would appear that the man has to have quite a substantial level of knowledge and tenacity to undertake these risk calculators.

- P28/ Paragraph 7

  "Although the Prostate Cancer Risk Management Programme (PCRMP) was launched in 2001 with the aim of providing men who are concerned about their risk of cancer to receive a balance view of the benefits and harms of PSA screening and treatment before making an informed choice to undertake screening, men may have accepted PSA testing without clearly understanding the harms because their GP did not adequately communicate the level of uncertainty of the test and treatment options. A study amongst GPs has shown that there is variation in the amount of information that is given to the patient and a full balanced view of harms and benefits of screening may not always be conveyed"

  The review of the PRCMP that is being undertaken is a good opportunity for an awareness programme for GPs and Practice Nurses to be fully aware of implications of PSA test, practicalities of test and in particular the 'at risk' groups. It is also an opportunity to update the information in the programme literature about key issues such as the importance of proactively identifying and ensuring that there is information for those most at risk of prostate cancer.

- P44 – ProtecT Study. *The study recruited 573 general practitioner (GP) practices (over 415,000 men) in England and Wales to be randomised into clusters of 10-12 neighbourhood practices to either a single round of PSA testing in ProtecT (intervention cluster) or to receive the UK NHS PCRMP advice 2 (comparison cluster) between 2001 and 2007.*

  We are surprised that there is only reference made to the ProtecT study taking place in England and Wales when the study is UK wide and has an arm of the study in Scotland.

4 September 2015

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[i] See Cancer in Scotland ISD NHS National services Scotland April 2015 pp5

[ii] ISD Cancer Incidence Projections for Scotland 2013-2027 18 August 2015. (These projections have been undertaken without assuming any increase in incidence from PSA testing but have been carried out purely reflecting demographic trends in size and age of population)

[iii] See Cancer in Scotland ISD NHS National services Scotland April 2015 pp12 -13

[iv] Johns LE, Houlston RS. A systematic review and meta-analysis of familial prostate cancer risk British Journal of Urology international 2003:91:789-794

[v] Ben-Shlomo Y, Evans S, Ibrahim F, Anson K, The risk of prostate cancer amongst black men in the united kingdom: the PROCESS cohort study EUR Urology 2008;53:99-105 Chinegwundoh F et al,. Risk and presenting features of

prostate cancer amongst African-Caribbean, South Asian and European men in North-east London. BJU International 2006; 98, 1216-1220

[vi] Thompson D., Easton DF, Cancer incidence in BRCA 1 mutation carriers Journal of National Cancer Institute 2002;94:1358-1365

[vii] See P5 UKNSC Screening for Prostate Cancer Review 2014 update Dr Karly Louie February 2015

[viii] Ibid See P5 UKNSC Screening for Prostate Cancer Review 2014 update Dr Karly Louie February 2015

[ix] See Page 40 UKNSC Screening for Prostate Cancer Review 2014 update Dr Karly Louie February 2015

[x] Vickers AJ. Cronin Bjork et al PSA concentration at age 60 and death or metastasis from prostate cancer : case control study BMJ 2010; 341:4521 and also Andrew J Vickers, Monique Roobol, and Hans Lilja Annual Rev Med 2012; 63: 161-170Screening for Prostate cancer: Early Detection or Over Detection

[xi] .Hans Lilja, Angel Cronin and Andrew J Vickers Predictions of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50 - Cancer 2011 Mar 15: 117(6): 1210-1219 also Lilja H, Ulmert D, Björk T et al Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50n years. J Clin Oncol. 207;25:431-6

6. xxxx xxxx

To preclude a possible problem or to ensure early diagnosis I ,wrongly, instigated a yearly fasting blood test . For 3 -4 years I was informed all ok. When diagnosed may 2013 with an aggressive prostate cancer ,I was naturally angry and upset that this had not been flagged up as my consultant was of the opinion that the disease had been active for some years. This was self evident to me that with the high incidence of PC in the over 50y that all the aforementioned should at least have been made aware of the advantages and short comings of the test. I was not given the prerequisite information sheet until after I was diagnosed. In my case an enlarged prostate led to a PSA test followed by a biopsy and then the bombshell visit to the consultant. Hence, I have had a 12 month correspondence exercise with my excellent GP-NHS England and NICE. This will obviously illustrate how strongly I feel about the subject. In Conclusion my proposals, from a very personal experience are as follows:

The objective: To ensure all the vulnerable group mentioned are given the data sheet by their GP's on turning 50y. A notice board advising same to be displayed in all practices similar as for the asymptomatic flu jab The patient will then have choice and be responsible and not the GP. This will free up valuable GP time as they will not have to plough through copious patient notes to determine if a correlation exists with other ailments which may attract censure to the GP or practice.

Whilst the PSA test is not definitive , a raised count will flag up a potential problem. As the MRI Scan shows up a cancer and their migration points, if any, then I suggest the problematic biopsy is eliminated-another saving for the NHS and as in my case serious and unpleasant post op experiences. I certainly do not think that all men over 50 should be screened as the cost benefit could not be justified in my opinion. I respectfully suggest that GP time is taken as a major factor in this excercise as the morale factor is becoming critical due to a much increased work load.

I trust my comments prove helpful as it mean that many patients across the UK may not have to experience the mental trauma as is the case with my family. I trust I will get a response and do not hesitate to contact me ,by phone if you wish.

xxxx xxxx xxxx xxxx

7. ROYAL COLLEGE OF RADIOLOGISTS

The Royal College of Radiologists

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From the Office of the President
Dr Giles Maskell MA FRCP FRCR

14 August 2015

Mr Adrian Byrtus
Evidence Review and Policy Development Manager
UK National Screening Committee
Floor 2, Zone B , Skipton House
80 London Road
London SE1 6LH

By email: ***adrian.byrtus@nhs.net***

Dear Mr Byrtus

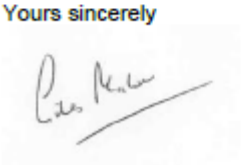
The NSC Recommendation on Oral Cancer Screening
The NSC Recommendation on Prostate Cancer Screening

In response to the two consultations above, The Royal College of Radiologists supports the UK National Screening Committee's recommendation that there should be no national screening programme for oral cancer or prostate cancer at this stage.

This can be considered to be the College's formal response, and it has no further comments to add.

With kind regards,

Yours sincerely



Dr Giles Maskell
President
president@rcr.ac.uk

7. ROYAL COLLEGE OF PHYSICIANS

Dear Adrian,

The RCP is grateful for the opportunity to respond to the above consultation.

We have liaised with our experts who have noted that the forthcoming results from the Stockholm 3 study, which will be published in a matter of weeks, will have a major impact on prostate cancer screening. We would suggest that any recommendations made about prostate cancer screening will need to be revisited in the light of the Stockholm results.

If you could confirm receipt of my email that would be greatly appreciated.

Best wishes,

Rochelle Keenaghan | Committee manager
Membership Support and Global Engagement Department| Royal College of Physicians
11 St Andrews Place | Regent's Park | London NW1 4LE

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8. NHSE NATIONAL CLINICAL DIRECTOR FOR DIAGNOSTICS

Thanks for this Adrian.

Another excellent review, nothing contentious from my perspective.

For prostate cancer from a diagnostic perspective we will need to revisit the evidence once PROMIS concludes and publishes its findings – I expect this will be mid 2016 at the earliest. I anticipate some changes in recommended pathways then and we may need to ask NICE to update guidance then too

Best wishes
Erika

Professor Erika Denton FRCP, FRCR

National Clinical Director for Diagnostics, NHS England
Honorary Professor of Radiology
University of East Anglia and Norfolk & Norwich University Hospital