UKNSC

Screening for Prostate Cancer Review

2015 Update

Review against programme appraisal criteria for the

UK National Screening Committee (UKNSC)

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15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment). 56

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 this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource. 60

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available. 65

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Introduction

Since the introduction of the PSA (prostate specific antigen) test in the 1980s, there has been a debate as to whether men should be routinely screened to detect prostate cancer early for the purpose of reducing prostate cancer mortality. Although prostate cancer is the most common cancer in men and responsible for over 10,000 deaths annually in the UK, the evidence had been inconclusive about whether screening actually reduces mortality. In addition, the PSA test itself has poor specificity to discriminate between clinically insignificant and significant prostate cancers[1]. Although the PSA test is a marker of indication for prostate biopsy that can lead to prostate cancer diagnosis for which curative treatment could be offered, increased PSA levels may be associated with the presence of prostate cancer but many men with increased levels do not actually have cancer and have other conditions (e.g. older men with benign prostatic hyperplasia). About 7 out of 10 men with a raised PSA level do not have prostate cancer. Or they are low-risk men with clinically insignificant disease in which the tumour is relatively indolent and unlikely to progress or require treatment. The lack of specificity for PSA leads to major harms of overdiagnosis and overtreatment in about 5-44% of men[2]. More careful selection of patients for screening to detect clinically significant prostate cancer is needed to reduce overtreatment and harms of screening.

The UK National Screening Committee (UKNSC) first reviewed the evidence for a national prostate screening programme in 1997 and then in 2010. The reviews showed no clear evidence that prostate cancer screening using the PSA test brings more benefits than harm, and the Committee recommended against offering prostate cancer screening. However an informed choice programme is available for men over the age of 50 who ask for a PSA test after careful consideration of the benefits and harms of PSA testing[3]. Considerable advances have been made in our understanding of prostate cancer screening since the last policy review in 2010, however, there remains significant uncertainties about the overall benefits of screening of detecting prostate cancer early. In this evidence review update, we review and appraise the emerging evidence for early detection and treatment of prostate cancer against the UKNSC Criteria.

Aims and objectives

Aims

The aim of the review is to advise the UKNSC whether there is any updated evidence since 2010 to change the current policy recommendation against a national prostate cancer screening policy.

Objectives

Objective 1: To conduct a comprehensive review to summarise the evidence for a prostate cancer screening from the most recent systematic reviews, meta-analyses, narrative reviews (non-systematic), epidemiological studies, modelling and practice guidelines.

Objective 2: To critically appraise the identified literature against the UKNSC criteria.

Methods

Prostate cancer screening remains controversial[4, 5]. A comprehensive synthesis review of peer-reviewed literature was carried out to critically appraise prostate cancer screening against the programme appraisal criteria for the UKNSC.

The evaluation of the evidence on the potential benefits of PSA testing for prostate cancer has been rigorously and extensively reviewed. Literature from a recent Cochrane Review in 2013 on prostate cancer screening[6] and a NICE (National Institute for Health and Care Excellence) review in 2014 on prostate cancer diagnosis and treatment[7] were used to critically appraise screening against the programme appraisal criteria. Both the Cochrane and NICE reviews are regarded as the highest standard of evidence-based reviews which help to inform on the evidence of prevention effectiveness and to develop recommendations for public health guidance in the UK. Given the rigour of these reviews, a separate systematic review was not warranted.

Besides these guidelines, publications from major societies on prostate screening who have carried out systematic reviews were reviewed and references were hand-searched to identify any additional relevant literature that could be used to critically appraise prostate cancer screening (Appendix A).

An additional search was conducted in OvidMedline up to December 2014 to identify relevant literature to appraise the programme criteria addressing 'epidemiology', 'natural history', 'risk factors', 'diagnosis', and 'treatment' of prostate cancer. The medical subject heading (MESH) and text words 'prostate cancer' was used in combination with the above terms. Articles were limited to the English language and humans. Where possible, relevant articles were selected following a framework of hierarchical evidence, ranking evidence from systematic reviews and meta-analyses at the top, followed by randomised controlled trials, cohort studies, case-control studies, cross-sectional studies and case-reports.

The review also summarises the updated work of , the School of Health and Related Research at Sheffield (ScHARR) [8] which investigated the impact of four policy options for PSA-based prostate screening in the UK on costs and resources.

The Condition

1. The condition should be an important health problem

1.1. Incidence and mortality

Prostate cancer is an important public health problem in the UK. It is the most common cancer in men and represents about a quarter of all new male cancer diagnoses in the UK[9-12]. It is also 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. In comparison, mortality rate is substantially lower, about 35 deaths per 100,000 men. Incidence and mortality are also significantly higher in Black Caribbean and Black African men in the UK[13, 14]. The lifetime risk of being diagnosed with prostate cancer is 1 in 4 (29.3%) for Black men compared to 1 in 8 (13.3%) for White men and 1 in 13 (7.9%) for Asian men[15]. And the lifetime risk of dying from prostate cancer is 1 in 12 (8.7%) for Black men compared to 1 in 24 (4.2%) for White and 1 in 44 (2.3%) for Asian men.

Prostate cancer is also strongly associated with increasing age. Diagnosis in young men (<50 years) is rare, about 1% of those diagnosed with prostate cancer. Incidence sharply increases starting at ages 50-54 with the highest incidence found in older men, peaking at ages 75-79 **(Figure 1).** The rate among men aged 75-79 is about five-fold higher (800 per 100,000 population of men) than men aged 55-59 (166 per 100,000 population of men).

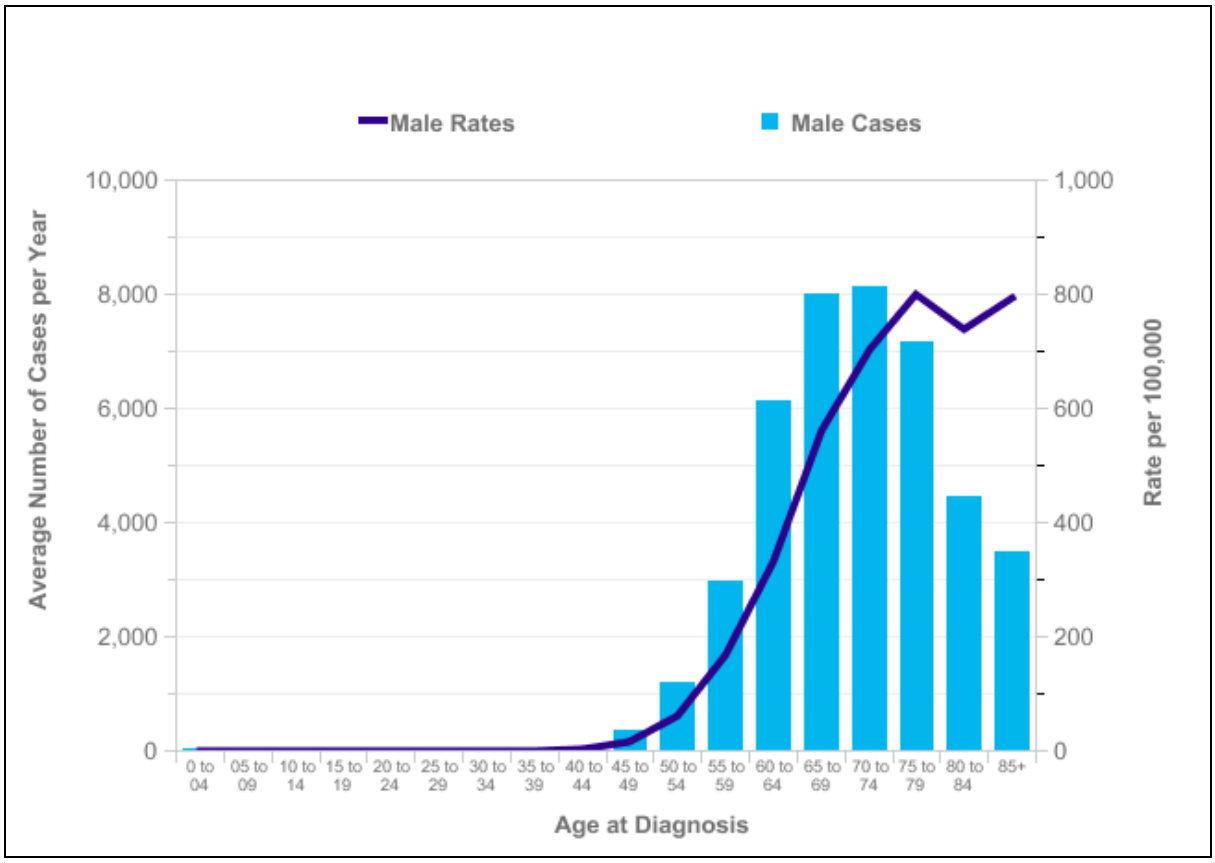

Figure 1. Average number of new cases of prostate cancer per year and age-specific incidence rates for men in the UK, 2009-2011. Cancer Research UK, http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/incidence/#source1, June 2014.

Similar to incidence, age-specific mortality sharply rises at age 50-54 years with the highest rate peaking at age 85+. About 75% of prostate cancer deaths occur in those aged 75+.

1.2. Trends over time

The UK has seen substantial increases in prostate cancer incidence in the last two decades reflecting similar observations worldwide[16]. Estimates show that incidence has increased by nearly 70% from 1993 to 2011 **(Figure 2),** and this corresponds to an annual percentage change of +3.1% per year. This pattern of increase can be attributable to the introduction of PSA testing since the late 1980s[17, 18] and increased use of transurethral resection of the prostate (TURP) for treatment of benign disease[19] which has resulted in increased detection of cancers .

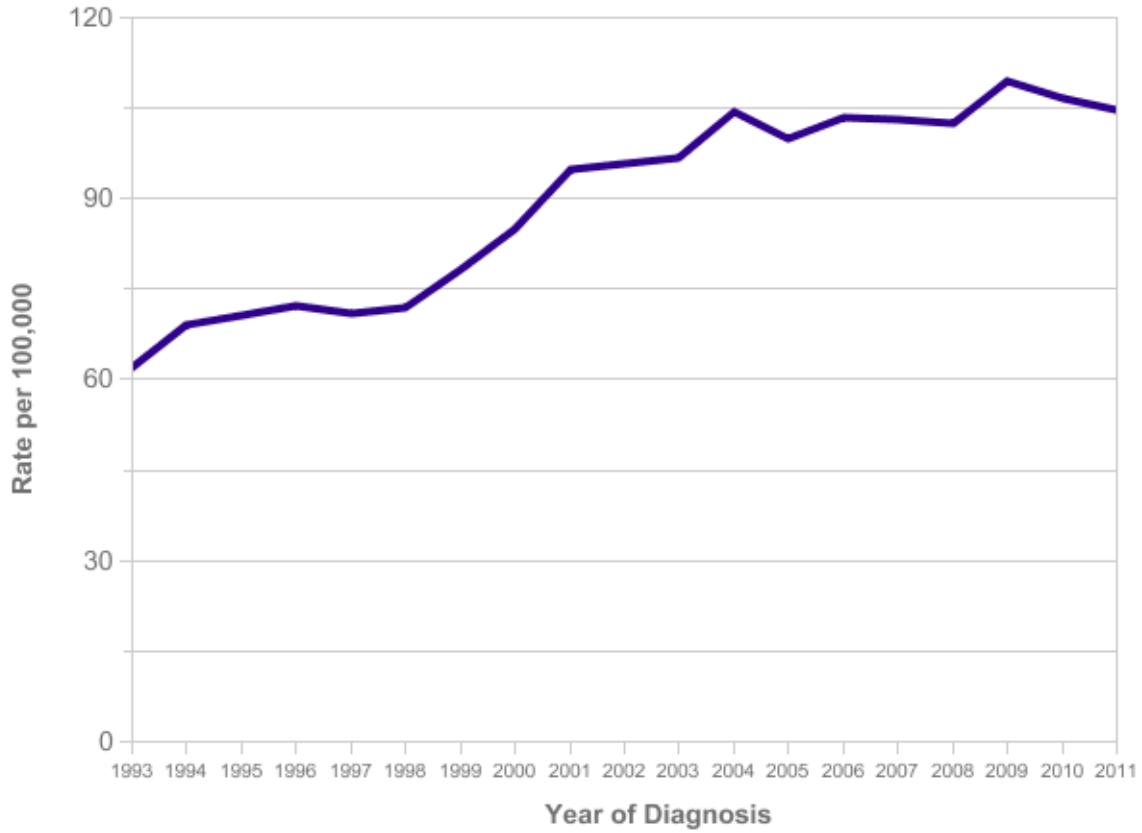

Figure 2. Age-standardised incidence (European) rates of prostate cancer from 1993 to 2011 in the UK. Cancer Research UK, http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/incidence/#source1, June 2014.

1.3. Burden of clinically significant and insignificant prostate cancer

Although prostate cancer incidence has increased, it is unclear what burden is represented by clinically significant (aggressive) and insignificant (localised non-metastatic) tumours at the national level. More specifically, clinically insignificant prostate cancer is a low-grade, small-volume and organ-confined prostate cancer that is unlikely to progress to clinical or biological significance without treatment[20] . In other words, clinically insignificant prostate cancer is diagnosed in the absence of cancer-related symptoms that would not cause disease-specific morbidity or mortality if the tumour was left untreated. Insignificant prostate cancers could avoid overtreatment given the low-risk malignancy potential of the tumour that will have little impact on the natural course of a man's life expectancy. Greenberg *et al* (2013)[21] recently examined the trends in histological presentation of tumours between 2000 and 2010 in one region of the UK, East of England, which covers approximately 2.7 million people, of which 49% are men. The study found that the incidence of low grade (Gleason score ≤6) cancer decreased in the last decade (91 vs. 81 per 100,000 men). In

contrast, intermediate (Gleason score 7) and high grade tumours (Gleason score 8-10) increased by 220% (65 vs. 81) and 64% (44 vs. 72) in the last decade, respectively. Despite the upward grade migration during this period, there was no change in clinical stages and metastasis rates were falling. This may be explained by the changes in histological reporting of diagnostic prostate biopsies[22] rather than aggressiveness of disease. However, this increased high-risk profile of disease has implications for provision of clinical services for treatment and management. Some data already suggest that the number of men requiring radical treatment have increased substantially in the UK[23].

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 stage.

2.1. Natural history

The natural history of prostate cancer is poorly understood. **Figure 3** shows the different stages of prostate cancer development[24]. Much research and progress has been made to understand the clinical progression pathway to identify prognostic markers that will distinguish between clinically significant and non-significant cancers, to elucidate why circulating androgens are necessary for cancer development, as well as why prostate cancer preferentially metastasizes to the bone[25]. However, underlying these clinical challenges are the molecular mechanisms that influence prostate cancer development (e.g. cell signalling, cell cycle regulators, and survival/apoptotic molecules), which have been studied less and are under investigation[25] Elucidation of the molecular mechanisms that influence prostate cancer initiation, progression and metastasis are necessary for identifying appropriate preventative and therapeutic strategies.

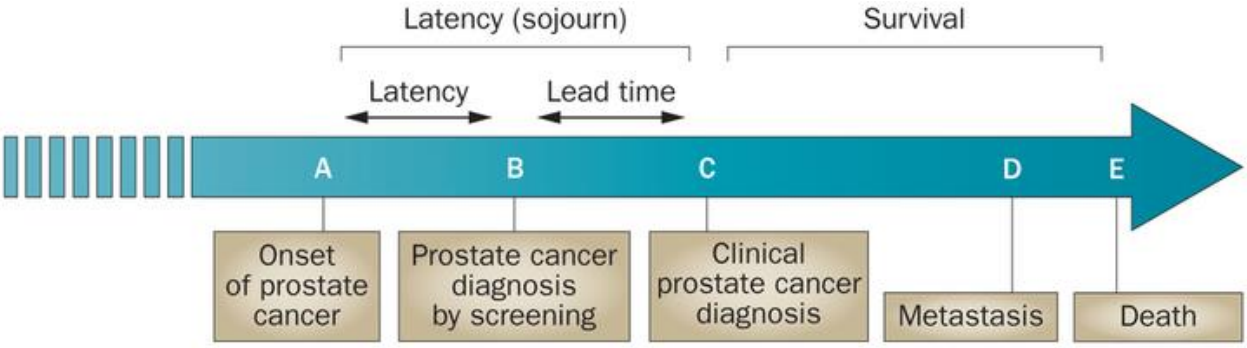

Figure 3. Natural history of prostate cancer. This figure illustrates the course of prostate cancer from initiation (A), to diagnosis by screening (B), to diagnosis by clinical symptoms (C), to clinically detectable metastatic disease (D), and finally to death from prostate cancer (E). Reproduced from Salinas C *et al* (2014)[24].

Due to the complicated aetiology of prostate cancer, treatment and management are difficult without characterising the broad spectrum of disease, defined by the rate of tumour growth, ranging from slow-growing "clinically insignificant" tumours in asymptomatic men that are unlikely to progress or require treatment to rapidly growing "clinically significant" tumours that have potential to progress and metastasize. The reasons why some tumours are more aggressive are unknown. Depending on whether prostate cancer is localised or locally advanced at the point of diagnosis, a number of treatment options are available (see **Criteria 10-12**).

2.2. Risk factors

Factors that contribute to a man's increase risk of developing prostate cancer include three well-established risk factors: increasing age, ethnicity and family history/genetics[26]. There is evidence that other exposures, such as diet and obesity, may also play a role. These risk factors suggest potential different clinical management strategies.

Age

A strong risk factor is increasing age **(Figure 1).** Autopsy studies have shown that prostate cancer can have a long latent period and that men show evidence of cancer cells in their prostate as early as in their 20s and 30s **(Figure 4)[27, 28].** By age 80, about 80% of men will have evidence of cancer cells in their prostate. However, only 2 in 50 men (all) will die from prostate cancer, which supports the evidence that men will likely die from other causes rather than from prostate cancer[27, 29].

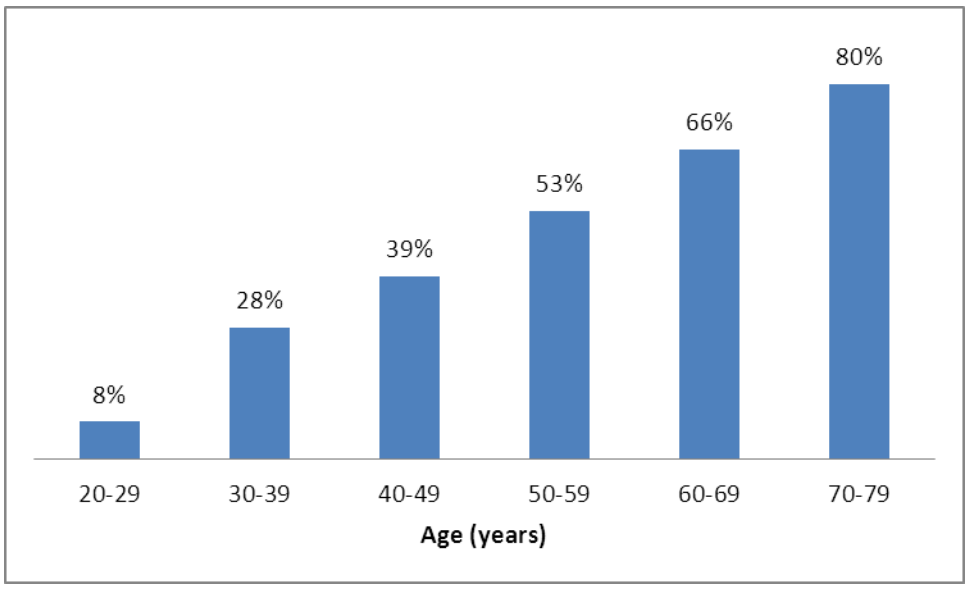

Figure 4. Percentage of men with evidence of prostate cancer by age[27, 28]

Ethnicity

Men of Black African descent are at disproportionately greater risk of prostate cancer than White men worldwide[30]. According to the UK's PROCESS (Prostate Cancer in Ethnic Subgroups) Study, Black men have an incidence that is three times greater than White men (age-standardised incidence rate, ASR, 166 vs. 56.4 per 100,000 male population, respectively) with insignificant differences between Black-African and Black-Caribbean origin[13]. Black men presented about 5 years younger (70.4 vs. 75.6 years) and are more likely to have higher PSA levels than whites. In comparison, men of South Asian descent have shown lower risks than whites (ASR=50 per 100,000 male population)[31, 32].

Although Black men in the UK present with higher rates of prostate cancer than other races, they also appear to have a 30% higher mortality rate than white men (age-standardised mortality rate, 91.6 vs. 70.5 per 100,000 men, respectively)[14]. Poorer survival rates suggest that there might be socioeconomic disparities in health-seeking behaviours to receive timely effective treatment. However, although Black men with prostate cancer are more likely to come from a lower socioeconomic group than their White counterparts, this had no effect on their accessibility to care[33]. Differences in access to diagnostic services[33], clinical presentation (except PSA level) and management of prostate cancer[34] were similar in all ethnic groups. In addition, there are no differences in prostate cancer-specific survival between Black men and White men (hazard ratio 0.93, p=0.238)[35].

Studies suggest that the greater disease burden among Black men may be explained by biological (e.g. ethnic variation in testosterone levels)[36-38]and genetic factors that are more common in men with African ancestry[39-41], making them more susceptible to prostate cancer than other ethnic groups. Also, a number of genetic variations have been identified (e.g. chromosome 8q24) [42-45]and may explain the higher frequency of disease in African men. The evidence is inconclusive and further investigation is needed before understanding the usefulness of these markers in genetic screening.

Family history and genetics

Studies dating back to the 1950s show family history is a strong risk factor for prostate cancer [46]. It was shown early on that men were at an increased risk of death if their father or brother died from prostate cancer[47]. Overall lifetime risk of a prostate cancer diagnosis according to family history is summarised below in **Table 1[48].** A man without a family history has an absolute lifetime risk of prostate cancer of 8%. This risk increases to 12% if the father was affected at age 60 years or above and the risk is further increased with increasing number of relatives affected with prostate cancer.

Table 1. Effect of family history of prostate cancer on lifetime risk of prostate cancer[48]

Family History of prostate cancer	Lifetime risk (%)
No history	8%
Father with prostate cancer at ≥60 yrs	12%
1 Brother affected at ≥60 yrs	15%
Father affected before age 60 yrs	20%
1 Brother affected before age 60 yrs	25%
2 male relatives with prostate cancer*	30%
3 or more affected male relatives	35-45%

***Father and brother, or 2 brothers, or a brother and a maternal grandfather or uncle, or a father and a paternal grandfather or uncle

Several meta-analyses have been conducted to summarise the association between family history and prostate cancer[49-52]. The most recent meta-analysis[51] of 33 case-control and cohort studies reports that men with first degree relatives (*brother or father*) with prostate cancer have more than 2.5-fold increased risk compared to men with no history **(Table 2)**. The risk is higher if the first-degree relative is a brother (relative risk, RR=3.14) than the father (RR=2.35) and if they had early onset of disease (<65 years). In comparison, men with second-degree relatives (*grandfather or uncle*) showed a similar risk with first-degree relatives overall but this association should be interpreted with caution as there were a small number of studies. Generally, previous reviews showed a lower risk overall compared to first-degree relatives.

Table 2. Estimates of relative risk depending for men with different family histories of prostate cancer[51]

Family history of prostate cancer	Relative Risk (95% CI)
1st degree relative (brother or father)	
For all men	2.48 (2.25-2.74)
For men <age 65	2.87 (2.21-3.74)
For men ≥age 65	1.92 (1.49-2.47)
Affected father	2.35 (2.02-2.72)
Affected brother(s)	3.14 (2.37-4.15)
2+ 1st degree relatives	4.39 (2.61-7.39)
2nd degree relatives (grandfather or uncle)	2.52 (0.99-6.46)

About 5-10% of all prostate cancers diagnosed are associated with hereditary prostate cancer genes[53, 54]Studies have identified a number of common heritable genetic changes that may contribute to a man's risk of prostate cancer[53, 55-61]. There is some evidence that some men with these genetic mutations are particularly susceptible to early onset of disease (age ≤50) [57, 62]. To what extent these genetic mutations are causing disease is unclear. However, data show that men with early onset of disease are more likely to die from prostate cancer compared to older men with similar clinical diagnoses[63], particularly those with high grade or locally advanced disease[64]. 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 disease[61].

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[57, 65-68], poorer prognosis[69], and increased mortality rates [70, 71]compared to non-carriers, particularly those with *BRCA2.* However, the burden of *BRCA* gene carriers represent <1% of all prostate cancer cases[66].

Obesity and diet

A 2014 review from the World Cancer Research Fund/American Institute for Cancer Research summarises the level of evidence available linking diet, nutrition, and physical activity risk factors with prostate cancer in **Table 3[72].**

There is strong evidence linking obesity with advanced prostate cancer. With a quarter of men in the UK considered obese (24%)[73] and prostate cancer being the most common cancer in men, the association between the two raises an important public health concern. A meta-analysis of two million men in prospective cohort studies showed that the relative risk of advanced prostate cancer increases by 9% for every 5 kg/m^2 increase in BMI, whereas the relative risk of localised prostate cancer decreases by 6% for every 5 kg/m^2 increase in BMI[74]. The biological mechanisms behind these findings are thought to relate to the lower levels of testosterone in obese men and that these are associated with lower risk of localised (non-aggressive tumours) but higher risk for more aggressive tumours. Besides being at higher risk for more aggressive tumours, obese men are more prone to treatment failure and complications, and prostate cancer-related deaths[75-79]. Specifically, men have a 15-20% increased risk of dying from prostate cancer with every 5 kg/m^2 increase in BMI[77]. Although obesity is a modifiable risk factor, few data exist on the effectiveness of weight loss and exercise interventions to reduce prostate cancer risk[78, 80, 81].

There is also strong evidence to suggest that adult height, attributable to developmental factors in childhood) influences the risk of prostate cancer[82-84]. In a meta-analysis of 31 cohort studies, the relative risk of prostate cancer incidence increases by 9% per 10 cm increase[85]. The Emerging Risk Factors Collaboration observed a 7% increased risk of dying from prostate cancer per 6.5 cm increase in height in a pooled analysis of nearly 1.1 million men from 121 prospective cohort studies[86].

There is strong evidence that show no association between consumption of beta-carotene in food or supplements and prostate cancer in a review of 11 and 5 cohort studies, respectively[72]

There is limited evidence that consumption of dairy products and diets high in calcium are associated with an increased risk of prostate cancer. In a meta-analysis of 45 observational studies, there was no association between dairy or milk intake and risk of prostate cancer[87]. However, in a meta-analysis of 13 studies, the relative risk of prostate cancer increased by 13% when comparing the highest with the lowest quintile of milk consumption.

There is also limited evidence that high consumption of plasma alpha-tocopherol concentrations reduces the risk of prostate cancer. In a review of 17 studies, the relative risk of prostate cancer decreased by 1% for any prostate cancer and 2% for aggressive prostate cancer per 1mg/ml of serum alpha-tocopherol[72].

The SELECT trial did not identify an association between selenium and prostate cancer risk[88, 89]. However, the US Nutritional Prevention of Cancer Trial, a randomised controlled trial of selenium (intervention) vs. yeast (placebo), found that after 7.5 years of follow-up that the relative risk of prostate cancer decreased by 49%. However, the summarised evidence suggests that the link between selenium and prostate cancer risk is limited[90].

Table 3. WCRF/AICR evaluation of endogenous prostate cancer risk factors

LEVEL OF EVIDENCE		DECREASES PROSTATE CANCER RISK	INCREASES PROSTATE CANCER RISK
STRONG EVIDENCE	Convincing		
	Probable		Body fatness (BMI, waist conference and waist-hip ratio) for advanced prostate cancer only Adult attained height (likely due to genetic, environmental, hormonal and nutritional factors)
LIMITED EVIDENCE	Limited-suggestive		Dairy products Diets high in calcium Low plasma alpha-tocopherol concentrations Low plasma selenium concentrations
	Limited-no conclusion	Cereals (grains) and their products, dietary fibre, potatoes, non-starchy vegetables, fruits, pulses (legumes), processed meat, red meat, poultry, fish, eggs, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, plant oils, sugar (sucrose), sugary foods and drinks, coffee, tea, alcoholic drinks, carbohydrate, protein, vitamin A, retinol, alpha carotene, lycopene, folate, thiamine, riboflavin, niacin, vitamin C, vitamin D, vitamin E supplements, gamma-tocopheraol, multivitamins, selenium supplements, iron, phosphorous, calcium supplements, zinc, physical activity, energy expenditure, vegetarian diets, Seventh-day Adventist diets, individual dietary patterns, body fatness (non-advanced prostate cancer), birth weight, energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely	Beta-carotene	

*Reproduced from the World Cancer Research Fund International/American Institute for Cancer Research Continuous Update Project Report: Diet, Nutrition, Physical Activity, and Prostate Cancer. 2014.[72]

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

There is a strong link between obesity and prostate cancer[74-79]. This suggests that lifestyle changes with weight loss and exercise could prevent or reduce prostate cancer risk. It is unknown whether a weight loss and exercise prevention intervention for obese men could be a cost-effective way to prevent or delay prostate cancer and other obesity-related diseases.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

Not applicable

The Test

5. There should be a simple, safe, precise and validated screening test.

The most common screening test used for determining the presence or absence of prostate cancer is prostate specific antigen (PSA) blood testing. PSA is a serum tumour marker which is produced by both normal and cancerous glands. Another procedure used to determine the presence or extent of prostate cancer is a digital rectal examination (DRE) of the prostate. Normally, either elevated levels of PSA testing and/or abnormal DRE will prompt further clinical investigation with a transrectal ultrasound (TRUS)-guided biopsy to confirm diagnosis. Prior to further investigation, the Prostate Cancer Management Programme (PCRMP), which provides GPs and primary care professionals with guidelines to help a man make an informed decision about screening,[91] recommends that serum PSA level alone should not automatically lead to a prostate biopsy. Consideration of other risk factors such as age, ethnicity, family history, DRE findings, and comorbidities should be taken into account with serum PSA levels. It is recommended that doctors involve their patients in the decision-making process.

In men with prostate cancer, PSA is elevated in those with localised and advanced disease. Levels of PSA are normally proportional to prostate volume of the tumour. However, there is significant overlap between PSA levels found in men with benign prostatic hyperplasia (ie. enlarged prostate) and cancer tumours, limiting the use of PSA because of its lack of specificity. Similarly, DRE is not very specific and may suggest that changes to the prostate gland surface are due to prostatic hyperplasia or prostate cancer. Symptoms for both conditions are the same and DRE cannot be used solely to diagnose prostate cancer. A combination of PSA blood testing and biopsy with DRE is normally required for diagnosis.

Challenges of PSA testing to differentiate between clinically significant prostate cancers have motivated research advances into the development of risk prediction models and identification of

novel biomarkers to improve prostate cancer screening. The application of these risk prediction models and novel biomarkers are currently under research and their utility in clinical practice is not yet known.

5.1. Prostate specific antigen (PSA) testing

The PSA test measures the prostate specific antigen in the blood. PSA testing is widely used for prostate cancer screening but the test has its limitations. The PSA test is not a diagnostic test. Increased levels of PSA will require further diagnostic evaluation with a TRUS-guided biopsy and histology to confirm the presence of prostate cancer. It is important to note that although PSA is organ-specific, it is not a tumour specific marker for prostate cancer[92]. About 15 out of every 100 men who have a normal PSA test result do not have prostate cancer[1]. An increased PSA level may indicate the presence of other prostatic diseases, such as benign prostatic hyperplasia (enlargement of the prostate without malignancy) or prostatitis (inflammation of the prostate). A normal PSA test may also provide false reassurances that there is no prostate cancer[1]. It has been found that men with abnormal PSA levels had up to 75% false-positive results (in the ERSPC trial)[93] . Factors other than prostate cancer can influence elevated PSA levels which include increasing age, race/ethnicity, medications, prostate gland inflammation, benign prostatic hyperplasia, lab variability and body mass index. A systematic review of the literature has been carried out to assess the diagnostic performance of PSA testing to detect prostate cancer[94]. **Table 4** summarises the pooled analysis of studies to evaluate the trade-offs of test performance between using a PSA cut-off of 4.0 ng/ml vs. 3.0 ng/mL to indicate prostate biopsy[94]. With a PSA cut-off of 4.0ng/mL to indicate biopsy, the pooled sensitivity to detect any prostate cancer was 21% and 51% for detecting any high-grade cancers (Gleason ≥8)**.** Using a PSA cut-off of 3.0ng/mL increased the sensitivity to detect any cancer and high-grade cancers to 32% and 68%, respectively. The specificity was 91% for a PSA cut-off of 4.0 ng/mL and 85% for a cut-off of 3.0 ng/mL. The positive predictive value (PPV) is defined as the proportion of men who are 'true' positive with prostate cancer amongst those who tested positive (number of true positives plus number of false positive). The PPV is 30% with a PSA >4 ng/ml and 28% with a PSA >3 ng/mL. This low PPV translates into significant increases in false-positive screen results (≥70%), leading to overdiagnosis and overtreatment. These results show that lowering the PSA cut-off threshold from 4.0 to 3.0 ng/mL increases test positivity and cancer detection rates but at the expense of lowers specificity. Overall, the results highlight that there is no distinct PSA cut-off to distinguish between the presence and absence of prostate cancer.

Table 4. PSA testing characteristics as a function of different threshold cut-offs[94]

Test characteristic	PSA (normal <4 ng/mL)	PSA (normal <3 ng/mL)
Test positivity (%)	12	18
Cancer detection rate (%)	3	4
Sensitivity (%) for detecting any prostate cancer (%)	21	32
Sensitivity (%) for detecting high-grade cancer (Gleason score ≥8)	51	68
Specificity (%)	91	85
Positive predictive value for detecting any prostate cancer (%)	30	28

5.2. Digital rectal examination of the prostate

The PCRMP guidelines[91] state that increased levels of serum PSA level alone should not automatically lead to a prostate biopsy. The digital rectal examination (DRE) could be a useful complementary test for detecting abnormalities, particularly for men with lower urinary tract symptoms or symptoms suggestive of advanced metastatic disease[91]. The examination can assess the prostate for signs of cancer (hard gland or palpable nodules) or benign enlargement (smooth, firm, enlarged gland). Even if a gland feels normal this does not exclude the presence of a tumour. Tumour development may produce changes detected on DRE but these changes are not specific, particularly for many early prostate cancers. The majority of cancers detected with DRE are advanced cases of prostate cancer[95].

A meta-analysis was carried out for 47,791 men included in thirteen studies who underwent DRE as a screening test for detection of prostate cancer[96]. Five percent of the study population had an abnormal DRE and prostate cancer was detected in 1.8% based on positive biopsy. The pooled sensitivity, specificity, and positive predictive value, PPV, for DRE were 53.2%, 83.6% and 17.8%. When compared to the meta-analysis of PSA in the same study, PSA had higher predictive values than DRE (PPV=25.1% vs. 17.8%). However, there are no randomised controlled studies to support DRE testing to reduce morbidity or mortality of prostate cancer at any age[97].

Combining PSA and DRE

Several studies have suggested that the diagnostic accuracy to detect prostate cancer can improve when both PSA testing and DRE are carried out during screening[98-101]. For example, in a study carried out among 6630 men aged >50 years who had a PSA test and DRE performed, cancer detection was 3.2% for DRE, 4.6% for PSA and 5.8% for both tests[98]. Overall, only 45% of the cases of cancers were detected only by PSA testing and only 18% by DRE. Combining PSA with DRE has the potential to increase overall detection of prostate cancer, however this has not been confirmed in randomised controlled trials and it has not been shown to be effective in reducing morbidity or mortality of prostate cancer.

5.3. Transrectal ultrasound (TRUS)

Transrectal ultrasound (TRUS) is used to examine and determine the size and volume of the prostate accurately, to detect hyperechoic lesions to indicate cancer or primarily to enable precise guidance of the needle during prostate biopsy. It is not reliable to exclude the presence of cancer. About 40% of tumours could be missed if the performance of the biopsy was dependent on TRUS suspicious findings only[98]. The Prostate Cancer Management Programme does not recommend using TRUS for screening asymptomatic men[91].

5.4. Prostate cancer risk prediction models

Over the last 20 years, there has been extensive development of risk prediction models to aid clinicians and patients in predicting prostate cancer diagnosis, stage and prognosis. The aim of these risk prediction models is to improve the accuracy of screening to detect prostate cancer. Besides PSA testing, models consider other factors such as age, ethnicity, DRE result, or other risk factors to predict a man's risk of having detectable prostate cancer. A number of these 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[102] and the European Randomized Study of Screening for Prostate Cancer (ERSPC) Risk Calculator[103]. A recent review by Louie *et al* 2014[104] identified over 120 unique risk prediction models. However, only six models to detect any prostate cancer[102, 103, 105-108]and only one model, PCPT, to detect clinically significant prostate cancer[102] have been evaluated in ≥5 study populations. This suggests that many poorly validated models exist.

Table 5 describes the characteristics of the study population and the predictor variables that were used to develop the identified six prostate cancer models used to predict any prostate cancer. Besides PSA, DRE was the most common predictor variable (5 of 6 models) to be included in the risk model, followed by age and % free prostate-specific antigen (fPSA) (4 out of 6 models) and TRUS-PV (3 of 6 models). PCPT was the only model to consider family history, ethnicity and previous negative biopsy results and Chun was the only model to consider PSA sampling density. Also Karakiewicz and

PCPT were the only two models that did not require a TRUS procedure. Including TRUS prostate volume as a predictor in a risk model to be used in a routine screening programme would be impractical. Currently, TRUS cannot be performed in general practices. Patients are referred to urology specialists, who are unlikely to be adequately resourced to sustain a population-based screening programme. This would have additional cost implications that would need to be evaluated. In addition, it is possible that patients would be unwilling to undergo TRUS-PV at screening and have an additional TRUS performed to guide biopsy for diagnosis. This could increase or cause additional psychosocial distress that may already occur in screening[109]. A strong prostate cancer prediction model used for decision-making should include predictors that are feasible for use in clinical practice in a population-based screening programme and produces a reliable test result.

Table 5. Characteristics of the six risk calculator development models to discriminate men at risk of being diagnosed with any prostate cancer

Author, Year	Model	N	Total PSA (ng/mL)	PSA range (ng/mL)	No. of biopsy cores	% with PCa	Population	Type of model	Predictor variables included in the development model
Stephan, 2002[108]	Prostataclass	1118	7.3	2-10	6-8	60.7	Germany &Canada	artificial neural network	PSA, DRE, Age, %fPSA, TRUS-PV
Finne, 2004[106]	Finne	1175	Not reported	4-10	≥6	22.7	ERSPC (Finland, The Netherlands & Sweden)	logistic regression	PSA, DRE, %fPSA, TRUS-PV
Karakiewicz, 2005[107]	Karakiewicz nomogram 2	1762	7.1	≤50	6	41.9	Germany	logistic regression	PSA, DRE, Age, %fPSA
Thompson, 2006[102]	PCPT	5519	1.5	0.3-287	≥6	21.9	USA	logistic regression	PSA, DRE, Age, Ethnicity, Family History, No. of previous negative biopsies
Chun, 2007[105]	Chun	1162	5.4	≤50	≥10	41.7	Germany	logistic regression	PSA, Age, %fPSA, sampling density (TRUS-derived gland volume by the number of cores taken at initial biopsy)

Table 5. Characteristics of the six risk calculator development models to discriminate men at risk of being diagnosed with any prostate cancer (continued)

Table 5. Characteristics of the six risk calculator development models to discriminate men at risk of being diagnosed with any prostate cancer (continued)

Author, Year	Model	N	Total PSA (ng/mL)	PSA range (ng/mL)	No. of biopsy cores	% with PCa	Population	Type of model	Predictor variables included in the development model
Roobol, 2010[103]	ERSPC Risk Calculator 3	1850	Not reported	≥3	6	29.2	The Netherlands	logistic regression	PSA, DRE, TRUS, TRUS-PV

DRE, digital rectal examination; fPSA, free prostate-specific antigen; PSA, prostate-specific antigen; TRUS-PV, transrectal ultrasonography prostate volume
Adapted for Louie et al[110]

The review[104] also carried out a meta-analysis to evaluate the predictive accuracy of risk prediction models to discriminate any prostate cancer compared to PSA testing. In general, compared to PSA testing (area under the curve, AUC=0.66), prediction models have a higher predictive accuracy to detect any prostate cancer **(Figure 5).** Among the six models, Prostataclass and ERSPC RC3 have the highest discriminative value to predict any prostate cancer (AUC=0.79), suggesting them to be the best performing models. PCPT is better at discriminating clinically significant prostate cancer than any prostate cancer (AUC=0.71 vs. 0.66, respectively). However, without applying and comparing all six prediction models in a cohort of men undergoing prostate cancer screening, conclusions cannot be made about the superiority of one model over another.

The sensitivity of PSA testing to detect prostate cancer is about 21%[94]. Although the superiority of a model to predict prostate cancer is unclear, this meta-analysis suggests that prediction models have the potential to double the sensitivity of PSA testing (44% vs. 21%).

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. Furthermore, the effect of these predictive risk models on reducing mortality and side effects related to overdiagnosis and overtreatment are unknown. Additional evaluations of the clinical effectiveness of these prostate cancer risk prediction models in clinical practice are needed before they are recommended for use in screening.

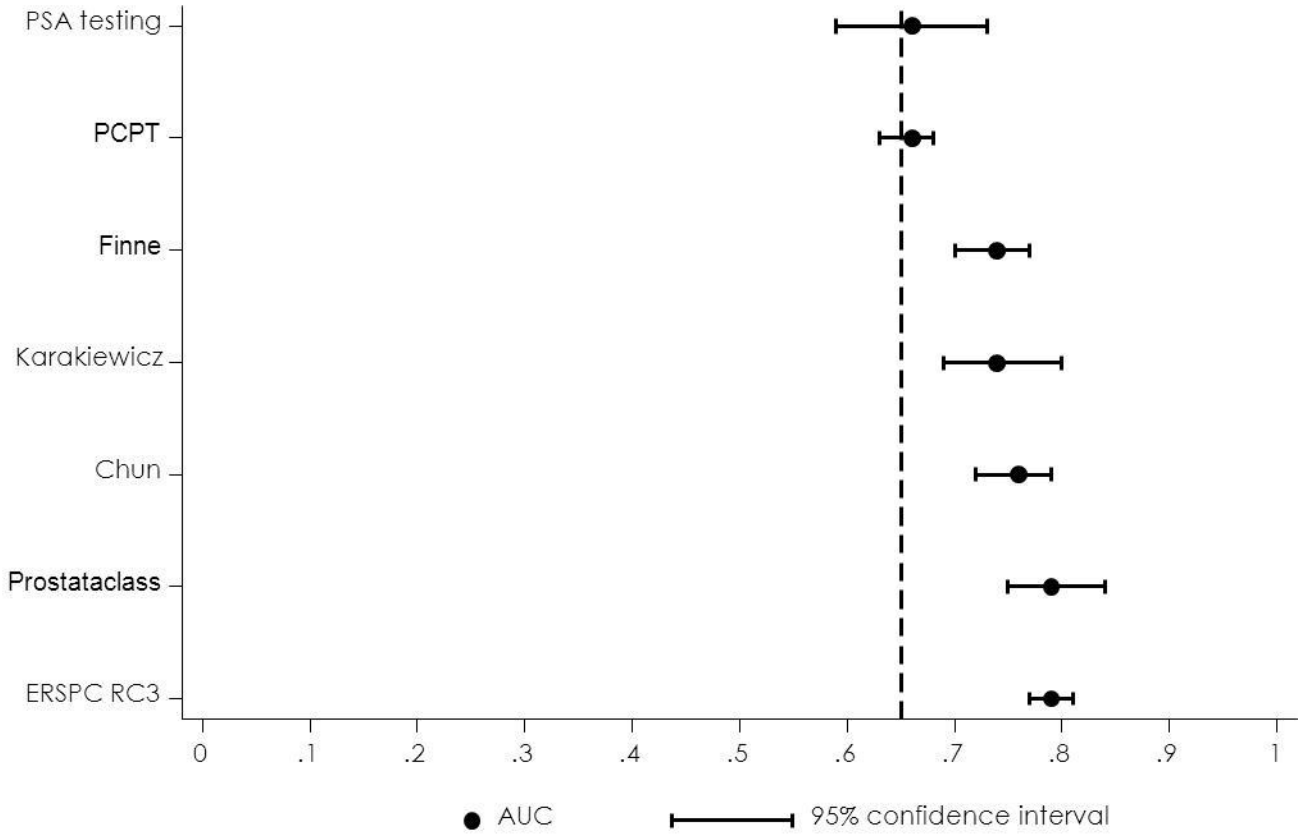

Figure 5. Summary of meta-analysis of the area under the curve (AUC) of PSA testing vs. PCa risk models to discriminate men at risk of being diagnosed with any prostate cancer[110]

5.5. New screening and triage biomarkers

Recent research advances have focussed on identifying biomarkers to stratify men with low-risk and high-risk aggressive disease so that men can be managed appropriately, minimising potential harms of overdiagnosis and overtreatment[111].

Two of the most promising urinary RNA biomarkers[112] are prostate cancer antigen, PCA3 and fusion gene TMPRSS2:ERG, to identify men with low-risk (indolent) and aggressive (clinically significant) cancers[112]. PCA3 is highly overexpressed in over 95% of prostate cancer tumours, or up to 100 times greater in men with cancer than in those with a normal prostate[113, 114]. PCA3 assay quantifies PCA3 messenger ribonucleic acid (mRNA) and PSA mRNA in urine. PCA3 mRNA is overexpressed in prostate cancer cells whereas PSA mRNA remains constant in normal prostate cells; and a ratio of these two markers will generate a score to indicate the probability of a positive prostate biopsy (PCA3 score ≥25). A review identified 11 clinical trials that evaluated the diagnostic performance of PCA3[115]. The sensitivity of PCA3 test (54-82%) was found to be less than PSA testing (81-98%), however, the specificity for PCA3 was much better than PSA (66-89% vs. 5-28%). Therefore, the higher specificity would reduce the number of overdiagnosis and overtreatment cases. A weakness of these studies was that none of them used PCA3 scores as a screening test to indicate prostate biopsy, making it difficult to understand its clinical value. However, in a recent report from the ERSPC screening trial arm in Rotterdam, compared to a PSA ≥3 ng/ml cut-off, a PCA3 score ≥35missedfewer cancers (32% vs. 64.7%), detected fewer aggressive tumours (26.3% vs. 68.2%) and reduced the number of unnecessary biopsies (51.7% vs. 68.2%)[116]. Results suggest that PCA3 performed marginally better than PSA testing (AUC 0.64 vs. 0.58, p-value=0.14). Surprisingly, in a subsequent study carried out in Rotterdam [117], only 38.9% (35 of 90) of men with a PCA3 score ≥100 had prostate cancer, leaving the remaining 61.1% of men with a PCA3 score ≥100 unexplained. The reasons for low detection rates of prostate cancer among men with high PCA3 scores are unclear and, as such, its clinical utility as a screening tool remains unclear.

Prostate gene fusion between TMPRSS2 and *ERG*, anETS (e-twenty-six) transcription factor is overexpressed in about 50% of prostate cancers from PSA-screened cohorts[118, 119]. However, population-based cohorts have shown a much lower prevalence of TMPRSS2:ER (15%).[119] The reasons for these differences in prevalence are not well understood, however, the prevalence of TMPRSS2:ERG was found to be lowest in men with early stages tumours (T1), suggesting that this marker may be useful in identifying men at risk for more aggressive disease. Further research is still needed to fully understand its clinical utility in screening and its potential use in prostate cancer management (i.e. prognosis).

Recent results from the prospective population-based Stockholm 3 (STHLM3) screening study suggest that a combination of plasma protein biomarkers (PSA, free PSA, intact PSA, hk2, MSMB, M1C1), genetic polymorphisms (232 SNPS) and clinical variables (age, family, history, previous

prostate biopsy, prostate exam) and PSA concentration would increase the specificity of screening without decreasing the sensitivity of PSA testing using a cut-off of at least 3 ng/mL to diagnose high-risk prostate cancers [120]. This could reduce the number of men undergoing prostate biopsy. The STHLM3 model was developed and validated using data from over 145,000 men aged 50-69 years who were randomly invited for screening. The model performed significantly better than PSA alone for detection of clinically significant cancers (Gleason score ≥7) with an AUC of 0.74 (95% CI: 0.72-0.75) compared to 0.56 (95% CI: 0.55-0.60), respectively. The clinical usefulness of these data suggests that the STHLM3 model could reduce the number of biopsies by 32% and avoid 44% of benign biopsies. Despite these promising results, the study was only carried out in Stockholm, Sweden, where the population is relatively homogenous and men were mainly of northern European descent. Further investigations are needed to validate the STHLM3 model in other populations and in ethnic groups (e.g. Blacks).

5.6. Reflex testing for diagnosing prostate cancer

A number of developments have been made to try to try improve the use of the PSA assay for screening and diagnosis. A PSA test cut-off of 4 ng/mL is the generally accepted threshold to indicate prostate biopsy, however, specificity is poor. Detection rates of prostate cancer are low at first biopsy, around 14-25%, and a significant number of negative or inconclusive biopsy results will require further assessments, including a second biopsy to confirm the absence of prostate cancer [121]. To avoid associated complications from biopsy and diagnosis of clinically insignificant prostate cancers, reflex testing with PSA isoforms, PROGENSA PCA3 assay (PCA3 assay) and the Prostate Health Index (PHI) may avoid unnecessary second biopsies.

Studies have suggested that reflex testing with PSA isoforms, such as ratio of free to total PSA (f/tPSA) or complex PSA (cPSA),for men with PSA values <10 ng/mL (known as the diagnostic “grey zone”) could improve specificity and reduce the number of unnecessary biopsies. A systematic review and meta-analysis of reflex testing with PSA isoforms[122] found that f/tPSA or cPSA improved the diagnostic performance of detecting prostate cancer for men with a total PSA (tPSA) of 2-4 or 4-10 ng/ml compared to tPSA alone. f/t PSA also performed better among men with a tPSA 4-10 ng/ml compared to 2-4 ng/mL. Assuming a sensitivity of 95%, the specificity of f/tPSA more than doubled for men with a tPSA range of 4-10 ng/mL compared to men with 2-4 ng/ml (18% vs. 6%). When both tests, f/t PSA and cPSA, were performed, the diagnostic performance to detect prostate cancer was equivalent for both 2-4 ng/ml and 4-10 ng/ml tPSA ranges. Results suggest that triage of men in the “grey zone” with tPSA 2-10 ng/ml using PSA isoforms could potentially reduce overdiagnosis and maintain a high cancer detection rate. A review of another PSA isoform, specifically [-2]proPSA, suggests that it has the potential to detect clinically significant and non-significant prostate cancer among those with a PSA level of <10 ng/mL[123]. However, the studies identified in this review were mainly small and retrospective. In general, larger prospective studies are required to fully evaluate the clinical application of these PSA isoforms as markers for screening.

Two non-invasive tests, the PROGENSA® prostate cancer antigen (PCA3 assay; Hologic Gen-Probe, Marlborough, MA, USA) urinary test and the Prostate Health Index (PHI; Beckman Coulter In., Brea, CA, USA) blood test have been developed to aid in the decision as to whether a second biopsy should be recommended[124]. In the previous section 5.5, PCA3 was reviewed as a potential test for initial screening. Although its clinical utility as a screening test is unclear, PCA3 has also been considered for use as a reflex test. In comparison to PCA3 test, PHI calculates a composite score using total PSA, free PSA and [-2]proPSA that can be used in the clinical decision-making process[125]. The PHI is a risk prediction model that predicts whether a man has clinically significant prostate cancer, specifically if they have a higher total PSA and [-2]proPSA with a low free PSA. A recent review of studies found that PHI performed better at discriminating prostate cancer on biopsy compared to PSA, percentage free PSA (%fPSA) or p2PSA among men in the grey zone[126]. It also found that PHI also improves the prediction of clinically significant prostate cancer among men with PSA 2-10 ng/ml.

Given the high potential of these two markers to improve PSA screening, NICE, in collaboration with NIHR HTA (National Institute of Health Research Health Technology Assessment) investigated the clinical and cost effectiveness of PCA3 and PHI as a reflex test to inform the decision to perform a second biopsy[124]. After reviewing the clinical validity of both biomarkers, the review found that there was no additional clinical benefit for adding either test in combination with existing tests that would improve the accuracy of diagnosing prostate cancer. Economic modelling results also showed that these tests were not cost-effective for clinical assessment. Although there are a number of ongoing trials evaluating these two markers, the evidence showed any added benefits of using these tests would be small and were unlikely to offset sufficient costs and reduce the number of men undergoing unnecessary repeat biopsies. Results for PCA3 were consistent with findings from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group in which evidence on clinical validity was rated inadequate to inform on decisions for when to repeat biopsy for previously biopsy-negative men[127]. NICE has not recommended PCA3 assay and PHI for clinical assessment of suspected prostate cancer, who previously had a negative or inconclusive TRUS biopsy[124]. It was also recommended that no further research should be carried out to consider PCA3 and PHI as reflex tests.

Aside from the effort to identify biomarkers to improve careful selection of patients for screening to detect clinically significant prostate cancer, the use of imaging or multiparametic MRI (mp-MRI) has also emerged as a potential non-invasive triage test for refining patient selection. See section 8.2 for a more detailed discussion.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

6.1. PSA testing

Elevated PSAs can be due to a number of factors other than prostate cancer, such as increasing age and ethnicity[128], medications (e.g. finasteride)[129], prostatitis[130], urinary tract infection[131], benign prostatic hyperplasia (BPH)[132], body mass index[133-135] and variations in laboratory assays[136]. It is widely accepted that PSA levels increase naturally with increasing age.

There is no consensus on suitable PSA cut-off levels for detecting prostate cancer. An informative threshold value for recommending prostate biopsy is the compromise between false positive and false negative results. A review by Luboldt et al[137], reported a number of studies recommending upper age-specific limits for PSA testing in populations that are predominantly White **(Table 6)**. The upper limits of PSA testing are highly variable by age which may reflect differences in demographically and clinically heterogenous populations. Although these studies have recommended age-specific reference range for PSA, the clinical usefulness of these ranges has not been evaluated and cannot be considered in practice. There is also evidence that suggests PSA levels will vary depending on race with black men having higher PSA levels compared to white men[138, 139]. .

Table 6. Studies recommended age-specific upper reference ranges for PSA (ng/ml) testing. Adapted from Luboldt H et al[137].

Author	Country	21-30 yrs	31-40 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs	80-89 yrs
Osterling[140]	USA			2.4	3.5	4.5	6.5	
Dalkin[141]	USA				3.5	5.4	6.3	
Anderson[142]	USA			1.5	2.5	4.5	7.5	
DeAntoni[138]	USA			2.3	3.8	5.6	6.9	
Oesterling[143]	USA			2.0	3.0	4.5	5.5	
Espana[144]	Spain			2.9	4.7	7.2	9.0	11.4

Table 6. Studies recommended age-specific upper reference ranges for PSA (ng/ml) testing. Adapted from Luboldt H et al[137] (continued)

Author	Country	21-30 yrs	31-40 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs	80-89 yrs
Lein[145]	9 European countries/ 8 non-European countries	1.16	1.78	1.75	2.27	3.48	4.26	2.64
Kalish[146]	USA				2.84	5.87	9.03	
Wolff[147]	Germany	0.93	1.10	1.15	2.35	3.55	3.95	
Chautard[148]	France	1.07	1.37	1.33	2.07	2.82		
Berger[149]*	Austria			1.94	3.5	6.4	8.8	

*With total PSA levels up to 20 ng/ml.

Besides the wide-ranging PSA references that exist in the literature, the PCRMP also recognises that there is a wide range of referral practice throughout the UK. Before a consensus can be found, the previously recommended age-related referral values by the Programme[91] **(Table 7)** are being reconsidered given the concern of missing a high proportion of clinically significant cancers in older men (low sensitivity) and the increase rate of unnecessary biopsies in younger men (low specificity)[137].

Table 7. Prostate Cancer Risk Management Programme (PCRMP) 2008 age-related prostate biopsy referral values for total PSA levels

Age (years)	PSA referral value (ng/mL)
50-59	≥3.0
60-69	≥4.0
≥70	>5.0

The two largest randomised PSA-based screening trials, ERSPC (European Randomised Study of Screening for Prostate Cancer) and PLCO (Prostate, Lung, Colorectal and Ovarian Cancer), have

evaluated PSA screening amongst men aged 50-69 years with biopsy indication amongst those with PSA ≥3.0 ng/mL. Recommended prostate biopsy referral values are being realigned to the evidence emerging from these two trials. Referral values are for men aged 50-69 years with a PSA value of ≥3.0 ng/mL **(Table 8).** Further diagnostic evaluation should consider the man's history of comorbidities, ethnicity, family history and abnormal DRE findings prior to biopsy.

Table 8. New recommended prostate biopsy referral values for total PSA levels

Age (years)	PSA referral value (ng/mL)
50-69 years	≥3.0

Repeat PSA testing

Although men with abnormal values can be referred for biopsy, a single PSA measurement may not be sufficiently precise for screening and diagnosis. The European Group on Tumor Markers conducted a systematic review of twenty-seven studies and found that the biological variation of serial PSA measurements can fluctuate from days, weeks, and months by up to 20% in men aged ≥50 years with PSA levels of 0.1 to 20 ng/mL [150]. The variability of PSA levels could be due to ejaculation within the last 48 hours[151], perineal trauma (e.g. cycling) [152], or prostatitis[153] rather than be indicative of disease. Men may consider deferring prostate biopsy and having a repeat PSA test after these conditions resolved. These results also suggest that a single PSA results should be interpreted cautiously and repeat PSA testing in ≥1 month with the same PSA assay and laboratory should be considered. Change in PSA measurement in subsequent testing should only be considered random if the change is <5%.

In terms of clinical outcomes, cancer detection rates and positive predictive values decline significantly with serial testing[154, 155]. Specifically, in the ERSPC trial where men were screened using a 4-year interval, the cancer detection rate decreased between the first and second round of screening from 5.1% to 4.4%; and the positive predictive value for PSA level ≥3.0 ng/ml decreased from 29.2% to 19.9%[155] The study also found that despite the long screening interval between rounds 1 and 2, localised prostate cancers were more likely to be found (81.3% to 96.3%) and the number of clinically significant tumours (Gleason score ≥7) reduced (8.1% to 3.3%). In comparison, the UK multi-centred ProtecT (Prostate testing for cancer and Treatment) randomised controlled trial evaluating different treatment strategies for localised prostate cancer, the study found that PSA levels that reduced by 20% at repeat testing at 7 weeks for men aged 50-70 years with initial PSA of 3.0-19.99 ng/ml were less likely to be diagnosed with clinically significant cancers[156]. Reduction was greatest amongst those aged ≤60 years and those who have high-grade disease had lower variability in PSA. However, repeat testing had poor specificity in predicting the absence of cancer. These data suggest that age and serial PSA results could potentially offer a simplistic approach to predict a man's risk of clinically significant disease[156]. However, the practicalities of this approach in clinical practice have not been evaluated, particularly because it requires manual monitoring of PSA concentrations[150].

Although prostate cancer risk prediction models appear to improve the accuracy of predicting a man's overall risk of prostate cancer, there are no published data, to our knowledge, whether these

models with age-specific cut-offs could improve the sensitivity and specificity for detecting clinically relevant disease. Additional research is needed to evaluate the effectiveness of risk prediction models with age-specific cut-offs to predict prostate cancer in clinical practice.

7. The test should be acceptable to the population.

When the PSA test was first introduced, an early study in 1994 showed that 95% of men attending their GP found PSA screening to be generally acceptable[157]. Despite the uncertainties of PSA screening, men in the UK may still want the PSA test because it's "just another blood test" or it's seen as responsible health behaviour to prevent prostate cancer[158].

Although the 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[91], 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[158, 159]. 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[160]. For men who required further investigation after a PSA test, increased anxiety and regret may often be experienced and uncertainty may still persist even if a man still receives a normal result[159]. In a randomised controlled trial where about 1000 men aged 40-75 in selected practices in England and Wales were randomised to receive either a patient decision aid that provided balanced information about the potential benefits and limitations of the PSA test (intervention) or no patient decision aid (controls), men who received the decision aid had improved knowledge of the PSA test and less positive attitudes towards the test[161]. Yet there was no difference in intention to be tested between the two groups, highlighting the acceptability of the PSA test irrespective of the level of information received by the man during the decision-making process.

On the other hand, results from a meta-analysis of PSA testing uptake following decision aids found that men who received decision aids were less likely to have a PSA test (-3.5%)[162]. However, this finding needs to be interpreted with caution as it is only a small effect and further studies are required for confirmation. Outside the clinical setting, men's social networks and media have also been found to be important factors in influencing a man's awareness of PSA testing and acceptability of the test[159].

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.

8.1. TRUS-guided diagnostic biopsy

A TRUS biopsy is considered the gold standard investigation for diagnosing prostate cancer. The procedure involves taking 10-12 cores of the prostatic tissue for histological analysis following the Prostate Cancer Management Programme's guidelines[163]. Histological examination will evaluate to what extent the tumour has differentiated and grade differentiation according to the Gleason score (2 to 10). Tumours are considered low-grade with Gleason ≤6, intermediate with Gleason score=7, and high-grade with Gleason 8-10. The sensitivity of detecting clinically significant prostate cancer (Gleason>6) using 12-core biopsy is 80%[164]. This suggests that about one in five prostate cancers (Gleason >6) are missed on TRUS biopsy and may require additional diagnostic evaluation if symptoms persist and PSA levels continue to increase.

8.2. Pre-biopsy imaging

TRUS is used to guide biopsy for investigating suspicious prostate cancer. Although TRUS is effective in showing the prostate and its four anatomic zones, it can be inaccurate at identifying suspicious lesions (e.g. small foci tumours). TRUS is performed in a 'blind' way that does not use imaging guidance to direct the biopsy to zones of the prostate where there are generally no suspicious lesions which can either lead to overdiagnosis of clinically insignificant prostate cancers[165, 166], lead to sampling of tissue that can miss clinically significant lesions [167, 168] or lead to random sampling of tissue that is imprecise in measuring the tumour that can underestimate the size and grading of the cancer[169]. False negative rates associated with TRUS guided biopsy can be as high as 30-45%[167, 168, 170] or up to half of men who are initially diagnosed with low-risk disease are under-staged and actually have a higher burden of high-risk disease[170-176]. However, diagnosis and staging of disease has the potential to improve with magnetic resonance imaging (MRI) before prostate biopsy[177]. MRI is a non-invasive test that uses a powerful magnetic field, radio frequency pulses and a computer to provide a detailed image of the prostate. Lesions seen on a pre-biopsy MRI could be used to select appropriate targets for TRUS-biopsy.

Triage of men with clinical suspicion of prostate cancer (elevated PSA and abnormal DRE) to MRI prior to prostate biopsy could be more specific in selecting those with clinically significant cancer that requires treatment. This strategy could potentially reduce the number of men who undergo unnecessary biopsy and treatment among men with clinically insignificant disease. This would also reduce the rate of complications that could interfere with accurate disease staging and improve disease risk stratification to manage appropriate treatment with active surveillance or radical therapies. A systematic review of 50 studies compared (MRI) to standard TRUS biopsy to detect clinically significant prostate cancer[178]. The review found that MRI and TRUS-biopsy have the same

detection rate (43%) of clinically significant cancers, however, with reduced number of biopsies and reduced number of clinically insignificant prostate cancers. It is estimated that MRI prior to targeted biopsy can reduce the number of biopsy procedures carried out by one-third if men are normal on MRI. Also 10% of men who were diagnosed with clinically insignificant prostate cancer by standard TRUS biopsy could have potentially been avoided if they had a MRI targeted biopsy. Despite the accumulating evidence that MRI can improve diagnosis of clinically significant prostate cancer and minimise overdiagnosis, the heterogeneity in study design limits establishing strong recommendations for MRI until large multi-centred studies are carried out using clearly defined MRI methods, standardised sampling and definitions of disease.

Advances in MRI technology, such as multiparametric MRI (mpMRI), combine additional imaging parameters such as T2W (*T2-weighted image*), DWI (*diffusion-weighted imaging*) and DCE (*dynamic contrast-enhanced imaging*) provides better visualisation of the prostate to detect clinically significant prostate cancers[179], however, provide lower accuracy in detecting smaller tumours with low grade disease[180]. Lesions suspicious on mpMRI can be used as targets for biopsy. A systematic review of twelve studies found that the rate of clinically significant prostate cancer with mpMRI ranged from 44% to 87% which is higher than the rate of blind standard TRUS-biopsy and it has a high negative predictive value (NPV) for significant disease ranging from 63% to 98%[181]. High NPV is important for clinicians to rule out significant disease. Similar to the review on MRI described above, there was considerable heterogeneity between studies in terms of patient characteristics, MRI criteria for reference standard and scoring/interpretation of images, making it difficult to establish recommendations for mPMRI in clinical practice.

In addition, few studies have reported on the role of mpMRI in biopsy naïve patients with no history of prostate cancer[178, 182-188]. In general, the studies show that mpMRI improves detection of clinically significant disease and reduces the detection of low-risk disease. However, these studies have generally been carried out in small sample sizes and follow-up has been short, and therefore, difficult to understand whether the benefits of reducing overdiagnosis outweigh diagnosis of a few clinically significant tumours that were missed at initial diagnosis using mpMRI with targeted MRI biopsy.

To address some of the challenges of using mpMRI in clinical practice, the UK PROMIS (Prostate MR imaging study) prospective trial is underway to investigate whether targeted biopsy with mpMRI is better than 10-12 cores TRUS biopsy (standard procedure) to discriminate men with and without clinically significant prostate cancer[170]. About 700 men who have never had a prostate biopsy before and have clinical suspicion of prostate cancer (i.e. abnormal DRE, elevated PSA, family history or ethnic risk group) are being recruited. Men who participate will have an mpMRI, template prostate mapping (TPM) biopsy and a 10-12 core TRUS biopsy. TPM is a more accurate biopsy which is not routinely offered to patients as part of standard care but it involves taking biopsy cores from the whole prostate. The performance of both mpMRI and TRUS-biopsy will be compared against the

TPM biopsy as the "gold standard" reference. TPM will be performed before TRUS-biopsy. PROMIS will standardise MRI reporting to European Society of Uro-Radiology[189] and British Society of Uro-Radiology[190] guidelines to avoid variation in interpretation, results of the mpMRI will be blinded to the patient and the clinician during TRUS biopsy to minimise bias, and long-term follow-up will be carried out using the Office for National Statistics and NHS databases. If results favour mpMRI, important changes will be made to the diagnostic pathway for prostate cancer in the future. Recruitment initiated in 2012 and is expected to end in the latter part of 2015.

Until more evidence becomes available to recommend mpMRI to biopsy naïve men with clinical suspicion of prostate cancer, NICE guidelines recommends that men who are negative on TRUS 10-12 cores biopsy should be further evaluated with mpMRI to consider whether a repeat biopsy with targeted biopsy is needed[7]. If the man is negative on mpMRI, then another biopsy should not be offered unless they are positive for other risk factors (e.g. abnormal DRE or have pathological features of high-grade prostatic intra-epithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) at first biopsy*)*. Evidence suggests this strategy will reduce the number of repeat biopsies required compared to routine systematic TRUS re-biopsy. A systematic review of 51 studies with 10,000 men estimates that the sensitivity of mpMRI to detect prostate cancer among men with prior negative biopsy ranges from 79-96% which means about 4-21% of prostate cancers will still be missed using this strategy[191]. However, in a meta-regression analysis of 46 studies, cancer detection after repeat biopsy with mpMRI was 37.6% compared to 36.8% for transperineal saturation biopsy (median 29 cores) and 30% for transrectal saturation biopsy (median 24 cores)[192]. Although cancer detection rates appear to be more sensitive for mpMRI compared to transrectal saturation biopsy, this was not significantly different after adjusting for the number of previous biopsies. On the other hand, mpMRI was able to achieve similar cancer detection rates at repeat biopsy compared to other strategies by taking fewer targeted cores at biopsy. In general, considerable heterogeneity exists between studies with limited prospective data or common reporting formats to determine the optimum re-biopsy strategy to manage patients who are negative at initial biopsy.

8.3. Diagnosis and treatment guidance

The National Institute of Health and Care Excellence (NICE) has developed guidance on the best available evidence for *Prostate cancer: diagnosis and treatment* that is summarised in NICE clinical guideline 175[7]. The guidelines apply to men with suspected or diagnosed prostate cancer who have been referred to secondary care or men with diagnosed cancer who are in follow-up in primary care. These recommendations do not apply to asymptomatic men with an abnormal PSA level detected in primary care who are not referred further clinical investigation.

The decision for a man to undergo prostate biopsy should not be based on abnormal serum PSA level screening alone. During the patient-centred informed decision-making process, the responsible

clinician should discuss the following with the patient: his PSA level and DRE findings as well as comorbidities and other risk factors (such as increasing age and black African-Caribbean family origin) and history of a previous negative prostate biopsy. The benefits and harms of prostate biopsy should be explained. A biopsy should not be offered to men with a high PSA level and evidence of bone metastases unless this is required for taking part in a clinical trial.

The biopsy procedure for diagnosis of prostate cancer follows the guidelines by the PCRMP in *Undertaking a transrectal ultrasound guided biopsy of the prostate*[163] which recommends 10 to 12 core samples of the midlobe peripheral zone and the lateral peripheral zone of the prostate to be taken. Prostate cancer is classified as early localised prostate cancer, locally advanced prostate cancer or advanced (metastatic) prostate cancer.

Grading and staging

If cancer is found on diagnosis, the prostate biopsy sample will be used to grade and stage the tumour.

Grading is scored using the Gleason grading system[193-198] which measures the level of disease aggressiveness of the cancer and it is used to inform on prognosis and appropriate treatment **(Figure 6)**. The grading system is used to look at the pattern of cancer cells within the prostate. By visual inspection, two of the most common patterns are graded on a scale of 1 (most like normal cells) to 5 (least like normal cells) to generate an overall summed score ranging from 2 to 10. For example, if the biopsy shows that most of the cancer cells is grade 3 and the highest grade of any other cancer cells seen is grade 4, then the overall Gleason score is 7 (3+4). There is increasing evidence that a Gleason score of 4+3 is slightly more aggressive than 3+4 because there is more grade 4 cancer[199]. With increasing Gleason score, the more aggressive the cancer is likely to be and the more likely it is to spread. The NICE clinical guideline 175, *Prostate cancer: diagnosis and treatment*[7], outlines the recommended strategies for treatment depending on disease stage.

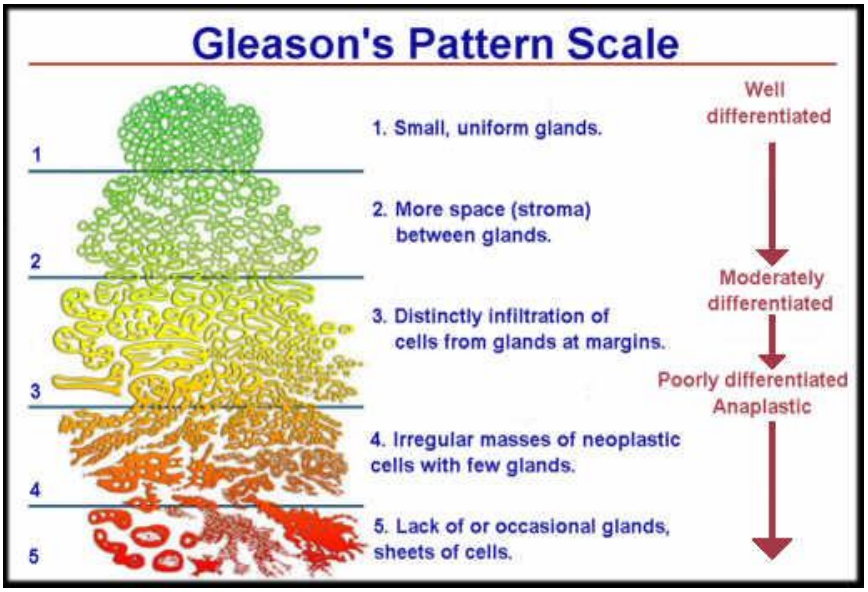

Figure 6. Gleason grading system for prostate cancer

Staging of the tumour defines the size and spread of the cancer[200]. The TNM (Tumour-Node-Metastases) staging system is used to define how much the cancer has spread in and around the prostate (T) and whether the cancer has spread to the lymph nodes (N) or metastasized (M) to other parts of the body **(Table 9)**.

Table 9. TNM Staging for Prostate Cancer[201]

Stage	Definition
TUMOUR	**Primary Turmour**
TX	Primary tumour cannot be assessed
T1[a]	Clinically inapparent tumour, neither palpable nor visible by imaging
T2[a]	Tumour confined within prostate
T3[a]	Tumour extends through the prostatic capsule
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and /or pelvic wall
NODE	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Regional lymph node metastasis
METASTASIS	**Distant metastasis**
M0	No distant metastasis
M1[a]	Distant metastasis

[a] Within each stage, there are subgroupings a–d, which defines the extent of spread within that group.

The grading and staging of the tumour will stratify men diagnosed with localised prostate cancer into the following low, intermediate and high risk categories **(Table 10)** to help guide and manage appropriate treatment. Men of low-risk prostate cancer are commonly defined as having insignificant prostate cancer that would unlikely cause disease-specific morbidity and mortality if left untreated[20].

Table 10. Risk stratification of men with localised prostate cancer

Level of risk	PSA		Gleason		Clinical stage
Low	<10 ng/ml	and	≤6	and	T1-T2a
Intermediate	10-20 ng/ml	or	7	or	T2b
High[1]	>20 ng/ml	or	8-10	or	≥T2c
[1]High-risk localised prostate cancer is also included in the definition of localised advanced prostate cancer. T, tumour stage, to describe the size and spread of the cancer					

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

Although genetic testing is currently not available, ongoing research is being carried out by the UK Genetic Prostate Cancer Study[202] to identify genetic variants that may increase a man's prostate cancer risk. Target recruitment of 26,000 men with prostate cancer is expected by 2017. Results will help inform the UK about the possibility of genetic screening for prostate cancer in the future which could potentially help in risk stratification for clinical management, treatment decision-making and prediction in prognosis.

Because the benefits of targeted screening for high-risk men is unknown, there is also an international multi-centric study (being coordinated in the UK) involving 62 centres from 20 countries called the IMPACT study (Identification of Men with a genetic predisposition to Prostate Cancer,) that is aimed at evaluating the role of targeted PSA screening in men with *BRCA1/2* mutations[203]. The study is evaluating the predictive value of biopsy using a PSA threshold of 3.0 ng/ml in *BRCA1* and *BRCA2* carriers aged 40-69 years to detect clinically significant prostate cancer. Results will demonstrate whether targeted screening of *BRCA1/2* carriers could lead to earlier diagnosis and improved survival. Initial results from the first of five rounds of annual screening show that the positive predictive value (PPV) of biopsy with a PSA threshold of 3.0 ng/ml is higher in *BRCA1* (41% vs 23%) *and BRCA2* (48% vs 33%) than controls (without *BRCA* mutations)[204]; and better at detecting high-grade disease for *BRCA2*. The PPV in *BRCA2* mutation carriers is double that in the general population (24.1%). This suggests that the benefits of PSA screening is improved for *BRCA1/2* carriers, however, additional data from IMPACT are needed from the subsequent screening rounds to fully determine the value of testing in these groups.

The Treatment

10. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

The NICE clinical guideline 175, *Prostate cancer: diagnosis and treatment*[7], outlines the recommended treatment for men with prostate cancer depending on disease stage: early localised prostate cancer, locally advanced prostate cancer or advanced metastatic prostate cancer **(Figure 7)**.

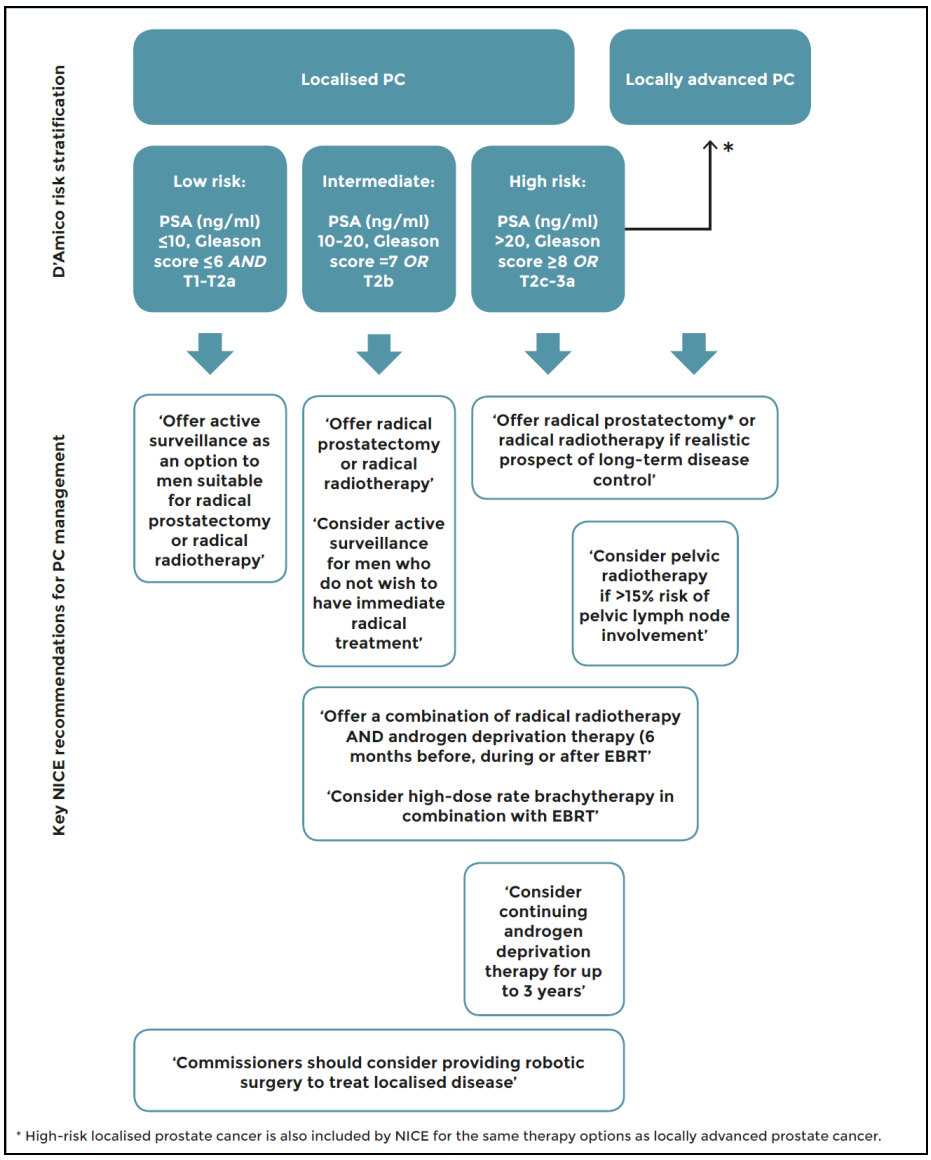

Figure 7. Prostate cancer staging, risk stratification and key NICE recommendations for the management of localised or locally advanced disease. Reproduced from[205].

Early localised prostate cancer

Men with low-risk localised prostate cancer will normally be offered active surveillance (*monitoring of PSA kinetics, DRE, and prostate rebiopsy*) or treatment with radical prostatectomy or radical radiotherapy **(Table 11)**. In the case where a man is under active surveillance, a decision to proceed with radical treatment should be made based on the man's preferences, comorbidities and life expectancy. Radical treatment may also be offered if there is evidence of disease progression.

Men with intermediate localised prostate cancer can consider active surveillance (if the man does not wish to undergo radical treatment immediately) or be offered radical treatment.

Men with high-risk localised prostate cancer are offered radical treatment if there is a realistic probability for long-term disease control. They should not be offered active surveillance.

Because prostate cancers are slow growing and treatment can cause side effects and impact a man's daily life (e.g. sexual dysfunction and urinary incontinence), asymptomatic men with localised prostate cancer may elect for watchful waiting. A man under watchful waiting will have a member of the urological MDT (multidisciplinary team) monitor him over the long-term for disease progression in order to avoid treatment unless symptoms appear.

Table 11. Protocol for active surveillance

Timing	Tests
Year 1	**Every 3-4 months:** • PSA • PSA kinetics (PSA doubling time and velocity) **Every 6-12 months:** • DRE **At 12 months: prostate rebiopsy**
Year 2-4	**Every 3-6 months:** • PSA • PSA kinetics (PSA doubling time and velocity) **Every 6-12 months:** • DRE
Year 5 and every year thereafter	**Every 6 months:** • PSA • PSA kinetics (PSA doubling time and velocity) **Every 12 months:** • DRE

Locally advanced prostate cancer

Men with locally advanced prostate cancer should consider pelvic radiotherapy and receive neoadjuvant hormonal therapy and radical radiotherapy.

Advanced metastatic prostate cancer

Men with advanced metastatic prostate cancer will be offered individualised information and access to specialist urology and palliative care teams to address each man's specific needs. All men are offered bilateral orchidectomy. Alternative individualised hormone, bone-targeted and pelvic-target therapies are considered for preventing or reducing complications of metastases.

11. 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.

The effectiveness of treatment for men with early localised prostate cancer remains uncertain. Current UK guidelines for treatment are outlined in the NICE clinical guideline 175, *Prostate cancer: diagnosis and treatment* summarised above.[7] A recent meta-analysis of 16 randomised clinical trials comparing the efficacy and safety of different treatments (observational management, prostatectomy, conventional radiotherapy, conventional radiotherapy hypofractionated, conformal low dose radiotherapy (<68 Gy), conformal high dose (HD) radiotherapy (refers to >74Gy), conformal LD radiotherapy hypofractionated and cryotherapy) for patients with localised prostate cancer found no reduction in 5-year all-cause mortality for all compared treatment groups[206]. However, conformal HD radiotherapy appeared superior to conventional radiotherapy (odds ratio, OR=0.21; 95% CI: 0.03-0.97) and prostatectomy was superior to observational management (OR=0.60; 95% CI: 0.37-0.98) in reducing 5-year prostate cancer-related mortality **(Table 12).**

Table 12. Comparison of each pair-wise intervention to reduce five year prostate cancer-related mortality

	Odds ratio (95% CI)
Prostatectomy vs. observational management	0.60 (0.37-0.98)
Conventional radiotherapy vs. Prostatectomy	1.65 (0.53-5.44)
Conventional radiotherapy fractionated vs. conventional radiotherapy	0.65 (0.28-1.43)
Conformal LD radiotherapy vs. observational management	0.70 (0.31-1.57)
Conformal HD radiotherapy vs. conventional radiotherapy	0.21 (0.03-0.97)
Conformal HD radiotherapy vs. conformal LD radiotherapy	0.86 (0.53-1.37)
Conformal LD radiotherapy vs. conformal HD radiotherapy	0.22 (0.00-6.85)
Cryotherapy vs. conventional radiotherapy	0.96 (0.27-3.46)

*Adapted from Xiong T, BMJ Open 2014[206]. HD, high dose; LD, low dose

However, there are randomised controlled trials with longer follow-up that have compared the efficacy of treatments and the results are inconclusive. The SPCG-4 (Scandinavian Prostate Cancer Group Study 4) trial followed 700 men randomised to either radical prostatectomy or watchful waiting for early prostate cancer and found that after 23.2-years of follow-up, radical prostatectomy significantly reduced prostate cancer-related mortality compared to watchful waiting (relative risk, RR=0.56; 95% CI: 0.41-0.77)[207]. Surgery was particularly beneficial for men age <65 years (RR=0.45) and men with intermediate-risk prostate cancer (RR=0.38) as well as reducing the risk of metastasis for older men (RR=0.68).

In contrast, the Prostate Cancer Intervention versus Observation Trial (PIVOT) in the United States also compared the effectiveness of radical prostatectomy vs. watchful waiting in about 700 men with PSA-detected cancers and found that surgery did not reduce all-cause (hazard ratio, HR=0.88 ; 95% CI: 0.71-1.08) or prostate-cancer mortality (HR=0.63; 95% CI: 0.36-1.09) as compared with observation after 12 years of follow-up[208]. Specifically among 296 men with low-risk prostate cancer, results suggest that men who underwent radical prostatectomy have a greater risk of all-cause (HR=1.48; 95% CI:0.42-5.24) and prostate cancer-related mortality (HR=1.15; 95% CI: 0.80-1.66) than those observed by watchful waiting although these results were not statistically significant.

In the UK, the ProtecT trial screened over 82000 population-based men aged 50-69 years and randomised over 1600 men who have PSA-detected localised prostate cancer to receive one of three of frequently used treatments, active monitoring, radical prostatectomy, or radical radiotherapy, in order to evaluate its impact on 10-year survival[209]. The recruitment phase of the trial has been completed however data are not yet available as follow-up has not been completed. The first outcome results will be reported in 2016. ProtecT differs from the other two randomised trials because participants in this trial have the lowest PSA levels, age and fewer high-grade cancers at randomisation in comparison. Also, randomisation to treatment was more highly acceptable among participants in ProtecT (62%) than in SPCG-4 (not reported) and PIVOT (15%). These differences in patient characteristics will help minimise the level of bias in results compared to SPCG-4 and PIVOT. To date, this is the largest randomised controlled trial investigating the effects of treatment for localised prostate cancer detected after PSA testing. Results will provide key information needed to manage localised prostate cancer as well as quantifying the potential harms of over-detection and overtreatment vs. the survival gains in PSA-detected prostate cancer.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

The latest evidence and best practices for management of men with prostate cancer were first reviewed by NICE in 2008 and updated recently in 2014[7]. As new results from clinical trials become available, guidelines will be reviewed and updated as required.

The first National Prostate Cancer Audit[205] was carried out in England and Wales in 2013 to audit the organisation of services delivery and prostate cancer care in order to assess the process of care and its outcomes in men diagnosed with prostate cancer. The audit was established to determine whether the care delivered to prostate cancer patients is aligned with recommended practice for diagnosis, treatment, care and support as well as to identify areas where improvements can be made. The audit will prospectively continue for a minimum of 5 years. The audit composed of carrying out (i) an organisational audit of services delivery and prostate cancer care, (ii) an analysis of existing datasets to provide comparative baseline data for the prospective audit, (iii) a prospective audit of men newly diagnosed with prostate cancer, (iv) an audit of patient-reported outcomes and experience measures for those with localised prostate cancer eligible for radical prostatectomy, (v) and an evaluation of the feasibility of a PSA testing audit in primary care. The audit will serve to ensure and improve optimal patient outcomes for those who make an informed choice to be screened in the informed choice programme. Detailed results of the first audit can be found in the report[205]. Participation in the audit included all providers of prostate cancer services in England Wales which included 143 NHS trusts in England and 10 NHS hospitals in Wales.

Key findings include:

- The organisational audit of provider cancer services in England and Wales found:
    - Nearly all provider cancer services have diagnostic access to onsite MRI imaging (99%) and isotope bone scanning facilities onsite (92.5%). All multi-disciplinary teams (MDTs) have access to staging modality to comply with recommendations.
    - The availability of surgical treatment (40%) and radical radiotherapy (52%)is centralised amongst provider cancer services and was found to be in line with national guidelines. About 92% of centres offered intensity-modulated radiotherapy (IMRT) which is considered the new standard of treatment. For patients with intermediate to high-risk localised or locally advanced prostate cancer, the recommended high-rate brachytherapy in combination with external beam radiotherapy is only available at 20% of the 54 radiation centres in England and none in Wales.
    - The provision of personal support services such as cancer advisory centres, sexual function and continence services and psychological/counselling services is available in half of the NHS trusts in England and 60% of hospitals in Wales. Over 95% of provider cancer services have urological clinical nurse specialists available to provide cancer in line with national recommendations. However, less than half of the services have oncological clinical nurse specialists available. About half of the specialist MDTs offers specialist clinics that allow patients to have a joint consultation with a surgeon, oncologist and a clinical nurse specialist.
- The feasibility study to evaluate the variation in use of PSA testing in men who are asymptomatic or symptomatic, the proportion of PSA tests that yield a prostate cancer diagnosis and the timeliness of the diagnostic process (ie. time between initial testing and actual cancer diagnosis date) is in progress. Results will help inform on the impact of the current informed choice programme.

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. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

The rationale for screening asymptomatic men is the potential for early detection of disease to reduce mortality and improve a person's quality of life. When considering mass population screening, the benefits and harms must be carefully evaluated and the benefits should always

outweigh the harms. There was no clear evidence in the last UKNSC policy review in 2010 that the benefits of a national prostate screening programme will bring more benefit than harm, however, a Prostate Cancer Risk Management Programme is available, to help men make an informed choice about screening after having reviewed the benefits, harms and implications of PSA test for prostate cancer.

The PSA test is routinely used for prostate cancer screening. Prostate cancer is usually suspected with increased levels of PSA and with or without digital rectal examination. Follow-up with prostate biopsy is needed for diagnosis confirmation.

Meta-analysis of Randomised Controlled Trials

The Cochrane Collaboration, has reviewed the clinical utility of PSA testing in randomised controlled trials. PSA-based screening for prostate cancer was initially reviewed in 2006[210] and 2010. These initial reviews identified insufficient evidence to support PSA-based screening. The recent 2013 Cochrane Review[6] provided an updated systematic review of five-randomised controlled trials: The European Randomized Study of Screening for Prostate Cancer (ERSPC)[93], the US Prostate Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial[211], The Norrkoping and Stockholm studies in Sweden, and the Quebec study in Canada. The objective of the review was to determine whether screening for prostate cancer reduces prostate cancer-specific mortality or all-cause mortality and to assess its impact on quality of life and adverse events.

Table 13 summarises the study population characteristics of the five RCTs included in the meta-analysis and estimated risk ratios of prostate cancer-specific mortality and all-cause mortality. The five RCTs included in the meta-analysis included 341,342 participants. Screening used PSA with or without DRE. Studies varied according to screening interval, follow-up time and threshold cut-off for further diagnostic evaluation with prostate biopsy.

Among the RCTs, the ERSPC and PLCO were the largest and were considered to have a low risk of bias, however, contradicting results were found. The ERSPC study found that PSA screening significantly reduced prostate-specific mortality (rate ratio, RR=0.84; 95% confidence interval (CI): 0.73-0.95) as compared to the controls; where the PLCO concluded that there was no significant difference between the screening and control groups (RR=1.15; 95% CI: 0.86-1.54). When the ERSPC study was limited to a sub-group of men who were screened aged 55-69, a 21% reduction of prostate cancer-specific mortality was observed. However, both ERSPC and PLCO did not find a reduction in all-cause mortality.

Overall, the meta-analysis found that PSA screening does not reduce prostate-cancer specific mortality (RR=1.00; 95%CI: 0.86-1.17) and all-cause mortality (RR=1.00; 95% CI: 0.96-1.03).

Prostate cancer diagnosis was 30% greater among men randomised to screening compared to controls (RR=1.30; 95%CI: 1.02-1.65). Men randomised to screening were more commonly

diagnosed with localised prostate cancer (RR=1.79; 95 CI: 1.19-2.70). In contrast, advanced cancer diagnosis was significantly lower among men in the screening groups compared to the controls (RR=0.80; 95%CI: 0.73-0.87).

Table 13. Randomised controlled trials evaluating the impact of screening vs. no screening on prostate cancer-specific mortality

Trial	No. screened	No. of controls	Age for screening	Screening interval	Screening test	PSA (ng/mL) cut-off for biopsy	Follow-up period	PCa-specific mortality Risk ratio (95% CI)	All-cause mortality Risk Ratio (95% CI)	Prostate cancer diagnosis Risk Ratio (95% CI)
ERSPC trial	112569	128688	50-74 yrs	2-4 yrly	PSA	≥3.0	Mean: 10.5 yrs Median: 11 yrs	0.84 (0.73-0.95)	1.00 (0.98-1.02)	1.59 (1.54-1.64)
PLCO trial (USA)	38340	38345	55-74 yrs	Annual	DRE and PSA; PSA - annual for 6 yrs DRE - annual for 4 yrs	≥4.0	6-yrs	1.15 (0.86-1.54)	0.97 (0.94-1.01)	1.12 (1.08-1.18)
Sweden Stockholm	2374	24772	55-70 yrs	One-time screening	DRE, PSA, and TRUS; repeat TRUS for PSA≥7.0 ng/mL	≥10.0	15-yrs; Median: 12.9 yrs	1.09 (0.83-1.45)	1.00 (0.95-1.05)	1.10 (0.96-1.26)
Sweden Norrkoping	1494	7532	50-69 yrs	3-years	DRE and PSA; 1st and 2nd round - DRE only and 3rd and 4th round - DRE and PSA	≥4.0 or abnormal DRE	20-yrs	1.16 (0.79-1.72)	0.97 (0.94-1.01)	1.47 (1.16-1.86)

Table 13. Randomised controlled trials evaluating the impact of screening vs. no screening on prostate cancer-specific mortality (continued)

Trial	No. screened	No. of controls	Age for screening	Screening interval	Screening test	PSA (ng/mL) cut-off for biopsy	Follow-up period	PCa-specific mortality Risk ratio (95% CI)	All-cause mortality Risk Ratio (95% CI)	Prostate cancer diagnosis Risk Ratio (95% CI)
Canada Quebec	7348	14231	45-80 yrs	Annual	DRE and PSA; 1st round - PSA and DRE ≥2nd round- PSA only	1st round - ≥3.0 and/or abnormal DRE ≥2nd round - ≥3.0 ng/mL	11-yrs	1.01 (0.76-1.33)	-	-
Meta-analysis	156157	185185	50-80 yrs					1.00 (0.86-1.17)	1.00 (0.96-1.03)	1.30 (1.02-1.65)

Comparing the PLCO and ERSPC trials

Two large prospective and randomised controlled trials on prostate cancer screening, ERSPC[212] and PLCO[211, 213], arrived at two different conclusions. ERSPC showed significant reduction in mortality and PLCO did not. The differences between the two trials that could explain these conflicting conclusions have been examined[214-216].

Table 14 summarises the patient characteristics of the two trials. The ERSPC trial was initiated in 1993 with the objective of evaluating the effect of PSA screening on death rates from prostate cancer in eight European countries. A total of 182,000 men aged 55-69 years were randomised to screening with PSA and DRE every 4 years or no screening. Median follow-up time was 11-years. At 13 years of follow-up, there was a 21% significant reduction in prostate cancer mortality[211]. This translates to one prostate cancer death averted for every 781 men invited for screening or 1 averted death for every 27 prostate cancers detected. The PLCO trial was initiated in the early 1990s with the same objective to assess the utility of annual PSA and DRE testing to reduce prostate cancer-specific mortality. A total of 76,693 men aged 55-74 years were randomised to screening or usual care. Median follow-up time was 6 years and no significant reduction in prostate-specific mortality was observed.

Table 14. ERSPC and PLCO study characteristics

	ERSPC	PLCO
Population	Europe	United States
No. of patients	182,000	76,693
Age range	55-69 years	55-74 years
Randomisation	PSA and DRE every 4 years vs. no screening	Annual PSA and DRE vs. usual care
% screened prior to entering the study	Data no available[215]	53.1 in the screening arm 54.8% in the usual care arm[217]
Contamination (controls screened)	30.7%[218]	54.8%[217]
Median follow-up	11 years	6.1 years
Outcome	20% reduction in prostate cancer death	No significant difference in prostate cancer mortality

Three important factors that could explain the differences in mortality outcomes between ERSPC and PLCO: testing prior to randomisation, contamination and compliance[215].

- In the PLCO, PSA testing prior to randomisation was reported in 53.1% of the screening arm and 54.8% in the usual care ("control") arm[217]. These data were not available for the ERSPC

study, however, during this period from 1993 to 2000, it can be estimated that PSA testing was about 20%[215]. The high rate of screening prior to randomisation in the PLCO study would have introduced selection bias into the trial. Men who had a normal PSA test prior to randomisation would have a lower risk of prostate cancer, reducing the possibilities of observing any differences in prostate-specific mortality. However, compared to men who never had a PSA test prior to randomisation, those who had at least two PSA tests prior to randomisation saw a 25% reduction in death[217].

- Men in the control group, who were not actively screened in the trials, but received screening outside of the study resulted in a contaminated population. More than half of the PLCO study population was contaminated[217] and it is estimated that one-third of the ERSPC population was also contaminated[218]. However, the high contamination rate observed in the PLCO controls (representing the "never screened group") suggests that the increase in PSA testing in the screening group was not much greater than the controls, which most likely diluted any differences between the two arms and reduced the chances of identifying any benefits of prostate screening that would have been otherwise observed.

- Compliance with biopsy indication was another issue that may have reduce the power of PLCO to observe a reduction in mortality by screening. Among the 14-15% of men who tested positive in the PLCO screening arm, only 40.2% and 30.1% had a biopsy in the first and subsequent round of screening[154] In comparison, of the 16.6% of all men who tested positive at screening in the ERSPC trial, 82.7% were compliant and had biopsy[219].

These major differences in terms of contamination and compliance with biopsy can contribute to explaining the reasons why PLCO does not show a reduction in prostate cancer-specific mortality by screening. These reasons highlight the methodological flaws that exist in the PLCO trial and suggest that the ERSPC trial was better designed to address the benefits of PSA screening. After adjusting for non-participation bias, the ERSPC demonstrated a greater absolute risk reduction in prostate cancer mortality of 27% at 13 years[220]. Despite the significant reduction of prostate-cancer specific mortality by PSA screening in the ERSPC study, harmful impact of overdiagnosis and overtreatment need to be weighed (see Section 15).

The UK CAP Study

Although the ERSPC trial demonstrated a reduction in mortality, the benefits of PSA screening remain unresolved on issues of overdiagnosis and overtreatment of clinically insignificant prostate cancers as well as identifying the optimum treatment for localised prostate cancer. The UK Cluster randomised trial of PSA testing for Prostate Cancer (CAP) Study aims to address these unanswered questions by evaluating whether PSA testing of men aged 50-69 years will reduce prostate cancer mortality and be cost-effective. The study design is a cluster randomisation controlled trial of primary care centres to either PSA screening (intervention arm) or to standard clinical care

(comparison arm)[18, 221].The ProtecT trial, as described earlier, is the randomised controlled trial (comparison arm of CAP) that is evaluating active surveillance, conformal external beam radiotherapy and radical prostatectomy treatments for men with localised prostate cancers in men attending a GP practice randomised to PSA testing in the CAP trial. Both trials are measuring outcomes of prostate cancer-specific mortality as well as overall survival, costs and quality of life[18].

The study recruited 573 general practitioner (GP) practices (over 415,000 men) in England, Scotland 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 [3](comparison cluster) between 2001 and 2007[221]. Surveillance of prostate cancer diagnoses or death are carried out by sending details of participants to the Health and Social Care Information Centre (HSCIC) and regional cancer registries at randomisation so that they could provide regular notification to the study. Both CAP and ProtecT are expected to report major outcomes in 2016.

The cluster randomised study design was used to minimise the effects of contamination which is more likely to occur if men were individually randomised (e.g. ERSPC and PLCO trials) because they would be aware of the option of screening for prostate cancer[221]. However, initial results estimate contamination to be minimal unless it reaches 20% which would undermine the power of the trial[222]. The study sample size has at least 80% power to detect a 13% reduction in the odds of prostate cancer mortality.

Table 15 compares the study design characteristics of the CAP, ERSPC and PLCO studies. The major strengths of the CAP study will help overcome some of methodological design issues found in ERSPC and PLCO[18, 221]. For example,

- Cluster randomisation enhances the generalisability of the effectiveness of a PSA screening policy by minimising volunteer bias and reducing contamination in the comparison group.
- Unbiased estimates of mortality will be provided by the CAP and ProtecT trial and provide robust estimates of screening and treatment effectiveness.
- Rate of overdiagnosis will be determined for clinically insignificant prostate cancers in a screen-detected population by comparing incidence in both the intervention and comparison groups of CAP.
- The ProtecT trial will establish the effectiveness of active surveillance vs. radical therapies for PSA-detected disease in men diagnosed with localised prostate cancer; and the balance of benefits and harms of treatment will be determined. For example, overtreatment of disease will be estimated by comparing men under active surveillance and those randomised to radical therapies.

- Screening and treatment costs will be determined as well as lifetime costs, effects and cost-effectiveness

The impact of prostate cancer screening from the UK CAP and ProtecT trials will generate robust estimates of the effect of a population-based screening policy. The trials will enable evidence-based decisions on population-based PSA screening and the management and treatment of screen-detected prostate cancers.

Table 15. Comparison of study design characteristics of CAP, ERSPC and PLCO trials.

	CAP	ERSPC	PLCO
Age range (years)	50-69	50-69 (core group). Some 50-54, 70-74	55-74
Randomisation	General practice All men at participating GP practices were randomised (population-based effectiveness trial)	Individual In the Netherlands, Belgium, Switzerland, Spain, only men giving consent underwent randomisation (efficacy trial). In Finland, Sweden and Italy, all men identified from cancer registries were randomised (population-based effectiveness trial)	Individual Only men giving informed consent were randomised (efficacy trial)
PSA threshold	3.0 ng/ml	3.0 ng/ml or 4.0 ng/ml depending on centre	4.0 ng/ml
Biopsy protocol	10-core TRUS biopsy	Mainly 6-core TRUS biopsy	Diagnostic evaluation decided by patients and primary care physician
Screening interval	Single screen	4-yearly (some 2 years)	1 year
Treatment	Randomised (surgery, radiotherapy, active surveillance)	Variable usual care (radical advised)	Variable usual care (radical advised)
Outcome ascertainment	Independent blinded adjudication committee	Blinded committee (some centres used death certificates)	Blinded reviewers (prostate-cancer death)
Follow-up	Average 10 years (up to 2016	Median 9 years (up to 2007)	Median 12.4 years (up to 2009)

*Adapted from Lane[18] and Turner[221] .

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.

Currently, there is no conclusive evidence to support a PSA-based screening programme but there is an informed choice programme for PSA-testing in asymptomatic men[91]. To aid patients and clinicians in the decision-making progress, the NHS Shared Decision Making (SDM) programme, a part of the Quality Improvement Productivity and Prevention (QIPP) Right Care Programme, introduced a Patient Decision Aid (PSA) for PSA Testing (http://sdm.rightcare.nhs.uk/pda/psa-testing/) in 2012. The tool promotes patient-centred care and involves patients and clinicians in weighing the benefits and harms of PSA-testing. Acceptability of the PSA test as a tool for prostate cancer screening has been discussed in **Criteria 7** of this report.

Diagnosis, treatment and management have been outlined in the recent 2014 NICE guideline[7]. Although the evidence relating to outcomes from treatment and management of prostate cancer is not clear, NICE has developed a urological cancer service guidance that is based on research evidence to address clinical effectiveness and services delivery to ensure that health professionals are making optimum decisions on patient management[223]. In addition, NICE has consulted on key priorities to improve the quality standard for patients with prostate cancer [224].Due to ageing, the absolute number of cases of prostate cancer is expected to increase even if the incidence remains the same. This implies that the financial burden of treatment (e.g. treatment facilities and trained specialists) will increase with the increasing burden of men diagnosed with the disease. Moreover, men with prostate cancer have more emergency than elective hospital admissions during their last year of life and the total cost of inpatient care per men with prostate cancer in his last year of life is £6391. Therefore, this quality standard guidance will drive measurable quality improvements in outcomes to prevent men from dying prematurely from prostate cancer, to enhance quality of life by reducing adverse effects of treatment, delaying and reducing the need for care and support and improving patient experience in hospital care.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

Harms of screening

The 2013 Cochrane Review[6] evaluated harms of screening including both adverse events from false-positive or false-negative results and their results from treatment procedures. Harms ranged from minor to major in terms of severity and duration. Minor harms include bleeding, bruising, and short-term anxiety. Common major harms include overdiagnosis and overtreatment, resulting in infection, blood loss requiring transfusion, pneumonia, erectile dysfunction and incontinence.

Screening

In the ERSPC trial, no excess mortality was found in those patients who were PSA-screened positive (without biopsy) compared to controls.[225]

In the PLCO trial, pain or bleeding resulting from DRE occurred in 0.3 per 10,000 screenings[6]. PSA testing reported a complication rate of 26.2 per 10,000 screenings and were mainly dizziness, bruising, haematoma, and three episodes of fainting.

Diagnosis with prostate biopsy

In the ERSPC trial, 22,699 biopsies were performed and no deaths resulted from any direct complications (e.g. septicaemia or bleeding) from the biopsy procedure[6]. Fourteen men died within 120 days following biopsy but their deaths could not be attributed to the biopsy but other causes. The most common minor complications from biopsy were hematuria lasting longer than 3 days (22.6%) and hematospermia (50.4%); whereas, major complications such as fever (3.5%) after biopsy were considered rare [226].

In the PLCO trial, complications from diagnostic biopsy occurred in 68 of 10,000 evaluations after a positive result from PSA-screening and were mainly infection, bleeding, clot formation and urinary difficulties[6].

In the UK Prospective cohort study (Prostate Biopsy Effects:ProBE) nested within the ProtecT study, 1147 men underwent a 10-core TRUS-biopsy and were recruited to report adverse events at biopsy (baseline), 7 days and 35 days after the procedure[227]. Adverse events are reported at baseline and follow-up in **Table 16.**

Table 16. Summary of adverse events identified at biopsy, 7 days and 35 days after biopsy in the ProBE Study[227]

Immediately after biopsy	• 85% men described no pain or mild pain • 3% of men felt "lightheaded" or dizzy • 7% passed blood in their urine immediately after biopsy • 3% passed clots in their urine immediately after biopsy
Within 7 days after biopsy	• 39% of men had pain; 6% found this a moderate or serious problem • 12% had a fever; 4% found this a moderate or serious problem • 64% had blood in the urine; 5% found this a moderate or serious problem • 33% had blood in the motions; 2% found this a moderate or serious problem • 86% had blood in the semen; 20% found this a moderate or serious problem
Delayed effects (in 35 days after biopsy)	• 44% of men had pain; 7% found this a moderate or serious problem • 20% had a fever; 5% found this a moderate or serious problem • 66% had blood in the urine; 6% found this a moderate or serious problem • 37% had blood in the motions; 2% found this a moderate or serious problem • 90% had blood in the semen; 25% found this a moderate or serious problem

Overdiagnosis and overtreatment

Overdiagnosis represents the detection of tumours at prostate screening among asymptomatic men that would not be diagnosed otherwise or cause them harm (i.e. symptoms or death) within the patient's lifetime. In other words, in the absence of screening, these excess cases of prostate cancer would have never been detected clinically and would have never required treatment. Overdiagnosed cases face the harms of unnecessary costs, tests and side effects of treatment.

A recent systematic review of overdiagnosis and overtreatment of prostate cancer by Loeb *et al* 2014[228] reported that overdiagnosis is wide-ranging from 1.7% to 67% and factors influencing overdiagnosis include study population characteristics, screening protocol and background incidence of disease. Specifically, an updated report from the ERSPC trial [229]indicate that on average 12 to 36 excess cases of men will have to be diagnosed to avert one prostate cancer death at 13 years of follow-up.

The UK community-based ProtecT study (described earlier) screened 43,000 men aged 50-69 years. Data of PSA-detected cases were modelled to estimate the probability of overdiagnosis at 11-12 years and found that overdiagnosis ranges between 10-31% and increases with age **(Table 17)** [230]. Final results of the trial are expected in 2016 and risk of overdiagnosis at 10 years for a one-time PSA screening will be quantified.

Table 17. Probability of overdiagnosis by age group in the ProtecT study

Age	Probability (%) of overdiagnosis (95% CI)
50-54	10 (7-11)
55-59	15 (12-15)
60-64	23 (20-24)
65-69	31 (26-32)

*Adapted from Pashayan *et al* 2009[230]

Quality of life

Limited data are available on the impact of prostate cancer screening and quality of life. Research assessing the effectiveness of screening on quality of life is ongoing for the ERSPC and PLCO trial[6]. However, results have been reported for two centres of the ERSPC trial which modelled the impact of the presence and absence of annual screening over the lifetime of 1000 men aged 55 to 69 to predict number of prostate cancers, treatments, deaths and quality-adjusted life-years (QALYs) gained[231]. The model predicted that the impact of screening would lead to nine fewer prostate-cancer deaths and 73 life-years gained over the lifetime. Harms of screening would be the overdiagnosis and overtreatment of 45 cases and loss of 1134 life-years free of prostate cancer. After adjusting for the number of life-years gained from screening, only 56 QALYs would be gained, which is 23% reduction from the predicted number of life-years gained. Therefore, the benefits of screening were reduced significantly by the loss of QALYs due to its impact on overdiagnosis and overtreatment; rendering screening not cost-effective.

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 this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

Cost-effectiveness of screening in the UK

UK 2013 ScHARR Report

The ScHARR (University of Sheffield's School of Health And Related Research) has estimated the costs, benefits and resource implications of prostate screening in the UK based on the ERSPC screening trial data[8]. This is an update of the original ScHARR report published in 2009.

Four PSA screening policies were compared to no screening:

Policy 1: Single screen at age 50

Policy 2: Screening every four years from age 50 to 74

Policy 3: Screening every two years from age 50 to 74

Policy 4: Screening every year from age 50 to 74

The screening impact model included key parameters (utility values for prostate cancer, cost-effectiveness of treatments of prostate cancer at end of life, adverse events associated with prostate cancer biopsy and treatment), unit costs for biopsy and treatment, and treatment of sexual dysfunction.

Table 18 summarises the potential impact of prostate cancer screening at different screening intervals assuming different PSA sensitivity levels of 40-80%[8]. The model predicts that **Policy 1,** a one-off screen at age 50 years, is the same as no screening with the same estimated lifetime probability of prostate cancer (11%).Annual screening also has marginal impact on age-specific incidence when compared to longer repeat intervals (2- and 4-yearly for screening).

Overdiagnosis at screening intervals of 4-yrly, 2-yrly or annually (**Policy 2-4)** is greater than a one-off screen at age 50 years and is estimated within the range of 40-60%. When comparing between the different screening intervals assuming different PSA sensitivities, overdiagnosis of prostate cancer did not differ. The overdetection rate of prostate cancer can reduce with improved PSA sensitivity (e.g. with a PSA sensitivity of 40%, 50%, and 60%, the overdetection rate with a 2-yearly screening policy is 63%, 52%, and 46%)

The mean lead time for potentially relevant cancers that would have been diagnosed with clinically relevant prostate cancers later is between 15-18 years for men who were screened once at age 50 and 8-10 years for men who were screened at more frequent intervals. Early detection of these potentially relevant cancers is estimated to reduce the number of metastatic cancers by four-fold and double the number of localized cancers diagnosed.

The average life years gained by inviting people for screening ranges from 20-39 days if screened 4-yrly, 24-54 days if screened 2-yrly and 27-67 days if screened annually; whereas a one-off screen at age 50 estimates that there is an average of 2-4 extra days of life gained. Although the average life years gained increases with repeat screening policies, this will also have implications on disease management that would require 17-32 years of additional prostate cancer management for every life gained. For example, with no screening the estimated number of men requiring radical treatment (*radical prostatectomy, radical radiotherapy and radical radiotherapy plus hormone therapy*) is 20,014. With increasing frequency of prostate screening intervals, three times the number of men will require radical treatment and four times the number of men will require. In terms of QALYs, repeat prostate cancer screening **Policy 2-4** saw a loss of discounted QALYs ranging from 0.016 to 0.023 per man invited to screening. Once in a lifetime screen at age 50 will cost the UK around £58 million and this will increase to over £1 billion for an annual screening policy.

However, the model assumptions that PSA testing has a sensitivity ranging from 40-80% is high given that a meta-analysis carried out by Wolf et al[94] suggests that the sensitivity is about 20%. This would suggest that the burden and costs may be much higher than those estimated by ScHARR.

Table 18. Impact of screening on prostate cancer detection[8]

	PSA sensitivity, 40%					PSA sensitivity, 60%					PSA sensitivity, 80%				
Screening policy	No screening	Once at 50	Age 50-74 every 4 yrs	Age 50-74 every 2 yrs	Age 50-74 every yr	No screening	Once at 50	Age 50-74 every 4 yrs	Age 50-74 every 2 yrs	Age 50-74 every yr	No screening	Once at 50	Age 50-74 every 4 yrs	Age 50-74 every 2 yrs	Age 50-74 every yr
Lifetime probability of PCa	11.0%	11.3%	22.2%	25.2%	27.2%	11.1%	11.5%	19.3%	20.6%	21.5%	11.1%	11.4%	18.2%	19.0%	19.4%
Overdiagnosis (%)		44%	64%	63%	63%		33%	53%	52%	52%		28%	47%	46%	46%
Potentially clinically relevant		56%	36%	37%	37%		67%	47%	48%	48%		72%	53%	54%	54%
Mean lead time for PCa diagnosis in potentially relevant cases (yr)		18.2	9.2	9.7	10.2		15.9	8.5	9.0	9.3		15.2	8.2	8.5	8.8

Table 18. Impact of screening on prostate cancer detection (continued)[8]

	PSA sensitivity, 40%					PSA sensitivity, 60%					PSA sensitivity, 80%				
Screening policy	No screening	Once at 50	Age 50-74 every 4 yrs	Age 50-74 every 2 yrs	Age 50-74 every yr	No screening	Once at 50	Age 50-74 every 4 yrs	Age 50-74 every 2 yrs	Age 50-74 every yr	No screening	Once at 50	Age 50-74 every 4 yrs	Age 50-74 every 2 yrs	Age 50-74 every yr
Average life years gained per person invited for screening		0.01	0.11	0.15	0.18		0.01	0.08	0.10	0.12		0.01	0.05	0.07	0.07
Average days gained		3.5	38.8	54.3	67.4		4.0	29.2	37.1	42.9		2.2	19.9	24.0	26.6

Other cost-effectiveness models

ERSPC trial data were used to assess the cost-effectiveness of prostate cancer screening according to 68 different screening strategies (starting from the age of 55 with a PSA threshold of 3) in order to identify the optimal screening intervals and ages[232]. A MIcrosimulation Screening Analysis Model was applied to the population in the Netherlands to predict the number of prostate cancers diagnosed, prostate cancer deaths averted, and life-years and quality-adjusted life-years (QALY) gained. Screening intervals of ≤3 years were more efficient than longer screening intervals **(Table 19)**. The optimal screening strategy with an incremental cost-effectiveness ratio threshold of $100,000 per QALY gained was screening ages 55 to 59 years with two-year intervals. This strategy predicted a 13% reduction in prostate cancer deaths and an overdiagnosis of 33% of screen-detected prostate cancers. The study found that increasing the upper age limit eligible for screening to ages 65 to 72 years would be only be cost-effective if there was no loss in quality of life because of treatment, no overdiagnosis or a mortality reduction of 56% can be achieved.

Table 19. Efficient screening strategies per 1000 men according to prostate cancer mortality reduction, overdiagnosis, life-years gained, and incremental cost-effectiveness.

Screening strategy	Interval	Prostate cancer reduction, %	Overdiagnosis, as % of screen-detected men	Life-years gained	QALYs gained compared to no screening	Incremental cost-effectiveness in $
55 yrs	**One screen**	**5**	**29.7**	**8.4**	**5.4**	**31,467**
55-57 yrs	**2**	**9**	**31.1**	**13.4**	**7.9**	**53,593**
55-58 yrs	**3**	**10**	**32.1**	**14.8**	**8.4**	**72,567**
55-59 yrs	**2**	**13**	**33.0**	**18.2**	**9.9**	**72,971**
55-61 yrs	2	17	34.8	22.6	11.3	118,989
55-61 yrs	1	18	34.8	24.9	11.8	243,031
55-62 yrs	1	20	35.7	27.1	12.2	260,507
55-63 yrs	1	22	36.7	29.0	12.3	776,149

*Adapted from Heijnsdijk et al [232]. Bold indicates the most efficient screening strategy.

ERSPC trial data were also extrapolated to the US population to evaluate cost-effectiveness of PSA screening[233]. Assuming if the US achieves a similar 20% reduction in prostate cancer-specific mortality at 9-year follow-up as observed in ERSPC, this would cost $262,758 per life-year saved. This estimate is 140-fold above the threshold of lifelong treatment costs of cost-effectiveness (<$1868 per life-year).

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

- Not applicable

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

- Not applicable

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

- Not applicable

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.

The PCRMP has produced information that are publicly available to assist primary care teams in providing information to asymptomatic men about the benefits and harms of PSA testing[91]. This information was developed under the consultation of over 100 GPS and primary care cancer leads as well as a multidisciplinary group of experts set up by the Department of Health to advise the PCRMP.

As described earlier, to aid patients and clinicians in the decision-making progress, the NHS SDMprogramme developed a Patient Decision Aid (PSA) for PSA Testing (http://sdm.rightcare.nhs.uk/pda/psa-testing/) in 2012. The tool promotes patient-centred care and involves patients and clinicians in weighing the benefits and harms of PSA-testing to make an informed choice. An updated tool is under development and is expected to be launched in 2016.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

Not applicable

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

Not applicable

Conclusions

23. Implications for policy

In order for prostate cancer screening to be valuable, it must be effective in reducing prostate-cancer specific morbidity and/or mortality. Evidence from the ERSPC randomised trial showed a benefit of PSA screening to reduce prostate cancer mortality by at least 21%. Despite this significant reduction the evidence is not sufficient to justify introducing a national screening programme using PSA. The benefits of PSA screening remain unresolved on issues of overdiagnosis and overtreatment of clinically insignificant prostate cancers as well as identifying the optimum treatment for localised prostate cancer. The current evidence suggests that the major harms from prostate cancer screening using PSA 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

Strategies to reduce the number of unnecessary biopsy procedures and to reduce the large number of men that need to be screened, biopsied and treated to save one life remains unclear. Major reported outcomes from the CAP and ProtecT trials are expected in 2016. These studies will address these unresolved issues and provide robust evidence about the effectiveness of a population-based PSA screening policy 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 multiparmetric MRI with targeted biopsies could further reduce overdiagnosis and unnecessary biopsies. Outcomes will guide diagnostic guidelines following a positive PSA screen.

Besides PSA, the current evidence also 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 high potential to improve upon the specificity of PSA testing to discriminate men at greater risk for clinically significant prostate cancer. Targeted risk-based prostate screening could be considered in the future. However more evidence is needed to demonstrate the clinical usefulness of these markers to be considered effective for screening.

Although the current evidence does not support a population-based screening programme, this does not preclude a man from making an individual decision to be screened. The PCRMP exists to aid GPs and a man over the age of 50 to weigh his individual risk alongside the benefits and harms of having a PSA test. After careful consideration of the test implications, a man can make an informed decision and any man who requests a test should be given one.

The UKNSC evidence review on prostate cancer screening will monitor and evolve in a timely manner with the emerging evidence.

24. Implications for research

Obesity and diet

There is increasing evidence linking obesity to prostate cancer. The clear benefit of weight loss and exercise interventions to prevent or reduce prostate cancer risk is unclear. Intervention trials are needed to evaluate the effectiveness of weight loss and exercise interventions to reduce a man's risk of prostate cancer.

Reflex testing

There have been developments to improve the performance of PSA testing by triaging men with a total PSA between 2-10 ng/ml with reflex testing with PSA isoforms (free to total PSA or complex PSA). Data from the Stockholm 3 study suggest that the STHLM3 model which uses a combination of plasma protein biomarkers, genetic polymorphisms and clinical variables could significantly improve the specificity of screening and significantly reduce the number of unnecessary biopsies. However, further research is needed to validate the model in the UK population and ethnic sub-populations who are at greater risk of prostate cancer.

Prostate cancer risk prediction models

A catalogue of prostate cancer risk prediction models are available and have the potential to improve PSA screening. These models consider other factors such as age, ethnicity, family history, DRE, or prostate volume besides PSA testing. A number of these models are available online, however it is unclear whether these models help a man to make an informed decision about the need for a prostate biopsy or a repeat biopsy after PSA screening; or help a man understand his risk of detecting clinically relevant prostate cancer. Additional research is needed to evaluate the clinical effectiveness of these prostate cancer risk prediction models in clinical practice before they are recommended for use in screening.

New screening and triage markers

The TMPRSS2:ERG urinary marker has the potential to distinguish men with low-risk and clinically significant cancers. However, further research is still needed to fully understand its clinical utility in screening and its potential use in prostate cancer management.

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Appendix A. Prostate cancer screening recommendations and guidelines from major societies

Organisation	Literature review type	Data sources	Dates	Methods
US Preventive Services Task Force, 2012	Systematic review	Pubmed and Cochrane Library	January 2007 to January 2011	Randomized controlled trials, systematic reviews and meta-analyses of PSA-based screening
American Urological Association, 2013	Systematic reviews and meta-analysis	Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials and Scopus	Not reported	The search focused on DRE, serum biomarkers (PSA, PSA Isoforms, PSA kinetics, free PSA, complexed PSA, proPSA, prostate health index, PSA velocity, PSA doubling time), urine biomarkers (PCA3, TMPRSS2:ERG fusion), imaging (TRUS, MRI, MRS, MR-TRUS fusion), genetics (SNPs), shared-decision making and prostate biopsy
American College of Physicians, 2013	Appraisal of available guidelines for prostate cancer screening in the United States using the AGREE II (Appraisal of Guidelines, Research and Evaluation in Europe)	The National Guideline Clearinghouse	August 2012	Appraised screening guidelines: American College of Preventive Medicine, American Cancer Society, American Urological Association, and U.S. Preventive Services Task Force
American Society of Clinical Oncology, 2012	Systematic review from the Agency for Healthcare and Quality	Pubmed and Cochrane Library	Up to March 2012	Focussed on evidence on the benefits and harms of PSA-based screening

Canadian Urologic Society, 2011	Systematic review	MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials	Up to 2010	Focussed on prostate cancer, prostatic neoplasms, prostate tumour, PSA, DRE, mass screening, screening test, early detection of cancer, cancer screening, screening, TRUS, randomised, false-negative and false-positive.
American Cancer Society, 2010	Systematic evidence reviews	Not reported	Not reported	Focussed search on early detection of prostate cancer, harms of therapy for localized prostate cancer, and shared and informed decision making in prostate cancer screening
European Association of Urology, 2013	Systematic review	MEDLINE, EMBASE, and Web of Science	January 2010 and November 2011	Focussed on original articles, review articles an editorials addressing, 'epidemiology', 'risk factors', 'diagnosis, 'staging' and 'treatment' of prostate cancer. Additionally, publications from major urological (EAU, AUA) and oncological meetings (ASCO, ESMO, ASTRO) were considered.
European Society for Medical Oncology, 2010	Non-systematic review			
Prostate Cancer World Congress, 2013	Non-systematic review – expert review			

Updated Japanese Urological Association Guidelines, 2010	Non-systematic review – expert review

*Search was condcuted(as of 31 Jan 2013) by Ms Paula Coles, Information Scientist at UKNSC.