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CANCER RESEARCH UK

Together we are beating cancer

Earlier detection and diagnosis of prostate cancer

A technical summary of the challenges and evidence

Contents

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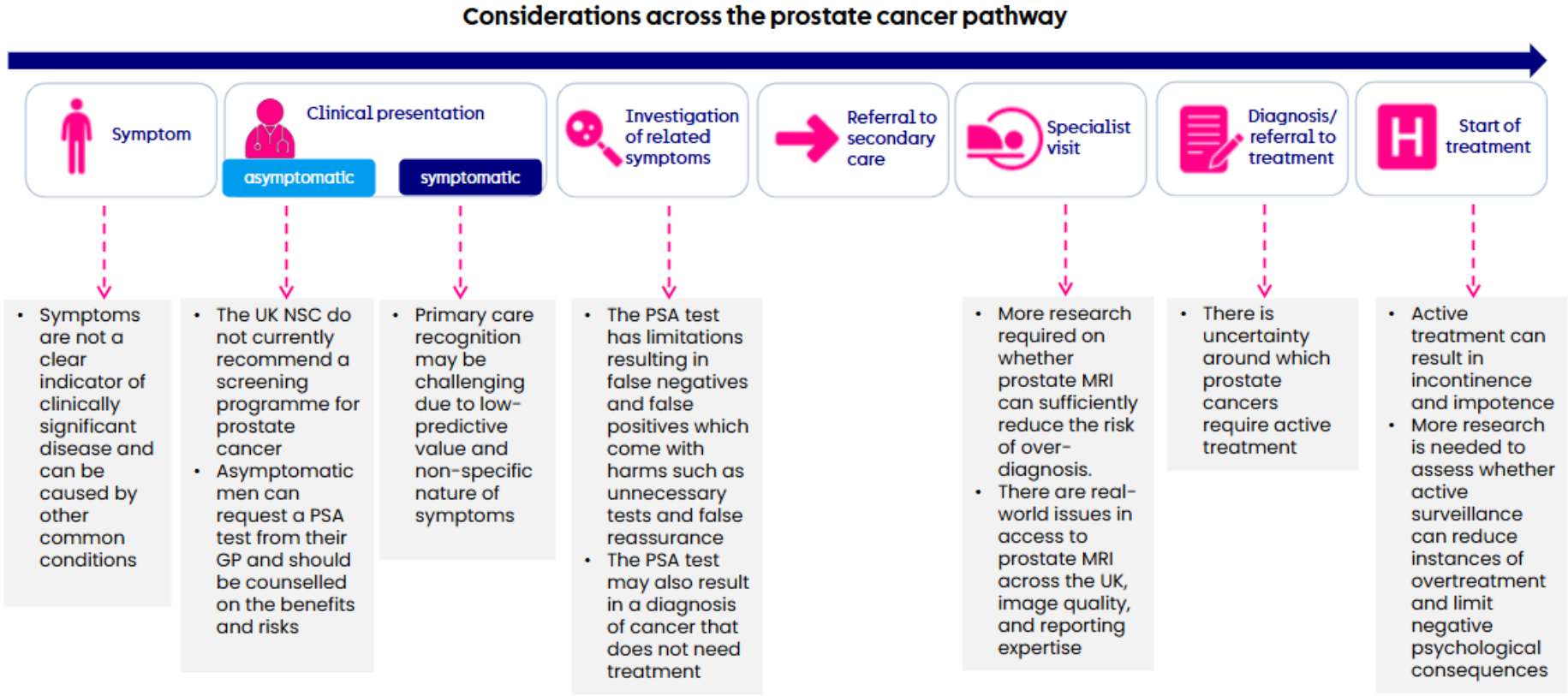
1.Foreword

Prostate cancer is the most common cancer in men in the UK. The early detection and diagnosis of prostate cancer is a topic that is actively debated amongst researchers, clinicians, policymakers and the wider cancer community. This is because there are several complexities associated with early detection and diagnosis of this disease. In our article *Detecting prostate cancer: why we need more research* we outline our position and the significant gaps in our understanding of this disease. This technical document expands on these gaps and summarises the existing evidence. The key references at the end represent the current evidence base that we have drawn from, but we are committed to updating this at regular intervals to capture any shifts and developments.

2. Key points

- Overdiagnosis is a significant problem in prostate cancer because not all prostate cancers will progress to cause harm, combined with the lack of an accurate test to identify prostate cancer that requires treatment.
- There are limitations to identification of prostate cancer on the basis of symptoms or the prostate-specific antigen (PSA) test.
- Current screening methods, primarily PSA testing, have not shown consistent benefit in reducing prostate cancer mortality due to issues with accuracy and contamination in the research trials. There are also considerations of overdiagnosis and overtreatment.
- The UK National Screening Committee (UK NSC) does not currently recommend PSA-based screening due to these concerns.
- New diagnostic pathways, including pre-biopsy MRI (mpMRI), offer improvements, reducing unnecessary biopsies and improving cancer detection, but their ability to reduce overdiagnosis and improve mortality is still under study.
- More research is needed to understand which individuals should be targeted for screening to avoid overdiagnosis and exacerbating health inequalities.

Figure 1: An overview of current considerations across the prostate cancer pathway



3. Overdiagnosis and overtreatment are issues for prostate cancer

There are different types of prostate cancer

While research is ongoing to better understand prostate tumour biology, it is generally agreed that prostate tumours can come in different forms that progress at different speeds (1,2). Some are 'aggressive' and often progress rapidly before a clinical diagnosis can be made or curative treatment can be considered. Other prostate tumours could be 'slowly progressive', meaning that the tumour could eventually grow and require treatment, whereas some are 'indolent' and are unlikely to ever cause symptoms or be diagnosed clinically in a person's lifetime.

There are challenges in identifying prostate cancers that will progress

While this is true for many cancers, prostate cancer is unique for a few reasons. First, we are currently unable to distinguish well enough between prostate cancer that requires treatment versus those that does not require treatment. It is also unclear how 'progression' of prostate cancer should be defined, which makes it challenging to know when to treat. Additionally, prostate cancer has been estimated to have a particularly long sojourn time, which is the duration that the cancer is detectable through asymptomatic tests but is not clinically detectable through symptoms. One study estimated the sojourn time for prostate cancer to be between 11.3-12.6 years and the more recent CAP trial estimated a similar number of between 12-15 years depending on patient's age(3,4). In comparison, one study estimated the sojourn time for breast cancer to be between 0-5 years, with a mean of 2 years (5). It should be noted that methods to calculating sojourn time can differ. In general, a longer sojourn time means that cancers that are not harmful at the time, but could go on to cause harm, may be detected earlier through interventions like screening. However, there would be no change to the person's outcome (known as 'lead-time bias'). This means that there was no benefit to earlier diagnosis and in many cases, the earlier diagnosis means people are more likely to get treatment prematurely, which can be harmful.

Consequences of overdiagnosis and overtreatment

Overdiagnosis is when cancer is diagnosed that would never have gone on to cause harm in a person's lifetime – i.e., the indolent cancers (6). It is a possible unintended consequence of early detection. Overdiagnosis is associated with psychological harms such as anxiety and stress from the uncertainty of identifying cancer that would not harm a person in their lifetime (7). Negative psychological consequences may be ongoing and linked to regular check-ups or testing

appointments that are used to monitor for progression of the disease (8). It can also lead to unnecessary treatment which is associated with physical harms. In the case of prostate cancer, radical treatment (e.g., radiotherapy or surgery) can cause long term consequences such as impotence or incontinence, which significantly decreases a person's quality of life (9,10). In addition to being harmful to individuals, treating cancer unnecessarily takes significant health system resource and can be costly (11). It is therefore important to make efforts to reduce instances of overdiagnosis and overtreatment.

It is difficult to measure overdiagnosis or identify who has been overdiagnosed. In prostate cancer, tumours are often graded using Gleason score (which looks at the histopathology of the tumour tissue) or Cambridge Prognostic Groups (which considers Gleason score, tumour morphology, and other clinical characteristics)(12). These more specific groupings give some indication of whether the tumour is 'clinically significant' (i.e., likely to progress and need treatment) or 'clinically insignificant' (i.e., more likely to be indolent or not require treatment yet). However, there is not a clear consensus amongst clinicians and researchers on where to draw the line between 'significant' and 'insignificant', and research studies to date have used varying definitions. In general, while these categorisations can be a helpful guide, more research is needed to strengthen the accuracy of them. For example, some tumours initially marked 'clinically insignificant' may still progress and require treatment, which is why regular monitoring is required (13).

Earlier diagnosis efforts can be helpful for slower progressing tumours, but accurate ways (e.g. symptoms or primary care tests) to distinguish between prostate cancer that is 'indolent' versus prostate cancer that is likely to progress, are lacking.

4. Symptoms aren't a clear indicator of prostate cancer

Progressive prostate tumours may not always present with symptoms, including those symptoms that are currently cited in NG12, the Scottish Referral Guidelines, and the Northern Ireland Referral Guidance for Suspected Cancer (e.g. symptoms like lower urinary tract symptoms (LUTS), erectile dysfunction, visible haematuria). A 2018 study found that 28.8% of prostate cancer patients had no recorded symptoms prior to diagnosis (14). This could be because symptoms of prostate cancer often emerge when the tumour presses on the urethra, but prostate tumours are found in the peripheral zone 70% of the time, and therefore would be unlikely to press on the urethra (15).

While a subset of tumours may cause LUTS, these symptoms have a low predictive value for prostate cancer (16). LUTS are highly prevalent in the general population, especially as men age, and can be associated with common conditions such as urinary tract infection or benign prostatic hyperplasia, the latter of which is the most common cause (17,18). Overall, this makes it difficult for health professionals to assess which patients need to be referred.

5. The limitations of Prostate-Specific Antigen

In the absence of symptoms, disease-associated biomarkers are another potential indicator of early disease. Analysis of disease-associated biomarkers could be used to screen for the disease. In prostate cancer, the main biomarker is known as Prostate-Specific Antigen (PSA). Serum PSA levels are analysed through a blood test known as the PSA test. However, the PSA test is not accurate enough at distinguishing people who have prostate cancer that is likely to progress, from those that do not have prostate cancer or who have indolent prostate cancer. The PSA test has a high rate of false positives, mainly driven by the fact that it is normal for all men to have some PSA in their blood and levels of this biomarker can be elevated by several common benign conditions/factors, including urinary tract infection, benign prostatic hyperplasia, vigorous exercise, or recent ejaculation (19). One meta-analysis suggests the false positive rate of the PSA test could be as high as 80%, meaning that 80% of people with elevated PSA do not actually have

prostate cancer (20).[1] Due to this, many men with elevated PSA levels may undergo unnecessary further investigation that could be invasive such as prostate MRI or biopsy. This also increases the risk of harm from overdiagnosis and overtreatment. Additionally, there is evidence to suggest that the PSA test could miss aggressive cancers ('false negatives') (19,21). Therefore, the overall utility of PSA for distinguishing between indolent versus potentially harmful prostate cancer as well as between cancer and no cancer is limited. More research and innovation is needed to find a new, more accurate test for prostate cancer or another biomarker that is more specific that can be used as early as possible in the diagnostic pathway.

6. The current evidence on prostate cancer screening

Given the need to reduce late-stage diagnosis to improve outcomes, coupled with the high likelihood that many people subsequently diagnosed with prostate cancer may not present with symptoms at all, there is significant interest in asymptomatic screening.

In the UK, the National Screening Committee (UK NSC) conducts independent, expert-led reviews of the evidence to appraise the viability, effectiveness, and appropriateness of a screening programme for a condition or disease. They then issue recommendations to the four UK governments on what screening programmes should be adopted. For a programme to be recommended, there must be high-quality evidence that (1) early intervention improves outcomes such as disease-specific mortality, and this outweighs harms associated from overdiagnosis and overtreatment, (2) there is a safe, effective, and acceptable test available, and (3) there is adequate onward follow-up care for those identified by screening (22). Based on their 2020 evidence review the UK NSC concluded that these criteria had not been met and therefore they do not currently recommend prostate cancer screening using the PSA test (22). The UK NSC based their decision on a few reasons, a major one being that most of the screening trials to date have employed the PSA test to screen asymptomatic men, and as noted above, there are inaccuracies and limitations to the test that increase the risk of harm from

[1] This study used a PSA cut-off threshold of 4ng/mL and only focused on symptomatic men. It should be noted that there is limited evidence for the diagnostic accuracy of the PSA test in the primary care setting, which is where the test is most commonly used. The test accuracy also depends on what PSA threshold is used and whether the patient is presenting with symptoms or not. Current symptomatic guidance (e.g., NICE NG12, NiCaN and SRG) suggest utilising age-specific thresholds as PSA levels rise with age, attributed to the benign enlargement of the prostate gland with age. However, evidence is currently limited on what the 'optimal' age thresholds should be. Therefore, the thresholds suggested in referral guidance are largely based on clinical consensus. For asymptomatic men, most research studies use a fixed threshold of 3 or 4 ng/mL, though this is also contested.

unnecessary investigations, overdiagnosis, and overtreatment. When considering the results from PSA-based screening trials (see Appendix), overall findings are mixed as to whether PSA testing in asymptomatic men reduces prostate-specific mortality. However, most studies have suggested a significant amount of potential overdiagnosis and excess incidence amongst those screened (24,25). Importantly, there are limitations to these trials, including contamination which are outlined in the Appendix. Additionally, the UK NSC's 2020 review notes that a superior treatment for early-stage prostate cancer has not been identified and radical treatment options come with adverse side effects that can significantly impact quality of life such as impotence and incontinence. It is therefore unclear whether early identification of men with prostate cancer would provide them with a therapeutic advantage. Read CRUK's PSA screening article for more information.

It should be noted that all the trials that employed PSA as a screening test were completed in the context of the older diagnostic pathway, which is considered to be more harmful because all patients with elevated PSA went straight to receiving a transrectal biopsy. Transrectal biopsies can result in complications such as bleeding, infection, and sepsis (26). There are also limitations with diagnostic accuracy because this biopsy technique largely consists of random sampling of prostate tissue (27,28). This means that aggressive cancer can get missed or indolent tumour tissue can get picked up, leading to overdiagnosis.

The next sections will discuss changes in the pathway and how they could impact future screening and the risk of harm through overdiagnosis and overtreatment.

7. Evolving diagnostic pathways - pre-biopsy prostate MRI

In recent years, the prostate cancer diagnostic pathway has evolved to include a pre-biopsy MRI scan of the prostate, known as a multi-parametric MRI (mpMRI) scan, which might mitigate some of the harms associated with the previous pathway, e.g. receiving a PSA test and going straight to transrectal biopsy if elevated (27). There have also been developments in biopsy techniques such as MRI-guided biopsy to help target tissue sampling to areas with high-grade lesions, as well as a shift towards transperineal biopsy which is associated with fewer complications than transrectal biopsy and may be more accurate (29,30).

The introduction of pre-biopsy MRI has likely improved the prostate cancer diagnostic pathway. The key study, known as the PROMIS trial, showed that using mpMRI to triage men for a biopsy reduced unnecessary biopsies by 27% and diagnosed 5% fewer 'clinically insignificant' cancers (defined as a Gleason 4 or

higher) (27). A meta-analysis supported the findings of this trial, with results showing that prostate MRI before targeted biopsy is superior to a biopsy-only approach and allows people to avoid unnecessary biopsies (31). While these are positive improvements to the diagnostic pathway for prostate cancer, it's important to consider that some MRI findings can be false negatives or may be indeterminate, meaning that it's unclear whether clinically significant prostate cancer is present (32). These cases present diagnostic challenges, and further invasive investigation such as biopsy may be required.

Pre-biopsy prostate MRI may have potential to form part of a screening strategy, but studies thus far have been varied, which makes it difficult to draw conclusions. The introduction of MRI would likely make screening safer and more effective but research from large-scale screening trials that employ pre-biopsy MRI are still required to establish a mortality benefit and reduction in overdiagnosis through testing this way. Emerging research suggests potential to reduce overdiagnosis, but there is a need to further understand this (33). Consideration must also be given to the feasibility and costs associated with a population-based screening programme that would involve MRI-scanning many more men with elevated PSA. Though some modelling has shown that screening incorporating MRI is likely to be cost-effective (34), it would require significant health system resource, capacity, and infrastructure, which must be weighed up within the context of the already overstretched NHS.

Challenges in access, image quality, and clinical expertise

There are real-world challenges with the current implementation of MRI that may mean that the benefits of it as demonstrated in trials may not be being realised in practice. For example, since the recommendation of pre-biopsy MRI in the prostate cancer diagnostic pathway, there has been variation in access and uptake across the UK. We are not aware of routine, publicly available data on this, but Prostate Cancer UK (PCUK) made a Freedom of Information (FOI) request in 2019 to find out more. Data showed that while there is widespread coverage of MRI that is up to PROMIS trial standard in England, there are still areas where MRI remains unavailable, is limited in availability, or is not up to PROMIS trial standard (35). As noted in the article, this is more apparent in Wales and Northern Ireland. Scotland publishes its performance of pre-biopsy MRIs in their Quality Performance Indicators. In 2021, 97.1% of patients had a pre-biopsy MRI, however only 77% had a pre-biopsy MRI which was reported on in line with standard guidelines (36).

MRI scanners must also be appropriately configured, and good MRI scan quality is vital for distinguishing high-grade lesions from low-grade lesions (37,38). A study in 14 hospitals within the Peninsula and Somerset, Wiltshire, Avon, and Gloucestershire Cancer Alliances evaluated prostate mpMRI quality and compliance and found that at least 40% of patients did not have a scan of

adequate quality (39). Some urologists note the importance of working alongside radiologists and being attentive to image quality to aid decision-making (40). Evidence also suggests that radiologist and clinician experience in reading and reporting mpMRI scans can impact whether a scan is reported on accurately (41). A formal consensus meeting comprised of UK experts in prostate cancer resulted in detailed recommendations for the implementation of mpMRI, including one that suggests that primarily urologists or radiologists with interest in mpMRI should report scans and that training courses should be offered (37).

Evidence and data suggests that while pre-biopsy prostate MRI is an improvement in the diagnostic pathway, more must be done to ensure that it is implemented effectively and equitably across the UK.

8. Developments in treatment for low-grade prostate cancer

In addition to changes in the diagnostic pathway, there have been advancements in how patients are treated for prostate cancer. Particularly, those diagnosed with low-grade disease that does not require treatment at the time of diagnosis are offered 'active surveillance' instead of radiotherapy or surgery. Active surveillance consists of regularly monitoring the disease for signs of progression (usually through regular PSA tests or prostate MRI) which allows some patients to avoid treatment consequences such as impotence and incontinence that could decrease their quality of life. Although this may reduce some harms associated with overtreatment, it should be noted that there is still uncertainty on how to define 'progression', especially to a point where active treatment is needed. As noted above, there is still an inability to reliably distinguish tumours that are indolent from tumours that are progressive meaning that sometimes radical treatment will still be needed down the line due to tumour progression or misclassification.

In the UK, the ProtecT trial studied prostate cancer mortality amongst men diagnosed with low-grade prostate cancer who received either active surveillance, surgery, or radiotherapy (42). Results showed no significant difference in prostate cancer mortality across the three groups at 15 years follow up. However, by follow up, over 60% of participants assigned to active surveillance had undergone either surgery or radiation but it's unclear whether this was due to disease progression or other factors such as anxiety or fear. It could be that patients opt for active treatment sooner than they need to because they are worried of progression. Some studies suggest that men on active surveillance feel anxious and uncertain, which could be attributed to the fact that they must cope with the difficult knowledge of being diagnosed with prostate cancer that does not yet need treatment (43,44). Evidence suggests that anxiety peaks around the time for monitoring

appointments or due to hypervigilance, indicating that the psychological harms may be present throughout surveillance (8). To note, there is contrasting research which suggests that risk of depression or anxiety does not differ between men who have active treatment versus men who have active surveillance (45). While the introduction of active surveillance can reduce some of the physical harms associated with overtreatment, more qualitative research on the psychological impacts is needed to better understand this issue.

Additionally, active surveillance is not without a healthcare burden, especially with the increasing role of MRI in active surveillance protocols to more accurately monitor patients. One study reported that patients are on active surveillance for at least 5 years (46). Whilst active surveillance is likely to be cost-effective compared to radical treatment initially (47), there needs to be a better understanding of how many people are receiving active surveillance without ever having their tumour progress enough to move towards treatment. The health system resource and costs associated with extended monitoring of this cohort must be considered alongside the opportunity for earlier diagnosis of progressive tumours that do require treatment. The aim must be to improve at diagnosing only tumours that are clinically significant in order to minimise healthcare burden and psychological harm.

9. Targeting screening at 'high risk' populations

Men of Black African or Black Caribbean Ethnicity

As mentioned in our *Detecting prostate cancer: why we need more research* article, data suggests that certain groups, such as Black men have approximately a 2-3 times greater incidence of prostate cancer than White men in the UK (48). Evidence also suggests that risk may vary for different ancestry groups within broad ethnicity categories (49), meaning that any interventions developed would need to be developed and implemented to take account of this emerging evidence. The UK-based PROCESS study found that Black Caribbean men had a slightly higher incidence of prostate cancer followed by Black African men (50).[2] The reason for higher incidence of prostate cancer among these groups is likely to be as a result of a mixture of environmental as well as biological factors, including genetics. Studies are attempting to elucidate if there are specific genetic drivers of risk across populations (51). There is also evidence to suggest that natural PSA levels amongst men without prostate cancer may differ based on ethnicity. One systematic review concluded that Black men without prostate cancer have higher

[2] It should be noted that the PROCESS study data is very outdated, with cases only being captured until 2001.

PSA levels than White men without prostate cancer, which could contribute to the higher rates of prostate cancer diagnosis amongst Black men (52). This may have implications for overdiagnosis.

Importantly, whilst Black men may have a higher incidence of prostate cancer, it is unclear whether they are at a higher risk of mortality compared to White men. An English study calculated that Black men had double the lifetime risk of dying of prostate cancer compared to White men, however Black men also had the highest incidence of prostate cancer (53). When comparing the lifetime risk of dying from prostate cancer to being diagnosed with it, a similar ratio was observed across different ethnic groups (53). Additionally, there is conflicting evidence on the link between advanced stage diagnosis and ethnicity. The 2025 National Prostate Cancer Audit reports that Black African and Black Caribbean men aged 65-84 with a recorded stage at diagnosis had a greater number of diagnoses per 1,000 across all stages, including stage 3 and 4, compared to White men (54). In contrast, an analysis of stage at diagnosis in England found that Caribbean and African men with prostate cancer had a decreased chance of late-stage cancer compared to the White-British cohort (55). Another study which looked at men with a raised PSA result found that the likeliness of diagnosis at an advanced stage was similar for Black and White men (56). The relationship between ethnicity and advanced stage diagnosis needs to be further explored in studies using tumour grading to provide a better understanding of potential overdiagnosis.

Another study in England found that having a higher income deprivation quintile was associated with higher risk of advanced stage prostate cancer diagnosis (57). Therefore, we need to understand more about how intersectionality and how the presence of multiple inequalities may impact the risk of being diagnosed with late-stage prostate cancer.

Men with a family history or genetic predisposition

Other groups that have a higher incidence of prostate cancer include men with a family history of prostate cancer, though mortality has been reported as lower amongst these men compared to men without a family history. This is commonly attributed to an increased awareness of the disease and therefore a higher likelihood to get a PSA test (58,59). One US-based study suggest that risk of lethal prostate cancer is higher amongst those with a family history of prostate cancer (58), though more specific research and data on tumour grade is required within this group. There is also some evidence suggesting that those with a family history of breast cancer could be at slightly higher risk of prostate cancer though similar research and data gaps exist (58). Genetic drivers of risk in this cohort are still largely unclear but are currently being investigated within studies like the PROFILE study which is explained more within the next section (60). Additionally, pathogenic variants in other cancer related genes such as BRCA1/2 have been shown to be

associated with increased risk of prostate cancer, similar to variants in other genes such as HOXB13.

More research is required prior to targeted screening programmes

Given the increased incidence of prostate cancer in these groups, there has been debate amongst clinicians, researchers and the public on whether a targeted prostate cancer screening programme in the UK would be beneficial. Clarity is needed on which cohorts would be included in such a programme, though Black men, men with a family history, and men with certain genetic predispositions (e.g., BRCA mutation or Lynch syndrome) have been suggested. However, prior to this we need more research to better understand the influence of genetics on prostate tumours that are likely to progress as well as which men specifically are at higher risk, given that research shows differences amongst ancestry groups within broad ethnicity categories.

Crucially we require better diagnostic technology that can distinguish indolent cancer from progressive cancer. Without this, introducing a targeted programme to these groups could risk harm through overdiagnosis and exacerbate existing health inequalities.

10. Overview of research and innovation in the pipeline

There is clearly a lot of complexity within prostate cancer early detection. However, there is promising research ongoing which might help resolve some of the uncertainty that currently exists.

Screening

CRUK supports the upcoming TRANSFORM trial, funded by PCUK and the National Institute for Health and Care Research (NIHR), which will study the effectiveness of different diagnostic tests for prostate cancer screening, including PSA, MRI, and polygenic risk scores (PRS). This trial is due to begin recruitment in 2025 and results will show whether prostate screening in the context of the new diagnostic pathway and with new diagnostic tools could be a possibility. It will be important to ensure that the TRANSFORM trial can limit contamination within the study in light of different efforts e.g. case-finding initiatives.

Genetics and men who are considered 'high-risk'

Additionally, the PROFILE study is ongoing to better understand the role of pathogenic variants (including in BRCA1, BRCA2, ATM, PALB2, MLH1, MSH2, MSH6, CHEK2) in screening for prostate cancer in men who have a family history of prostate cancer and men of Black African or Black African-Caribbean ancestry without a family history. This study will help shed light on which men might be at higher risk so that targeted diagnostic strategies which consider genetics may be developed. CRUK is also part funding the ReIMAGINE trial which combines the use of MRI, genotyping of prostate cancer cells, and genetic changes in the blood to predict clinically significant cancers. The BARCODE 1 study, also part-funded by CRUK, is assessing PRS to risk stratify men for targeted prostate cancer screening and initial findings have recently been published (61), but follow-up is still ongoing. As mentioned above, PRS will also be explored in the TRANSFORM trial.

Diagnostics

There are also developments occurring within pre-biopsy MRI, such as a shift from mpMRI towards bi-parametric MRI (bpMRI). The main difference between the two scans is that mpMRI utilises a contrast agent to complete the scan whereas bpMRI does not, which means that bpMRI is less expensive, quicker to complete, and does not have a risk of allergy or negative reactions to the contrast agent. The PACIFIC and PRIME trials are currently evaluating whether the diagnostic accuracy of bpMRI is similar to that of mpMRI, and if so, a shift may occur such that bpMRI is used instead which may save health system resource and costs. This may also have implications for the use of MRI in screening. Research is also evaluating the potential for MRI in active surveillance. For example, the ATLAS trial will explore whether MRI can improve detection of prostate cancer progression in patients undergoing active surveillance.

Treatment

There is research ongoing to find kinder and more effective treatments for prostate cancer, especially for late-stage disease which is associated with worse outcomes. An example of this is the STAMPEDE trial that has been ongoing since 2005 and has since produced results that have significantly changed standard practice (e.g., adding docetaxel, a type of chemotherapy, or abiraterone, a type of hormone therapy, to improve disease control and life-expectancy) (62). CRUK are also jointly funding STAMPEDE2 which is testing treatments for metastatic hormone sensitive prostate cancer.

11. Summary/conclusion

There are several complexities associated with early detection and diagnosis of this disease. Key drivers are limitations in existing interventions to distinguish between tumours that are likely to progress from those that are indolent. This means that there are significant concerns about harms associated with overdiagnosis and overtreatment, which is exacerbated by the fact that symptoms are not a good predictor of disease, and the significant limitations to the PSA test.

Evidence to support screening for prostate cancer using the PSA test is currently lacking, due to the risk of harm from overdiagnosis and overtreatment, coupled with the uncertain mortality benefit. However, new diagnostic technologies and innovation such as MRI and genetic tools, alone or in combination with PSA, may have potential in forming a future diagnostic and screening strategy, but more research is required to evaluate this in relation to the UK NSC's criteria for a screening programme.

12. Appendix

Trial name	Key findings	Notes and limitations
The Cluster Randomised Trial of PSA Testing for Prostate Cancer ('the CAP trial')	• After 15-years of follow-up, there was a 0.09% reduction in mortality amongst those screened compared to the control group. This equates to less than 1 life be saved for every 1,000 men invited for screening. • 15% (nearly 1 in 6) of men diagnosed through screening were likely to have been overdiagnosed	• Only employed a one-off test as opposed to repeat testing • Compliance with screening intervention was low (36%) • Contamination estimated to be 10-15%
The European Randomised Study for Prostate Screening (ERSPC)	• After 16 years of follow-up, a 20% reduction in mortality was seen amongst those screened compared to those in the control group. • Excess incidence of prostate cancer in the screening group was estimated to be 41%	• Conducted repeat testing, though frequency varied between centres/countries • PSA threshold used was reduced over time at some centres • Mortality reduction driven by Sweden and the Netherlands • Contamination rate quoted to be as high as 62.7%
The Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial (PLCO)	• No difference in mortality was found amongst those screened compared to those in the control group.	• Employed repeat testing • High contamination rate, quoted to be 54.8% in the rapid review for PLCO, but a re-evaluation concluded this was closer to 90%

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