Created by: Strategic Evidence, Cancer Research UK
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Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (Prostate)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected prostate cancer. Key themes have been determined from the literature. For each key theme e.g. individual symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NG12 and SRG guidelines can be found for reference.

This document includes evidence on the following topics:

- Individual symptoms
- Symptom combinations
- Diagnostic accuracy of Digital Rectal Examination (DRE)
- Diagnostic accuracy of PSA testing
- Factors impacting Prostate-specific antigen (PSA) levels (note that this section is subdivided by factor)
- Factors impacting risk of prostate cancer
- Safety netting
- Emerging topics
- Other insights

Background

Prostate cancer is the most common cancer among men in Scotland, accounting for around 4,200 diagnoses each year (2018, 2019, 2021).[1] Stage 4 was the most common stage of prostate cancer diagnosis in Scotland in 2021 (26.9%), followed by stage 3 (24.1%).[2] Overall survival of prostate cancer is high in Scotland with almost 9 in 10 (85.6%) of men surviving their disease for 5 years or more (2015-2019).[3] Survival and treatment options are generally better for those diagnosed at earlier stages. Specific survival by stage data is not available in Scotland, but in most UK nations, stage 4 diagnosis is associated with a significant drop in survival compared to stage 3 diagnosis. Of note, clinicians commonly determine how advanced prostate cancer is by using Gleason score or Cambridge Prognostic Group (CPG) instead of

[1] Public Health Scotland. Average annual prostate cancer (ICD10 C61) incidence in Scotland, based on incidence in the years 2018, 2019 and 2921. Accessed March 2023. Available from: https://publichealthscotland.scot/publications/cancer-incidence-in-scotland/cancer-incidence-in-scotland-to-december-2021
[2] Public Health Scotland. Cancer Incidence and Prevalence in Scotland. Public Health Scotland. March 2023. Available from: https://publichealthscotland.scot/media/20142/2023-03-28-cancer-incidence-report_revised.pdf (Note that the denominator for these proportions include those diagnosed at an unknown stage)
[3] Cancer Research UK. Cancer Statistics Data Hub. Available from: https://crukcancerintelligence.shinyapps.io/CancerStatsDataHub/

TNM staging. Gleason score is determined based on the histopathology of the tumour whereas CPG - which is used in NG12 - is a mixture of TNM staging, Gleason score, and prostate-specific antigen (PSA) level. These measures help discern whether prostate cancer is 'clinically insignificant' (i.e., likely to be slow-growing and does not require immediate active treatment) or 'clinically significant' (i.e., treatment is recommended). A Gleason score greater than or equal to 7 (may also be written as 3+4 or 4+3) or a CPG less than or equal to 2 is generally defined as 'clinically insignificant cancer', however there is a lack consensus in the literature and wider prostate cancer community on this definition.

Changes to urinary patterns, erectile dysfunction, unexplained visible haematuria, lower back pain, bone pain or weight loss are specified as symptoms of prostate cancer in the Scottish Referral Guidelines (SRG). SRG suggests completing a PSA test (a blood test to measure the concentration of PSA which may become elevated in the presence of prostate cancer) and a digital rectal examination (DRE, to feel abnormalities in the prostate) for men exhibiting these symptoms, while also cautioning that a PSA test may be raised due to recent ejaculation, urinary tract infection (UTI), or invasive procedures.

Whether early-stage prostate cancer presents with symptoms or is largely asymptomatic is unclear. Considering that prostate tumours are found in the peripheral zone 70% of the time, some researchers argue that anatomically, early-stage prostate cancer should not present with LUTS. [4] **The causal relationship between LUTS and prostate cancer is not well established**, meaning that LUTS may present due to other benign conditions.[3] Therefore, the focus on LUTS in cancer referral guidance has been debated by researchers and clinicians.[3] Additionally, LUTS is highly prevalent in the general population, especially as men age. The EPIC study included participants from Canada, Germany, Italy, Sweden, and the UK and found that 62.5% of men in the general sample experienced LUTS.[5] Given this high prevalence and the strong association between LUTS and benign conditions, some clinicians and researchers argue that LUTS should not be sufficient enough to warrant a prostate specific antigen (PSA) test.[6]

PSA levels can be elevated in several other benign conditions. The evidence on the reliability of the PSA test among symptomatic populations is limited but suggests that **many people with elevated PSA do not actually have prostate cancer**. The accuracy of DRE is

[4] Gnanapragasam VJ, Greenberg D, Burnet N. Urinary symptoms and prostate cancer-the misconception that may be preventing earlier presentation and better survival outcomes. BMC Med. 2022;20(1):264. Published 2022 Aug 4. doi:10.1186/s12916-022-02453-7
[5] Irwin DE, Milsom I, Kopp Z, Abrams P, Artibani W, Herschorn S. Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. Eur Urol. 2009;56(1):14-20. doi:10.1016/j.eururo.2009.02.026
[6] Just J, Osgun F, Knight C. Lower urinary tract symptoms and prostate cancer: is PSA testing in men with symptoms wise?. Br J Gen Pract. 2018;68(676):541-542. doi:10.3399/bjgp18X699689

flawed as well because many people with prostate cancer will have normal DREs. There is also concern that PSA testing, especially in asymptomatic contexts, can lead to overdiagnosis of prostate cancer (i.e., diagnosis of 'clinically insignificant' prostate cancer that would never have gone on to cause harm in a person's lifetime), however **not enough research currently evaluates the diagnostic accuracy of PSA in detecting clinically significant prostate cancer versus clinically insignificant prostate cancer.** There is also not enough research correlating the presence of symptoms to clinically significant or insignificant cancer.

Moreover, the prostate cancer diagnostic pathway now includes Multiparametric or Biparametric Magnetic Resonance Imaging (mpMRI and bpMRI) completed before biopsy to reduce the harms of unnecessary and invasive investigations and treatments. As these investigations become more established and widespread in the UK, more research is required to explore symptoms, PSA testing, risk stratification, and overdiagnosis in this new context. It should be noted that a large portion of current research into the diagnosis of prostate cancer and the PSA test comes from England and uses secondary care datasets or asymptomatic cohorts. Little evidence exists in a primary care, symptomatic context.

Search Strategy

Search terms: "prostate cancer", symptom, symptom*, diagnosis, detection, "lower urinary tract", urinary, urological, fatigue, "weight loss", haematuria, impotence, "erectile dysfunction", urgency, frequency, hesitancy, retention, nocturia, "abdominal pain", "positive predictive value", risk, prevalence, "diagnostic accuracy", "primary care", "general practice", GP, recognition, referral, ethnic*, PSA, "prostate specific antigen", "prostate-specific antigen", "level", "digital rectal exam*", DRE, age, old, older, aging, "body mass index", BMI, weight, obesity, obese, "early stage", "advanced stage", "late stage", comorbid*, "family history", lifestyle, death, mortality, stratification, tool, score, predict*

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences in Scottish Referral Guidelines (SRG) and NG12 guidelines. These have been drawn from the NG12 Evidence Review document or the NG12 Evidence Review document for diagnostic accuracy of PSA thresholds.

Peer-reviewed literature

Notes: grey rows in the table represent studies that have already been summarised earlier in the document. We have tried to use the same terminology as used in each study for describing the population **(i.e., either 'men' or 'people').** We have included one older publication

(Hamilton et al., 2006) as this paper was leaned on heavily in the NG12 evidence review and it is the only paper to quantify positive predictive values of prostate cancer symptoms in a UK primary care cohort.

Topic: Individual Symptoms
Summary: • The Scottish Referral Guidelines for Suspected Cancer (SRG) suggest a prostate-specific antigen (PSA) test and a digital rectal examination (DRE) if a patient is experiencing changes to urinary patterns, erectile dysfunction, unexplained visible haematuria, lower back pain, bone pain or weight loss. • While there is evidence to indicate that these symptoms can be common among people subsequently diagnosed with prostate cancer, a large proportion of patients do not experience any symptoms and the positive predictive values for some symptoms as specified in SRG are quite low. Hamilton et al. (2006) found that hesitancy, retention, impotence, elevated PSA and abnormal DRE were the only symptoms or findings with a positive predictive value (PPV) higher than the 3% threshold now used by NG12 guidance. This paper is dated, but there is no recent evidence that quantifies prostate symptom PPVs using data on symptomatic men in primary care compared to the wider population. • There is more recent evidence showing that LUTS are the most prevalent type of symptoms in people diagnosed with prostate cancer, and that many people presenting with LUTS are diagnosed with early-stage cancer. However, LUTS are very common as men age and are associated with many benign conditions.[7] Whether there is a causal relationship between LUTS and prostate cancer is unclear. Many diagnosed with prostate cancer could have experienced LUTS as a result of another benign condition and anatomically, it has been argued that early-stage prostate cancer is unlikely to cause LUTS.[8] LUTS may not be a good indicator for prostate cancer, and some argue that they should not be a sufficient reason to offer a PSA test.[9] • There was also evidence for differences in symptom presentation among men of different ethnicities, but more research is needed to determine why this is the case (i.e., genetic variation, symptom awareness, stigma, deprivation, etc.).

[7] Abdelmoteleb H, Jefferies ER, Drake MJ. Assessment and management of male lower urinary tract symptoms (LUTS). Int J Surg. 2016;25:164-171. doi:10.1016/j.ijsu.2015.11.043

[8] Gnanapragasam VJ, Greenberg D, Burnet N. Urinary symptoms and prostate cancer-the misconception that may be preventing earlier presentation and better survival outcomes. BMC Med. 2022;20(1):264. Published 2022 Aug 4. doi:10.1186/s12916-022-02453-7

[9] Just J, Osgun F, Knight C. Lower urinary tract symptoms and prostate cancer: is PSA testing in men with symptoms wise?. Br J Gen Pract. 2018;68(676):541-542. doi:10.3399/bjgp18X699689

Paper number	Study	Summary	Notes
1	Koo MM, Swann R, McPhail S, et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. Lancet Oncol. 2020;21(1):73-79. doi:10.1016/S1470-2045(19)30595-9	This paper examined associations between common presenting symptoms of cancer and stage at diagnosis. There has been debate around whether symptoms present at an early enough stage for there to be possibility for meaningful clinical intervention. Most people (86%) who presented with **lower urinary tract symptoms (LUTS)** were subsequently diagnosed with prostate cancer. 22% of people who presented with **haematuria,** 11% of people who presented with **lower abdominal pain**, 12% of people who presented with **fatigue**, and 11% of people who presented with **weight loss,** were all subsequently diagnosed with prostate cancer. Of the people who presented with LUTS in the study, 71% reported this as their only symptom and 15% were diagnosed with stage 4 cancer *(note: includes cancers other than prostate),* indicating that symptoms can present early enough for meaningful clinical intervention.	• Cross-sectional population-based study • N=7,997, aged 25 or older. Unclear how many of these were those diagnosed with prostate cancer. • National Cancer Diagnosis Audit (NCDA) and National Cancer Registration and Analysis Service (NCRAS) data (2014) • LUTS included: nocturia, frequency, hesitancy, urgency, retention • England only • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitation: recording of symptoms and extraction of information from primary care records might be incomplete or biased; • Did not report positive predictive values (PPV)

2	Zakkak N, Barclay ME, Swann R, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. Br J Cancer. 2024;130(2):297-307. doi:10.1038/s41416-023-02507-4	This paper examined (1) the frequency of presenting symptoms by cancer site and (2) the frequency of cancer site by presenting symptom. The researchers noted that a large proportion of patients diagnosed with prostate cancer had **no recorded symptoms** (28.8%). Prostate cancer had a wide symptom presentation: • 9% presented with **non-specific symptoms.** • 1.55% presented with **upper abdominal symptoms**. • 5.22% presented with **lower abdominal symptoms**. • 50.7% presented with **urological symptoms** such as **loin pain, LUTS, haematuria** (the paper did not specify whether this was visible or non-visible)**, dysuria, urinary tract infection**, **and renal colic**. • 5.45% presented **musculoskeletal** such as **back pain**, **bone pain** or **fracture**. Of note, the mean number of symptoms experienced by those diagnosed with prostate cancer was 1.3. *Note: These symptoms could have occurred individually or in combination with other symptoms.*	• Sample size: 55,122 patients; 8,747 prostate cancer patients • Aged 25 or older • NCDA 2018 data, England only • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • LUTS included: nocturia, frequency, hesitancy, urgency, retention • Limitations: case-only analysis so cannot make inferences about PPV; surveys for GPs regarding the presenting symptoms were filled out retrospectively and therefore, could be prone to bias.
3	Moore SF, Price SJ, Bostock J, Neal RD, Hamilton W. Incidence of 'Low-Risk but Not No-Risk' Features of Cancer Prior to High-Risk Feature Occurrence: An	This study explored whether patients who saw their GP with a high-risk cancer symptom had also seen their GP with a 'low-risk but not no-risk' symptom in the previous year (defined as having a risk threshold between 1-2.99%).	• Observational, descriptive, cross-sectional study • Clinical Research Practice Datalink (CPRD) data, England only

	Observational Cohort Study in Primary Care. Cancers (Basel). 2023;15(15):3936. Published 2023 Aug 2. doi:10.3390/cancers15153936	Results showed that, of the patients diagnosed with prostate cancer who exhibited a high-risk symptom with a risk threshold of 3% or higher: • 7.8% also experienced a symptom with a risk threshold between 2-2.99% in the year prior. These individual symptoms included an **enlarged prostate, frequency/urgency** (most common), **nocturia,** and **weight loss**. The median time of occurrence for these symptoms was 31.5 days prior to the high-risk symptom. • 2.0% also experienced a symptom with a risk threshold between 1-1.99% in the year prior. The only symptom included in this group was **haematuria** (the paper did not specify whether this was visible or non-visible)**.** The median time of occurrence for this symptom was 157 days prior to the high-risk symptom.	• N=150,921 of which 73,643 were male (unclear how many were diagnosed with prostate cancer). • Included data on patients 40 or older from 1 January 2015 to 31 December 2016 • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant)
4	Hamilton W, Sharp DJ, Peters TJ, Round AP. Clinical features of prostate cancer before diagnosis: a population-based, case-control study. Br J Gen Pract. 2006;56(531):756-762.	This was the first UK study completed that identifies and quantifies the pre-diagnostic clinical features of prostate cancer. Only factors occurring in 2.5% of cases or controls were analysed. Results showed the following positive predictive values for individual symptoms of prostate cancer: • **Haematuria** (not specified whether this was visible or non-visible)**:** 1.0 (95% Confidence Interval (CI): 0.57-1.8) • **Loss of weight:** 0.75 (95% CI: 0.38-1.4) • **Nocturia:** 2.2 (95% CI: 1.2-3.6) • **Hesitancy:** 3.0 (95% CI: 1.5-5.5) • **Frequency/urgency:** 2.2 (95% CI: 1.1-3.5)	• Population-based case-control study • 21 GP practices in Exeter, Devon, UK • Patients 40 or older diagnosed between 1998 to 2002 were included; 5 controls were matched to each case based on age and general practice. • N=217 cases, 1080 controls • Note this is the only paper to assess positive predictive

		• **Retention:** 3.1 (95% CI: 1.5-6.0) • **Impotence:** 3.0 (95% CI: 1.7-4.9) In some cases, weight loss (2nd presentation), frequency/urgency, impotence, and abnormal rectal examinations (benign) were present as far as 6 months prior to diagnosis. The authors note that it is unknown if earlier diagnosis by such a time period improves mortality. Note: this paper was used heavily in the 2005 NG12 guidelines review and the 2009 New Zealand Guidelines Group review for their suspected prostate cancer referral guidelines.	values of symptoms associated with prostate cancer among a primary care population. • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: recording of signs and symptoms may vary between practices; potential verification bias; large number of variables in multivariable analysis could lead to false positive associations.
5	Young SM, Bansal P, Vella ET, Finelli A, Levitt C, Loblaw A. Systematic review of clinical features of suspected prostate cancer in primary care. Can Fam Physician. 2015;61(1):e26-e35.	This study evaluated the clinical features of prostate cancer and the diagnostic accuracy of investigations for prostate cancer. The overall findings on symptoms and clinical features were mixed. The authors concluded that **LUTS** were not highly predictive of prostate cancer. It should be noted that only 2 studies in this review were conducted in a primary care setting (Hamilton et al., 2006; Baughan et al., 2011), so it's difficult to draw firm conclusions for a primary care population.	• Systematic review • Included studies from 2005-2012 • 28 papers included in the review (included cohort studies, guideline reviews, retrospective studies, and case control studies) • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant)

			• Limitations: searches are slightly outdated now; no meta-analysis (narrative summary only); limited to observational studies, all but 2 of the studies were not conducted in a primary care setting;
6	Chandra Engel J, Palsdottir T, Aly M, et al. Lower urinary tract symptoms (LUTS) are not associated with an increased risk of prostate cancer in men 50-69 years with PSA ≥3 ng/ml. *Scand J Urol*. 2020;54(1):1-6. doi:10.1080/21681805.2019.1703806	This study (1) described the prevalence of urinary symptoms in a prostate cancer screening population; and (2) investigated whether there was an association between urinary symptoms and the risk of prostate cancer. As part of the Stockholm3 PSA-based screening study, men completed the International Prostate Symptom Score (IPSS) questionnaire which collected data on LUTS, including **incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia**. Each question renders a score depending on symptom severity to contribute to an overall IPSS score. IPSS 0–7 points were considered mild symptoms, 8–19 moderate, and 20-35 severe. This study analysed the IPSS scores among the study cohort. The researchers concluded that there is no clinically meaningful association between urinary symptoms and risk of prostate cancer. Risk of prostate cancer did not increase with increasing LUTS. In fact, there was a slightly lower risk of any, ISUP grade ≥2, and advanced prostate cancer (OR 0.97–0.99) with increasing IPSS score.	• Based in Stockholm, Sweden • N=45,595 men aged 50-69 • Cohort is from the Stockholm3 study which was a **PSA based screening cohort** that ran from 2012-2015. In this study, all men with a PSA of 3ng/mL or higher were recommended to have a prostate biopsy. • They looked at diagnosis by International Society of Urological Pathologists (ISUP) Grade Group system. Although there is debate on what 'clinically significant' prostate cancer is, when using this system, it is generally considered as ISUP grade ≥2.

7	Solvang M, Elnegaard S, Jarbøl DE. Urological symptoms among 23,240 men in the general danish population - concerns about symptoms, their persistence and influence on primary care contacts. Scand J Prim Health Care. 2018;36(3):227-236. doi:10.1080/02813432.2018.1487377	This study analysed associations between men's likelihood of contacting a GP for **urological symptoms**, and linked findings to implications for prostate cancer and PSA testing. We decided to include this study because it is the only recent large population-based study providing important context to the prevalence of LUTS in the general population and the implications this may have for prostate cancer. Out of the study population of 23,240 men, 59.9% of respondents had at least one **urological symptom**, and 23.6% of these people contacted a GP regarding their symptoms. GP contact was higher among those who were older, and was also influenced by increased symptom concern, influence on daily activity, long-term persistence of symptoms, and number of symptoms experienced. The most frequently occurring urological symptom was **night-time urination** (prevalence 47.9%), while **blood in the urine or semen (visible)** was most infrequent among the general population of men. The researchers suggest that this has implications for PSA testing, as majority of men in the general population in this study experienced urological symptoms. Given such a high prevalence of urological symptoms in the general population, PSA testing guidelines may be challenged.	• Web-based Danish cross-sectional questionnaire study • N=23,240 men aged 20 or older • "Urological symptom" included: night-time urination, frequent urination, incontinence with or without stress/urge, difficulty in emptying the bladder, blood in urine, blood in semen, erectile dysfunction. • Limitations: did not study what percentage of people were later diagnosed with prostate cancer; recall bias may be present; willingness to answer questionnaire could be associated with presence of symptoms resulting in overestimation or underestimation; standardised symptom scales not used in this study; Danish study so may not be representative of barriers to accessing primary care that may exist in the UK.

8	Martins T, Ukoumunne OC, Lyratzopoulos G, Hamilton W, Abel G. Are There Ethnic Differences in Recorded Features among Patients Subsequently Diagnosed with Cancer? An English Longitudinal Data-Linked Study. Cancers (Basel). 2023;15(12):3100. Published 2023 Jun 7. doi:10.3390/cancers15123100	This study investigated possible ethnic differences in the number and type of cancer features (as defined by NG12) recorded in primary care before a cancer diagnosis. Results showed: • Asian (AOR = 1.38, 95% CI: 1.02–1.88) and Black men (AOR = 1.79, 95% CI: 1.46–2.19) were more likely than White men to have **erectile dysfunction** prior to a cancer diagnosis. • Black men were less likely than White men to have **LUTS** (AOR = 0.85, 95% CI: 0.73–0.98) and **visible haematuria** (AOR = 0.65, 95% CI: 0.50–0.85) prior to a cancer diagnosis. • Men in the Other ethnic group were less likely to have **erectile dysfunction** (AOR = 0.59, 95% CI: 0.40–0.99) prior to a cancer diagnosis. The researchers suggest that differences could be due to genetic variation, symptom awareness, stigma, health literacy, language barriers, or socioeconomic deprivation which affects help-seeking in ethnic minorities.	• Clinical Practice Research Datalink (CPRD-Aurum) • England only • Included cancers diagnosed between 1 January 2006 and 31 December 2016 in those 40 or older • N= 130,944 (92.3% White, 1.95% Black, 1.61% Asian, 1.88% Mixed, 2.27% Other) • LUTS included: frequency, urinary hesitancy, urinary retention, urinary urgency. • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: Sample size in ethnic minority groups is smaller compared to White ethnic group.

Topic: Symptom Combinations
Summary: Literature on symptom combinations for prostate cancer is lacking. Koo et al. (2020) suggested that those presenting with non-specific symptoms such as lower abdominal pain, fatigue, and weight loss are more likely to experience other symptoms as well, however these findings are not solely in relation to prostate cancer. There was also evidence for differences in symptom presentation

among men of different ethnicities, but more research is needed to determine why this is the case (i.e., cancer biology, symptom awareness, stigma, deprivation, etc.).			
Paper number	**Study**	**Summary**	**Notes**
1	Koo MM, Swann R, McPhail S, et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. Lancet Oncol. 2020;21(1):73-79. doi:10.1016/S1470-2045(19)30595-9 This paper is also summarised above, see paper 1.	This paper examined associations between common presenting symptoms of cancer and stage at diagnosis. There has been debate around whether symptoms present at an early enough stage for there to be possibility for meaningful clinical intervention. *Note that the following findings do not **only** apply to those that were subsequently diagnosed with prostate cancer. Other cancers are included as well, and a site-specific breakdown was not provided.* • 29% of those that reported **LUTS** reported other symptoms alongside LUTS. • 34% of those that reported **haematuria** reported other symptoms as well (note: the paper did not specify whether this was visible or non-visible haematuria) • 82% of those that reported **lower abdominal pain** reported other symptoms as well. • 84% of those that reported **fatigue** reported other symptoms as well. • 88% of those that reported **weight loss** reported other symptoms as well.	• Cross-sectional population-based study • Sample size: 7,997, aged 25 or older • National Cancer Diagnosis Audit (NCDA) and National Cancer Registration and Analysis Service (NCRAS) data (2014) • England only • LUTS included: nocturia, frequency, hesitancy, urgency, retention • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitation: recording of symptoms and extraction of information from primary care records might be incomplete or biased; did not report positive predictive values (PPV); did not provide

		Majority of these people were diagnosed with early-stage disease, except for those that presented with weight loss and fatigue in which 51% and 50%, respectively, were diagnosed with stage 4 cancer *(note: this does not only include prostate cancer, other cancers are included as well).*	specific breakdowns for combined symptoms, by cancer site or further breakdowns of other stages.
9	Martins T, Walter FM, Penfold C, Abel G, Hamilton W. Primary care use by men with symptoms of possible prostate cancer: A multi-method study with an ethnically diverse sample in London. Eur J Cancer Care (Engl). 2021;30(6):e13482. doi:10.1111/ecc.13482	This study investigated primary care use by men with recent onset of LUTS to identify any ethnic differences in care and investigations which could impact ethnic differences in prostate cancer outcomes. 72% of the study population self-identified as White, 15% as Black, and 13% as Asian. 53% of the study population had **only one first symptom**, 12% had **two first symptoms,** and 35% had **3 or more first symptoms**. **Nocturia** and **erectile dysfunction** were the most common symptom experienced (68% and 57%, respectively) although, they were only reported as the first symptom 30% and 22% of the time, respectively.	• Multi-method study involving a questionnaire and face-to-face interviews • Recruited 54 practices in London between March 2016-October 2017; • N=274 men included in analysis • LUTS included hesitancy, frequency of micturition, nocturia, urgency, urgency-with-dribble, retention, sexual/erectile dysfunction, visible haematuria, unexplained weight loss, and explained fatigue or tiredness • Limitations: very low response rate; large older population (70% were over 60 years old); lower participation from ethnic minority groups; limited

			ability to classify ethnic subgroups.
8	Martins T, Ukoumunne OC, Lyratzopoulos G, Hamilton W, Abel G. Are There Ethnic Differences in Recorded Features among Patients Subsequently Diagnosed with Cancer? An English Longitudinal Data-Linked Study. Cancers (Basel). 2023;15(12):3100. Published 2023 Jun 7. doi:10.3390/cancers15123100 This paper is also summarised above, see paper 8.	This study investigated possible ethnic differences in the number and type of cancer features (as defined by NG12) recorded in primary care before a cancer diagnosis. Results showed: • Asian men were more likely to experience multiple symptoms of prostate cancer (adjusted odds ratio (AOR) = 1.20, 95% CI: 1.04-2.33) while men in the other ethnic group were less likely to experience multiple symptoms (AOR = 0.82, 95% CI: 0.71-0.95) The researchers suggest that differences could be due to genetic variation, symptom awareness, stigma, health literacy, language barriers, or socioeconomic deprivation which affects help-seeking in ethnic minorities.	• Clinical Practice Research Datalink (CPRD-Aurum) • England only • Included cancers diagnosed between 1 January 2006 and 31 December 2016 in those 40 or older • N= 130,944 (92.3% White, 1.95% Black, 1.61% Asian, 1.88% Mixed, 2.27% Other) • LUTS included: frequency, urinary hesitancy, urinary retention, urinary urgency. • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: Sample size in ethnic minority groups is smaller compared to White ethnic group.

Topic: Diagnostic accuracy of Digital Rectal Examination (DRE)
Summary: Digital Rectal Examination (DRE) is recommended in both NG12 and SRG. There is a lack of recent high-quality evidence among a symptomatic population that evaluates the diagnostic accuracy of DRE in primary care. The only recent systematic review included only 4 studies all from over 10 years ago. The sensitivity of DRE was very low, indicating that many patients with prostate cancer have a normal

DRE, weakening the utility of DRE as a diagnostic test. PSA performs better than DRE but is not without its own limitations as noted in the previous section.			
Paper number	**Study**	**Summary**	**Notes**
10	Jones D, Friend C, Dreher A, Allgar V, Macleod U. The diagnostic test accuracy of rectal examination for prostate cancer diagnosis in symptomatic patients: a systematic review. BMC Fam Pract. 2018;19(1):79. Published 2018 Jun 2. doi:10.1186/s12875-018-0765-y	This systematic review evaluated the effectiveness of **Digital Rectal Examination (DRE)** performed in primary care for symptomatic patients on predicting prostate cancer. Pooled results for the diagnostic accuracy of DRE performed in primary care for a symptomatic population showed: • A 28.6% (95% CI 25.1-32.3%) sensitivity • A 90.7% (95% CI 89.5-91.8%) specificity • A 42.3% Positive Predictive Value (PPV) • A 84.2% Negative Predictive Value (NPV) These results support urgent referral if a DRE is abnormal, however the sensitivity indicates that many people with prostate cancer actually have a normal DRE. The authors conclude that DRE performed in primary care adds little to the decision to refer.	• Systematic review • 4 studies included from the US, UK and Spain (3 cohort, 1 case-control) • N=3225 total • All studies included were judged to be of high methodological quality by review authors. • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: Only 4 studies included all of which were published over 10 years ago; some papers had poor specification of symptoms patients experienced; often not clear who the DRE was performed by in primary care.
11	Okpua, N.C., Okekpa, S.I., Njaka, S. et al. Clinical	This systematic review compared the diagnostic accuracy of PSA test and DRE for diagnosing prostate cancer. Studies	• Systematic review and meta-analysis

	diagnosis of prostate cancer using digital rectal examination and prostate-specific antigen tests: a systematic review and meta-analysis of sensitivity and specificity. Afr J Urol 27, 32 (2021). https://doi.org/10.1186/s12301-021-00129-x	were included if they had information on both DRE and PSA for patients and the outcome was prostate cancer diagnosis. Results indicated that PSA test has a higher sensitivity (Risk ratio=0.74, P<0.00001, 95% CI 0.67-0.83) and specificity (Risk ratio=1.81, P<0.00001, 95% CI 1.54-2.12) compared to DRE for detection of prostate cancer. 22% of the included study population had an abnormal DRE while 94% had an elevated PSA test; however, 52% of the population with an abnormal DRE were diagnosed with prostate cancer compared to only 30% of those with an elevated PSA test. This suggests that an abnormal DRE may be a better predictor of prostate cancer than a raised PSA, especially when considering concerns around unnecessary investigations. *Note: included studies had symptomatic and asymptomatic study populations.*	• Included studies from 1 Jan 2006 to 31 Dec 2019 • 18 studies included in review, all considered high quality by authors. ○ Note that one study (Issa et al. 2006) is also included in the systematic review above. • Studies from Nigeria, Spain, USA, Qatar, Ireland, India and Sudan • N=3976 • All men were 40 years or older. • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: No UK studies so results may not be relevant or generalisable; included studies had symptomatic and asymptomatic study populations; PSA thresholds used in studies not specified; difficulty locating all relevant studies, including unpublished/grey literature;

			some studies included used a very small sample;
4	Hamilton W, Sharp DJ, Peters TJ, Round AP. Clinical features of prostate cancer before diagnosis: a population-based, case-control study. Br J Gen Pract. 2006;56(531):756-762. This paper is also summarised above, see paper 4.	This was the first UK study completed that identifies and quantifies the pre-diagnostic clinical features of prostate cancer. Only factors occurring in 2.5% of cases or controls were analysed. The study split up the diagnostic accuracy of DRE based on whether an exam was classified as abnormal but benign or abnormal but malignant by the doctor. An **abnormal rectal exam** that was classified as **benign** based on the doctor's notes and description had a positive predictive value for prostate cancer of 2.8 (95% CI: 1.6-4.6). An **abnormal rectal exam** that was classified as **malignant** based on the doctor's notes and description had a positive predictive value for prostate cancer of 12 (95% CI: 5.0-37). • Note: Hard, craggy or nodular glands were classified as malignant. Of note, in a separate multivariable model where PSA was added, the only factor that significantly predicted prostate cancer was PSA value.	• Population-based case-control study • 21 GP practices in Exeter, Devon, UK • Patients 40 or older diagnosed between 1998 to 2002 were included; 5 controls were matched to each case based on age and general practice • N=217 cases, 1080 controls • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: recording of signs and symptoms may vary between practices; potential verification bias; large number of variables in multivariable analysis could lead to false positive associations.
12	Ying Y, He W, Xiong Q, et al. Value of digital rectal examination in patients with suspected prostate cancer: a	The aim of this trial was to evaluate the diagnostic accuracy and role of DRE among patients suspected of prostate cancer (positive mpMRI or PSA above 4ng/mL).	• Prospective clinical trial • Based in Shanghai

	prospective cohort analysis study. Transl Androl Urol. 2023;12(11):1666-1672. doi:10.21037/tau-23-371	The diagnostic accuracy of DRE was as follows: • Sensitivity: 59.51% • Specificity: 67.23% • PPV: 63.53% • NPV: 63.38% Sensitivity of DRE increased when stratified by increasing PSA levels, but the specificity decreased. For example, PSA level between 4-10 showed a sensitivity and specificity of DRE to be 23.68% and 74.50%, respectively, compared to 63.29% and 60.58%, respectively, in those with PSA levels between 10-20. There was an association (P<0.001) between DRE positivity and clinically significant prostate cancer (Gleason Score ≥ 7). DRE had a sensitivity of 65.99% for recognising Gleason Score ≥7 prostate cancer. Overall, the findings showed that stratifying DRE by PSA did not improve diagnostic accuracy.	• Included patients with positive mpMRI or elevated PSA above 4ng/mL. • N=580 • Considered clinical significance as Gleason score ≥ 7. • Limitations: only investigated DRE performance in those that underwent biopsy; did not include patients with PSA levels <4ng/mL; did not consider prostate volume or tumour pathology; DRE can be subjective; Unclear if patients were suspected of cancer due to symptoms or screening PSA.

Topic: Diagnostic accuracy of Prostate Specific Antigen (PSA) testing

Summary:

- The PSA test has a high sensitivity for detecting the presence of **any** prostate cancer, but the specificity of the test is low. There is a lack of evidence investigating diagnostic accuracy of PSA for detecting clinically significant prostate cancer versus clinically insignificant prostate cancer in the symptomatic context. This limits the utility of PSA as a diagnostic test.
- The only systematic review on diagnostic accuracy conducted in a symptomatic population did not include any studies evaluating PSA in primary care. The included studies typically used a fixed threshold of 4ng/mL rather than the age-specific thresholds currently recommended in the SRG or NG12.
- The evidence suggesting the superiority of age-specific thresholds compared to a fixed threshold is limited in quality and quantity and reports mixed findings. NICE published an evidence review regarding the diagnostic accuracy of PSA testing when they updated

their NG12 guidance in 2021 to include age-specific thresholds. The committee noted that sensitivity and specificity was inconsistent among included studies due to poor quality and differences in study populations, and concluded there that there wasn't strong evidence for ***or*** against age-specific thresholds. In light of the variation in thresholds in use across the country at the time, the committee decided to recommend that age-specific PSA thresholds be considered in the update to the guidance, largely based on clinical consensus.			
Paper number	**Study**	**Summary**	**Notes**
13	Merriel SWD, Pocock L, Gilbert E, et al. Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. BMC Med. 2022;20(1):54. Published 2022 Feb 7. doi:10.1186/s12916-021-02230-y	This systematic review aimed to assess the diagnostic accuracy of PSA for detecting prostate cancer in patients exhibiting at least one symptom. Results of the meta-analysis showed a pooled sensitivity of 0.93 (95% CI 0.88-0.96) and a pooled specificity of 0.20 (95% CI 0.12-0.33) for a PSA test with a threshold greater than or equal to 4ng/mL for detecting prostate cancer. This suggests that the utility of PSA as a test to detect prostate cancer is limited. It should be noted that no studies included in the review assessed the performance of PSA in a primary care population. Data were not available to assess the diagnostic accuracy of PSA for detecting clinically significant prostate cancer.	• Systematic review and meta-analysis • 19 studies included in the review. • They included studies of both fixed and variable PSA thresholds, but for the meta-analysis, they used a fixed PSA threshold of 4ng/mL as this was used in most included studies. • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: did not look at Gleason grade or stage of diagnosis; no study was performed in the primary care population; all studies had a high risk of bias in at least one QUADAS domain;

14	Lophatananon A, Light A, Burns-Cox N, et al. Re-evaluating the diagnostic efficacy of PSA as a referral test to detect clinically significant prostate cancer in contemporary MRI-based image-guided biopsy pathways. J Clin Urol. 2023;16(4):264-273. doi:10.1177/20514158211059057	This study aimed to assess the diagnostic accuracy of PSA in the context of current practice i.e., following introduction of mpMRI into the prostate cancer pathway. Two threshold models were tested: (1) ⩽ 50 years: PSA ⩾ 2.5, 50–69 years: PSA ⩾ 3 ng/mL and 70–79 years: PSA ⩾ 5 ng/mL (2) PSA ⩾ 2.5 for men under 50 years or PSA ⩾ 3 everyone else. Results showed that, based on a single PSA threshold of ⩾ 3 ng/mL, the PPV was 40.3% for clinically significant prostate cancer. In comparison Model 1 and Model 2 as described above **both** produced an PPV of 40.2% for clinically significant prostate cancer. This suggests that the age-specific thresholds perform similar to a fixed cut-off of 3ng/mL, and therefore, the age-thresholds did not improve the PPV of PSA for clinically significant prostate cancer.	• Retrospective multicentre cohort study • Data from 3 UK secondary care diagnostics centres from 2013-2020 (referred from primary care based on abnormal DRE or elevated PSA). • N=2767 • 'Clinically significant' cancer was defined as ISUP Grade Group 2 or higher • Limitations: England based; cohorts were already referred to secondary care and may have been subject to different local PSA thresholds; unclear if men were symptomatic or not in primary care; analysis is limited to men who had all secondary care tests, including biopsy.
5	Young SM, Bansal P, Vella ET, Finelli A, Levitt C, Loblaw A. Systematic review of clinical features of suspected prostate cancer in primary	This study evaluated the clinical features of prostate cancer and the diagnostic accuracy of investigations for prostate cancer.	• Systematic review • Included studies from 2005-2012 • 28 papers included in the review (included cohort studies, guideline reviews,

	care. Can Fam Physician. 2015;61(1):e26-e35. This paper is also summarised above, see paper 5.	The overall findings showed that compared to LUTS and DRE, PSA testing had the highest predictive value for detecting prostate cancer, ranging from 34% to 47%. It should be noted that only 2 studies in this review were conducted in a primary care setting (Hamilton et al., 2006; Baughan et al., 2011), so it's difficult to draw firm conclusions for a primary care population.	retrospective studies, and case control studies) • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: searches are slightly outdated now; no meta-analysis (narrative summary only); limited to observational studies, all but 2 of the studies were not conducted in a primary care setting;
15	Gilbert R, Tilling K, Martin RM, et al. Developing new age-specific prostate-specific antigen thresholds for testing for prostate cancer. Cancer Causes Control. 2018;29(3):383-388. doi:10.1007/s10552-018-1014-3	This study examined whether age-specific thresholds for PSA in men without prostate cancer can be used to identify men's risk of prostate cancer (high-risk vs. low/no risk). They compared a model developed in the Krimpen longitudinal community-based study (Bosch et al., 2006)[10] to a fixed 3ng/mL threshold and the NG12 age-specific thresholds. The Krimpen study established a mathematical model which can be applied to predict normal PSA changes over time for an *individual* so long as you have the first measurement and age. This differs based on NICE thresholds because it can be personalised and individualised for each patient instead of a population-generic threshold.	• Nested Multicentre Randomised Controlled Trial (RCT) from the ProtecT study (Prostate testing for cancer and Treatment) RCT which compared treatments for men with localised prostate cancer in the UK. ○ Men recruited from primary care for a PSA test and then offered biopsy if PSA level was 3.0ng/mL or

[10] Bosch JL, Tilling K, Bohnen AM, Donovan JL; Krimpen Study. Establishing normal reference ranges for PSA change with age in a population-based study: The Krimpen study. Prostate. 2006;66(4):335-343. doi:10.1002/pros.20293

		Results suggest that using either the Krimpen or NICE age-specific thresholds to guide referral and further investigation resulted in fewer 'unnecessary' investigations compared to using a fixed threshold (5,579 fewer unnecessary investigations when using Krimpen thresholds and 2,235 fewer unnecessary investigations when using NICE thresholds). However, more high-risk cancers were missed (533 missed when using Krimpen thresholds and 155 missed when using NICE thresholds. The authors concluded that there was little benefit of using the Krimpen age-based threshold model or the NG12 age-thresholds due to the amount of high-risk cancers missed.	more. If they had cancer, they were recruited into ProtecT to follow treatment. • N= 81,553 aged 50 or older • Limitations: asymptomatic population

Topic: Factors impacting Prostate Specific Antigen (PSA) levels and testing			
Context: PSA is a protein produced by the prostate gland. Levels of PSA can be elevated in cases of prostate cancer but can also be elevated for a variety of other reasons, including benign conditions, age, exercise, sexual activity, and infection.[11] Historically, PSA levels were considered elevated if they were greater than a fixed threshold of 3 or 4 ng/mL, however, there has been a recent shift toward using age-based thresholds (present in both SRG and NG12 guidance, although specific thresholds are different between the two) following understanding that PSA levels increase naturally with age. **There is emerging evidence that other factors can impact PSA levels and that it might be beneficial to consider these factors when interpreting PSA test results. This section collates evidence on these topics.**			
Paper number	**Study**	**Summary**	**Notes**
Ethnicity, age, and PSA levels			

[11] Harrison S, Tilling K, Turner EL, et al. Investigating the prostate specific antigen, body mass index and age relationship: is an age-BMI-adjusted PSA model clinically useful?. Cancer Causes Control. 2016;27(12):1465-1474. doi:10.1007/s10552-016-0827-1

Sub-section summary: • Current guidance on interpreting PSA only considers age. SRG currently recommends using the following age-specific thresholds for interpreting PSA: Less than 60 years < 3 ng/mL; aged 60-69 years < 4 ng/mL; aged 70-79 years < 5 ng/mL; aged 80-85 years > 10 ng/mL; aged 86 years and over > 20 ng/mL. These figures are largely based on clinical consensus and they differ from NG12 PSA thresholds (which were also largely based on limited evidence and committee consensus). • The evidence suggests that PSA levels increase with age, which supports the use of age-specific PSA thresholds, although there is limited evidence on what threshold should be established for each age-group. Matti et al. (2022) conducted a systematic review which found the following pooled upper limits for PSA levels by age-group: 40-49 years - 2.1ng/mL; 50-59 years - 3.2ng/mL; 60-69 years - 4.9ng/mL; 70+ - 6.5ng/mL. • PSA levels may also be naturally higher among Black men without prostate cancer. The reason for this may be due to genetic variation among people of different ancestry which has been shown in genome-wide association studies.[12,13] For example, over 128 common single nucleotide polymorphisms (SNPs) have been identified that explain 8% of PSA variation.[14] However, more research is needed to determine the prevalence of this genetic variation in Black men, and within sub-ethnicities. • Black men also experienced a higher incidence of prostate cancer at younger ages, but no difference in advanced stage cancer diagnosis.[15] This may have implications for interpreting PSA test results for Black men, but further research investigating rates of **clinically significant vs. insignificant prostate cancer diagnosis by ethnicity is needed.** Evidence for ethnic sub-groups is also lacking.			
16	Barlow M, Down L, Mounce LTA, et al. Ethnic differences in prostate-specific antigen levels in men without prostate cancer: a systematic review. Prostate	This systematic review aimed to collate available evidence on PSA levels in men without cancer or without symptoms suggestive of prostate cancer from different ethnic groups. It was noted that there is no ethnicity-specific guidance for interpreting PSA in the UK although evidence has suggested	• Systematic review • 13 studies included; 7 studies were of good quality and the rest were poor quality. • Studies from the USA and New Zealand

[12] Kachuri L, Hoffmann TJ, Jiang Y, et al. Genetically adjusted PSA levels for prostate cancer screening. Nat Med. 2023;29(6):1412-1423. doi:10.1038/s41591-023-02277-9
[13] Wang A, Shen J, Rodriguez AA, et al. Characterizing prostate cancer risk through multi-ancestry genome-wide discovery of 187 novel risk variants. Nat Genet. 2023;55(12):2065-2074. doi:10.1038/s41588-023-01534-4
[14] Shi M, Shelley JP, Schaffer KR, et al. Clinical consequences of a genetic predisposition toward higher benign prostate-specific antigen levels. EBioMedicine. 2023;97:104838. doi:10.1016/j.ebiom.2023.104838
[15] Down L, Barlow M, Bailey SER, et al. Association between patient ethnicity and prostate cancer diagnosis following a prostate-specific antigen test: a cohort study of 730,000 men in primary care in the UK. BMC Med. 2024;22(1):82. Published 2024 Mar 1. Doi:10.1186/s12916-024-03283-5

	Cancer Prostatic Dis. 2023;26(2):249-256. doi:10.1038/s41391-022-00613-7	that PSA levels vary among ethnicities. Findings from this review show that: • Although evidence was mixed, the studies considered to be 'good' quality reported that Black males had higher baseline PSA levels than White males in the USA. • Hispanic men were found to have similar PSA levels to White men in the USA.	• N=654,197 men aged 40 or older, although 2,313 men may be duplicated • Across all studies, there were 82% White, 6% Black, 6% Asian, 3% Pacific Island, 2% Maori, 1% Hispanic <1% Other • Limitations: No UK or Europe based studies; limited representation of some ethnicities and limited/no breakdown within ethnic groups; did not conduct a meta-analysis due to heterogeneity of the studies.
17	Down L, Barlow M, Bailey SER, et al. Association between patient ethnicity and prostate cancer diagnosis following a prostate-specific antigen test: a cohort study of 730,000 men in primary care in the UK. BMC Med. 2024;22(1):82. Published 2024 Mar 1. Doi:10.1186/s12916-024-03283-5	This study investigated prostate cancer diagnosis in the year following a PSA test and the associated risk of advanced disease at diagnosis by ethnic group. Results showed that across the whole cohort, Asian men had the lowest PSA values while Black men and men of mixed ethnicity had the highest PSA values. The ethnic distribution of men with a raised PSA who were diagnosed with prostate cancer within a year was: • 19.8% of White men; 7.5% diagnosed with advanced prostate cancer. • 13.4% of Asian men; 4.5% diagnosed with advanced prostate cancer.	• CPRD Aurum dataset (England only) • N=730,515; 89% White, 5.4% Asian, 4.3% Black, 0.8% Mixed, 0.9% Other. • Included men aged 40 or older during 2010-2017 who had a PSA test in this period • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant)

		• 24.7% of Black men; 7.0% diagnosed with advanced prostate cancer. Of note, prostate cancer incidence was higher among younger Black men aged <70 compared to White and Asian men of the same age. Incidence of advanced prostate cancer diagnosis was similar among White and Black men less than 60 years old, but after age 65, White men had the highest incidence of advanced cancer. Asian men consistently had the lowest incidence.	• Limitations: Did not have data on Gleason score so unable to comment on clinically significant cancer; was not able to determine reasons for the PSA test; smaller sample size of some ethnic minority groups (Asian, Mixed, Other); unable to consider ethnic subgroups; could not examine ethnic differences in outcomes following a raised PSA test.
9	Martins T, Walter FM, Penfold C, Abel G, Hamilton W. Primary care use by men with symptoms of possible prostate cancer: A multi-method study with an ethnically diverse sample in London. Eur J Cancer Care (Engl). 2021;30(6):e13482. doi:10.1111/ecc.13482 This paper is also summarised above, see paper 9.	This study investigated primary care use by men with recent onset of LUTS to identify any ethnic differences in care and investigations which could impact ethnic differences in outcomes. No ethnic differences were found in the proportion of men who were offered a DRE, although compared to White and Asian men, fewer Black men were offered DRE at the first GP consultation. There was significant ethnic variation found in the proportions of men who were offered a PSA test (59% White, 49% Black, and 36% Asian).	• Multi-method study involving a questionnaire and face-to-face interviews • Recruited 54 practices in London between March 2016-October 2017; • N=274 men included in analysis • LUTS included hesitancy, frequency of micturition, nocturia, urgency, urgency-with-dribble, retention, sexual/erectile dysfunction, visible haematuria, unexplained weight loss,

			and explained fatigue or tiredness • Limitations: very low response rate; large older population (70% were over 60 years old); lower participation from ethnic minority groups; limited ability to classify ethnic subgroups.
18	Matti B, Zargar-Shoshtari K. Age-adjusted reference values for prostate-specific antigen in a multi-ethnic population. Int J Urol. 2021;28(5):578-583. doi:10.1111/iju.14519	This study aimed to establish age-specific thresholds for PSA among men of different major ethnicities present in New Zealand, including Māori, Pacific, Asian, and European. Although this paper is in a New Zealand context, we've decided to include it because there is very little UK evidence on age-specific PSA thresholds, especially considering ethnicity. International evidence may help to bridge this gap. Results showed that PSA levels increased with age, regardless of ethnicity (Pearson correlation = 0.362, P < 0.001). However, ethnicity was found to impact PSA levels. For example, PSA levels were higher for Māori and Pacific men compared to European and Asian men. The researchers speculate that this could be due to both biological and sociological factors. Due to the impact of ethnicity on PSA, different upper limits for age-specific PSA thresholds were proposed for different ethnic groups in the study. The researchers suggest that ethnic variation should	• Based in New Zealand • N=215,132 men aged 40-79 • Data collected from 2009-2017. • Limitations: Study took place in New Zealand so may not be generalisable to the UK population; unclear whether all patients were cancer-free but men with very abnormally high PSA were excluded; the reason for PSA testing among men in the cohort is unknown (so it is unclear whether the population was mostly symptomatic or mostly asymptomatic)

		be considered when PSA results are interpreted in clinical practice.	
19	Matti B, Xia W, van der Werf B, Zargar-Shoshtari K. Age-Adjusted Reference Values for Prostate Specific Antigen - A Systematic Review and Meta-Analysis. Clin Genitourin Cancer. 2022;20(2):e114-e125. doi:10.1016/j.clgc.2021.11.014	This systematic review evaluated different age-specific thresholds for PSA across different ethnicities of healthy men. Findings showed that while overall PSA levels did increase with age, there was significant variation in the specific PSA levels reported among studies. The analysis showed that this was largely attributed to age and ethnicity, as opposed to methodological factors such as study population or design. The following pooled upper limits for PSA thresholds for each age-group were found: • 40-49: 2.1ng/mL • 50-59: 3.2ng/mL • 60-69: 4.9ng/mL • 70+: 6.5ng/mL However, because ethnicity was a main driver of variation in PSA thresholds across studies, the researchers suggest that ethnicity should be accounted for when interpreting PSA test results.	• Systematic review and meta-analysis • Searched up to December 2019. • 43 studies included overall but only 37 were able to be included in the meta-analysis. • Studies from Asia, the Middle East, USA, Europe, Nigeria, and New Zealand. • N=325,514 • Moderate quality evidence according to researchers. • Limitations: heterogeneity suggests that other factors not considered in the study may contribute to the observed differences in PSA thresholds across studies; many of the included studies are older and dated.
Body Mass Index (BMI), weight, and PSA levels **Sub-section summary:**			

• Body mass index (BMI) is a measure that uses height and weight to determine whether an individual is at a 'healthy' weight. BMI is calculated by dividing a person's body weight in kilograms by their height in metres squared to produce their BMI in kilograms per metre squared (kg/m^2). • There is evidence suggesting an inverse relationship between body mass index (BMI) and PSA levels, however Harrison et al. (2016) found no difference between an age-BMI adjusted PSA model compared to the NICE age-specific thresholds. This indicates that adding BMI to the guidance for interpretation of PSA levels may not be useful. • There was no evidence to show that BMI impacts the likelihood of being diagnosed with prostate cancer.			
20	Bonn SE, Sjölander A, Tillander A, Wiklund F, Grönberg H, Bälter K. Body mass index in relation to serum prostate-specific antigen levels and prostate cancer risk. Int J Cancer. 2016;139(1):50-57. doi:10.1002/ijc.30052	This study assessed the association between BMI and PSA in men without prostate cancer at baseline. Men were then followed-up to investigate prostate cancer risk. Findings indicated that PSA values decline with increasing BMI. Specifically, PSA levels decreased by 1.6% (95% CI: -2.1 to -1.1) with every one unit (kg/m2) increase in BMI in the adjusted models. Of note, there was no statistically significant association between BMI and PSA among men who were diagnosed with prostate cancer, suggesting that while BMI can impact PSA levels, BMI does not impact the likelihood of being diagnosed with prostate cancer.	• Population-based STHLM-2 cohort study based in Sweden. • 2010-2012 • N= 15,827 • Looked at cancer risk by Gleason grade - Gleason score <7 was defined as low-grade and ≥7 was defined as high-grade • Limitations: Based in Sweden so may not be generalisable to UK population; short follow-up time; reasons for PSA testing were not clear – could be symptomatic or screening; lack of mortality data; self-reported height and weight used to calculate BMI.
21	Harrison S, Tilling K, Turner EL, et al. Systematic review and	This systematic review aimed to understand the association between BMI and (1) prostate cancer risk (2) advanced	• Systematic review and meta-analysis

	meta-analysis of the associations between body mass index, prostate cancer, advanced prostate cancer, and prostate-specific antigen. Cancer Causes Control. 2020;31(5):431-449. doi:10.1007/s10552-020-01291-3	prostate cancer risk, and (3) PSA levels. This summary focuses on the third objective – the association between BMI and PSA levels *(the other associations are discussed in the risk stratification section of this review).* • The random-effects meta-analysis showed that on average, for a 5kg/m^2 increase in BMI, the associated change in PSA levels was -5.88% (95% CI: -6.87 to -4.87, p<0.001.) There was heterogeneity in estimates across studies. Fixed-effect meta-analysis showed a similar result with smaller confidence intervals. • The association between BMI and PSA levels was found to be non-linear, meaning PSA values decreased more between overweight and obese individuals than between normal weight and overweight individuals. • Obese men had an estimated 12.9% lower PSA than normal weight men. • Overweight men had an estimated 3.4% lower PSA than normal weight men. Based on these results, the authors suggest that it could be beneficial to consider BMI when interpreting a PSA test.	• Included studies: 78 (association between BMI and prostate cancer); 21 (association between BMI and advanced prostate cancer); 35 (association between BMI and PSA) ○ *Note: This summary only considers the 35 papers assessing the association between BMI and PSA (the other associations are in the risk stratification section)* • N=264,970 among the 19 studies assessing the association between BMI and PSA included in the meta-analysis • Explored outcomes for advanced/clinically significant prostate cancer using individual study definitions (i.e., if the study labelled as “advanced” or “aggressive,” “locally advanced”, “extra-prostatic”, “nodular” or

			"metastatic" prostate cancer) • Limitations: Heterogeneity between studies evaluating associations between PSA and BMI; moderate risk of bias in most studies; some studies could not be included in the meta-analysis.
22	Harrison S, Tilling K, Turner EL, et al. Investigating the prostate specific antigen, body mass index and age relationship: is an age-BMI-adjusted PSA model clinically useful?. Cancer Causes Control. 2016;27(12):1465-1474. doi:10.1007/s10552-016-0827-1	This study examined the relationship between PSA and BMI (in men without diabetes) and developed and assessed an age-BMI-adjusted model for PSA for detecting prostate cancer. Results showed the following relationships: • As BMI increases, PSA levels tend to decline. • As age increases, PSA levels tend to increase. The NICE age-specific thresholds for PSA performed similarly (sensitivity/specificity) for detecting prostate cancer as the models adjusting for BMI alone, age alone, and age and BMI together, suggesting that the age-BMI model is no more useful than the NICE age-specific thresholds. It was not clear from the study whether there was a causal relationship between PSA and BMI, and the researchers noted that it is difficult to disentangle the relationship with underlying prostate cancer.	• Cross-sectional study nested within the ProtecT (Prostate testing for cancer and Treatment) RCT which compared treatments for men with localised prostate cancer in the UK. ○ Men recruited from primary care for a PSA test and then offered biopsy if PSA level was 3.0ng/mL or more. If they had cancer, they were recruited into ProtecT to follow treatment. • N= 11,293 (9,457 cases and 1,836 controls)

			○ Cases had prostate cancer and controls did not have prostate cancer. • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: not an ethnically diverse population; PSA values taken on one day which could have been influenced by other factors which were not considered.
Patient/GP factors and PSA testing **Sub-section summary:** • PSA testing is higher among some demographic groups, including, but not limited to: Black men, more highly educated men, men from less deprived areas, employed men, men with a family history, men with a wife/partner, and older men. • PSA testing was lower among: men who were from more deprived areas, current smokers, men who had a lower alcohol intake, men who had a higher BMI, men with diabetes/heart disease/stroke. • There is geographical variation in PSA testing rates across the UK. Young et al. (2017) found that there was a lower risk of PSA testing and diagnosis in Scotland than England.			
23	Littlejohns TJ, Travis RC, Key TJ, Allen NE. Lifestyle factors and prostate-specific antigen (PSA) testing in UK Biobank: Implications for epidemiological research.	This study explored the associations between sociodemographic, lifestyle and health-related characteristics and PSA testing. The following groups were more likely to have had a PSA test:	• Population-based cohort study • N=212,039 men from UK Biobank study • Limitations: UK Biobank has a higher proportion of men

	Cancer Epidemiol. 2016;45:40-46. doi:10.1016/j.canep.2016.09.010	• Older men (OR for 65–70 years vs. 40–44 years = 18.8) • Men with a family history of prostate cancer (brother or dad) (OR = 1.92) compared to men without a family history. • Men who were more highly educated. • Black men. • Men not in paid/self-employment. • Men living with a wife or partner. • Men who had private healthcare. • Men who were taller. • Men who had a vasectomy. • Men who were diagnosed with non-prostate cancer. • Men who had hypertension. The following groups were less likely to have had a PSA test: • Men living in socioeconomically deprived areas • Men who were current smokers, • Men who had a lower alcohol intake • Men with a higher BMI • Men who had been diagnosed with diabetes, heart disease or stroke PSA testing was also less common in the East Midlands and Northeast England and most common in Wales and South West England.	reporting ever having had a PSA test than previous studies report; undergoing a PSA test was self-reported; PSA test reason, frequency, outcome data was not collected.
24	Nderitu P, Van Hemelrijck M, Ashworth M, et al. Prostate-specific antigen testing in inner London general	This study investigated the association between PSA testing and factors that may influence testing (age, ethnicity, obesity, social deprivation, and comorbidity).	• Cross-sectional study • Data from general practices in London boroughs of

	practices: are those at higher risk most likely to get tested?. BMJ Open. 2016;6(7):e011356. Published 2016 Jul 12. doi:10.1136/bmjopen-2016-011356	Findings showed an overall PSA testing prevalence of 17.6% in the cohort. The following groups were more likely to undergo PSA testing: • Older groups. • Black patients (OR=1.78) and mixed Black patients (OR=2.25) compared to white patients • More deprived groups (OR=0.83 in the most deprived quintile) • Obese patients (OR=1.29) compared to normal weight patients. • Men with cardiovascular disease (OR=1.51) • Men with hypertension (OR=1.49)	Newham, City and Hackney and Tower Hamlets • N=150,481 men aged 40 or older • Limitations: unknown whether patients were symptomatic or asymptomatic at PSA test; unknown whether PSA test was initiated by patient or GP; other drugs that may impact PSA were not adjusted for in the study due to lack of data.
25	Young GJ, Harrison S, Turner EL, et al. Prostate-specific antigen (PSA) testing of men in UK general practice: a 10-year longitudinal cohort study. BMJ Open. 2017;7(10):e017729. Published 2017 Oct 30. doi:10.1136/bmjopen-2017-017729	Guidance for primary care physicians in the UK, USA, and Australia recommend counselling and shared decision making with patients about PSA testing for men who raise the issue, are high-risk, or have symptoms/clinical concern. Given this vague guidance, testing rates are likely to vary between GPs. Therefore, this study evaluated the cumulative risk of PSA testing of UK men without prostate cancer in primary care. Findings showed: • The cumulative 1-year, 5-year and 10-year risks of receiving a PSA test were 5.1% (95% CI 5.0% to 5.2%), 21.4% (95% CI 21.3% to 21.5%) and 39.2% (95% CI 39.0% to 39.4%), respectively.	• Retrospective cohort study • Data from CPRD from January 2002 to December 2011 • N=434,236 from 558 primary care practices in the UK; 37% of these men had a full 10-year follow-up • All areas in the UK were included except for London due to the though that PSA testing rates may be different in the capital • Limitations: Unclear which tests were due to symptoms

		• The risk of receiving a PSA test increased with age (25.2% in those aged 45-49 compared to 53% in those aged 65-69) • The risk of testing and diagnosis of prostate cancer was higher in the Southeast Coast (47.5% and 3.1% respectively) and Wales (45% and 2.8% respectively). • **The risk of testing and diagnosis were lowest in Scotland (23.8% and 2.4% respectively)** • Those in higher deprivation areas had a lower risk of testing and diagnosis compared to lower deprivation areas. • Of the men with complete 10-year follow-up, 36% underwent at least 1 PSA test. The authors write that the pattern of PSA testing in the cohort suggested that many PSA tests are being undertaken due to investigation of LUTS symptoms rather than screening, however, they were unable to separate which tests were opportunistic and which were symptomatic.	and which were opportunistic tests;
26	Moss S, Melia J, Sutton J, Mathews C, Kirby M. Prostate-specific antigen testing rates and referral patterns from general practice data in England. Int J Clin Pract. 2016;70(4):312-318. doi:10.1111/ijcp.12784	This study reports the proportion of men referred following a PSA test according to age and PSA level from 2010-2011 in England. • The rate of men tested at least once was 8.74 (95% CI 8.67–8.82) per 100 person-years in 2010, and 9.45 (95% CI 9.37–9.53) in 2011. • Rates of testing increased with age. • Rates decreased with increasing deprivation.	• CPRD data • England only • N=106,114 men aged 45-84 • Limitations: CPRD data was linked to HES data which may not be representative of all practices or the general population; unable to investigate variations by

		• Rates of testing varied by region, being lowest in the North East region and highest in the South East Coast region. • Rates of testing were higher in smaller practices. • 27.1% of men in 2010 had a relevant symptom recorded in the 12 months prior to the test with similar proportions in 2011 as well. • Referral rates after a raised PSA test in symptomatic men was 31.8%.	ethnicity; difficulty in identifying referrals linked to the PSA test; 'Raised PSA test' definition is unclear and could vary from practice to practice as it was before age-specific thresholds were introduced in guidance.

Topic: Factors impacting risk of prostate cancer diagnosis			
Summary: • More deprived patients, older patients, patients with renal disease, patients with peripheral vascular disease, and patients with higher BMI were at increased risk of advanced stage diagnosis. • Older men and those with higher PSA levels at diagnosis were at increased risk of prostate cancer death. • More evidence is required to determine whether Black men have a greater risk of dying from prostate cancer given their incidence of the disease is higher. However, evidence supports that Caribbean and African men have a lower risk of late-stage diagnosis, potentially due to the fact that Black men may be more likely to have a PSA test.			
Paper number	Study	Summary	Notes
27	Barclay ME, Abel GA, Greenberg DC, Rous B, Lyratzopoulos G. Socio-demographic variation in stage at diagnosis of breast, bladder, colon, endometrial, lung, melanoma, prostate,	This study examined the association between stage at diagnosis for common cancers in England and socio-demographic variation. The following associations were found:	• Cross sectional study • Data from the English cancer registry in 2015 • N=202,001 • Stage data was TNM staging – this may not be completely relevant to

	rectal, renal and ovarian cancer in England and its population impact. *Br J Cancer.* 2021;124(7):1320-1329. doi:10.1038/s41416-021-01279-z	• Increasing age was linked to increasing odds of advanced stage (stage 3 or 4) prostate cancer diagnosis. • More deprived patients were at higher risk of advanced stage prostate cancer. The authors estimated that a 9.1% absolute increase in stage 1 and 2 prostate cancer diagnoses may be seen if socio-demographic inequalities in stage at diagnosis were eliminated (note: this was the largest absolute difference across all cancer sites included). However, this should be noted with caution because the authors considered TNM staging instead of Gleason score, ISUP grade group, or Cambridge Prognostic Groups (CPG). So, this finding may not be representative of the shift of clinically significant or advanced prostate cancer to more localised disease.	prostate cancer as we talk about 'clinically significant' or 'clinically insignificant' disease using Gleason grading, ISUP grade groups, or Cambridge Prognostic Groups (CPG). TNM staging does not represent clinical significance. • Limitations: stage data missing for some patients; TNM staging used rather that Gleason, ISUP, or CPG; health-care related factors were not considered; could not adjust for PSA testing;
28	Boakye D, Günther K, Niedermaier T, Haug U, Ahrens W, Nagrani R. Associations between comorbidities and advanced stage diagnosis of lung, breast, colorectal, and prostate cancer: A systematic review and	This review analysed the association between comorbidities and incidence of advanced stage diagnosis for prostate, breast, lung, and colorectal cancer. Results showed the higher odds of advanced stage diagnosis of prostate cancer for the following comorbidities: • Renal disease (odds ratio (OR) = 2.02) • Peripheral vascular disease (OR=1.26)	• Systematic review and meta-analysis • Advanced stage was defined as stage 3 or 4 determined by TNM staging, not Gleason grade, ISUP or CPG. • 37 studies included; 4/37 examined prostate cancer.

	meta-analysis. *Cancer Epidemiol* 2021; 75: 102054.	There were slightly lower odds of advanced stage diagnosis of prostate cancer for patients with: • Hypertension (OR-0.84) • Myocardial infarction (OR=0.80) No association was found between diabetes or HIV, and advanced stage prostate cancer diagnosis. Note that advanced stage was defined using TNM staging and not Gleason grade, ISUP, or CPG so the findings may not be generalisable to clinically significant or insignificant disease,	• Studies included up to 3rd June 2021 • Limitations: Most studies based in the USA so maybe not generalisable to the UK; TNM staging rather than Gleason, ISUP or CPG; did not consider impact of screening or if populations had screening; did not consider psychiatric conditions.
29	MacKintosh FR, Sprenkle PC, Walter LC, et al. Age and Prostate-Specific Antigen Level Prior to Diagnosis Predict Risk of Death from Prostate Cancer. Front Oncol. 2016;6:157. Published 2016 Jun 28. doi:10.3389/fonc.2016.00157	This study evaluated the risk of prostate cancer death according to age and PSA level at diagnosis. Findings showed that higher PSA levels (Area Under the Curve (AUC)=0.72) and older age (AUC=0.67) at diagnosis were associated with a higher risk of prostate cancer death. Older men had increased mortality, regardless of PSA level at diagnosis. When both age and PSA level at diagnosis was combined to predict prostate cancer death, the AUC was 0.79.	• Cohort study • N=230,081 men, aged 50-89 • Veterans Administration database from 1999-2009 • USA-based • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: Not UK-based cohort so maybe not generalisable; observational study which did not control for treatment/other factors; unclear whether PSA prior to diagnosis was due to screening or due to

			symptoms; stage or grade information at diagnosis was not provided; short mean follow-up time (3.7 years);
21	Harrison S, Tilling K, Turner EL, et al. Systematic review and meta-analysis of the associations between body mass index, prostate cancer, advanced prostate cancer, and prostate-specific antigen. Cancer Causes Control. 2020;31(5):431-449. doi:10.1007/s10552-020-01291-3 This paper is also summarised above, see paper 21.	This systematic review aimed to understand the association between BMI and (1) prostate cancer risk (2) advanced prostate cancer risk, and (3) PSA levels. This summary focuses on the first and second objective *(the third objective is included in the PSA levels and considerations section).* • There was no association between BMI and increased prostate cancer risk. However, there is a reduced risk of being diagnosed, or a higher chance of missed diagnosis *(note: the researchers do not define what 'missed diagnosis' is)*, in overweight or obese men due to the nature of PSA testing in prostate cancer diagnosis, and the existing inverse relationship between BMI and PSA which is not currently considered in guidance. • There was some evidence to suggest a linear association between BMI and increased risk of advanced prostate cancer, but only among studies that reported Hazard Ratios and not among studies that reported Odds Ratios. This could be due to differences in study populations or study designs.	• Systematic review and meta-analysis • Included studies: 78 (association between BMI and prostate cancer); 21 (association between BMI and advanced prostate cancer); 35 (association between BMI and PSA) ○ *Note: This summary only considers the 78 and 21 papers assessing the association between BMI, prostate cancer risk, and advanced prostate cancer risk.* • For the 67 studies included in the meta-analysis assessing BMI and prostate cancer risk: N=9,513,326 • For the 18 studies included in the meta-analysis assessing BMI and advanced prostate cancer risk: N=1,146,847

			• Explored outcomes for advanced/clinically significant prostate cancer using individual study definitions (i.e., if the study labelled as "advanced" or "aggressive," "locally advanced", "extra-prostatic", "nodular" or "metastatic" prostate cancer) • Limitations: Some studies were screening studies so not all men were biopsied; heterogeneity between studies; varying definitions of "advanced prostate cancer" among studies.
30	Lloyd T, Hounsome L, Mehay A, Mee S, Verne J, Cooper A. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008-2010. BMC Med. 2015;13:171. Published 2015 Jul 30. doi:10.1186/s12916-015-0405-5	This study calculated the lifetime risk of being diagnosed with and dying from prostate cancer among White, Black and Asian men in England between 2008-2010. Black men had double the lifetime risk of being diagnosed and dying from prostate cancer when compared to White men in England. However, Black men also had the highest incidence of prostate cancer. When this was considered, all ethnic groups had the same chance of dying (33%) once diagnosed.	• England only • Combined data from the Public Health England Cancer Registries, the Office for National Statistics, the 1990-2010 England National Cancer Data Repository Analysis dataset, the Hospital Episodic Statistics dataset, and the census. • Only looked at broad diagnosis of prostate cancer

			(not by clinically significant vs. insignificant) • Limitations: there was a general lack of high-quality complete ethnicity data; could not consider mixed ethnic group; mortality data was from deaths between 2008-2010 meaning that these men could have been diagnosed prior to 2008 which means that the ratio of deaths to diagnoses should be interpreted with caution; did not consider stage at diagnosis (only lifetime risk).
31	Fry A, White B, Nagarwalla D, Shelton J, Jack RH. Relationship between ethnicity and stage at diagnosis in England: a national analysis of six cancer sites. BMJ Open. 2023;13(1):e062079. Published 2023 Jan 26. doi:10.1136/bmjopen-2022-062079	This study assessed the associations between ethnicity and stage at diagnosis across England for six cancer sites, including prostate cancer. After adjustment, results showed that Caribbean (OR 0.74 (95% CI 0.68 to 0.80)) and African (OR 0.79 (95% CI 0.71 to 0.88)) men with prostate cancer were less likely to be diagnosed at a late stage than White British men. The researchers suggested that this may be because evidence suggests that Black men are more likely to have a PSA test which can increase the proportion of early-stage diagnosis.	• N=199,818 people with prostate cancer • England only • Data from NHS Digital's National Cancer Registration and Analysis Service. • Only looked at broad diagnosis of prostate cancer (not by clinically significant vs. insignificant) • Limitations: Could not control for tumour subtype; used TNM staging as opposed to

			Gleason or CPG; data on education, country of birth, language, was unavailable which could have affected help-seeking;
32	Barber L, Gerke T, Markt SC, et al. Family History of Breast or Prostate Cancer and Prostate Cancer Risk. Clin Cancer Res. 2018;24(23):5910-5917. doi:10.1158/1078-0432.CCR-18-0370	This study explored the relationship between familial prostate or breast cancer and risk of total and lethal prostate cancer. Results showed: • Men with a family history of prostate or breast cancer were more likely to have had PSA testing in the prior two years before diagnosis than men with no family history. • Men who only had a family history of breast cancer had an 21% higher risk of any prostate cancer (95% CI 1.10–1.34) compared to those with no family history. • Men with a family history of prostate cancer had a 68% (95% CI 1.53–1.83) greater risk of developing any prostate cancer compared to men with no family history. • A history of both prostate and breast cancer was associated with a 61% (95% CI 1.30–1.98) increased prostate cancer risk compared to men with neither family history. • A positive family history of prostate cancer increased risk of lethal disease by 72% (95% CI 1.25–2.38). Of note, the observed differences between men with a family history and men without a family history was not explained by PSA screening patterns.	• U.S.-based study • 254,626 person-years • Cases who were diagnosed with or developed metastases during follow-up, or died from prostate cancer were considered 'lethal' cases. • Limitations: US-based so may not be generalisable to UK population; results only generalisable to White men as that was the majority of the study population;

Topic: Safety Netting			
Summary: There isn't a lot of evidence on safety netting in primary care for patients with suspected prostate cancer. Much of the evidence on repeated PSA tests is in the context of asymptomatic screening cohorts. One paper found that patients with a persistent raised PSA or abnormal DRE but who had a negative biopsy or mpMRI had a higher incidence of prostate cancer during follow-up than the general population, however the authors suggested that the increased diagnostic surveillance (including repeated PSA testing) increased rates of overdiagnosis.			
Paper number	**Study**	**Summary**	**Notes**
33	Exterkate L, Wegelin O, Barentsz JO, et al. Incidence of significant prostate cancer after negative MRI and systematic biopsy in the FUTURE trial. BJU Int. 2023;131(3):313-320. doi:10.1111/bju.15876	This study assessed the proportion of clinically significant prostate cancer cases diagnosed during follow-up of patients after negative systematic biopsy and negative mpMRI with persistent raised PSA or abnormal DRE. Follow-up consisted of a PSA test 6 months after a negative mpMRI, and then annual measurements after that. If the PSA value was raised above the baseline value at any point or if PSA density was 0.15, then mpMRI was completed again. Patients with mpMRI scans of PI-RADS 2 or greater underwent biopsy. 8.8% of patients were diagnosed with prostate cancer, of which 3% were clinically significant prostate cancer. Clinically significant prostate cancer was diagnosed after a median follow-up of 44 months compared to 27 months for clinically insignificant prostate cancer. Of note, the incidence of prostate cancer among this cohort was higher than the incidence of prostate cancer in the general Dutch population suggesting potentially higher risk among those with previous negative biopsy or mpMRI but persistent raised PSA/abnormal DRE. The authors compared the	• Based in the Netherlands • Sub-analysis of the FUTURE trial (a multicentre RCT comparing biopsy techniques in patients suspected of prostate cancer). • N=431 • Median follow-up was 41 months. • Considered clinically significant prostate cancer to be Gleason ≥3 + 4 or ISUP grade group ≥2 • Limitations: small sample size, inconsistent follow-up on some patients as they bounced from primary to secondary care; variation in technique for reading MRI

		standardised incidence ratios of clinically insignificant prostate cancer versus clinically significant prostate cancer in the study and noted that the increased diagnostic surveillance may have increased overdiagnosis of indolent cancer.	scans or completing biopsies; there was overall a low number of clinically significant cancers diagnosed reducing the power of the study; patients were originally referred to mpMRI/biopsy due to raised PSA or abnormal DRE but it is unclear if these tests were completed due to symptoms.

Emerging Topics

Risk prediction tools/scores

- There is lots of innovation and emerging research for risk prediction tools or risk scores to better identify a patient's risk for prostate cancer and determine whether further investigations are necessary. These risk prediction tools can incorporate a variety of factors including: Age, ethnicity, family history, PSA test results, DRE results, PSA volume, previous biopsy results, and Polygenic Risk Scores (PRS). Most studies evaluate these risk prediction tools for the purpose of stratifying patients according to risk prior to determining whether further investigation is necessary. This may be helpful considering that a less invasive and more accurate primary care test for prostate cancer does not currently exist. The goal of these tools would be to reduce the number of unnecessary investigations occurring in men with little risk of prostate cancer. Many of these tools are currently still in development, evaluation, and validation stages.

Upcoming research

- Dr. Sam Merriel, a UK researcher and GP, is currently conducting research on prostate cancer, symptom presentation, and PSA testing in a primary care context. His upcoming studies are described below. He will be presenting the results from these studies at

Ca-PRI 2024 in Melbourne and the 2024 SAPC ASM conferences in Bristol. We can liaison with Sam on how results may feed into the SRG review process – he is happy to be involved.

- **Presenting Complaints for Prostate Cancer in Primary Care: The PC3 study**[16] **–** This study will explore the early-stage symptoms of prostate cancer and whether outcomes differ among those who were symptomatic at diagnosis compared to those who were asymptomatic at diagnosis.
- **Primary care models for the detection of clinically significant prostate cancer: the ProsDetect study**[17] **–** This study will explore the diagnostic accuracy of the PSA test for detecting clinically significant prostate cancer, and if the accuracy can be improved using a multivariable model.

NG12 vs. SRG

NG12	**SRG**
Refer people using a **suspected cancer pathway referral** for prostate cancer if their prostate feels malignant on digital rectal examination. [2015] 1.6.2 Consider a prostate-specific antigen (PSA) test and digital rectal examination to assess for prostate cancer in people with: • any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention or • erectile dysfunction or • visible haematuria. [2015] 1.6.3 Consider referring people with possible symptoms of prostate cancer, as specified in recommendation 1.6.2, using a **suspected cancer pathway referral** for prostate cancer if their PSA levels are	Men presenting with **unexplained** possible symptoms and signs suggestive of prostate cancer such as changes to urinary patterns, erectile dysfunction, unexplained visible haematuria, lower back pain, bone pain or weight loss should have a digital rectal examination and a prostate specific antigen (PSA) test with counselling. A PSA test may be raised within three days of ejaculation or six weeks of a proven UTI, catheterisation or other invasive procedure, such as prostate biopsy. 5 alpha reductase inhibitors such as finasteride may reduce the PSA level. It should be noted that the majority of men with prostate cancer have no symptoms at all. An urgent suspected cancer referral if there is:

[16] NIHR. Presenting Complaints for Prostate Cancer in Primary Care: The PC3 study. Available from: https://www.spcr.nihr.ac.uk/research/projects/prostate-cancer-in-primary-care-the-pc2-studies

[17] NIHR. Primary care models for the detection of clinically significant prostate cancer: the ProsDetect study. Available from: https://fundingawards.nihr.ac.uk/award/NIHR202734

above the threshold for their age in table 1. Take into account the person's preferences and any comorbidities when making the decision. [2021]

Table 1
Age-specific PSA thresholds for people with possible symptoms of prostate cancer

Age (years)	Prostate-specific antigen threshold (micrograms/litre)
Below 40	Use clinical judgement
40 to 49	More than 2.5
50 to 59	More than 3.5
60 to 69	More than 4.5
70 to 79	More than 6.5
Above 79	Use clinical judgement

- Evidence from digital rectal examination of a hard, irregular prostate
- Elevated or rising age-specific PSA. Rough guide to normal PSA levels (ng/ml):
    - Less than 60 years < 3
    - Aged 60-69 years < 4
    - Aged 70-79 years < 5

These figures are a pragmatic aid based on clinical consensus. The principles of Realistic Medicine should be applied when considering referral and, in older men, routine or no referral may be appropriate for PSA levels of:

- Aged 80-85 years > 10
- Aged 86 years and over > 20

A routine referral if there is:

- Elevated age-specific PSA where urgent referral will not affect outcome due to age or comorbidity.