Prostate cancer (update)

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Advanced Accelerator Applications	Comments form	Question 2	General	**Would implementation of any of the draft recommendations have significant cost implications?** The expansion of PET-CT services in the UK is required to meet the current needs of health care professionals and physicians. Please see below for further background on the development of PET-CT services which AAA has proposed to the NHS to be included in the "Levelling Up" agenda. **[This text was identified as confidential and has been removed]**	Thank you for your comment. We didn't review the evidence on PET-CT for this update as it is outside the scope of this update, we only looked at risk stratification tools and also amended the treatment recommendations for consistency with the new stratification scheme. We will pass the additional research you highlight to our surveillance team for consideration of any future updates.
Advanced Accelerator Applications	NG131 Evidence Review	General	General	We agree with the committee that prostate cancer (PC) specific mortality is an important outcome in people newly diagnosed with localised or locally advanced PC, and we commend the committee on the recommended risk stratification for localised and locally advanced prostate cancer. We would like to take this opportunity to comment on the fact that although multiple studies have shown that more sensitive emerging PET-CT technologies, such as [^{68}Ga]GaPSMA PET-CT radiotracers, have a substantial impact on clinical management, [13, 15, 16, 20] and enable non-invasive PSMA assessment in clinical indications such as staging of intermediate-to-high risk patients,[21] only one study was considered, and ultimately excluded, in the evidence review.[25] We would suggest that this does not fully represent the significant and relevant body of work on [^{68}Ga]GaPSMA PET-CT in PC and the role that it may have in improving PC specific mortality outcomes.	Thank you for your comment in support of the recommendation on risk stratification We didn't review the evidence on PET-CT for this update as it is outside the scope of this update, we only looked at risk stratification tools and also amended the treatment recommendations for consistency with the new stratification scheme. However, we will pass on the details of the identified trials to the surveillance team to decide whether a future guideline update is needed in this area.

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				Beyond traditional staging techniques (e.g., Tumour, Node, Metastasis Classification system; Gleason score; numbered staging [Stage I-IV]; prostate-specific antigen [PSA] levels), the expression of prostate-specific membrane antigen (PSMA) has been identified as an indicator of PC disease stage. PSMA is a transmembrane folate hydrolase that is highly overexpressed in PC tissue but has limited expression in normal tissues. [1-5] High PSMA expression correlates with tumour grade, pathological stage, biochemical recurrence (BCR) and Gleason score. [1, 6] Furthermore, PSMA is an independent predictor of poor prognosis, [7, 8] with significantly shorter PSA progression-free survival and overall survival (OS), as well as a higher risk of disease recurrence reported in patients with high levels of PSMA expression. [8, 9] In routine clinical practice, current diagnostic methods are not reliable in diagnosing PC accurately. Digital rectal examination (DRE) is widely used but associated with low diagnostic sensitivity (<30%),[10] while conventional imaging modalities (e.g., bone scans and CT are prone to underestimating the presence and extent of disease.[11] Bone scans are capable of evaluating bone metastases only, and up to 41% of scanned patients return a false negative (sensitivity: 59%-90%; specificity: 75-85%).[11] Alternatively, CT can present challenges in distinguishing between small bone metastases and bone marrow; PC metastases are missed in around a third of patients (sensitivity: 56%; specificity: 74%),[12] while more than half of all patients with nodal metastases (0.5-2 cm) are not identified (diagnostic sensitivity as low as 40%),	

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				largely due to high prevalence of micro-metastases. A similarly low diagnostic sensitivity of 55%-65% has also been reported for MRI in the evaluation of lymph node metastases.[11] Limitations in the resolution of current diagnostic methods could have severe ramifications that include inappropriate disease staging (occurring in 32%-51% of patients with PC following conventional imaging),[13, 14] and missed metastases, with nodal metastases missed in 39% and distant metastases missed in 16% of patients with PC.[15] This leads to suboptimal selection of treatments.[11] Approximately half of all patients are estimated to receive an inappropriate treatment plan due to limitations in diagnostic accuracy,[13, 15, 16] and just under 1 in 10 patients (9%) eligible for curative treatment are assigned to palliative care only due to misdiagnosis.[14] More sensitive diagnostic methods are therefore needed to ensure the timely delivery of appropriate treatment and ensure optimal outcomes in patients with PC.[15] [^{68}Ga]GaPSMA is a particularly promising emerging PET-CT radiotracer that is associated with significantly higher PC detection rates than choline PET-CT in patients with recurrent PC and low PSA levels,[17, 18] due to an excellent contract-to-noise ratio, and high specificity to prostate tissue.[19] This can partly be explained by their differing mechanisms of action. [^{68}Ga]GaPSMA PET-CT radiotracers specifically reveal the location of PC tumours by binding PSMA which is highly overexpressed on the PC tumour cell surface.[18] Whereas choline-based radiotracers are precursors for the biosynthesis of cellular metabolism phospholipids, and therefore reveal the	

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				location of general membrane metabolism and turnover only (a process which is increased in many malignancies, including PC).[18] Multiple studies have shown that more sensitive emerging PET-CT technologies, such as [^{68}Ga]GaPSMA PET-CT radiotracers, have a substantial impact on clinical management.[13, 15, 16, 20] Due to the ability of [^{68}Ga]GaPSMA PET-CT imaging to detect PSMA expression, it would be ideally placed to establish a diagnostic pathway with the aim of improving PC specific mortality outcomes in people newly diagnosed with localised or locally advanced PC. The use of PSMA PET and ^{68}Ga-PSMA-11 has also been recognised in recent updates to clinical guidelines including the National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®). The NCCN is a not-for-profit alliance of 31 cancer centres, are comprised of recommendations for the prevention, diagnosis and management of malignancies across the continuum of care.[22] The Guidelines provide evidence-based, consensus-driven guidance for cancer management to ensure that all patients receive preventative, diagnostic, therapeutic, and supportive services that are most likely to lead to optimal outcomes.[23] In September 2021, the NCCN included prostate-specific membrane antigen (PSMA) PET imaging with ^{68}Ga-PSMA-11 and piflufolastat ^{18}F in their updated guidelines for prostate cancer.[24] The updated guidelines now include ^{68}Ga-PSMA-11 and piflufolastat ^{18}F PET-CT imaging to be considered as an alternative to standard imaging (i.e., chest CT,	

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				abdominal/pelvic CT, abdominal/pelvic MRI and/or mpMRI) of bone and soft tissue (full body) imaging. Additionally, due to the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (i.e., CT, MRI) at both initial staging and biochemical recurrence, the NCCN Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that it can serve as an equally effective, if not more effective front-line imaging tool for these patients.[24] The use of PSMA PET and ^{68}Ga-PSMA-11 has also been recognised in recent updates to clinical guidelines including the National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®). The NCCN is a not-for-profit alliance of 31 cancer centres, are comprised of recommendations for the prevention, diagnosis and management of malignancies across the continuum of care.[22] The Guidelines provide evidence-based, consensus-driven guidance for cancer management to ensure that all patients receive preventative, diagnostic, therapeutic, and supportive services that are most likely to lead to optimal outcomes.[23] In September 2021, the NCCN included prostate-specific membrane antigen (PSMA) PET imaging with ^{68}Ga-PSMA-11 and piflufolastat ^{18}F in their updated guidelines for prostate cancer.[24] The updated guidelines now include ^{68}Ga-PSMA-11 and piflufolastat ^{18}F PET-CT imaging to be considered as an alternative to standard imaging (i.e., chest CT, abdominal/pelvic CT, abdominal/pelvic MRI and/or	

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				mpMRI) of bone and soft tissue (full body) imaging. Additionally, due to the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (i.e., CT, MRI) at both initial staging and biochemical recurrence, the NCCN Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that it can serve as an equally effective, if not more effective front-line imaging tool for these patients.[24]	
Advanced Accelerator Applications	NG131 Guideline	019	012	We agree with the additional research recommendation on improving the diagnostic accuracy of staging investigations for CPG2 and 3 prostate cancer (PC). We would like to take this opportunity to highlight the relevant body of research on [^{68}Ga]GaPSMA positron emission tomography-computed tomography (PET-CT) to the committee. Beyond traditional staging techniques (e.g., Tumour, Node, Metastasis Classification system; Gleason score; numbered staging [Stage I-IV]; prostate-specific antigen [PSA] levels), the expression of prostate-specific membrane antigen (PSMA) has been identified as an indicator of PC disease stage. PSMA is a transmembrane folate hydrolase that is highly overexpressed in PC tissue but has limited expression in normal tissues. [1-5] High PSMA expression correlates with tumour grade, pathological stage, biochemical recurrence (BCR) and Gleason score. [1, 6] Furthermore, PSMA is an independent predictor of poor prognosis, [7, 8] with significantly shorter PSA progression-free survival and overall survival (OS), as well as a higher risk of	Thank you for your comment. We will pass the additional research you highlight to our surveillance team for consideration of any future updates.

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				disease recurrence reported in patients with high levels of PSMA expression. [8, 9] In routine clinical practice, current diagnostic methods are not reliable in diagnosing PC accurately. Digital rectal examination (DRE) is widely used but associated with low diagnostic sensitivity (<30%),[10] while conventional imaging modalities (e.g., bone scans and CT are prone to underestimating the presence and extent of disease.[11] Bone scans are capable of evaluating bone metastases only, and up to 41% of scanned patients return a false negative (sensitivity: 59%-90%; specificity: 75-85%).[11] Alternatively, CT can present challenges in distinguishing between small bone metastases and bone marrow; PC metastases are missed in around a third of patients (sensitivity: 56%; specificity: 74%),[12] while more than half of all patients with nodal metastases (0.5-2 cm) are not identified (diagnostic sensitivity as low as 40%), largely due to high prevalence of micro-metastases. A similarly low diagnostic sensitivity of 55%-65% has also been reported for magnetic resonance imaging (MRI) in the evaluation of lymph node metastases.[11] Limitations in the resolution of current diagnostic methods could have severe ramifications that include inappropriate disease staging (occurring in 32%-51% of patients with PC following conventional imaging),[13, 14] and missed metastases, with nodal metastases missed in 39% and distant metastases missed in 16% of patients with PC.[15] This leads to suboptimal selection of treatments.[11] Approximately half of all patients are estimated to receive an inappropriate treatment plan due to limitations in diagnostic accuracy,[13, 15, 16] and just under 1 in 10	

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				patients (9%) eligible for curative treatment are assigned to palliative care only due to misdiagnosis.[14] More sensitive diagnostic methods are therefore needed to ensure the timely delivery of appropriate treatment and ensure optimal outcomes in patients with PC.[15] [^{68}Ga]GaPSMA is a particularly promising emerging PET-CT radiotracer that is associated with significantly improved metastases detection rates than choline PET-CT in patients with recurrent PC and low PSA levels,[17, 18] due to an excellent contract-to-noise ratio, and high specificity to prostate tissue.[19] This can partly be explained by their differing mechanisms of action. [^{68}Ga]GaPSMA PET-CT radiotracers specifically reveal the location of PC tumours by binding PSMA which is highly overexpressed on the PC tumour cell surface.[18] Whereas choline-based radiotracers are precursors for the biosynthesis of cellular metabolism phospholipids, and therefore reveal the location of general membrane metabolism and turnover only (a process which is increased in many malignancies, including PC).[18] Multiple studies have shown that more sensitive emerging PET-CT technologies, such as [^{68}Ga]GaPSMA PET-CT radiotracers, have a substantial impact on clinical management.[13, 15, 16, 20] Due to the ability of [^{68}Ga]GaPSMA PET-CT imaging to detect PSMA expression, it would be ideally placed to establish a diagnostic pathway. Under the proposed 5-tier Cambridge Prognostic Group (CPG) risk stratification model, the previous "intermediate-risk" group now consists of some people in CPG1, and all people in CPG2 and CPG3. As [^{68}Ga]GaPSMA PET-CT enables non-	

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				invasive PSMA assessment in clinical indications such as staging of intermediate-to-high risk patients,[21] which encompass those with CPG2 and CPG3 PC, its establishment within a diagnostic pathway may therefore allow earlier detection of primary tumours and/or the extent of metastases, enabling greater staging accuracy which is aligned with the research recommendation of improving the diagnostic accuracy of staging investigations for CPG2 and 3 PC. The use of PSMA PET and ^{68}Ga-PSMA-11 has also been recognised in recent updates to clinical guidelines including the National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®). The NCCN is a not-for-profit alliance of 31 cancer centres, are comprised of recommendations for the prevention, diagnosis and management of malignancies across the continuum of care.[22] The Guidelines provide evidence-based, consensus-driven guidance for cancer management to ensure that all patients receive preventative, diagnostic, therapeutic, and supportive services that are most likely to lead to optimal outcomes.[23] In September 2021, the NCCN included prostate-specific membrane antigen (PSMA) PET imaging with ^{68}Ga-PSMA-11 and piflufolastat ^{18}F in their updated guidelines for prostate cancer.[24] The updated guidelines now include ^{68}Ga-PSMA-11 and piflufolastat ^{18}F PET-CT imaging to be considered as an alternative to standard imaging (i.e., chest CT, abdominal/pelvic CT, abdominal/pelvic MRI and/or mpMRI) of bone and soft tissue (full body) imaging. Additionally, due to the increased sensitivity and	

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				specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (i.e., CT, MRI) at both initial staging and biochemical recurrence, the NCCN Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that it can serve as an equally effective, if not more effective front-line imaging tool for these patients.[24]	
Association of Chartered Physiotherapists in Oncology and Palliative Care (ACPOPC)	NG131 Guideline	019	General	Active Surveillance Recommendations for Research • Request recommendation to research lifestyle characteristics influencing length of time men remaining on AS window rather than progress to radical treatments. Question – does healthy lifestyle influence this? • There is evidence that management of pelvic floor function is beneficial following radial prostatectomies. Can this be added/included or added as a recommendation for research? • Can there be expansion/inclusion of self-management strategies including signposting of where to seek advice if required?	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to incorporate the new tiers. In order to draft a research recommendation, we need to have reviewed evidence in that area and identified a gap that the committee feels is a priority.
Bayer HealthCare	NG12 Guideline	General	General	Bayer is concerned that the age-adjusted PSA thresholds specified in the update could negatively impact patient care overall compared to a fixed PSA threshold (of 3 nanograms/mL for example). This	Thank you for your comment. We agree that not including the cost of false negatives is a limitation, however we do not have the information to calculate these costs as it is unknown at what point a patient who received a false negative would be correctly diagnosed, and what the effect of a delayed

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				concern has also been previously raised[1] by the clinical community. Furthermore, there is evidence[2] showing that age-adjusted PSA thresholds, while saving some healthcare resources by being more discriminatory and referring fewer people to unnecessary biopsy, also result in too many high-risk cancers being missed: a threshold of PSA = 3 ng/ml for all ages identified more high-risk prostate cancers, recommending biopsy in 9.8% of men, of which 10.3% (n = 823) had high-risk prostate cancer; whereas, using age-specific thresholds, 2.3% men were recommended for biopsy, of which 15.2% (n = 290) had high-risk prostate cancer; that is a drop of **65%** in the number of people with high-risk prostate cancer identified. Although the impact of false positives was costed and considered by the committee in the guideline update, the impact of false negatives was not given full consideration. There are likely to be more false negatives with the age-specific thresholds as if a patient is older then there is a higher threshold for referral, therefore a person with prostate cancer would require a higher PSA value to be referred and the cancer discovered. From an economic perspective this is important because people with prostate cancer that is discovered later could have disease progression and require higher levels of care which would incur higher	diagnosis would have on disease progression and treatment. This was noted as a limitation during discussion and the committee were aware of this when making their recommendations. Thank you also for highlighting the Gilbert R 2018 study on age specific PSA which did meet our inclusion criteria. The committee have considered this evidence but do not think the positive predictive value for a UK symptomatic population (as estimated using the Qcancer model) with either age adjusted threshold analysed by the authors warranted a change the committee's recommended thresholds. Note that the paper did present evidence on a fixed test threshold of 3 ng/ml, but this was based on the assumption that those with a PSA <3ng/ml did not have prostate cancer. This population did not have a biopsy or multiparametric MRI. This did not match the reference standard for our review for having prostate cancer, so we reanalysed the data, removing the participants who did not have a biopsy or multiparametric MRI from the analysis. This meant that data was no longer available for a fixed test threshold of 3ng/ml.

[1] https://www.nice.org.uk/guidance/ng12/resources/2021-exceptional-surveillance-of-suspected-cancer-recognition-and-referral-nice-guideline-ng12-9070300909/chapter/Surveillance-decision?tab=evidence

[2] Gilbert, Rebecca, et al. "Developing new age-specific prostate-specific antigen thresholds for testing for prostate cancer." *Cancer Causes & Control* 29.3 (2018): 383-388.

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				costs as well as negative consequences for the disease outcomes and quality of life of patients. Bayer urges the committee to take further considerations around this proposed update and its implications for patients' care. The committee should consider the evidence in its totality and should not aim to make specific recommendations on PSA thresholds without a comprehensive assessment of the cost-effectiveness of these recommendations. Such an assessment should be aiming to quantify the healthcare resource utilisation, disease outcomes and quality of life implications linked to false negatives and put them into balance against the resource implications linked to false positives. This is the only way to ensure cost-effective use of NHS resources and that patients receive the best quality of care possible.	
Bayer HealthCare	NG131 Guideline	General	General	Bayer welcomes the use of the CPG 5-tier risk stratification model instead of the old 3-tier model. This approach should allow better judgement of patient risk levels while decreasing the potential of over or under treatment. However, with a patient centred approach to care in mind, it is important the patient is informed about the treatment choices available (including the alternative options available when the first option recommended is not acceptable to the patient)	Thank you for your comment. We agree with a patient centred approach, and this is why we recommend in 1.3.7 that box 2 should be used to discuss the benefits and harms with patients. We have now also added a reference to the NICE shared decision making guideline which should be referred to.
Beckman Coulter (UK) Ltd	NG12 Guideline	004	017	We suggest that the committee consider not only PSA but other serum tests such as the FDA approved and CE marked Prostate Health Index (PHI) for men with PSA between 2 – 10 ng/mL in addition to age specific PSA threshold for referral as recommended by the recent	Thank you for your comment. The scope for this update was limited to considering the threshold for PSA testing that should prompt referral to secondary care (see https://www.nice.org.uk/guidance/gid-ng10194/documents/final-scope for details), so we

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				European Urology Association guidelines (https://uroweb.org/guideline/prostate-cancer/#5_1) in order to avoid unnecessary negative biopsies (see §5.2.3.1 and §5.2.3.4) and multiparametric MRI as demonstrated in published evidence in the UK (Kim et al. BMC Medicine (2020) 18:95 https://doi.org/10.1186/s12916-020-01548-3).	did not consider other serum tests as part of this update. However, we have passed your comment to the surveillance team at NICE for consideration to inform future updates of the guideline.
Beckman Coulter (UK) Ltd	NG12 Guideline	005	006	We suggest that recommendations should be made for additional research on new and innovative biomarkers such as the FDA approved and CE marked Prostate Health Index (PHI) which as demonstrated superior performance over PSA testing to improve sensitivity and specificity for prostate cancer detection, reduction of unnecessary negative prostate biopsies and cost effectiveness in UK clinical settings (Kim et al. BMC Medicine (2020) 18:95 https://doi.org/10.1186/s12916-020-01548-3).	Thank you for your comment. The scope for this update was limited to considering the threshold for PSA testing that should prompt referral to secondary care (see https://www.nice.org.uk/guidance/gid-ng10194/documents/final-scope for details), so we did not consider other biomarkers or the prostate health index as part of this update. However, we have passed your comment to the surveillance team at NICE for consideration to inform future updates of the guideline.
Beckman Coulter (UK) Ltd	NG12 Guideline	007	002	The FDA approved and CE marked Prostate Health Index (PHI) has demonstrated in the context of UK clinical practice to be an effective way to reduce mpMRI and biopsies without compromising detection of significant prostate cancers and therefore constitute a cost-effective approach to improve early detection of prostate cancer (Kim et al. BMC Medicine (2020) 18:95 https://doi.org/10.1186/s12916-020-01548-3).	Thank you for your comment. The scope for this update was limited to considering the threshold for PSA testing that should prompt referral to secondary care (see https://www.nice.org.uk/guidance/gid-ng10194/documents/final-scope for details), so we did not consider other the prostate health index as part of this update. However, we have passed your comment to the surveillance team at NICE for consideration to inform future updates of the guideline.
British Association of Urological	NG12 Guideline	001	001	Title My only comment regards the title which relates to localised and locally advance cancer ie. non metastatic	Thank you for your comment. We think that this comment refers to the update of the NICE prostate cancer guideline (NG 131) rather than the NICE guideline on suspected cancer (NG 12). The

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Surgeons (BAUS)				and I wonder if this should be made clear in the title eg 'Prostate cancer: localised and locally advanced' Presumably there will be a guideline which will address metastatic cancer and this would have an appropriate title It's a very good and clear document	aspects of the NICE guideline on prostate cancer that were updated only related to localised and locally advanced prostate cancer, and only the aspects that were updated were included in the consultation document for clarity and ease of commenting. However, there are other aspects of the guideline that relate to metastatic prostate cancer and the updated recommendations have now been incorporated into this guideline for final publication. For details, see https://www.nice.org.uk/guidance/ng131.
British Association of Urological Surgeons (BAUS)	NG12 Guideline	004	014	Consider referring people with possible symptoms of prostate cancer, as specified in recommendation 1.6.2 The symptoms listed are not in general related to prostate cancer and should not be used to alert men to a possible risk of prostate cancer. The majority of men with clinically significant prostate cancer do not have any symptoms relating to their cancer, and the majority of men with LUTs do not have clinically significant prostate cancer. The studies below have actually shown tha the relationship is inverse- i.e. the absence of symptoms is associated with prostate cancer. Encouraging GPs to only test men with these symptoms may actually deny men more at risk from being tested. Frånlund M, Carlsson S, Stranne J, Aus G, Hugosson J. The absence of voiding symptoms in men with a prostate-specific antigen (PSA) concentration of≥ 3.0 ng/mL is an independent risk factor for prostate cancer: results from the Gothenburg Randomized Screening Trial. BJU international. 2012 Sep;110(5):638-43.	Thank you for your comment. The scope of this update was to consider PSA referral thresholds for people presenting in primary care with symptoms and therefore we were unable to look at an asymptomatic population. The population in the Franlund, M study highlighted does not match our population, as this was limited to men with PSA ≥ 3.0 ng/mL (and the population of NG12 is not limited by PSA level) and therefore disagree that for this population, an absence of symptoms is associated with prostate cancer. In relation to the Collin SM study, the authors conclude that 'A history of LUTS before PSA testing marginally improves the prediction of an individual's risk for prostate cancer'.

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				Collin SM, Metcalfe C, Donovan J, Lane JA, Davis M, Neal D, Hamdy F, Martin RM. Associations of lower urinary tract symptoms with prostate-specific antigen levels, and screen-detected localized and advanced prostate cancer: a case-control study nested within the UK population-based ProtecT (Prostate testing for cancer and Treatment) study. BJU international. 2008 Nov;102(10):1400-6.	
British Association of Urological Surgeons (BAUS)	NG12 Guideline	005	002 - 005	Do not routinely offer isotope bone scans to people with Cambridge Prognostic Group (CPG) 1 localised prostate cancer. It would be reasonable to avoid Bone Scans in CPG 2 disease as well. I have seen the explanatory notes and appreciate this is an evidence free area and therefore am comfortable with it.	Thank you for your comment. On discussion with the committee, we have decided to extend this recommendation to include CPG2 and remove CPG2 from the research recommendation. Although we didn't systematically review evidence in this area, the committee were aware of evidence that supported this decision, and they were also confident this accurately reflected current practice.
British Association of Urological Surgeons (BAUS)	NG12 Guideline	005	002 - 005	Do not routinely offer isotope bone scans to people with Cambridge Prognostic Group (CPG) 1 localised prostate cancer. The following study made use of the CPG system, before it had been termed 'CPG'. It found that the chance of bone scan being positive for men with CPG<3 was exceedingly low. Based on this, I think it would be better to recommend that bone scan is not undertaken for men with CPG 1-2. Thurtle, D., Hsu, R., Chetan, M. et al. Incorporating multiparametric MRI staging and the new histological Grade Group system improves risk-stratified detection of bone metastasis in prostate	Thank you for your comment. On discussion with the committee, we have decided to extend this recommendation to include CPG2 and remove CPG2 from the research recommendation. Although we didn't systematically review evidence in this area, the committee were aware of evidence that supported this decision, and they were also confident this accurately reflected current practice.

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British Association of Urological Surgeons (BAUS)	NG12 Guideline	006	006 - 008	For people with CPG 2 localised prostate cancer, offer a choice between active surveillance, radical prostatectomy or radical radiotherapy if radical treatment is suitable. It may be important to specify GG2 patients who are suitable for AS. Suitable cohort include patients with <10% GG2, absence of Cribriform and Intraductal patterns	Thank you for your comment. We did not review evidence on individual risk factors for better or worse prognosis within the CP2 category and so have not made a recommendation on this. We have passed your comment to the NICE surveillance team for consideration to inform future updates of the guideline. We acknowledge that decisions on treatment for individuals needs to be made based on a number of factors in discussion between the clinician and patient.
British Association of Urological Surgeons (BAUS)	NG12 Guideline	009	009 - 012	It may be important to specify GG2 patients who are suitable for AS. Suitable cohort include patients with <10% GG2, absence of Cribriform and Intraductal patterns. I am slightly anxious with this statement. The evidence for this is weak. Suggested line: Consider active surveillance (in line with recommendation 1.3.9) for people who choose not to have immediate radical treatment explaining higher potential for progression/metastasis in the surveillance period	Thank you for your comment. We did not review evidence on individual risk factors for better or worse prognosis within the CP2 category and so have not made a recommendation on this. , We have passed your comment to the NICE surveillance team for consideration to inform future updates of the guideline. We acknowledge that decisions on treatment for individuals needs to be made based on a number of factors in discussion between the clinician and patient.
British Association of Urological Surgeons (BAUS)	NG12 Guideline	012	001 - 003	Offer radical prostatectomy or radical radiotherapy to people with CPG 4 and 5 localised and locally advanced prostate cancer when it is likely the person's cancer can be controlled in the long term. CG-5 includes T4 disease. I don't think group should be offered RP as SOC	Thank you for your comment. While the committee agreed that those with T4 disease would rarely be offered radical prostatectomy, they felt this could still be appropriate for a minority, and so it was important not to exclude this option. The committee highlighted that CPG5 includes a spectrum of disease severity

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					and any decisions for or against treatment should be discussed carefully with the patient and informed by clinical judgement.
British Association of Urological Surgeons (BAUS)	NG12 Guideline	012	009 - 012	Commissioners should base robotic systems for the surgical treatment of localised prostate cancer in centres that are expected to perform at least 150 robot-assisted laparoscopic radical prostatectomies per year to ensure they are cost effective. This data was based on a relatively old HTA SR. Is this statement still valid, considering the wider applicability and indications for the Robotic technique? Suggested recommendation: Commissioners should base robotic systems for the surgical treatment of localised prostate cancer in centres that are expected to perform at least 150 robot-assisted laparoscopic procedures per year to ensure they are cost effective	Thank you for your comment. The recommendation you are referring to is out of scope for this partial update regarding risk stratification and therefore no new evidence was reviewed in this area. We have passed your comment to the NICE surveillance team for consideration to inform future updates of the guideline.
British Association of Urological Surgeons (BAUS)	NG12 Guideline	013	005 - 008	Offer people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone. There is the option of SABR without the need for ADT in CPG2,3 (PACE Trial)	Thank you for your comment. We didn't review the evidence on this, we only amended the recommendation for consistency with the new stratification scheme. However, we will pass on the details of the identified trial to the surveillance team to decide whether a further update is needed in this area.
British Association of Urological Surgeons (BAUS)	NG12 Guideline	General	General	I have one comment about the NICE guidlines NG12 with the age adjusted PSA levels. I am aware that the prostate cancer risk management programme is being re-written, currently it has a threshold of 3ng/ml which doesn't fit with the NICE guidance PSA levels. Do you have any idea of what threshold the new PCRMP is going to use, and if it is not going to be the same as	Thank you for your comment. We agree that the prostate cancer risk management group (external to NICE) recommended referral for people with a PSA > 3 micrograms/litre, however this recommendation was made for people who received a PSA test

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				NICE it is very confusing for primary care that the two are different.	without symptoms of prostate cancer as part of the prostate cancer risk management programme. We do acknowledge that having different guidance for people with and without symptoms could be confusing for GPs. NICE is currently liaising with the Prostate cancer risk management programme (PCRMP) to try to ensure that the guidance from the 2 organisations (for people with, and without, the symptoms listed in NG12 rec 1.6.2 respectively) is coherent., and to make it clear to stakeholders which populations are covered by which sets of guidance. Also note that the PCRMP guidance is currently under review
British Association of Urological Surgeons (BAUS)	NG12 Guideline	General	General	Back to Olmsted County then. The wheel of life.. No doubt there will be a backlash from PCUK etc. but it's a pragmatic move.	Thank you for your comment.
Cambridge University Hospitals NHS Foundation Trust	NG12 Evidence Review	005	General	Suspected cancer: recognition and referral [B] Evidence reviews for diagnostic accuracy of prostate specific antigen (PSA) thresholds for referring people with suspected prostate cancer It is odd as to why there is a distinction between symptomatic and asymptomatic for PSA levels? There is no such distinction in clinical practice? These listed on this page are also not symptoms for prostate cancer on page 5? Though may co-exist.	Thank you for your comment. We do not think that the presence or absence of symptoms is unrelated to whether a person has prostate cancer. The review that was done as part of the 2015 update of the NICE guideline on suspected cancer found having any lower urinary tract symptom, erectile dysfunction or visible haematuria increased the risk of prostate cancer and recommended that a PSA test should be considered for people with these symptoms. This evidence was not reviewed as part of this update, but it is also consistent with the QCancer risk prediction model, which calculates a person's risk an

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					as yet undiagnosed cancer based on symptoms and other factors. The symptoms identified by the review in the suspected cancer guideline also significantly increase the risk of prostate cancer in the QCancer model, which is based on UK general practice data. This data set has been used to estimate the prevalence of prostate cancer in people with symptoms that might suggest prostate cancer to calculate positive predictive values in this update. We therefore think it is appropriate to prioritise evidence from people with symptoms of prostate cancer for this review
Cambridge University Hospitals NHS Foundation Trust	NG12 Evidence Review	009 - 011	General	NG12-Suspected cancer: recognition and referral [B] Evidence reviews for diagnostic accuracy of prostate specific antigen (PSA) thresholds for referring people with suspected prostate cancer All these papers cited are quite old and pre- MRI. None include cancers diagnosed through MRI pathways in the modern era 1. We have a paper which has <u>just this month</u> been accepted for publication in the Journal of Clinical Urology (In press) which addresses this gap in the knowledge and was done in the UK – the paper can be found here as open access in the meanwhile or by email to vjg29@cam.ac.uk : https://www.repository.cam.ac.uk/handle/1810/330267 *Re-evaluating the diagnostic efficacy of PSA as a referral test to detect clinically significant prostate cancer*	Thank you for your comment. This paper has become available after the search dates for the review and so was not considered as part of the evidence review. However, we have now obtained the paper and considered whether it would impact on the recommendations that have been made. This paper would not have met the inclusion criteria for our review because data presented provides sensitivity and specificity, but no confidence intervals or other means of extracting the numbers of true positives, false positives, true negatives and false negatives that would be needed for us to incorporate the data into our review. The second paper you highlight appears to be a review of the same study and also does not present sensitivity and specificity data with confidence intervals in order to calculate

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				in contemporary MRI based image-guided biopsy pathways- Artitaya Lophatananon, Alexander Light, Nicholas Burns-Cox, Angus MacCormick, Joseph John, Vanessa Otti, John McGrath, Pete Archer, Jonathan Anning, Stuart McCracken, Toby Page, Ken Muir1 and Vincent J Gnanapragasam. **Journal of Clinical Urology 2021(In press)** This paper looked at the validity of current PSA cut-offs and age referenced thresholds in men investigated through an MRI based pathway in the UK in 3 geographically distinct centres (2767 men in primary cohort + 554 men in a validation cohort). These represented a real-life cohort of men presenting for investigations in prostate diagnostic centre. The key endpoint was detection of clinically significant prostate cancer. This paper specifically looked at PPV of PSA and utility of age referenced PSA when using MRI based targeting and biopsies. 2 This short review on the current impact of different PSA thresholds across the UK and its impact on diagnostics may also be of help: Light A, Burns-Cox N, MacCormick A, John J, McGrath J, Gnanapragasam VJ. *The diagnostic impact of UK regional variations in age-specific prostate-specific antigen guidelines*. BJU Int. 2021 Sep;128(3):298-300. doi: 10.1111/bju.15484. This latter paper was not in your list of excluded papers	true positives, false positives, true negatives, and false negatives. Additionally, both papers specifically consider people who had an MRI as part of investigations for prostate cancer, and only those with a positive MRI or ongoing clinical suspicion of prostate cancer were included in the analysis. As our review question was about referral criteria from primary care, we think this population is indirectly relevant to our review.

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Cambridge University Hospitals NHS Foundation Trust	NG12 Evidence Review	021	044 - 044	NG12-Suspected cancer: recognition and referral [B] Evidence reviews for diagnostic accuracy of prostate specific antigen (PSA) thresholds for referring people with suspected prostate cancer The paper mentioned above in point 2 addresses the concern from the committee that all the reviewed information was so far based without use of MRI. This has now been looked at as mentioned (*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*- Artitaya Lophatananon, Alexander Light, Nicholas Burns-Cox, Angus MacCormick, Joseph John, Vanessa Otti, John McGrath, Pete Archer, Jonathan Anning, Stuart McCracken, Toby Page, Ken Muir1 and Vincent J Gnanapragasam. **Journal of Clinical Urology 2021**) https://www.repository.cam.ac.uk/handle/1810/330267	Thank you for your comment. This paper has become available after the search dates for the review and so was not considered as part of the evidence review. However, we have now obtained the paper and considered whether it would impact on the recommendations that have been made. This paper would not have met the inclusion criteria for our review because it specifically considered people who had an MRI as part of investigations for prostate cancer, and only those with a positive MRI or ongoing clinical suspicion of prostate cancer were included in the analysis. Our review question was about referral criteria from primary care and so we do not think that the population matches our review. Additionally, the data presented provides sensitivity and specificity, but no confidence intervals or other means of extracting the numbers of true positives, false positives, true negatives and true positives that would be needed for us to incorporate the data into our review.
Cambridge University Hospitals NHS Foundation Trust	NG12 Evidence Review	022	042	NG12-Suspected cancer: recognition and referral [B] Evidence reviews for diagnostic accuracy of prostate specific antigen (PSA) thresholds for referring people with suspected prostate cancer Agree there is variation not only in age ranges but also thresholds and this impacts detection - a single national age reference should be used (if this is to be retained) - see : Light A, Burns-Cox N, MacCormick A, John J,	Thank you for your comment. We acknowledge that many different referral criteria were used across the UK. Because of this, the committee recommended 1 set of criteria to reduce this variation. This paper would not have met the inclusion criteria for our review. The data presented does not provide sensitivity and specificity with confidence intervals or other means of extracting the numbers of true

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				McGrath J, Gnanapragasam VJ. The diagnostic impact of UK regional variations in age-specific prostate-specific antigen guidelines. BJU Int. 2021 Sep;128(3):298-300. doi: 10.1111/bju.15484.	positives, false positives, true negatives, and false negatives that would be needed for us to incorporate the data into our review.
Cambridge University Hospitals NHS Foundation Trust	NG12 Guideline	004	014 - 019	The symptoms listed are not in general related to prostate cancer and should not be used to alert men to a possible risk of prostate cancer. The majority of men with clinically significant prostate cancer do not have any symptoms relating to their cancer, and the majority of men with LUTs do not have clinically significant prostate cancer. The studies below have actually shown that the relationship is inverse- i.e. the absence of symptoms is associated with prostate cancer. Encouraging GPs to only test men with these symptoms may actually deny men more at risk from being tested. Frånlund M, Carlsson S, Stranne J, Aus G, Hugosson J. The absence of voiding symptoms in men with a prostate-specific antigen (PSA) concentration of≥ 3.0 ng/mL is an independent risk factor for prostate cancer: results from the Gothenburg Randomized Screening Trial. BJU international. 2012 Sep;110(5):638-43. Collin SM, Metcalfe C, Donovan J, Lane JA, Davis M, Neal D, Hamdy F, Martin RM. Associations of lower urinary tract symptoms with prostate-specific antigen levels, and screen-detected localized and advanced prostate cancer: a case-control study nested within the UK population-based ProtecT (Prostate testing for	Thank you for your comment. The scope of this update was to consider PSA referral thresholds for people presenting in primary care with symptoms and therefore we were unable to look at an asymptomatic population. The population in the Franlund, M study highlighted does not match our population, as this was limited to men with PSA ≥ 3.0 ng/mL (and the population of NG12 is not limited by PSA level) and therefore disagree that for this population, an absence of symptoms is associated with prostate cancer. In relation to the Collin SM study, the authors conclude that 'A history of LUTS before PSA testing marginally improves the prediction of an individual's risk for prostate cancer'.

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				cancer and Treatment) study. BJU international. 2008 Nov;102(10):1400-6.	
Cambridge University Hospitals NHS Foundation Trust	NG12 Guideline	004	014 - 019	Family history and black ethnicity are established risk factors for the development of prostate cancer. These should receive some mention in the guidance on who GPs should discuss PSA testing with, rather than men with symptoms unrelated to prostate cancer (such as those referred to in this section of the guidance)	Thank you for your comment. The committee did not find evidence on whether the presence or absence of a family history of prostate cancer or ethnicity should influence the PSA threshold at which referral to secondary care should be considered, but made a research recommendation for research into the diagnostic accuracy of PSA testing that was stratified by ethnicity and family history of prostate or breast cancer.
Cambridge University Hospitals NHS Foundation Trust	NG12 Guideline	005	001	The age specific PSA thresholds are at odds with those recommended by Public Health England and the Prostate Cancer Risk Management Program, which use a threshold of 3.0 for men aged 50-69. This risks creating confusion for GPs. Use of the lower threshold in primary care, along with further discriminators such as MRI in secondary care, are likely together to reduce false negative and false positives.	We agree, the prostate cancer risk management group (external to NICE) recommended referral for people with a PSA > 3 micrograms/litre, however this recommendation was made for people who received a PSA test without symptoms of prostate cancer as part of the prostate cancer risk management programme. This recommendation is also currently under review and NICE is working with the prostate cancer risk management programme to make sure that the guidance from the 2 organisations is coherent.
Cambridge University Hospitals NHS Foundation Trust	NG131 Guideline	005	001 - 005	The following study made use of the CPG system, before it had been termed 'CPG'. It found that the chance of bone scan being positive for men with CPG<3 was exceedingly low. Based on this, I think it would be better to recommend that bone scan is not undertaken for men with CPG 1-2.	Thank you for your comment. On discussion with the committee, this recommendation has been extended to include CPG2. CPG2 has been removed from the research recommendation. Although we didn't systematically review evidence in this area, the committee were aware of evidence that supported

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				Thurtle, D., Hsu, R., Chetan, M. et al. Incorporating multiparametric MRI staging and the new histological Grade Group system improves risk-stratified detection of bone metastasis in prostate cancer. Br J Cancer 115, 1285–1288 (2016). https://doi.org/10.1038/bjc.2016.353	this decision, and they were also confident this accurately reflected current practice
Cambridge University Hospitals NHS Foundation Trust	NG131 Guideline	General	General	I use CPG in all my decision making discussions. I find it really helpful and give patient a better understanding and put things in to perspective for them. The decision making discussion used to be 40—45minutes in majority of cases in the past but now 20minutes. There will be always some patients who take longer regardless. I haven't had any treatment regression discussion recently. I have noticed the psychological and emotional reaction to the cancer diagnosis especially with low and intermediate risk is reduced when I use CPG figures. I Think that is important so that patients can make a decision that is right for them. Prostate Cancer CNS.	Thank you for your comment in support of the recommendation on risk stratification.
Cambridge University Hospitals NHS Foundation Trust	NG131 Guideline	General	General	In my experience, CPG provides reassurance and confidence to patients and clinicians in proceeding with active surveillance for men with CPG1, and some men with CPG2.	Thank you for your comment in support of the recommendation on risk stratification.
Cambridge University Hospitals NHS Foundation Trust	NG131 Guideline	General	General	The CPG system also helps to provide improved prognostication for men with prostate cancer of any CPG group. This is particularly important for men with CPG 2-5, who can now be split into 4 groups, rather than 2 using the previous risk system. The new guideline is an improvement.	Thank you for your comment in support of the recommendation on risk stratification.

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Cancer Research UK	NG12 Evidence review	General	General	There is evidence to suggest regional variation in the use of age-specific thresholds for PSA testing and that this causes variation in referral rates and missed diagnoses[1] and acknowledge that PSA levels rise with age. However, we agree that the evidence is not strong to inform PSA age-specific thresholds. Therefore overall, we support the setting of a national 'consider' recommendation. 1. Light, A., Burns-Cox, N., Maccormick, A., John, J., McGrath, J. and Gnanapragasam, V.J. (2021), *The diagnostic impact of UK regional variations in age-specific prostate-specific antigen guidelines*. BJU Int, 128: 298-300.	Thank you for your comment
Cancer Research UK	NG12 Guideline	004	017 - 019	We think it is positive that this recommendation allows leeway to using clinical judgement when deciding whether a referral is needed or not in a person has a raised PSA level. Could the 'clinical judgement' be clarified, and more considerations added (as well as preferences and comorbidities), such as risk factors (ethnicity, family history).	Thank you for your comment. The committee did not find evidence on whether the presence or absence of a family history of prostate cancer or ethnicity should influence the PSA threshold at which referral to secondary care should be considered, but made a research recommendation for research into the diagnostic accuracy of PSA testing that was stratified by ethnicity and family history of prostate or breast cancer.
Cancer Research UK	NG12 Guideline	005	001	The new guidance covers people aged 40-79, have you considered providing direction for the younger and older people? Could incorporate some messaging for management of these groups <40 and ≥80, particularly flagging use of clinical judgement.	Thank you for your comment. As the committee were unable to find evidence for PSA thresholds in ages >79 and <40, they felt unable to recommend a specific threshold. They did recognise however that this does and should not exclude people from referral in these age groups, and therefore agreed to

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					add to the table that 'clinical judgement' should be used when considering referring people >79 or <40.
Cancer Research UK	NG12 Guideline	005	001	Could it be specified that the threshold is either e.g. for aged 40-49, >2.5, or ≥2.5?	Thank you for your comment. We have amended these to add the greater than > symbol, as the studies these were taken from indicate these thresholds as the top of the normal reference range for these age groups.
Cancer Research UK	NG12 Guideline	005	006	Given the known limitations of the PSA test, an additional research recommendation could be around discovering new primary care tests to investigate possible prostate cancer symptoms, particularly ones which can distinguish clinically significant cancers and reduce the likelihood of overdiagnosis. For example, PSA density and the Stockholm3 blood test which have been shown to perform superior to PSA in patients with lower urinary tract symptoms[1]. 1. Nordström, T., Engel, J. C., Bergman, M., Egevad, L., Aly, M., Eklund, M., Palsdottir, T. and Grönberg, H. (2021) *Identifying Prostate Cancer Among Men with Lower Urinary Tract Symptoms*. European Urology Open Science, 24, pp. 11-16.	Thank you for your comment. The scope for this update was limited to considering the threshold for PSA testing that should prompt referral to secondary care (see https://www.nice.org.uk/guidance/gid-ng10194/documents/final-scope for details), so we did not review evidence of biomarkers or the prostate health index as part of this update. Our process for research recommendations is that a gap in the evidence should be identified first before drafting a research recommendation in order to generate new evidence in a specific area. However, we have passed your comment to the surveillance team at NICE for consideration to inform future updates of the guideline.
Cancer Research UK	NG12 Guideline	General	General	Ongoing research could inform a future update to this guideline: • The IMPACT trial – a large-scale international trial to evaluate annual PSA screening in men with germline BRCA1/2 mutations using PSA. Interim	Thank you for your comment. We have passed your comment to the surveillance team at NICE to consider this evidence. However, please note that screening is outside of the remit for NICE and is instead considered by the National Screening Committee..

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				results suggest the research group are including people with symptoms in the trial[1]. 1. Page, E.C, etal. (2019) *Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers*. Eur Urol, 76(6), pp. 831-842.	
London cancer alliance - South East London	NG131 Guideline	021	General	1.3.26 In this setting docetaxel in addition to ADT improves failure-free survival, and this translates into higher QALYs and lower costs compared to standard of care only (Addition of Docetaxel to First-line Long-term Hormone Therapy in Prostate Cancer (STAMPEDE): Modelling to Estimate Long-term Survival, Quality-adjusted Survival, and Cost-effectiveness; Eur Urol Oncol. 2018 Dec;1(6):449-458)	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated in future.
London cancer alliance - South East London	NG131 Guideline	021	General	1.3.26 According to a recent update (2495 - Docetaxel for hormone-naïve prostate cancer (PCa): results from long-term follow-up of non-metastatic (M0) patients in the STAMPEDE randomised trial (NCT00268476); Annals of Oncology (2019) 30 (suppl_5): v325-v355. 10.1093/annonc/mdz248) this does not translate into an improvement in PFS or OS; in addition, in patients who receive radiotherapy, docetaxel seems to eliminate the additional benefit from radiotherapy	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated in future.
London cancer alliance -	NG131 Guideline	021	General	1.3.26 In the same group of patients with high-risk non-metastatic prostate cancer, abiraterone/prednisolone alongside 3 years of ADT improves metastasis-free	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to

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South East London				survival (MFS) and OS and should be a new standard of care (LBA4_PR - Abiraterone acetate plus prednisolone (AAP) with or without enzalutamide (ENZ) added to androgen deprivation therapy (ADT) compared to ADT alone for men with high-risk non-metastatic (M0) prostate cancer (PCa): Combined analysis from two comparisons in the STAMPEDE platform protocol. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741)	incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated in future.
London cancer alliance - South East London	NG131 Guideline	General	General	The recommendation for docetaxel in high risk M0 prostate cancer is based on data published in 2016 which has now been superseded.	Thank you for your comment. Evidence was not reviewed in this area as part of this update. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated.
London cancer alliance - South East London	NG131 Guideline	General	General	39% were node positive in the AAP analysis. However, only 70% of node positive patients received radiotherapy (not clear if was to the prostate alone or prostate plus nodes as nodal radiotherapy). It implies that quite a large proportion of patients did not receive radiotherapy and even if they did not sure if they received nodal radiotherapy as it was not mandated.	Thank you for your comment. Evidence was not reviewed in this area as part of this update. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated.
London cancer alliance - South East London	NG131 Guideline	General	General	Drawing comparisons with the node positive patients from the docetaxel arm we know that if we offered radiotherapy to prostate and pelvic nodes in the N1 setting then there is perhaps no additional benefit of docetaxel. The latitude trial did not show a survival advantage in the over 70 years in the M1 setting which makes me think the benefit would be even less in the M0 or N1 in this age group. These patients were staged with conventional imaging. With routine use of PSMA there	Thank you for your comment. Evidence was not reviewed in this area as part of this update. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated.

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				will be a Will Roger effect implying more patients will be given AAP now.	
NHS Horsham and Mid Sussex CCG	NG12 Guideline	005	001	The Table I am concerned that the tablet only includes patients aged up to 79. We have an ageing population and several patients aged >79 may be fit & well, with a life expectancy of >10 years. In the interests of fairness & inclusion, could an age-specified PSA referral threshold be made available for patients aged >79 too please?	Thank you for your comment. As the committee were unable to find evidence for PSA thresholds in ages >79 and <40, they felt unable to recommend a specific threshold. They did recognise however that this does and should not exclude people from referral in these age groups, and therefore agreed to add to the table that 'clinical judgement' should be used when considering referring people >79 or <40.
Northern Ireland Cancer Network	NG131 Guideline	004 – 005, 013, 017	General	On page 4 and 5 it states "microgram/litre" On page 13 "nanogram/mL" / On page 17 "milligram/litre" The one used on page 17 is incorrect. Although microgram/litre (µg/L) and nanogram/mL are the same amount, the agreed standardised units that should be used is microgram/litre (µg/L).	Thank you for your comment. We agree and this has been amended.
Northern Ireland Cancer Network	NG131 Guideline	005	001	1 Table There is no guidance of a PSA threshold for age 80 and above – leaves uncertainty. Suggest a threshold or explain why none stated.	Thank you for your comment. As the committee were unable to find evidence for PSA thresholds in ages >79 and <40, they felt unable to recommend a specific threshold. They did recognise however that this does not exclude people from referral in these age groups, and therefore agreed to add to the table that 'clinical judgement' should be used when considering referring people >79 or <40.
Prostate Cancer UK	NG12 Evidence Review	005	004	We are unsure why the scope of this change has been restricted to symptomatic patients. Whilst we recognise that symptoms should change the referral level for some cancers, that is normally because symptoms increase	Thank you for your comment. This review was for an update of recommendations in the NICE guideline on suspected cancer, which is specifically on signs and symptoms that warrant further investigation and

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				the likelihood of cancer being present – thus the referral threshold is **lower** if symptoms are present. These guidelines would make the referral threshold **higher** for symptomatic patients age 50+. The creation of two different tiers of PSA test referral levels for symptomatic and asymptomatic men will likely lead to confusion among men and GPs. Further, it does not make sense based on the evidence that the majority of localised prostate cancers are asymptomatic, and when LUTS are present they are often independent to prostate cancer with an entirely different cause e.g. enlarged prostate.[1,2] Relating symptoms to prostate cancer in this way and therefore implementing a detailed referral threshold structure for symptomatic men does not make sense. For example, consider the scenario of a GP faced with a 60-year-old man who mentions getting up at night to pee and has a PSA of 4 – the GP has to make a judgement as to whether peeing at night should be considered a symptom of prostate cancer – at which point on this guidance they would not refer – or is incidental and they should refer the man according to the lower referral threshold. Inevitably there would be variation in how GPs would interpret that, thus making this challenging to implement and defeated the point of trying to give guidance to create consistency.	referral for suspected cancer. The 2015 update of the guideline reviewed evidence on symptoms that increase the probability of a person having prostate cancer. They found having any lower urinary tract symptom, erectile dysfunction or visible haematuria increased the risk of prostate cancer and recommended that a PSA test should be considered for people with these symptoms. This evidence was not reviewed as part of this update, but it is also consistent with the QCancer risk prediction model, which calculates a person's risk an as yet undiagnosed cancer based on symptoms and other factors. The symptoms identified by the review in the suspected cancer guideline also significantly increase the risk of prostate cancer in the QCancer model, which is based on UK general practice data. This data set has been used to estimate the prevalence of prostate cancer in people with symptoms that might suggest prostate cancer, to calculate positive predictive values in this update. We do acknowledge that having different guidance for people with and without symptoms could be confusing for GPs. NICE is currently liaising with the Prostate cancer risk management programme (PCRMP) to try to ensure that the guidance from the 2 organisations (for people with, and without, the symptoms listed in NG12 rec 1.6.2 respectively) is coherent., and to make it clear to stakeholders which populations are covered by which sets of guidance.

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					Also note that the PCRMP guidance is currently under review.
Prostate Cancer UK	NG12 Evidence Review	006	009	The positive predictive values (used as the primary outcome) are generated using the prevalence figures calculated with the Qcancer Risk calculator. This uses a range of symptoms to estimate as yet undetected prostate cancer by age group. However, we know that urinary symptoms are generally incidental, and prevalence of these symptoms is extremely high.[1,2] There are concerns over the accuracy of these cancer prevalence values. Therefore, there are significant concerns of the accuracy of the primary outcome.	Thank you for your comment. We used the QCancer risk model as a source of prevalence estimates for this work because we believe it to be the best source of prevalence data for people with symptoms of prostate cancer. It is based on UK general practice data, and so directly applicable to this review question about referral from primary care. Note that the prevalence estimates are for people who have consulted their GP with symptoms rather than symptoms that are incidental, which are likely to be much more common.
Prostate Cancer UK	NG12 Evidence Review	007	003	Limiting the study population to symptomatic patients means that studies have been downgraded if they include asymptomatic patients. This downgrading may be inappropriate given, as detailed above, that lower urinary tract symptoms are incidental to the presence or absence of prostate cancer. We support widening the evidence review to include studies with asymptomatic patients, and not downgrading these for indirectness.	Thank you for your comment. We do not think that the presence or absence of symptoms is unrelated to whether a person has prostate cancer. The review that was done as part of the 2015 update of the NICE guideline on suspected cancer found having any lower urinary tract symptom, erectile dysfunction or visible haematuria increased the risk of prostate cancer and recommended that a PSA test should be considered for people with these symptoms. This evidence was not reviewed as part of this update, but it is also consistent with the QCancer risk prediction model, which calculates a person's risk an as yet undiagnosed cancer based on symptoms and other factors. The symptoms identified by the review in the suspected cancer guideline also significantly increase the risk of prostate cancer in the QCancer model, which is based on UK general practice data. This data set has been used to estimate the

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					prevalence of prostate cancer in people with symptoms that might suggest prostate cancer to calculate positive predictive values in this update. We therefore think it is appropriate to prioritise evidence from people with symptoms of prostate cancer for this review. However, in line with the review protocol we did include evidence on age adjusted and age stratified threshold from asymptomatic populations because of a lack of evidence in people with possible symptoms of prostate cancer. This evidence was downgraded to 'partially applicable' if the asymptomatic population also included <30% people with a positive digital rectal examination (DRE) and indirectly applicable if >30% of the study population had a positive DRE.
Prostate Cancer UK	NG12 Evidence Review	015	002	Table 6 The proposed age-related thresholds will have a big impact on practice as they differ considerably from existing practice: 50-59, 3.5 ng/ml; 60-69, 4.5 ng/ml against the existing threshold of 50-69, 3 ng/ml. This means the new guidelines will exclude many men from referral for suspected cancer who currently would be referred. Justification for this is given as "appropriate based on [the committee's] knowledge of practice and marginally higher PPV". However, our significant concerns about the strength of the evidence means we feel the "marginal" difference in PPV is not enough to be used to make this decision. We remain concerned by the level of uncertainty over the impact of the proposed	Thank you for your comment. The recommendation in the previous version of the NICE guideline was that people should be referred using a suspected cancer pathway referral for prostate cancer if their PSA thresholds were above the age-specific reference range, although the reference range was not specified. Committee members reported that there was a wide range of practice across the country with different reference ranges being used. The new recommendation is intended to provide consistency across the country but is not intended to be a major change in practice. The prostate cancer risk management group (external to NICE) recommended referral for people

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				changes, particularly in the age ranges 50-70, and thus the possibility of missed cancers in men who would previously have been referred for further investigation.	with a PSA > 3 micrograms/litre, however this recommendation was made for people who received a PSA test without symptoms of prostate cancer as part of the prostate cancer risk management programme. We do acknowledge that having different guidance for people with and without symptoms could be confusing for GPs. NICE is currently liaising with the Prostate cancer risk management programme (PCRMP) to try to ensure that the guidance from the 2 organisations (for people with, and without, the symptoms listed in NG12 rec 1.6.2 respectively) is coherent., and to make it clear to stakeholders which populations are covered by which sets of guidance. Also note that the PCRMP guidance is currently under review
Prostate Cancer UK	NG12 Evidence Review	021	028	As the Evidence Review itself states, the quality of the available evidence is very poor. This not only makes it difficult to make the case for either age adjusted or fixed PSA thresholds, but also to assess whether the age adjust thresholds suggested by the committee are acceptable. In particular, the positive predictive values quoted in older populations appear to be contradictory (a higher threshold having a lower PPV in some cases), which is likely a result of low quality evidence.	Thank you for your comment. We agree that the evidence assessed was of low or very low quality. For this reason, the committee decided to recommend age-specific reference ranges, as in the previous version of the guideline, as they did not think that the evidence was strong enough to change practice. The previous version of the guideline did not specify what the reference ranges should be, and this led to variation in practice across the county. The committee thought that it would be helpful to specify reference ranges to reduce unjustified variation, and so chose to recommend the age-specific reference ranges that were used in the evidence for people with symptoms of prostate cancer.

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Prostate Cancer UK	NG12 Evidence Review	022	003	009, 043 It is disingenuous to state that the current guidelines use age-related thresholds, given that there is only one age category specified (50-69, limit 3 ng/ml) and outside of this age category no guidance is given. The Prostate Cancer Risk Management Programme simply states "If the PSA is over 3ng/ml, the GP is advised to refer."[3] Therefore, adopting the proposed age-related thresholds is in fact a change to existing practice and should be considered as such.	Thank you for your comment. The current guidance recommends referral if PSA levels are above 'the age specific reference range'. The recommendation is not explicit in defining what these ranges were and therefore the committee were keen to make these explicit in the new recommendation to reduce unwarranted variation in how these are interpreted. The prostate cancer risk management group (external to NICE) recommended referral for people with a PSA > 3 micrograms/litre, however this recommendation was made for people who received a PSA test without symptoms of prostate cancer as part of the prostate cancer risk management programme. We do acknowledge that having different guidance for people with and without symptoms could be confusing for GPs. NICE is currently liaising with the Prostate cancer risk management programme (PCRMP) to try to ensure that the guidance from the 2 organisations (for people with, and without, the symptoms listed in NG12 rec 1.6.2 respectively) is coherent., and to make it clear to stakeholders which populations are covered by which sets of guidance. Also note that the PCRMP guidance is currently under review

[3] https://www.gov.uk/government/publications/prostate-specific-antigen-testing-explanation-and-implementation/advising-well-men-about-the-psa-test-for-prostate-cancer-information-for-gps

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Prostate Cancer UK	NG12 Evidence Review	022	045	We acknowledge there is significant variation in referral practices around the country, however the existing Prostate Cancer Risk Management Programme guidance states that a referral threshold of 3 ng/ml should be used for asymptomatic men. Implementing this proposed NICE guideline change for symptomatic men will lead to two sets of national guidance and may make confusion, and thus variation, worse rather than better. This is particularly the case because urinary symptoms are usually incidental to prostate cancer, leading to ambiguity over which set of thresholds to apply.[4,5]	Thank you for your comment. We agree that the prostate cancer risk management group (external to NICE) recommended referral for people with a PSA > 3 micrograms/litre, however this recommendation was made for people who received a PSA test without symptoms of prostate cancer as part of the prostate cancer risk management programme. We do acknowledge that having different guidance for people with and without symptoms could be confusing for GPs. NICE is currently liaising with the Prostate cancer risk management programme (PCRMP) to try to ensure that the guidance from the 2 organisations (for people with, and without, the symptoms listed in NG12 rec 1.6.2 respectively) is coherent., and to make it clear to stakeholders which populations are covered by which sets of guidance. Also note that the PCRMP guidance is currently under review.
Prostate Cancer UK	NG12 Evidence Review	General	General	We recognise that existing practice in many areas of the country uses age-specific PSA thresholds as a means to control the number of referrals made for suspected	Thank you for your comment. The committee recognised that when using PSA thresholds for referral, there was a fine balance between identifying

[4] Frånlund M, Carlsson S, Stranne J, Aus G, Hugosson J. The absence of voiding symptoms in men with a prostate-specific antigen (PSA) concentration of ≥3.0 ng/mL is an independent risk factor for prostate cancer: results from the Gothenburg Randomized Screening Trial. BJU Int. 2012 Sep;110(5):638-43. doi: 10.1111/j.1464-410X.2012.10962.x. Epub 2012 Apr 30. PMID: 22540895; PMCID: PMC5629001.

[5] Collin SM, Metcalfe C, Donovan J, Lane JA, Davis M, Neal D, Hamdy F, Martin RM. Associations of lower urinary tract symptoms with prostate-specific antigen levels, and screen-detected localized and advanced prostate cancer: a case-control study nested within the UK population-based ProtecT (Prostate testing for cancer and Treatment) study. BJU Int. 2008 Nov;102(10):1400-6. doi: 10.1111/j.1464-410X.2008.07817.x. Epub 2008 Jun 6. PMID: 18540932.

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				prostate cancer, when diagnostic resources in hospital are stretched as never before. However, other ways are possible to reduce the diagnostic burden, such as clinical triage when engaging with secondary care and considering additional factors such as PSA density. Limiting referrals through age-related thresholds may stop some false positives in healthy older men reaching secondary care, but can also cause missed diagnoses in cancer cases with lower PSA. This provides false reassurance and means the cancer may not now be discovered until it has reached an advanced stage. Increasing the risk of this happening goes against the government's stated objective to improve cancer outcomes by reducing late-stage diagnosis.	the maximum number of clinically significant cases possible while avoiding the burden of overtreatment and overdiagnosis. There was no strong evidence to suggest moving practice to a fixed threshold model, and in recognition that the evidence for age-adjusted thresholds was also weak, the committee felt that the recommendation should change to 'consider' and that any approach to referral should be patient centred with comorbidities and patient preference taken into consideration. The committee were unable to consider PSA density as this was not within the scope of this update.
Prostate Cancer UK	NG12 Evidence Review	General	General	Given the low quality of the evidence base and the lack of consensus on the ideal balance of avoiding overdiagnosis in younger men vs missing cancer in older men, we are not confident that an appropriate decision to set national standards can be reached through this process as detailed. The review document calls for further research; this, as well as including further studies with asymptomatic men, will increase the statistical power of the evidence base and allow safer conclusions to be drawn.	Thank you for your comment. We agree that the quality of the evidence was low, however we think clear national guidance on the specific PSA thresholds is important in order to reduce regional variation in how these are applied. The current guidance recommends age specific thresholds but does not specify what these thresholds should be; this has led to different thresholds being applied unevenly. The new recommendation is explicit about the thresholds and aims to reduce this unwarranted variation.
Prostate Cancer UK	NG131 Evidence Review	14	43	We are happy with the strength and application of the review methods used in this process, and the consideration of bias within the sources.	Thank you for your comment.

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Prostate Cancer UK	NG131 Evidence Review	General	General	We support the adoption of Cambridge Prognostic Groupings as these will result in more effective risk stratification, meaning the right men should get the right treatments. The clarity provided on treatment pathways could reduce prostate cancer undertreatment and overtreatment. Use of active surveillance must be promoted as best practice for low-risk prostate cancers.	Thank you for your comment in support of the recommendation on risk stratification.
Prostate Cancer UK	NG131 Evidence Review	General	General	We are happy with the transformation of treatment recommendations from the 3-tier risk grouping to the 5-tier risk grouping.	Thank you for your comment in support of the recommendation on risk stratification.
Royal College of Nursing	General	General	General	We do not have any comments on this consultation. Thank you for the opportunity to contribute.	Thank you for your comment
Royal College of Physicians	NG131 Guideline	General	General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as below. We agree that more needs to be done to lower over-treatment of prostate cancer particularly those with small amounts of Gleason 3+4 cancer / ISUP Grade Group 2. We have some overall comments: There is some concern that such a whole-sale change is based on quality of evidence that is 'moderate to very low' with an over reliance on panel member opinion. This is particularly so given the statements that there might not be a significant impact on care. - the validation evidence lacks contemporaneous evidence linked to the NICE recommended changes in	Thank you for your comment. Although the quality of evidence was rated as moderate to very low, the committee agreed that there was sufficient evidence to warrant a change in practice, and that the limitations in the evidence were not so serious as to be likely to change the conclusions of the review. They acknowledged that validation evidence for the CPG model was collected before the NICE-recommended changes in MRI and targeted biopsy became current practice, however the committee did not think that these changes were likely to change the conclusions of the review and that further research (with associated delay in implementation) was not warranted. They noted that the information that needs to be collected for the 5-tier stratification scheme is the same as for the 3-tier scheme and so thought that there would be a minimal cost impact,

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				MRI and targeted biopsy in the diagnostic setting so this change may be perceived by many as premature. - the designation of Grade Group 2 versus 3 should be done on an overall assessment of all the positive tissue taken at biopsy whereas some assign the Grade Group on the maximal involvement which is incorrect. The NICE guidance should incorporate a key statement on this as it will do more to minimise over-treatment in the era of targeting cores and concentrating these on one area	and that even modest improvements in prognosis were worthwhile. We have not included a statement on how GRADE Group should be designated as this is a good practice point that is beyond the scope of this update and the evidence that has been reviewed here.
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	004	013	Table 1. Risk stratification. In CPG 3 it is unclear what the PSA ranges are for the second option i.e. Gleason 4+3 AND Stages T1-T2	Thank you for your comment. The table states 'or' for the second option, therefore PSA isn't relevant if the risk level is *Gleason 4 + 3 = 7 (grade group 3) and Stages T1–T2*.
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	013	016	Section 1.3.25 Low dose rate brachytherapy (LDR/permanent seed implantation) should be offered as monotherapy in CPG 2 and 3. This is based on the following: The 2008 and 2014 NICE clinical guidelines for localised prostate cancer (2014 update No.58 page 19) recommended brachytherapy as an option for low and intermediate risk prostate cancer which in the NG 131 draft would be considered CPG 1, 2, 3. The 2014 guideline recommended further research into clinical and cost effectiveness for localised prostate cancer, including the value of procedures such as	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated in future.

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				brachytherapy based on survival, local recurrence, toxicity, and quality of life outcomes as end points. We and others have published UK population series on all these end points. Our own work in this regard can be viewed on PubMed links PMID: **34448332,** PMID: **2960760,** PMID: **29054374,** PMID: **28670842,** PMID: **22841018,** PMID: **21854533.**	
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	026	015	"***low - dose brachytherapy*** *plus external beam radiotherapy*" - please amend to '**low dose rate'** brachytherapy. As the sentence stands it misleadingly gives the impression that a low dose of radiotherapy is delivered during low dose rate brachytherapy, when in fact a high prescription dose (110 Gy when combined with EBRT or 145Gy as monotherapy) is delivered as a continuous *dose* of radiation released over a long period of time.	Thank you for your comment. The committee agree with this, and the amendment has been made.
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	026	018	"***high-dose brachytherapy***" - please amend to "**high dose rate**" brachytherapy. Low and high dose RATE brachytherapy refer to the rate at which the dose is delivered over time NOT to the magnitude of the dose per se.	Thank you for your comment. The committee agree with this, and the amendment has been made.
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	026	019	Nowadays most brachytherapy centres do offer both types of brachytherapy although the indications may differ. High dose rate in combination with external beam radiotherapy is particularly suitable for locally advanced prostate cancer with seminal vesicle invasion, whereas low dose rate is indicated as boost combined with external beam radiotherapy for high-risk localised prostate cancer as noted in the guideline.	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to

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				As discussed above in points 2,7 and 8 of this form, low dose rate brachytherapy is indicated as monotherapy for low and intermediate risk cancer.	consider whether this recommendation should be updated in future.
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	030	002	1.3.8 - "*consider radical prostatectomy or radical radiotherapy if active surveillance is not suitable or acceptable to the person*." Low Dose Rate brachytherapy should also be an option if active surveillance is not suitable or acceptable to the person.	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated in future.
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	031	002	1.3.9 - *"offer a choice between active surveillance, radical prostatectomy or radical radiotherapy to people with CPG 2 localised prostate cancer if radical treatment is suitable".* Low Dose Rate brachytherapy alone should also be offered to this risk group if radical treatment is suitable. The RTOG 0232 randomised controlled trial compared LDR brachytherapy monotherapy vs EBRT + LDR brachytherapy in 579 intermediate risk patients. LDR monotherapy was as efficacious in terms of disease control as the combined treatment. LDR monotherapy had a lower toxicity profile and better patient responded outcomes based on the EPIC questionnaire. The trial design and results can be viewed at https://www.clinicaltrials.gov/ct2/home Trial ID = NCT 00063882	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated in future.
Royal Surrey County Hospital	NG131 Guideline	031	002	1.3.10 - *"For people with CPG 3 localised prostate cancer: offer radical prostatectomy or radical radiotherapy"*	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and

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NHS Foundation Trust				Low Dose Rate brachytherapy alone should also be offered to this risk group. The RTOG 0232 randomised controlled trial compared LDR brachytherapy monotherapy vs EBRT + LDR brachytherapy in 579 intermediate risk patients. LDR monotherapy was as efficacious in terms of disease control as the combined treatment. LDR monotherapy had a lower toxicity profile and better patient responded outcomes based on the EPIC questionnaire. The trial design and results can be viewed at https://www.clinicaltrials.gov/ct2/home Trial ID = NCT 00063882	treatment recommendations were only updated to incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated in future.
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	033	002	1.3.24 - *"Consider brachytherapy in combination with external beam radiotherapy for people with CPG 2, 3 4 and 5 localised or locally advanced prostate cancer"* We concur with this recommendation based on external beam radiotherapy plus low dose rate brachytherapy boost as documented in the ASCEND RT trial (PMID: **28262473)**	Thank you for your comment.
Royal Surrey County Hospital NHS Foundation Trust	NG131 Guideline	033	002	1.3.25 - *"Do not offer brachytherapy alone to people with CPG 4 and 5 localised or locally advanced prostate cancer."* We concur with this recommendation.	Thank you for your comment.
UK Cancer Genetics Group	NG12 Guideline	004	General	General and specifically 1.6.3 We note that these recommendations do not make any mention of the higher *a priori* risk of prostate cancer in individuals with increased genetic susceptibility to prostate cancer such as *BRCA2* carriers. In the context	Thank you for your comment. We recognise that risk factors will increase a person's chances of developing cancer, but as the scope of this update is specifically about referral of people with symptoms presenting to primary care, the committee didn't feel this recommendation was an appropriate place for

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				of an individual having a disease causing variant in known prostate cancer susceptibility gene the thresholds for further investigations may be lower than they would be in non carriers. We accept you have not reviewed the greyed out evidence but think the omission to acknowledge individuals at increased genetic risk of prostate cancer in these guidelines is significant for this cohort, and poses a potential clinical risk to individuals at increased genetic risk, particularly younger individuals in whom GPs may have a lower index of suspicion. You could highlight the need to consider genetic background in 1.6.3: Lines 17,18,19: "Take into account the person's preferences, confirmed or potential genetic predisposition to prostate cancer (e.g. those with family history or confirmed high risk gene carriers, for example *BRCA2* carriers) and any comorbidities when making the decision."	this consideration. Risk factors make a person more likely to develop cancer, but do not affect the way the cancer presents. Please see the section on 'the use of risk factors as well as symptoms' as considered by the committee in the original NG12 guideline here. The committee did not find evidence on whether the presence or absence of a family history of prostate cancer should influence the PSA threshold at which referral to secondary care should be considered but made a research recommendation for research into the diagnostic accuracy of PSA testing that was stratified by ethnicity and family history of prostate or breast cancer. In the absence of evidence, the committee did not think that family history or ethnicity should be taken into account when deciding whether to refer to secondary care based on the PSA test result.
UK Cancer Genetics Group	NG131 Guideline	General	General	We note that this document does not anywhere reference individuals who may have a higher chance of having younger onset and more aggressive prostate cancer due to germline genetic susceptibility e.g. *BRCA2* carriers. Information about treatment options and the risk figures quoted may be different for high risk gene carriers. Has the committee thought about highlighting these differences between individuals with inherited susceptibility versus those without as part of a management and treatment decision strategy? We feel it is important that this document references that	Thank you for your comment. We did not review evidence on individual risk factors for treatment as the scope of this update was to look at the risk stratification model. We acknowledge that decisions on treatment for individuals needs to be made based on a number of factors in discussion between the clinician and patient.

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				individuals with genetic susceptibility may require more detailed discussions about their personal risks of different treatment options.	
UK National Screening Committee	NG12 Guideline	006	General	**The evidence on fixed and age-adjusted thresholds for prostate-specific antigen testing** The purpose of the guidance on Prostate specific antigen (PSA) testing from the Prostate Cancer Risk Management Programme (PCRMP) is to help primary care teams give asymptomatic men information about the potential benefits, limitations and implications of having a prostate specific antigen (PSA) test for prostate cancer and to provide men with clear and balanced information about the risks and benefits of PSA testing in the context of early detection of prostate cancer. The PCRMP was set up in response to an increasing trend for PSA testing in the context of detecting early prostate cancer. In 2002, more than 100 GPs and primary care cancer leads as well as an expert multidisciplinary group set up by the Department of Health were consulted before the publication of the first edition of this guidance. A critical distinction between the PCRMP guidance and the NICE guidance appears to be the presence or absence of lower urinary tract symptoms. Many men who consult their GPs with lower urinary tract symptoms (LUTS) may do so concerned as to whether or not they might have prostate cancer. The relationship between symptoms and prostate cancer is unclear, but there is general consensus that the presence of symptoms does not of itself represent a risk factor for the presence of prostate cancer (1). Such men might undergo	Thank you for your comment. Discussions are ongoing between NICE and the UKNSC and the PCRMP to make sure that the guidance from the 2 organisations is coherent, and that the PCRMP threshold recommendation is currently under review. This review was for an update of recommendations in the NICE guideline on suspected cancer, which is specifically on signs and symptoms that warrant further investigation and referral for suspected cancer. The 2015 update of the guideline reviewed evidence on symptoms that increase the probability of a person having prostate cancer. They found having any lower urinary tract symptom, erectile dysfunction or visible haematuria increased the risk of prostate cancer and recommended that a PSA test should be considered for people with these symptoms. This evidence was not reviewed as part of this update, but it is also consistent with the QCancer risk prediction model, which calculates a person's risk an as yet undiagnosed cancer based on symptoms and other factors. The symptoms identified by the review in the suspected cancer guideline also significantly increase the risk of prostate cancer in the QCancer model, which is based on UK general practice data. This data set has been used to estimate the prevalence of prostate cancer in people with symptoms that might

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				PSA testing without clearly understanding the potential harms (2, 3). There is variation in the amount of information given to the patient and a full and balanced view of potential harms and benefits may not always be conveyed (4). Men undergoing further investigation after a PSA test often experience increased anxiety, regret and uncertainty (3). In 2008, the PCRMP recommended the NICE age-related referral values. In the 2016 update, we recommended a referral value for men aged 50-69 years of 3ng/mL. In doing so, we took the following into account I. The two largest randomised PSA-based screening trials – ERSPC (5) and Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) (6) – have evaluated PSA testing with biopsy indication among those with PSA ≥3.0 ng/mL. There is no similar dataset evaluating any age-related PSA levels and outcomes from prostate cancer. The upper age limit within ERSPC was 75 years. II. The UK ProtecT study into treatment of prostate cancer used the cut-off of PSA ≥3.0 ng/mL (7). The evidence from this study helps drive decision-making in the treatment of localised prostate cancer that is detected on PSA testing is based on this cut-off in a UK population. This is reflected in NICE NG131. III. Within the age range 50-69 years, there appears to be no benefit to using reference ranges that change with age (8). Specifically, within that age range, the NICE-age-related reference ranges result in missing a high number of high-grade cancers in older men than in	suggest prostate cancer to calculate positive predictive values in this update. Thank you for explaining the basis of the PCRMP recommendations in 2016. However, we do not think that this evidence means that a fixed test threshold of 3 ng/ml should be used when deciding whether to refer someone with symptoms of prostate cancer to secondary care. Thank you also for highlighting the Gilbert R 2018 study on age specific PSA which did meet our inclusion criteria. The committee have considered this evidence but do not think the positive predictive value for a UK symptomatic population (as estimated using the Qcancer model) with either age adjusted threshold analysed by the authors warranted a change to the committee's recommended thresholds. Note that the paper did present evidence on a fixed test threshold of 3 ng/ml, but this was based on the assumption that those with a PSA <3ng/ml did not have prostate cancer. This population did not have a biopsy or multiparametric MRI. This did not match the reference standard for our review for having prostate cancer, so we reanalysed the data, removing the participants who did not have a biopsy or multiparametric MRI from the analysis. This meant that data was no longer available for a fixed test threshold of 3ng/ml.

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				younger men (9). Indeed these data have suggested that PSA performs better as a diagnostic test in the older cohort (60 to 69 years) than those aged 50 to 59 years. IV. There is little evidence to support PSA testing below the age of 50. It would be helpful for patients and the healthcare community if matters around PSA testing could be harmonised and simplified. Having differential cut-offs between guidance for asymptomatic and symptomatic men and multiple age-related variable cut-offs is likely to create confusion. Against this we have considered the likely impact on referral rates but feedback from alliances that have used the PCRMP single cut-off (e.g., South Yorkshire/ North Derbyshire) have found the referral rates manageable. The PSA-level suggested should be taken in conjunction with the advice NOT to carry out routine PSA testing as part of health promotion. A PSA level should not automatically lead to referral – indeed there is evidence collected in a large UK population to suggest that, in the absence of other risk factors, more than one PSA level establishes risk of high-grade prostate cancer far better than a single test in the PSA range between 3 and 19.99 ng/mL (10). The decision whether to refer or not at any age should be based on other factors, including a patient's risk factors, general condition, expectations and life-expectancy rather than the PSA level alone – the guidance issued by PCRMP makes this clear. Finally, in the absence of definitive data demonstrating a benefit of age-specific PSA levels, it is difficult to refute an	

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				allegation of systemic age-related discrimination, particularly if the UK data points in the opposite direction. 1. BMJ 2018;361:k1202 doi: 10.1136/bmj.k1202 2. Qual Health Res 2008;18(1):56-64. 3. Br J Gen Pract 2007;57(537):303-10. 4. BMC Fam Pract 2007;8:35. 5. Lancet 2014;384(9959):2027-35. 6. J Natl Cancer Inst 2012;104(2):125-32. 7. N Engl J Med 2016; 375:1415-1424 DOI: 10.1056/NEJMoa1606220. 8. Cancer Causes Control. 2018; 29(3): 383–388. 2018. 9. https://abstracts.ncri.org.uk/abstract/are-age-specific-psa-reference-ranges-justified-results-from-the-protect-study-2/) (2008). 10. European Urology 2008; 53:777-784. https://doi.org/10.1016/j.eururo.2007.11.064.	
Wales Cancer Network	NG12 Guideline	General	General	Supportive of the new age specific reference ranges	Thank you for your comment
Wales Cancer Network	NG12 Guideline	General	General	Happy to see inclusion of co morbidities as a factor to be considered when making USC referral. This would enable clinicians to down grade referrals on this basis if required ie marginally raised PSA in patient with numerous co morbidities would not need to be seen as USC.	Thank you for your comment

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Wales Cancer Network	NG12 Guideline	General	General	Doesn't include anything about repeating PSA levels and checking for UTIs etc before referring as suspected cancer as that is what urology have been encouraging GPs to do in Wales, or at least South Wales.	Thank you for your comment. The committee discussed repeat PSA testing, but felt if the recommendation specified this it would lead to some patients not returning for their second test and follow up, meaning diagnosis could be delayed in these people. We agree that checking for UTIs is an important good practice point for GPs, but the scope of this update was limited to considering PSA thresholds for referral to secondary care. We have passed your comment to the NICE surveillance team to consider for consideration to inform future updates of the guideline.
Wales Cancer Network	NG131 Guideline	005	002 - 005	We feel that bone scanning could be safely omitted in CPG 1 and 2 groups & group 3 - excluding Gleason 4+3=7 cancers i.e. should be performed in patients with CPG groups 4, 5 + Gleason 4+3=7 cancers.	Thank you for your comment. On discussion with the committee, we have decided to extend this recommendation to include CPG2 and remove CPG2 from the research recommendation. Although we didn't systematically review evidence in this area, the committee were aware of evidence that supported this decision, and they were also confident this accurately reflected current practice. The committee felt that CPG3 should remain in the research recommendation.
Wales Cancer Network	NG131 Guideline	005	002 - 005	We are concerned that there are no recommendations for staging of high-risk prostate cancers (CPG 4 & 5) using PSMA-PET-CT scans which greatly improves the accuracy of baseline staging and alters management /	Thank you for your comment. Evidence was not reviewed in this area as part of this update. However, we have passed your comment to the

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				treatment options in a significant proportion of these cases.	surveillance team at NICE to consider whether this recommendation should be updated
Wales Cancer Network	NG131 Guideline	011	006	Happy to see the inclusion of GI 3+4 in active surveillance as a recognised option	Thank you for your comment.
Wales Cancer Network	NG131 Guideline	011	009 - 013	We are concerned that this recommendation may imply that active surveillance is an equally valid treatment option for CPG 3 cancers (particularly GI 4+3=7 cancers) which is misleading	Thank you for your comment. While the committee agreed that active surveillance is not the preferred option for CPG 3, they felt there might be a small number of patients for whom radical treatment is high-risk or unacceptable to them. They also felt that not providing active surveillance as an option could lead to people refusing all treatment, which would have a worse impact than active surveillance, where progression could be monitored. The recommendation reflects this by using 'offer' for radical treatment and 'consider' for active surveillance for people who choose not to have radical treatment. Any decision should be made with the patient and family using box 2 which we have highlighted at the beginning of this section. We have also now added referring to the NICE guideline on shared decision making.
Wales Cancer Network	NG131 Guideline	013	005 - 011	We are concerned that this recommendation may result in more men receiving neoadjuvant ADT for CPG 2 cancers with attendant side effects	Thank you for your comment. CPG2 maps to 'intermediate risk' in the previous 3 tier risk stratification tool. As this was already recommended for people in this intermediate risk group, we don't feel this recommendation changes practice.

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Wales Cancer Network	NG131 Guideline	013	016 - 018	We are concerned that this recommendation may result in more men requesting / receiving brachytherapy boost for CPG 2 / 3 cancers which could have significant resource implications	Thank you for your comment. CPG2 maps to 'intermediate risk' in the previous 3 tier risk stratification tool. As this was already recommended for people in this intermediate risk group, we don't feel this recommendation changes practice.
Wales Cancer Network	NG131 Guideline	013	021 - 029	We are concerned that the guidelines do not include any recommendations on early Androgen Receptor Targeted Agents as an alternative to Docetaxel chemotherapy.	Thank you for your comment. Evidence was not reviewed in this area as part of this update. Our scope was to look at the risk stratification model, and treatment recommendations were only updated to incorporate the new tiers. However, we have passed your comment to the surveillance team at NICE to consider whether this recommendation should be updated in future.
Wales Cancer Network	NG131 Guideline	General	General	The change in risk criteria is slightly cumbersome but is likely to work well when adopted. It has made it more objective by removing subcategorization of T2 a,b and c. CPG 3 I think the inclusion criteria are reasonable but it needs to be clarified/worded better.	Thank you for your comment. The committee feel using and/or is the best way to convey the spectrum of risk within each category, and this reflects the wording used in the CPG risk prediction model.
Wales Cancer Network	NG131 Guideline	General	General	I would be uncertain about offering active surveillance to patients with primary pattern 4 disease in CPG 3. I know it is temporary/potentially for primary pattern 3 and would be assessed on a per patient basis but the wording suggests you could offer it to primary pattern 4 patients.	Thank you for your comment. While the committee agreed that active surveillance is not the preferred option for CPG 3, they felt there might be a small number of patients for whom radical treatment is high-risk or unacceptable to them. They also felt that not providing active surveillance as an option could lead to people refusing all treatment, which would

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					have a worse impact than active surveillance, where progression could be monitored. The recommendation reflects this by using 'offer' for radical treatment and 'consider' for active surveillance for people who choose not to have radical treatment. Any decision should be made with the patient and family using box 2 which we have highlighted at the beginning of this section. We have also now added referring to the NICE guideline on shared decision making.
Wales Cancer Network	NG131 Guideline	General	General	The guideline acknowledges that the chance of cure in GI 8 and above is low and uses disease control rather than cure as treatment goal. This is good.	Thank you for your comment.
Wales Cancer Network	NG131 Guideline	General	General	Neoadjuvant hormonal therapy for all CPG 2 patients will add workload to oncology/Urology plus potential side effects.	Thank you for your comment. CPG2 maps to 'intermediate risk' in the previous 3 tier risk stratification tool. As this was already recommended for people in this intermediate risk group, we don't feel this recommendation changes practice.
Wales Cancer Network	NG131 Guideline	General	General	We do not routinely offer bone scans to pys who would be in CPG 2. This will increase workload without good quality evidence to support this step.	Thank you for your comment. On discussion with the committee, this recommendation has been extended to include CPG2. CPG2 has been removed from the research recommendation. Although we didn't systematically review evidence in this area, the committee were aware of evidence that supported this decision, and they were also confident this accurately reflected current practice.

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Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
Yes	Bayer HealthCare	**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012	Nil	No further action required