

## Appendix B: Stakeholder consultation comments table

2018 surveillance of [Bladder cancer: diagnosis and management](#) (2015)

Consultation dates: 12 to 25 February 2019

Do you agree with the proposal not to update the guideline?			
Stakeholder	Overall response	Comments	NICE response
University of Exeter	Yes	No comments provided	Thank you for your response.
Roche Products Ltd & Roche Diagnostics Ltd- comprises feedback from both pharmaceutical and diagnostic divisions	No	<p>We believe that this guideline should be updated to reflect the immunotherapies and diagnostics that are available and recommended in NICE Technology Appraisals.</p> <p><b><u>Current NICE pathway recommendations:</u></b></p> <ol style="list-style-type: none"> <li><b>First-line chemotherapy:</b> <ul style="list-style-type: none"> <li>Cisplatin-based chemotherapy or carboplatin in combination with gemcitabine were previously</li> </ul> </li> </ol>	<p>Thank you for your response. We appreciate you highlighting the importance of the new immunotherapies. As you mention these are covered by technology appraisals, all of which are linked with the guideline content in the <a href="#">bladder cancer pathway</a>. NICE pathways aim to bring together all NICE content on a particular topic in an interactive flow chart. We agree that these immunotherapies are important in the treatment of bladder cancer, and as such we are providing a cross-referral from recommendations 1.7.7 and 1.7.8 in NG2 directly to the bladder cancer pathway to ensure that service users are able to quickly access these technology appraisals and other information within the pathway.</p>

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		<p>recognised as the recommended first-line regimens in the 2015 Bladder cancer: diagnosis and management guidelines.</p> <ul style="list-style-type: none"> <li>● Since, there have been 2 developments that should be incorporated in to an updated guideline: <ul style="list-style-type: none"> <li>▪ NICE technology appraisal guidance on atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA492)<sup>1</sup>: Atezolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial carcinoma in adults when cisplatin-containing chemotherapy is unsuitable, only if: <ul style="list-style-type: none"> <li>- their tumours express PD-L1 at a level of 5% or more and</li> <li>- the conditions of the managed access agreement for atezolizumab are followed.<sup>2</sup></li> </ul> </li> <li>▪ NICE technology appraisal guidance on pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA522)<sup>3</sup>: Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated locally advanced or metastatic urothelial carcinoma in adults when cisplatin-containing chemotherapy is unsuitable, only if: <ul style="list-style-type: none"> <li>- their tumours express PD-L1 with a combined positive score of 10 or more</li> </ul> </li> </ul> </li> </ul>	
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		<ul style="list-style-type: none"> <li>- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses and the conditions of the managed access agreement for pembrolizumab are followed</li> </ul> <p><b>2. Second-line chemotherapy:</b></p> <ul style="list-style-type: none"> <li>● Gemcitabine in combination with cisplatin, carboplatin in combination with paclitaxel, or gemcitabine in combination with paclitaxel were previously recognised as the recommended second-line regimens in the 2015 Bladder cancer: diagnosis and management guidelines.</li> <li>● Since, there have been 2 developments that should be incorporated in to an updated guideline:</li> </ul> <p>NICE technology appraisal guidance on atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA525)<sup>4</sup>:  Atezolizumab is recommended as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:</p> <ul style="list-style-type: none"> <li>- atezolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses, and</li> <li>- the company provides atezolizumab with the discount agreed in the patient access scheme.<sup>5</sup></li> </ul> <p>NICE technology appraisal guidance on pembrolizumab for treating locally advanced or metastatic urothelial carcinoma</p>	
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		<p>after platinum-containing chemotherapy (TA519)<sup>6</sup>: Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:</p> <ul style="list-style-type: none"> <li>- pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression and</li> <li>- the conditions in the managed access agreement for pembrolizumab are followed.</li> </ul> <ol style="list-style-type: none"> <li>1. NICE guidance TA492. Available at: <a href="https://www.nice.org.uk/guidance/ta492">https://www.nice.org.uk/guidance/ta492</a> [Last accessed 21/02/19]</li> <li>2. NICE guidance TA492. Tools and resources. Available at: <a href="https://www.nice.org.uk/guidance/TA492/Resources">https://www.nice.org.uk/guidance/TA492/Resources</a> [Last accessed 21/02/19]</li> <li>3. NICE guidance TA522. Available at: <a href="https://www.nice.org.uk/guidance/ta522">https://www.nice.org.uk/guidance/ta522</a> [Last accessed 21/02/19]</li> <li>4. NICE guidance TA525. Available at: <a href="https://www.nice.org.uk/guidance/ta525">https://www.nice.org.uk/guidance/ta525</a>. [Last accessed 21/02/19]</li> <li>5. NICE guidance TA525. Tools and resources. Available at: <a href="https://www.nice.org.uk/guidance/ta525/resources">https://www.nice.org.uk/guidance/ta525/resources</a>. [Last accessed 21/02/19]</li> </ol> <p>NICE guidance TA519. Available at: <a href="https://www.nice.org.uk/guidance/ta519">https://www.nice.org.uk/guidance/ta519</a> [Last accessed 21/02/19]</p>	
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Fight Bladder Cancer	No	<p>Page 9. There are many recommendations for research in the existing guidelines. It is essential that an update analysis of research that has been carried out subsequent to the 2015 guidelines either as completed studies or studies currently being carried out.</p> <p>Pages 27-29: The epidemiology of bladder cancer is illustrated only using the code C67 for invasive bladder cancer. The true epidemiology of bladder cancer should be illustrated using D09.0 and D41.4 as well as C67, in order to also capture the incidence, mortality, and relative survival rates of non-invasive bladder cancer</p> <p>Page 78. The difference between TURBT for diagnosis and TURBT for treatment of some early forms of bladder cancer is not well differentiated in the guidelines. There is a growing body of evidence to suggest that TURBT is widely being classed as a definitive treatment irrespective of the fact that cancer remains in the patient and that the patient requires further treatment as a matter of urgency. In such cases, the 'clock' is erroneously stopped on the 62-day waiting time target, which removes the incentive for providers to deliver the definitive treatment that patients need.</p> <p>Page 78. There is currently no guidance in this document on hospital-based investigation of haematuria, which forms</p>	<p>Thank you for highlighting the importance of research recommendations. At this surveillance review no evidence was found to suggest any of the research recommendations for this guideline had been addressed. We did, however, identify some ongoing research in the areas identified by the research recommendations and these studies will be check for impact on the guideline when results are available.</p> <p>The information relating to epidemiology was correct at the time of writing the guideline, and was important in shaping the evidence reviews, however it is not within the remit of the surveillance process to determine whether epidemiology cited in the full guideline is up to date</p> <p>Time to definitive diagnosis has been raised by a topic expert in addition to stakeholders during this surveillance review. NG2 lists TURBT as an option in section 1.2 diagnosing and staging bladder cancer. It is also mentioned in section 1.3 – treating non-muscle-invasive bladder cancer, but under the subheading of risk classification, with further bullet points following giving the choice of treatment options. Topic experts were consulted on this issue who suggest that the definition of TURBT is relative to the individual and their tumour status. Stakeholder feedback received during this consultation indicates that this is an implementation issue, as such we will provide feedback to NHS England. However, the <a href="#">NHS England guidance</a> on delivering cancer wait times suggests that trusts should develop their own separate pathways for different urological cancers, such as bladder cancer, rather than applying one pathway to all 5 (renal, prostate, bladder, testicular and penile.)</p> <p>Investigation of haematuria is covered by NICE guideline NG12 – suspected cancer recognition and referral, recommendation 1.6.4. NG12 is linked to NG2 in the <a href="#">bladder cancer pathway</a>.</p>
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	<p>an important part of the diagnostic pathway for most cases of bladder cancer</p> <p>Page 79: There is now new evidence of narrow band imaging (NBI) versus white light cystoscopy (WLC), such as:</p> <p>Xiong Y, Li J, Ma S, Ge J, Zhou L, Li D, et al. (2017) A meta-analysis of narrow band imaging for the diagnosis and therapeutic outcome of non-muscle-invasive bladder cancer. PLoS ONE 12(2): e0170819</p> <p>Joo Yong Lee, Kang Su Cho, Dong Hyuk Kang, Hae Do Jung, Jong Kyou Kwon, Cheol Kyu Oh, Won Sik Ham and Young Deuk Choi. (2015) A network meta-analysis of therapeutic outcomes after new image technology-assisted transurethral resection for non-muscle-invasive bladder cancer: 5-aminolaevulinic acid fluorescence vs hexylaminolevulinic acid fluorescence vs narrow band imaging. BMC Cancer 2015;15:566</p> <p>Anna Kołodziej, Wojciech Krajewski, corresponding author Michał Matuszewski, and Krzysztof Tupikowski. (2016) Review of current optical diagnostic techniques for non-muscle-invasive bladder cancer Cent European J Urol. 69(2): 150–156.</p> <p>Page 101. The diagnostic accuracy of urine biomarkers has significantly improved since the last review published by Mowatt et al., 2010. The sensitivity and specificity of certain tests, particularly those using DNA or RNA, can match that of cystoscopy. An updated assessment of their</p>	<p>Thank you for providing studies relating to narrow band imaging. These 3 studies do not meet our inclusion criteria, as they do not state the sources of their searches, are review articles or do not analyse randomised controlled trials. We are tracking an ongoing study due to publish in 2021 regarding photodynamic versus white light guided treatment and several others on diagnostic imaging which will be considered when available.</p> <p>We also felt that urinary biomarkers were a potential area where new evidence may be available, and as such it formed one of our focussed searches for this surveillance review. However, the evidence found was for a broad selection of tests, none of which were found to be more accurate than the current gold standard method of cystoscopy. This issue will be noted for consideration at the next review. We are also tracking an ongoing study for the Xpert bladder cancer monitor test which we will review when the results are available. The study by Mowatt et al is outside our search dates for this review. Thank you for highlighting the study by Chou et al, this was identified in the surveillance review and has already been included in our evidence summary.</p> <p>Recommendations 1.3.6-1.3.9 detail treatment options for high risk non-muscle-invasive bladder cancer, and states to offer the choice of intravesical BCG or radical cystectomy based on a full discussion with the person and their clinical team. No evidence has been identified to suggest changing these recommendations at this time. We sympathise with the supply issues however the role of guidelines are to provide evidence based recommendations of best practice and it's the role of commissioners to ensure availability of recommended treatment options.</p> <p>Thank you for highlighting the study by Kassouf et al. This study was considered in our surveillance review; however, it did not meet our</p>
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	<p>role in the diagnosis and staging of bladder cancer is needed. See:</p> <p>Chou, R., Gore, J. L., Buckley, D., Fu, R., Gustafson, K., Griffin, J. C.,... &amp; Selph, S. (2015). Urinary biomarkers for diagnosis of bladder cancer: a systematic review and meta-analysis. <i>Annals of internal medicine</i>, 163(12), 922-931.</p> <p>Page 139. Treatment of high risk non-invasive bladder cancer discusses the recommended use of BCG as the standard of care. Over recent years there has been period of shortages of this drug that has led to clinicians stopping treatment in accordance with the current guidelines, using treatments not currently recommended of recommending radical surgery due to the non- availability of BCG. Clear guidance as to the recommended treatment options are essential in an update of the guidelines.</p> <p>Page 239. There is now additional evidence examining the optimal follow up non-muscle-invasive bladder cancer. For example:</p> <p>Kassouf, W., Traboulsi, S. L., Schmitz-Dräger, B., Palou, J., Witjes, J. A., van Rhijn, B. W.,... &amp; Kamat, A. M. (2016, October). Follow up in non-muscle-invasive bladder cancer—International Bladder Cancer Network recommendations. In <i>Urologic Oncology: Seminars and Original Investigations</i> (Vol. 34, No. 10, pp. 460-468). Elsevier.</p>	<p>inclusion criteria. On reviewing this study, it supports the recommendations for low risk NMIBC follow up (recommendations 1.4.3-1.4.6) and high risk NMIBC follow up (recommendations 1.4.9-1.4.10).</p> <p>Thank you for highlighting the studies relating to alternatives to radical cystectomy, however these studies do not meet our inclusion criteria for this surveillance review as they do not state the sources for their searches or analyse studies that are not randomised controlled trials.</p> <p>Regarding new immunotherapy for advanced/metastatic bladder cancer, we are making an editorial amendment to recommendations 1.7.7 and 1.7.8 which will direct readers to the <a href="#">bladder cancer pathway</a>. The new technology appraisals for immunotherapy are clearly linked within the bladder cancer pathway and as such provide a source of information for newly available therapies.</p>
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		<p>Page 273. There is now additional evidence addressing the question “In which patient groups with muscle-invasive bladder cancer would radical cystectomy produce better outcomes than radical radiotherapy and in which groups would radical radiotherapy produce better outcomes?”</p> <p>Arcangeli, G., Strigari, L., &amp; Arcangeli, S. (2015). Radical cystectomy versus organ-sparing trimodality treatment in muscle-invasive bladder cancer: A systematic review of clinical trials. <i>Critical reviews in oncology/hematology</i>, 95(3), 387-396</p> <p>Vashistha, V., Wang, H., Mazzone, A., Liss, M. A., Svatek, R. S., Schleicher, M., &amp; Kaushik, D. (2017). Radical cystectomy compared to combined modality treatment for muscle-invasive bladder cancer: a systematic review and meta-analysis. <i>International Journal of Radiation Oncology Biology Physics</i>, 97(5), 1002-1020.</p> <p>Page 319. The current guidelines do not consider the newly approved immunotherapy oncology for advanced/metastatic bladder cancer. It is essential that this section is updated to give clarity on treatments recommended for advanced/ metastatic bladder cancer.</p>	
British Association of Urological Surgeons (BAUS)	No	There are a number of things that need to be clarified or updated.	Thank you for your feedback. No evidence was identified at this surveillance review to suggest the guideline recommendations should be updated. However, without any further details we are unable to provide a more in-depth response to this comment.
Action Bladder Cancer UK	No	It is a matter of grave concern that, in the period of 4 years since the Bladder Cancer guideline was completed, there	Thank you for highlighting the funding issues for bladder cancer research. There are 18 research recommendations in the bladder

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	<p>has apparently been no significant improvement in evidence to support the current – or any new – guideline recommendations. This really does reflect the ‘Cinderella Cancer’ status of bladder cancer – relative to the ‘Big Four’ and a number of other cancers where there has been much better investment in research. Many of the current guideline recommendations were based on limited evidence and could only justify a “Consider” recommendation – and we are, essentially, no further on.</p> <p>Bladder cancer continues to be one of those cancers where survival statistics and early presentation have not improved at the same speed or level that other cancers have. The low level of research and evidence to guide practice is very relevant.</p> <p>This situation is actually a scandal and something that NICE and the NHS should be bringing to the attention of national decision makers and funders. Failure to review and strengthen the guidelines, and also to facilitate their implementation, continues to ensure poor outcomes for those with bladder cancer.</p> <p>Meanwhile, implementation of the current guideline recommendations has been slow, inconsistent and only partial – especially with respect to those relating to patient experience. A ‘postcode lottery’ continues to apply.</p> <p>What is of even more concern is that, in the absence of definitive evidence, changes to treatment practice have emerged with some areas of bladder cancer treatment – based on local judgements, some European research papers and, possibly, workload pressures and expedience.</p>	<p>cancer full guideline which aim to highlight areas for research priorities in order to improve NICE guidance and patient care in the future. We are also monitoring 15 ongoing trials in this area and will assess the results for impact on the guideline when available.</p> <p>Regarding early presentation, NICE guideline NG12 – suspected cancer: recognition and referral has recommendations for bladder cancer, which are aimed at primary care for improving diagnosis. NG12 also has a research recommendation on <a href="#">‘primary care testing’</a> which includes non-visible haematuria. The research recommendation states this is important to inform clinicians on the choice of investigation for symptomatic patients.</p> <p>We did not find any evidence at this surveillance review to suggest the recommendations should be updated. We will pass on your concerns about implementation to the relevant NICE team.</p> <p>NG2 recommendations 1.3.5-1.3.9 contain guidance regarding the use of BCG for high risk NMIBC.</p> <p>The use of hyperthermic mitomycin C has been reviewed as part of this surveillance. There is a recent NICE interventional procedures guidance, <a href="#">Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer</a> IP628, which does not currently recommend intravesical microwave hyperthermia due to evidence of well-recognised adverse events. IP628 is linked in the bladder cancer pathway. The recommendations relating to mitomycin C in NG2 do not currently suggest using a hyperthermic approach.</p> <p>Robotic cystectomy was highlighted by topic experts as an area where improvements to patient outcomes may be seen. The evidence found at this review supports the views of topic experts, however increased costs and operative times were also seen. We are tracking an ongoing Cochrane study which may provide further</p>
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	<p>Examples of this would include the introduction of a shorter programme of BCG treatment and/or the use of hyper-thermic Mitomycin for High Risk Non-Muscle-Invasive Bladder Cancer.</p> <p>As a consequence, the treatment a high risk NMIBC patient receives in their local area may be very different to that experienced elsewhere. And this makes it extremely difficult for patients to be confident that the treatment they are subject to is the best available – the ‘gold standard’.</p> <p>Reference is made to the improvements to some aspects of patient outcome for those receiving robotic cystectomy surgery. Whilst that is encouraging, we might ask if it is sufficient evidence to justify the significant shift to this robotic surgery that is seen across the UK.</p> <p>Practice is also changing with respect to the emerging use of chemo/radiation and some of the new immunological treatments for some more advanced bladder cancer cases.</p> <p>It is likely that, in the absence of definitive evidence and clear NICE recommendations that practice in the field of bladder cancer will continue to evolve on a Trust by Trust basis. And patients struggle to be well informed as to what they receive in their local or Specialist Trust is the only – or best – option.</p> <p>Even a set of consensus-based recommendations would be helpful at this critical point in time – where practice is changing around us.</p>	<p>evidence once the results are available. An interventional procedure is also linked in the bladder cancer pathway, <a href="#">laparoscopic cystectomy</a> - IP287, which states that it may be performed robotically.</p> <p>Thank you for highlighting the importance of new immunotherapies. We are making an editorial amendment to recommendations 1.7.7 and 1.7.8 which will direct readers to the bladder cancer pathway. The new technology appraisals for immunotherapy are clearly linked within the bladder cancer pathway and as such provide a source of information for newly available therapies.</p> <p>Our guidelines are periodically reviewed according to the <a href="#">NICE manual</a>, however exceptional reviews can be generated if substantial new evidence is identified between the scheduled review dates.</p>
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		<p>There is also now a new class of immunotherapy treatments for bladder cancer. NICE has approved the use of both atezolizumab and Pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma after failed platinum-based chemotherapy. These recommendations were evidence based yet aren't part of the current guidelines. Surely, as a minimum, the guidelines should be reviewed to correct this omission and include guidance relating to the new treatments which are now approved and for the further new treatments coming forward.</p> <p>It has been 4 years since the current guidelines were published. <b>If a full review is not undertaken now, how long will it be before it is?</b> Practices and treatment options are emerging and evolving as we speak – without the certainty of definitive evidence. An early timescale for a review – whatever the evidence available – and a commitment to press for and fund evidence gathering in readiness should be the minimum that bladder cancer patients ought to expect from this process.</p>	
Reading Bladder Cancer Support Group Trust	No	Updating to include comments at 2. is essential to raise GP and public awareness of the symptoms, mainly haematuria.	Thank you for highlighting symptom awareness. No evidence was found at this review regarding increasing awareness, and this may be more appropriate to NICE guideline NG12, suspected cancer: diagnosis and referral. This will be noted for consideration at the next surveillance review for both NG2 and NG12.
The Urology Foundation	No	Not to update the guideline with a refocus on TURBT is a missed opportunity. At the moment the first operation for	Time to definitive diagnosis has been raised by a topic expert in addition to stakeholders during this surveillance review. This

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		bladder cancer (TURBT) stops the 31-day cancer clock, and because it does, hospitals often then take their eye off the ball and inevitably patients face delays including long delays for chemo and cystectomy. There is unanimous opinion among both bladder cancer surgeons and patients that NHSE needs to reclassify TURBT as a diagnostic procedure (as with prostate biopsy which does not stop the clock) with the clock only stopping once the patient has received definitive treatment such as cystectomy.	appears to be an issue with NHS England (NHSE) and cancer waiting times, rather than the guidance, as such we will look into feeding back to NHSE regarding this issue. NG2 lists TURBT as an option in section 1.2 diagnosing and staging bladder cancer. It is also mentioned in section 1.3 – treating non-muscle-invasive bladder cancer, but under the subheading of risk classification, with further bullet points following giving the choice of treatment options. It does not define TURBT as either diagnostic or treatment, however it is part of the recommendations on diagnosis. Advice from topic experts suggests that TURBT may be a suitable definitive treatment for NMIBC but not MIBC.
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**Do you have any comments on areas excluded from the scope of the guideline?**

Stakeholder	Overall response	Comments	NICE response
University of Exeter	Yes	I've looked at the old NG2, and it starts 'diagnosis' with secondary care testing for patients referred (presumably) by GPs. There is no part of NG2 that covers the selection of patients for testing. Of course, NG12 covers that (and it is a remarkably clean split between NG2 and NG12!).	Thank you for your response. We agree that NG12 covers these aspects of diagnosis. The <a href="#">bladder cancer pathway</a> brings together these 2 guidelines for service users.
Roche Products Ltd & Roche Diagnostics Ltd- comprises feedback from both pharmaceutical and diagnostic divisions	Yes	<b><u>Current NG2 - Bladder Cancer: diagnosis and management consultation document recommendations:</u></b>  Under first-line chemotherapy and second-line chemotherapy we would recommend including the most recent Technology Appraisals.	We appreciate the feedback on new immunotherapy treatments. We are adding a cross-referral to the bladder cancer pathway in order to highlight the new technology appraisals from the recommendations on second-line chemotherapy. The bladder cancer pathway brings together all guidance on bladder cancer and is

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	<p><b><u>Suggestions to update the consultation document:</u></b></p> <ul style="list-style-type: none"> <li>- <u>Page 3</u>: View of topic experts</li> </ul> <p>Current situation: "Topic experts highlighted the new evidence available for immunotherapy such as pembrolizumab; however, this area is covered by technology appraisals, TA519 and TA522 and is currently limited to use within the cancer drugs fund. As such we will not be covering immunotherapy in this surveillance review."<sup>1,2</sup></p> <p>If the reason not to update the surveillance is that the area is covered by TA and some indications are only available within CDF. We would like to emphasise that atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA525) is covered by NICE and not within CDF.<sup>3</sup> Therefore, we would suggest that atezolizumab (if not for both indications) would be added to the second-line chemotherapy recommendations. We would also suggest that atezolizumab and pembrolizumab are added to the surveillance review.</p> <ul style="list-style-type: none"> <li>- <u>Page 7</u>: Diagnosis</li> </ul> <p>Current situation: PD-L1 testing is not considered</p> <p>The EMA has recommended that atezolizumab and pembrolizumab should now only be used for first-line treatment of urothelial cancer in patients with high levels of PD-L1 (see definitions below) and the marketing authorisations have been updated to reflect this.<sup>4</sup> The</p>	<p>regularly updated when new technology appraisals and other NICE guidance is created.</p> <p>As PD-L1 testing is specific to atezolizumab and pembrolizumab, the most appropriate place for information relating to this testing is in the relevant technology appraisals, all of which are linked in the bladder cancer pathway. We will however log this issue for consideration at the next review.</p> <p>Thank you for the suggestion regarding the chapter heading for section 1.7 - Managing locally advanced or metastatic muscle-invasive bladder cancer. No evidence was identified at this review to suggest changing the terminology at this time.</p> <p>We will amend our response to the research recommendation to detail our proposed cross-referral to the bladder cancer pathway in light of the new technology appraisals.</p>
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	<p>changes to the respective marketing authorisations for atezolizumab and pembrolizumab are different because the respective trials used different definitions of higher PD-L1 expression. These definitions and the updated marketing authorisations are listed below:</p> <p>Atezolizumab is licensed as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression <math>\geq 5\%</math>. This is defined as the presence of discernible PD-L1 staining of any intensity in tumour infiltrating immune cells covering <math>\geq 5\%</math> of tumour area occupied by tumour cells, associated intratumoural and contiguous peri-tumoural desmoplastic stroma.<sup>5</sup></p> <p>Pembrolizumab is now licensed as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) <math>\geq 10</math>. This is defined as <math>\geq 10\%</math> of tumour cells and mononuclear inflammatory cells within tumour nests and adjacent supporting stroma expressing PD-L1 at any intensity.<sup>6</sup> The CPS is thus the addition of the numbers of positive tumour and mononuclear inflammatory cells and then this sum is divided by the number of all tumour cells, the result being expressed as a percentage (the maximum of which is 100%).</p> <p>NICE updated the relevant guidance (TA492 and TA522) to reflect the new marketing authorisations and NHS England has modified its treatment criteria for use in the Cancer</p>	
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	<p>Drugs Fund.<sup>2,7</sup> The updated treatment criteria can be found on the national CDF list at <a href="https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/">https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/</a> or on the application form(s) on the Blueteq site.<sup>8</sup> PD-L1 testing is also referenced in the 2019/20 National Tariff Payment System under high cost devices and listed procedures 2019/20.<sup>9</sup></p> <p>We would also suggest that PD-L1 testing is recommended for patients before initiating first-line chemotherapy thus treating oncologists can consider available immunotherapies as first-line treatment for their patients with PD-L1 positive tumours samples.</p> <ul style="list-style-type: none"> <li>- <u>Page 25</u>: Managing locally advanced or metastatic muscle-invasive bladder cancer</li> </ul> <p>Current situation: “locally advanced or metastatic <u>muscle-invasive bladder cancer</u>” is used in the title.</p> <p>We would suggest that “locally advanced or metastatic <u>bladder cancer</u>” or “locally advanced or metastatic <u>urothelial bladder cancer</u>” is used as in first-line chemotherapy and second-line chemotherapy recommendations on the same page further below.</p> <ul style="list-style-type: none"> <li>- <u>Page 25</u>: First-line chemotherapy</li> </ul> <p>Current situation: cancer immunotherapies not included.</p> <p>We would suggest that atezolizumab and pembrolizumab are recommended to be offered as first-line treatment for patients with untreated locally advanced or metastatic urothelial carcinoma when cisplatin-containing</p>	
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		<p>chemotherapy is unsuitable, and their tumours express PD-L1 at a level of 5% or more.</p> <ul style="list-style-type: none"> <li>- <u>Page 25-26</u>: Second-line chemotherapy</li> </ul> <p>Current situation: cancer immunotherapies not included.</p> <p>We would suggest that atezolizumab and pembrolizumab are recommended to be offered as second-line treatment for patients with locally advanced or metastatic urothelial carcinoma who have had platinum-containing chemotherapy.</p> <ul style="list-style-type: none"> <li>- <u>Page 36</u>: In patients with incurable locally advanced or metastatic bladder cancer after first-line chemotherapy what is the most effective second-line therapy (including single agent, combination therapy, novel agents or best supportive care)</li> </ul> <p>Current situation: No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</p> <p>We would suggest that immunotherapies are considered in this section based on the NICE pathway recommendations; TA525 and TA519.<sup>1,3</sup></p> <ol style="list-style-type: none"> <li>1. NICE guidance TA519. Available at: <a href="https://www.nice.org.uk/guidance/ta519">https://www.nice.org.uk/guidance/ta519</a> [Last accessed 21/02/19]</li> <li>2. NICE guidance TA522. Available at: <a href="https://www.nice.org.uk/guidance/ta522">https://www.nice.org.uk/guidance/ta522</a> [Last accessed 21/02/19]</li> </ol>	
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		<p>3. NICE guidance TA525. Available at: <a href="https://www.nice.org.uk/guidance/ta525">https://www.nice.org.uk/guidance/ta525</a>. [Last accessed 21/02/19]</p> <p>4. European Medicines Agency. EMA restricts use of Keytruda and Tecentriq in bladder cancer. Available at: <a href="https://www.ema.europa.eu/en/news/ema-restricts-use-keytruda-tecentriq-bladder-cancer">https://www.ema.europa.eu/en/news/ema-restricts-use-keytruda-tecentriq-bladder-cancer</a> [Last accessed 20/02/19]</p> <p>5. NICE Technology Appraisal Programme: Cancer Drugs Fund Data collection arrangement for the single technology appraisal of atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma patients who are considered cisplatin ineligible Re-issue date: July 2018</p> <p>6. NICE Technology Appraisal Programme: Cancer Drugs Fund Data collection arrangement for the single technology appraisal of pembrolizumab for locally advanced or metastatic urothelial cancer where cisplatin is unsuitable Re-issue date: July 2018</p> <p>7. NICE guidance TA492. Available at: <a href="https://www.nice.org.uk/guidance/ta492">https://www.nice.org.uk/guidance/ta492</a> [Last accessed 21/02/19]</p> <p>8. NHS England. Cancer Drugs Fund list. Available at: <a href="https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/">https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/</a> [Last accessed 25/02/19]</p> <p>NHS Improvement. National Tariff Payment System 2019/20: a consultation notice. Available at: <a href="https://improvement.nhs.uk/resources/national-tariff-1920-consultation/">https://improvement.nhs.uk/resources/national-tariff-1920-consultation/</a> [Last accessed 25/02/19]c</p>	
Fight Bladder Cancer	Yes	<p>Apart from the effect of smoking, the current guidelines do not contain advice on prevention of bladder cancer.</p>	<p>Thank you for highlighting the issue of bladder cancer prevention, however this is outside the remit which was for the diagnosis and</p>

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		Current evidence needs to be evaluated in order to help prevent the incidence of bladder cancer in the population.	management of bladder cancer only. However, please note that NICE also has a number of public health guidelines covering primary prevention of lifestyle factors that may be associated with bladder cancer.
British Association of Urological Surgeons (BAUS)	Yes	<p>There has always been a huge gap in the original guideline because the hospital investigation of haematuria was excluded from the scope of the guideline. The updated guidance for TWR is for primary care and does not cover it. This absence has led to confusion and variations in practice that needs addressing.</p> <p>robotic cystectomy had not taken off when the first guidelines were drawn up and should now be reviewed.</p> <p>BAUS and patient groups are concerned about TURBT being defined as a first treatment – this should have been addressed at the last update and was not – it continues to mean patients spend on average about 3 months before they start any treatment in these target driven times.</p> <p>There are now some new biomarkers, and there is some further data about treatments for NMIBC, and MIBC. e.g. device-assisted chemotherapy, Immunotherapy.</p> <p>There is concern about the risk categories for NMIBC. It appears to stem from a lack of understanding of the 2004 ISUP vs 1973 WHO grading systems. A pTaG2 (high grade) bladder cancer is indistinguishable from a TaG3 NMIBC pathologically and as far as we are aware there is no published evidence to demonstrate a difference in behaviour – but the former is intermediate risk and the</p>	<p>Thank you for raising the issue of hospital investigation of haematuria. The scope of NG2 only excludes primary care investigation of haematuria, and as such evidence for hospital investigation could be considered. The evidence found for haematuria at this review was inconclusive and related largely to the use of urinary biomarkers. We will note this issue for consideration at the next surveillance review.</p> <p>We have reviewed new evidence for robotic cystectomy as part of this surveillance review, as it was raised by topic experts as an emerging area. The evidence showed improvements in a number of patient outcomes with robotic cystectomy compared to open cystectomy, and a potential cost saving due to a reduction in transfusions compared to open cystectomy. The bladder cancer pathway contains a link to an interventional procedure guidance, IPG287 – laparoscopic cystectomy which states the procedure can also be performed using robotic methods. We are also tracking an ongoing Cochrane study in this area and will assess any impact when the results are available.</p> <p>Thank you for highlighting the issues regarding definitive treatment for bladder cancer. The recommendations in NG2 state to offer TURBT in sections 1.2 – diagnosing and staging bladder cancer, and section 1.3 states to offer a second TURBT within 6 weeks if the first showed high risk NMIBC. Advice from topic experts suggests that TURBT may be suitable as definitive treatment for NMIBC but not for MIBC. For high risk NMIBC a second TURBT could be</p>

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		<p>latter high risk. In addition, the risk categorisation adopted omits T1 High grade altogether - some labs will report this instead of T1G3. In our opinion the guidance needs to acknowledge that the 2 systems exist and either support 1 or adopt a classification that covers both. In effect the NICE guideline appears to have adopted a new and different risk classification to the standard (EAU) classification and the one adopted in the NICE guideline has never been validated. BAUS believes this should be changed.</p>	<p>offered which may result in reclassification to MIBC or could be considered definitive treatment, as could commencement of NMIBC. The guideline indicates which treatments are effective for the relevant stages of bladder cancer, with NHSE being responsible for appropriately commissioning those services. We will look in to feeding back this information to NHSE.</p> <p>Evidence for urinary biomarkers was considered in our surveillance review, however the results were not as accurate as cystoscopy. We are providing a cross-referral from recommendations 1.7.7 and 1.7.8 to the bladder cancer pathway to further highlight the new technology appraisals available regarding immunotherapy.</p> <p>Thank you for the feedback on tumour classification. The risk categories in the guideline were developed in order to make clear recommendations for management of NMIBC. They were created by the Guideline Committee based on evidence reviews and clinical opinion. This surveillance review did not find any evidence relating to pTaG2/TaG3 classification. We will log this issue for consideration at the next surveillance review.</p>
Action Bladder Cancer UK	Yes	<p>The scope of the previous guidelines was constrained to the part of the pathway from diagnosis on. In the absence, currently, of a screening option for bladder cancer the detection and investigation of bladder cancer is critical and should be included in any review.</p>	<p>Thank you for highlighting the issue of bladder cancer screening and detection, however it is outside the remit which was for the diagnosis and management of bladder cancer only. Other guidelines contain cross-referrals for bladder cancer, including the draft guidance on urinary incontinence and pelvic organ prolapse, which highlights for women with haematuria or recurrent UTI that the recommendations in NG12 – <a href="#">suspected bladder cancer</a> should be followed. NG12 also has a research recommendation which highlights the need for further studies on primary care testing of haematuria.</p>

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Reading Bladder Cancer Support Group Trust	Yes	We believe that at diagnosis stage, the guidelines should include the recommendation to GPs that patients over 35 years old who present with haematuria, be referred automatically for cystoscopy, not just treated with antibiotics for suspected UTI. Bladder cancer is increasing in the population, often diagnosed late (especially in women) due to lack of urological referral and thus expensive to treat.	Thank you for raising the issue of age for automatic cystoscopy referral. Recommendations for GP referral are covered by NICE guideline NG12, suspected cancer: recognition and referral. The issue of age has been added to the issue log for NG2 for consideration at the next surveillance review.
The Urology Foundation	Yes	There is currently nothing in the guideline about what investigations should be done in the haematuria clinic for maximum cost-effectiveness. This was not part of the scope of the original guideline and was left out and is a glaring omission.	Thank you for highlighting the issue of haematuria. Haematuria testing in primary care is outside the scope of this guideline. Some evidence was found at this review regarding haematuria and urinary biomarkers however the results were not as accurate as cystoscopy for bladder cancer investigation. As such no impact is anticipated at this time. We will note this issue for consideration at the next surveillance review.

### Do you have any comments on equalities issues?

Stakeholder	Overall response	Comments	NICE response
University of Exeter	Yes	We all recognise the gender differences in diagnosis, and some of them clearly reside in primary care (the classic being the mis-attribution of cancer symptoms to recurrent UTIs in elderly women). There may be similar structural problems in secondary care that disadvantage women – though I don't feel qualified to comment.	Thank you for the studies provided by Yin Zhou and Yoryos Lyratzopoulos. The study on gender inequalities is outside of the search dates for this review and as such will not be included. The study on fast track referrals is not specific to bladder cancer, and instead refers more generally to all cancer types. As such this does not meet our inclusion criteria for this review. As you note, referral from primary care is more relevant to NG12: Suspected cancer,

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		<p>Awkwardly, there's been little published from primary care since we did the NG12 searches that would allow a 'NG12 new' or NG2-new to give new bladder recommendations. Yin Zhou and Yoryos Lyratzopoulos have shown there is a 'problem' but not provided gender-specific PPVs that would have led to gender-specific recommendations. My view is that NG12 recommendations were pretty good – but that there is differential <u>application</u> of them by GPs.</p> <p>Overall, I have no problem with no revision of NG2, though eliminating the gender inequalities may be tricky. Perhaps NG2 should bring across the NG12 recommendations into a first chapter – and add to them a pointer about 'emerging evidence that women are disproportionately under-referred'.</p>	<p>recognition and referral. This issue has been added to the issue log for both NG2 and NG12 for consideration at the next surveillance review.</p> <p>The <a href="#">bladder cancer pathway</a> brings together recommendations from both guidelines in an interactive flowchart. From the bladder cancer pathway, NG12 is accessible following the link 'adult referred to secondary care with suspected bladder cancer'.</p>
Roche Products Ltd & Roche Diagnostics Ltd- comprises feedback from both pharmaceutical and diagnostic divisions	No	None	Thank you for your response.
Fight Bladder Cancer	Yes	<p>Women are much more likely have late diagnosis and late referral due to misdiagnosis</p> <p>Indeed, the 2015 guidelines state that:</p> <p>Women have between 15% and 45% higher odds of advanced disease depending on the country and whether non-malignant bladder tumours (D41.4, D09.0) are included in analysis. Survival at both 1 and 5 years is higher</p>	<p>Thank you for your feedback in this area. No evidence regarding gender issues was found at this surveillance review. Several guidelines provide cross-referrals to NG12 – suspected cancer to highlight the process for investigation potential bladder cancer. A guideline is currently in development for urinary incontinence in women which includes a recommendation on investigation of potential bladder cancer symptoms. We will request that the urinary</p>

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		in men than in women. In England in 2006-10 one-year survival in men was 77% compared to 64% in women. In 2006-10 five-year survival in men was 58% compared to 47% (Figure 21). In Wales in 2007-11 one-year survival in men was 76% compared to 60% in women, and in 2007-11 five-year survival in men was 54% compared to 50%	incontinence in women pathway includes a link to NG2 – bladder cancer.  This issue will be considered at the next surveillance review.
British Association of Urological Surgeons (BAUS)	Not answered	No comments provided	Thank you.
Action Bladder Cancer UK	Yes	<p>Poorer survival and later presentation for women continues to be a serious concern. Specific measures and recommendations are required to address this issue – notably at the level of Primary Care.</p> <p>Bladder cancer patients are disadvantaged by the perverse use of the 1<sup>st</sup> TURBT (Transurethral Resection of a Bladder Tumour) as the 62-day target timescale for waiting times – for all patients – when for many patient’s definitive further treatment is required – usually very urgently. Serious delays are a continuing major issue and they have a significant impact, inevitably, on outcomes.</p> <p>And there is a more general issue that bladder cancer does not attract the level of funding or focus that it merits on the basis of its mortality and survival statistics.</p>	<p>Thank you for your feedback. The issue of later presentation for women has been logged for consideration at the next surveillance review. Several guidelines link to NG12 – suspected cancer which includes recommendations on suspected bladder cancer. This includes draft guidance for urinary incontinence in women which has a recommendation specifically for bladder cancer investigation.</p> <p>Thank you for highlighting the issues regarding waiting times. This appears to be an issue with commissioning of treatment services and as such we will look into feeding back information on this issue to NHSE. The recommendations in NG2 state to offer TURBT in sections 1.2 – diagnosing and staging bladder cancer, and section 1.3 states to offer a second TURBT within 6 weeks if the first showed high risk NMIBC. Advice from topic experts suggests that TURBT may be suitable as definitive treatment for NMIBC but not for MIBC.</p> <p>NG2 has 18 research recommendations which may help to direct areas for future research. We have also identified 15 ongoing studies, including imaging alternatives to TURBT and photodynamic</p>

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			light guided TURBT. We will track these studies and evaluate the results for impact when available.
Reading Bladder Cancer Support Group Trust	No	No comments provided	Thank you for your response.
The Urology Foundation	Yes	While men are twice as likely to contract bladder cancer, it remains the case that women are more likely to die early from it and this is largely due to late diagnosis. Women present with symptoms at primary care level many more times before they are referred. A guideline that includes more information about what investigations should be done at primary and secondary care level and in haematuria clinics may help in that regard.	Thank you for highlighting this issue. Several guidelines have cross-referrals to NG12- suspected cancer. This includes an in development guideline for women with urinary incontinence with a specific recommendation for bladder cancer. There is also a research recommendation in NG12 requesting evidence on primary care diagnosis of haematuria which is hoped to increase awareness of bladder cancer in women. No new evidence was found at this review, as such the issue will be logged for consideration at the next surveillance review.

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