NICE National Institute for Health and Care Excellence

2023 surveillance of metastatic malignant disease of unknown primary origin in adults: diagnosis and management (NICE guideline CG104)

Surveillance report

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Surveillance decision

We will not update the NICE guideline on metastatic malignant disease of unknown primary origin in adults at this time.

We will actively monitor the availability of new evidence on:

- diagnosis of carcinoma of unknown primary (CUP) in adults using 'molecular diagnostic tests' (this includes gene-expression-based profiling), diagnostic imaging techniques (MRI and PET/CT scans), and immunohistochemical methods.
- molecular diagnostic tests for informing the management of CUP in adults.

The impact of evidence on current recommendations will be evaluated as soon as possible following publication to inform decisions on the appropriate time for a full update of the guideline. A randomised controlled trial (RCT) investigating molecular diagnostic tests and guided therapy is due for completion in 2024 and will be actively monitored (CUPISCO trial).

Due to changes in practice, we will replace recommendation 1.2.2.9 that says not to use gene-expression-based profiling for diagnosis, with a cross-reference to the NHS Genomic Medicine Service, which provides information on available options for gene-expression-based profiling. We will also withdraw recommendation 1.3.2.4, as while insufficient evidence exists for a recommendation on treatment options informed by the results of gene-expression-based profiling, we wish to remove the 'do not use' statement as there is ongoing research within this area.

Reasons for the decision

The primary focus of this surveillance review has been on molecular diagnostic tests (gene-expression-based profiling) following an external enquiry which questioned whether recommendations 1.2.2.9 and 1.3.2.4 were out of date. All other areas of recommendations within the NICE guideline were considered for the need to update. Topic experts expressed that although some recommendations could be updated now, it would be appropriate to wait until the evidence is available around molecular diagnostics and guided therapy before a full update of the NICE guideline. They thought that recommendations on organisation of services and support, diagnosis, factors influencing management

decisions, managing specific presentations and systemic treatment should be considered for update when the molecular diagnostic test evidence is available.

The evidence that will be actively monitored as a result of the findings of this surveillance review relate to recommendations in the diagnosis and management decisions sections of the guideline. Active monitoring refers to the process of continual checks for the publication of evidence.

Overview of 2023 surveillance methods

The surveillance process considered evidence presented from:

- The evidence review that informed the development of the guideline in 2010.
- The 2017 exceptional surveillance review.
- The intelligence (related NICE guidance, NICE quality standards, NIHR signals, Cochrane reviews) and topic expert views reported in a standard surveillance review which commenced in 2020, but was paused due to the COVID pandemic. The responses from topic experts are included in this report (see views of topic experts from 2020).
- Feedback from topic experts completed for this surveillance review (see views of topic experts from 2023).
- A search for ongoing research on CUP was completed on ClinicalTrials.gov, the ISRCTN Registry, the Cochrane CENTRAL database of ongoing clinical trials and the Cancer Research Database (provided by the National Cancer Research Institute).
- Examining the NICE event tracker for relevant ongoing and published events.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Summary of recommendations considered during the surveillance review

Gene-expression-based profiling to identify primary tumours in patients with provisional CUP

Recommendation 1.2.2.9 states that gene-expression-based profiling should not be used to identify primary tumours in patients with a provisional diagnosis of CUP. This recommendation was published in 2010 and was based on evidence from 19 studies, which were of low quality. This was due to the studies being designed to report on diagnostic development and to validate tests, so the link to patient benefit had not been established.

An exceptional surveillance review in 2017 assessed evidence on the use of gene-expression-based profiling for the diagnosis of CUP. It was reported to be associated with high rates of accuracy in classifying tumours and as 'showing promise'. Despite this, the evidence base was assessed as not being sufficient to confirm a benefit of gene-expression-based profiling over the immunohistochemistry techniques in recommendation 1.2.2.7.

A surveillance review of the NICE guideline was started in 2020, which included a consultation with topic experts. Topic experts raised the issue that the recommendation on gene-expression-based profiling for the identification of primary tumours was not reflective of clinical practice and an update maybe required. This was paused due to the COVID-19 pandemic.

An external enquiry was received in 2022, which highlighted that recommendation 1.2.2.9 did not reflect current practice and that genetic testing is available within the NHS (National Genomic Test Directory). However, evidence provided as part of the external enquiry and from topic experts is limited to observational studies and technology development studies (see evidence considered in surveillance). These studies report the proportion of patients in which the primary origin of cancer is successfully identified but do not report on the impact that this diagnosis has on patient outcomes. The current level of RCT evidence in this area is limited, but a large RCT (CUPISCO) is due to complete and publish in 2024 (see ongoing research). This is a phase 2 trial for people who receive disease control with initial platinum based therapy for 3 cycles and are then randomised to more platinum or targeted/immunotherapy based on genomic profile. The primary outcome

is progression free survival. The results of this trial are seen as directly relevant to the decision on whether this guideline is updated, therefore we will actively monitor the availability of this trial's results.

Topic experts also identified that the term 'gene-expression-based profiling' may not be a true representation of the processes used in the genomic testing that is currently available. They suggested that a more appropriate terminology is 'molecular diagnostic test' or 'molecular profiling' as this reflects the molecular and genetic testing which is available to CUP patients. These molecular diagnostic tests include not only gene-expression-based profiling but also next-generation genetic or genomic profiling for actionable mutations and immuno-oncology profiling. The terminology of 'gene-expression-based profiling' will therefore be changed to 'molecular diagnostic test'.

Molecular diagnostic testing when deciding which treatment to offer patients with confirmed CUP

We will withdraw recommendation 1.3.2.4, which states that gene-expression-based profiling should not be used when deciding which treatment to offer patients with confirmed CUP. Topic experts highlighted the need to remove the 'do not use' statement on gene-expression-based profiling as it is currently being used to guide treatment both inside and outside of trials in the UK. The removal of this recommendation also aligns with the European Society for Medical Oncology (ESMO) guideline, which advises that next-generation-sequencing findings are discussed at a molecular tumour board to guide treatment. These ESMO recommendations are based on studies, which report the success of genomic profiling or next-generation-sequencing to identify the primary origin and inform treatment for CUP. Further studies on whether this results in improved outcomes for CUP patients are required before the evidence for these techniques can be considered in an update of the NICE guideline. The CAPSICO study has potential to provide these results, so this and the other studies described in the ongoing research section will be actively monitored.

Diagnostic tests

Topic experts highlighted advances in the evidence base for MRI, PET/CT and immunohistochemistry since the publication of the NICE guideline in 2010. For example the ESMO guidelines recommend a PET/CT and brain MRI for patients with single-site or oligometastatic CUP. In comparison the NICE guideline only recommends breast MRI for patients with adenocarcinoma involving the axillary nodes (recommendation 1.2.2.4).

Similarly the NICE guideline only recommends a PET/CT scan for patients with provisional CUP presenting with cervical lymphadenopathy or extra-cervical presentations (recommendations 1.2.2.5 and 1.2.2.6).

The Royal College of Pathologists published a dataset for histopathological reporting of CUP in 2018. This provides a broader set of markers to be used in immunohistochemistry panels than those provided in the NICE guideline, which recommends cytokeratin 7 (CK7), CK20, thyroid transcription factor-1, placental alkaline phosphatase, oestrogen receptor and PSA (recommendation 1.2.2.7). This dataset is currently being updated and will be monitored for further advances and this will inform the timing of the guideline update. There is an ongoing study on PET/CT scanning for CUP, this is due to complete in 2024 (FAPI-CUP, see the ongoing research section) and is part of the active monitoring planned for this area of recommendations. A search for ongoing studies will be established in this area to identify other relevant studies for active surveillance.

Evidence considered in surveillance

During this surveillance review we considered studies identified by the external enquiry received in 2022. This highlighted the role of genomic hubs in the NHS and raised concerns that an update was needed of the NICE guideline. There are 2 additional studies that were identified by topic experts in 2023 that have also been considered and summarised below.

The evidence available on molecular diagnostics (gene-expression-based profiling) for the identification of primary tumours and treatment planning currently includes retrospective analyses, prospective observational studies and an RCT with a low number of participants. These focus on the proportions of patients that received molecular guided therapy or genomic profiling. This evidence is not currently sufficient to change our recommendations, we would need to see the impact on patient related outcomes and cost effectiveness. Other studies report on the development of algorithms for molecular analysis, the success of using a specialist CUP team or the development of genomic profiling technologies. The evidence reviewed is summarised here:

- Fusco et al. 2022 is a retrospective review of patients with a CUP diagnosis, between 2017 and 2019. The study identified 95 patients who received next-generation sequencing. It then presents results on those that went on to have molecularly guided therapy. Molecularly guided therapy was an option for 52 (55%) of these patients, but only 17 were prescribed molecularly guided therapy. The median overall survival for those receiving molecularly guided therapy was 23.6 months compared to 14.7 months for those receiving standard treatment, although this was not statistically significant (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.27 to 1.21; p=0.13). A primary tumour type was suggested by the next-generation sequencing results in 14 patients (15% of total patient group) of the total CUP participants.

- Ross et al. 2020 is a retrospective analysis of adenocarcinoma and undifferentiated CUP specimens (n=303) from a real-world comprehensive genomic profiling database (FoundationCore). The samples had been previously referred for comprehensive genomic profiling. A hybrid capture-based CDx assay was used to determine the presence of genomic alterations, microsatellite instability, tumour mutational burden, genomic loss of heterozygosity and programmed death-ligand 1 positivity. Results report that 32% of patients were eligible for targeted therapy.

- Kato et al. 2021 reports on 1,931 samples from CUP patients assessed non-invasively with liquid biopsies interrogating cell-free DNA (cfDNA). The next-generation sequencing panel (73-74 genes) is designed to identify (cfDNA) alterations. One or more cfDNA alterations were found in 1,739 (90%) patients. This high frequency of cfDNA alterations suggests the potential for a high degree of matching to therapy.

- Westphalen et al. 2022 is a descriptive molecular analysis of 346 people with unfavourable CUP recruited to the CUPISCO trial. Comprehensive genomic profiling was performed using the F1CDx assay. Gene alterations were analysed using multiple correspondence analyses and hierarchical clustering. The most frequent gene alterations were TP53 (44%), CDKN2A (32%), KRAS (21%; 2% G12C), CDKN2B (21%), ARID1A (13%), STK11 (13%), MTAP (12%), PIK3CA (10%), MYC (8%), PBRM1 (8%), BAP1 (8%) and FGFR2 (8%). This study reported that 30% of patients carried a gene alteration that could be targeted in personalised therapies and that CUP can be clustered based on molecular profiling.

- Nguyen et al. 2022 reports on the development of a machine learning classifier for whole-genome sequencing. The dataset was based on 6,756 whole-genome sequenced primary and metastatic tumour samples. This used simple and complex somatic drivers and passenger mutations to develop a tumour of unknown origin classifier. The classifier distinguished 35 cancer subtypes. Results suggest that 58% of tumours of unknown of origin would be determined.

- Stares et al. 2021 is a UK based study on prospectively gathered data from 1,225 patients referred to a regional CUP team over a 10 year period. The study reported on the benefits of referral to a specialist CUP service. Confirmed CUP was diagnosed in 25% of patients and primary metastatic cancer was identified in 36% of cases. Median survival of patients was 4 months in those with a confirmed CUP diagnosis and 9 months where a primary metastatic cancer had been identified.

- Fizazi et al. 2019 is an RCT of 243 patients with pathologically-confirmed metastatic CUP. Patients were randomised to either empiric chemotherapy (Cisplatin 100 mg/m² d and Gemcitabine 1250 mg/m²) or systemic treatment tailored by molecular gene expression analysis. Treatment was tailored by molecular test results in 91 of the 123 patients in the systemic treatment group. Median progression free survival was 5.3 months for the empiric chemotherapy group and 4.6 months for the systemic treatment group, this showed no significant difference between the 2 groups (HR 0.95; 95% CI 0.72 to 1.25; p=0.7).

Ongoing research

We checked for relevant ongoing research registered on ClinicalTrials.gov, on ISRCTN registry and on the Cochrane CENTRAL database of ongoing clinical trials. The National Cancer Research Institute provided results from a search of the Cancer Research Database, which aims to track all ongoing UK cancer research studies. The searches returned 55 results, 8 of these are relevant to the CUP guideline and are being monitored by the NICE surveillance team:

- CUPISCO is a phase 2, multicentre RCT that compares the efficacy and safety of molecular diagnosis and guided therapy for CUP, based on genomic profiling, with an active comparator of platinum-based chemotherapy (NCT03498521). The sample size is 790 across 141 study locations. Study completion is due in October 2023.

- CUP-COMP is a UK based cohort study, recruiting patients with a confirmed diagnosis of CUP (NCT04750109). It aims to assess genomic sequencing (both in tissue and blood) for diagnosis and to inform treatment in CUP patients, including a comparison of the effectiveness of tissue and blood-based biomarkers.
- CUPem is a non-randomised trial aiming to establish how well tolerated pembrolizumab is in comparison to conventional chemotherapy in CUP patients (NCT03752333). The study completion date was estimated to be November 2022, but results are still to be published.
- IMPACT is a retrospective observational study of 3,026 patients using previously collected biopsy samples to provide biomarker data about a patient's cancer; CUP is a subgroup (NCT01505400). This is then used to inform molecularly targeted therapies. The study completed in January 2023 and is run by the same group as the OCTANE study, described below.
- OCTANE is a prospective observational study with 10,000 participants with advanced, incurable tumours, including CUP (NCT02906943). Archival formalin-fixed paraffin embedded tumour tissue is collected and targeted DNA sequencing completed. Samples are used for future research purposes, so there is a likelihood that the guidance of therapies for CUP will be investigated. Recruitment is expected to continue until August 2026.
- UCSD_PREDICT is a cohort study assessing 10,000 patients with a cancer diagnosis, including a subgroup of CUP (NCT02477931). Genetic or molecular profiling is used to provide personalised care and treatment. Patient outcomes include tumour response, time to treatment failure, survival and toxicity.
- FAPI-CUP is a single arm cohort study aiming to evaluate the diagnostic ability of PET-CT scans for CUP. This study is evaluating the use of fibroblast activation protein as a radiotracer that can bind to CUP (NCT05263700). It aims to recruit 150 patients and is estimated to complete in February 2024.

These studies may have the potential to change recommendations. Therefore, we plan to regularly check whether they have published results and evaluate the impact on current recommendations as quickly as possible.

2020 surveillance review

Intelligence gathering was completed during the surveillance review that was paused in

2020 due to the COVID-19 pandemic. This did not identify any directly relevant Cochrane reviews, NIHR alerts or Campbell collaboration reviews. There were 2 other guidelines highlighted by topic experts, detailed in the section below.

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. Responses were received from 14 topic experts on the need to update the NICE guideline, 7 said that an update was required and 7 said an update was not required. The 14 topic experts were made up of 4 consultant radiologists, 3 consultants in palliative medicine, 3 consultant histopathologists, 3 consultant clinical oncologists and a consultant respiratory physician. The responses to the questionnaire have been grouped into recommendation areas:

Organisation of services

Concern was raised by 1 topic expert over the concept of a CUP team at the hospital or cancer-centre level, as recommended in section 1.1.1. They suggested a potential alternative could be that 1 team or department take the lead role for each site, this would be decided locally, an example could be the Upper-Gastrointestinal tract team as they are possibly already the most diverse staff group. It was considered that this would make administrative and clinical ownership less costly, but could have other advantages such as in reducing delay.

It was reported by 1 topic expert that over 55% of CUP patients present at A&E (no reference provided). They said that a clear directive would be beneficial to emphasise the working relationship between the CUP team and the A&E team in the guideline. This could also consider the role of the GP and how the NICE guideline on metastatic malignant disease of unknown primary origin links to the NICE guideline on recognition and referral of suspected cancer.

Diagnosis

Six of the topic experts stated that the diagnosis section of the NICE guideline needed updating. One topic expert said that a review of all tests included in the section was needed. Two topic experts suggested that the NICE guideline should be updated to reflect the Royal College of Pathologists guidance, educational information and reporting proformas for histopathological reporting of CUP, published in 2018. The gene expression-

based-profiling (recommendation 1.2.2.9) was highlighted as being out of date by 2 topic experts.

One topic expert highlighted emerging evidence on the role of whole-body MRI and PET/MRI which could provide a second diagnostic phase (no reference was provided). MRI is currently only recommended for patients with breast cancer involving the axillary nodes (recommendation 1.2.2.4). Similarly PET-CT scans are currently only recommended for patients with specific presentations of extra-cervical or cervical lymphadenopathy with no primary tumour identified on ear, nose and throat panendoscopy (recommendations 1.2.2.5 and 1.2.2.6). This highlights the need for active surveillance in this diagnostic area.

A topic expert suggested that the evidence base for FDG-PET scanning needs reviewing as it may lead to an increase in diagnostic accuracy, reduced delays and a lower number of investigations needed. Although it was highlighted by a different topic expert that a lack of availability of FDG-PET scanning and significant cost may be a potential barrier to implementation in many NHS hospitals.

The need to include recommendations on somatostatin receptor scintigraphy (also called 'octreotide scan') for neuroendocrine tumours was suggested by 1 topic expert.

A topic expert commented that Whole-Body-Diffusion Weighted Imaging (WB-DWI) should be investigated as a possible addition to the recommendations, but did note that significant further research may be needed.

Treatment

One topic expert identified that a large amount of research is ongoing in personalised therapies. They suggested that the use of biomarkers to give personalised treatments for specific tumours and cancers needed to be accounted for in the recommendations. The use of circulating tumour DNA as markers of tumour recurrence and behaviour also has a growing evidence base that could impact on the guideline. This is relevant to recommendation 1.3.2.4.

A review of all treatments used to manage CUP was proposed by 1 topic expert as they thought that new evidence was likely in this area, although no references were provided. There was also a suggestion of a flowchart to inform the clinical management or a prognosticator scheme for patients presenting with CUP.

General

Two topic experts identified guidelines that have been updated recently, ESMO's CUP: Clinical practice guideline for diagnosis, treatment and follow-up (2022) and the American Cancer Society's guidance on the causes, risk factors, prevention, early detection, diagnosis, staging and treatment of CUP (2018). Guideline development and healthcare systems differ and as such European or US guidance may not be directly applicable to the UK setting. The topic experts commented that these include diagnostic and treatment regimens not detailed in the NICE guideline. Examples of the recommendations included by ESMO and not detailed in the NICE guidelines are provided below. The ESMO guideline provides the level of evidence that has informed their recommendations. This applies an adapted version of the Infectious Diseases Society of America - United States Public Health Service Grading System, which ranges from level 1: large RCTs of good methodological quality, to level 5: case reports or studies with no control group. This highlights that many of the ESMO recommendations are based on low quality evidence. The ESMO guideline recommends that:

- Next-generation-sequencing be carried out for diagnostic purposes, the evidence arises from retrospective or case control studies (level 4 evidence).
- MRI imaging of neck, thorax, abdomen and pelvis is completed for all patients, based on evidence from retrospective or case control studies (level 4 evidence).
- A strategy for prognosis should be assessed using risk score based on ECOG PS and serum LDH levels, based on evidence from retrospective or case control studies (level 4 evidence).
- FDG-PET–CT imaging is generally recommended for single-site/oligometastatic cases that warrant ablative locoregional treatment as well as for patients with head and neck CUP, based on evidence from retrospective or case control studies (level 4 evidence).
- Hyperthermic intraperitoneal chemotherapy may be an option for patients with ovary-like and colon-like CUP, based on evidence from retrospective or case control studies (level 4 evidence).

There are also recommendations based on higher quality evidence in the ESMO guideline that do not exist in the NICE guideline, 2 examples are:

- FDG-PET-CT imaging is generally recommended for single-site/oligometastatic cases that warrant ablative locoregional treatment as well as for patients with head and neck CUP, based on small RCTs or RCTs with lower methodological quality (level 2 evidence).
- In patients with NTRK fusion-positive CUP, treatment with an NTRK inhibitor is recommended, based on evidence from prospective cohort studies (level 3 evidence).

Views of topic experts 2023

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. In addition we received completed questionnaires from topic experts involved with the Royal College of Pathologists dataset for CUP. We also received a response from the senior clinical lecturer who raised the enquiry with NICE in 2022, which prompted this surveillance review. The topic experts completed a questionnaire about developments in evidence for diagnostics, treatment and services related to the guidelines.

We received 7 questionnaire responses from topic experts including: 2 consultant radiologists, 2 consultants in palliative medicine, a clinical oncologist, a senior clinical lecturer in experimental cancer medicine and a combined response from a professor and a consultant of pathology.

Molecular diagnostic tests (gene-expression-based profiling) to identify primary tumours

We asked topic experts if they agreed that the evidence base on molecular diagnostic tests (gene-expression-based profiling) should be monitored, with a view to updating this area as and when 'sufficient' evidence is available. All agreed with this statement. It was noted that ongoing research is likely to influence future management of this area and an update to the guideline once evidence is available will be necessary, timely and helpful. Reference was made to the current paucity of RCT evidence and that the CUPISCO study may provide practice changing evidence. One topic expert confirmed that the ESMO guidelines also make a similar statement: 'The clinical utility of gene expression profiling to help elucidate the likely primary is not currently supported by high-level evidence. Consequently, it is not generally recommended outside of clinical research'.

Following this, topic experts were asked whether they agreed that the wording of

recommendation 1.2.2.9 should be changed from 'Do not use gene-expression-based profiling to identify primary tumours in patients with provisional CUP' to 'For information on gene-expression-based profiling to identify primary tumours in patients with provisional CUP, see the NHS Genomic Medicine Service'.

Five topic experts agreed that the wording should be changed and that it is a clinically appropriate update for UK NHS practice at this juncture.

There was however a concern raised by 1 topic expert that this wording may result in inappropriate use of genetic profiling. This focussed on the potential of a 'free for all' scenario to be created unless a clear directive was in place. They suggested a flowchart to demonstrate where the application could be considered or whether it should be restricted to research. It is not considered possible for NICE to develop a flowchart at this time, due to a lack of evidence on the effectiveness of molecular diagnostic testing to identify primary tumours in patients with provisional CUP. This could be considered for the updated guidelines, with the evidence from the CUPISCO trial likely to be crucial in developing a flowchart.

A further concern was raised by 1 topic expert that the labelling of techniques as gene-expression-based profiling may not be the most accurate terminology. They highlighted that in this area of research there are many non-gene-expression-based profiling techniques that aim to identify likely primary sites which are mostly DNA-based and could be used to inform therapeutic options. They suggested a change to 'molecular diagnostic tests' or 'molecular profiling'. The need for this change is confirmed by the language used in the evidence we have considered during this surveillance review. These studies used terms that may not be covered by gene-expression-based profiling, such as: next-generation-sequencing, molecular guided therapy, genomic alterations, molecular analysis and whole-genomic sequencing.

One consideration when making a change is the consistency of terms across NICE guidelines. The term 'gene-expression-based profiling' is not used in any other NICE guideline so consistency in terminology across other guidelines is not seen as a barrier to removing this description. 'Molecular diagnostics' is a term currently used in NICE's guidelines on brain tumours (primary) and brain metastases in over 16s and haematological cancers: improving outcomes. Another potential alternative is 'genomic biomarker-based', this is used in 3 NICE guidelines which all refer to cancer treatment with a link to the NICE topic page on genomic biomarker-based cancer treatments. These are NICE's guidelines on advanced breast cancer: diagnosis and treatment, oesophago-gastric

cancer: assessment and management in adults and prostate cancer: diagnosis and management. The recommendation we are considering here is focussed on the identification of tumours rather than treatment, so this description with a link to the genomic biomarker-based treatments page is not relevant to this recommendation. It therefore seems reasonable to use the molecular diagnostic tests terminology for this recommendation.

We will therefore adopt the molecular diagnostic test terminology and incorporate this into the recommendation wording that was agreed by 5 of the 7 topic experts:

1.2.2.9 For information on molecular diagnostic tests to identify primary tumours in patients with provisional CUP, see the NHS Genomic Medicine Service.

Molecular diagnostic tests (gene-expression-based profiling) when deciding on treatment

The topic experts were asked whether they agreed that recommendation 1.3.2.4 should be withdrawn. Six of the 7 topic experts agreed that this recommendation should be withdrawn and that the evidence be monitored to inform when an update will be appropriate. The topic expert that didn't agree with the proposal was concerned this may result in the inappropriate use of genetic profiling, suggesting that clear guidance on when the application could be used would help to avoid a 'free for all' approach. This could be considered in future updates but currently there is no evidence to direct this development.

The topic experts were then asked whether each of the areas of the guideline required an immediate update or could wait until we have sufficient evidence on gene-expression-based profiling, so that a full review can be completed at this later date. Their responses are summarised in the recommendation areas:

Organisation of services and support

All topic experts agreed that the recommendation section on organisation of services and support could be updated when the molecular diagnostic tests evidence becomes available.

Diagnosis

There was agreement from 6 of the 7 topic experts that the recommendations on

diagnosis should be updated when the molecular diagnostic tests evidence becomes available. The use of positron emission tomography–computed tomography (PET/CT) was raised by 1 topic expert. They reported that although the evidence base is low quality, PET-CT scans are seen as an appropriate test for CUP by clinicians. Given the increased availability of PET/CT in the NHS it would be reasonable to update the guidance. The search for ongoing studies conducted as part of this surveillance review identified a study that is assessing PET-CT scans in CUP patients. Although it is a cohort study with no active comparison, the results might inform recommendations 1.2.2.5 and 1.2.2.6, so it would be beneficial to perform active surveillance on this area of evidence.

Immunohistochemistry was also identified as an area for ongoing active surveillance by 1 topic expert. It was suggested that markers recommended for diagnosis have increased in number and a broader panel of markers are now available to pathologists. As identified in 2020 by topic experts, a key data source to consider when updating this area would be the Royal College of Pathologists guidance on histopathological reporting of CUP and malignancy of unknown primary origin. This dataset was published in 2018 and a second edition is in preparation.

Whole-body diffusion weighted MRI (WB-DWI) was also identified as an area for update by 1 topic expert. WB-DWI has shown promise in the diagnosis of multiple myeloma and gastric cancer due to a high contrast resolution which may provide a higher diagnostic performance. A case report has shown potential for WB-DWI to be useful in CUP patients, but further research would be required before this could be considered for our recommendations.

As a result of these issues being raised by topic experts it was decided that a search would be developed for these diagnostic areas and the evidence actively monitored.

Factors influencing management decisions

All topic experts agreed that an update of recommendations on factors influencing management decisions could be delayed until the molecular diagnostic tests evidence becomes available. It is anticipated that the new evidence on molecular diagnostics (if found to be effective) would feed into management decisions.

Managing specific presentations

There were comments from 2 topic experts that the ESMO guidance has been updated

recently with specific presentations and the NICE guidelines may need to incorporate these. The section on managing specific presentations in the NICE guideline provides detail on presentations that may benefit from radical treatment. The presentations covered are squamous carcinoma involving upper- or mid-neck nodes and the inguinal nodes, adenocarcinoma involving the axillary nodes and solitary metastases. The ESMO guidance provides specific therapies for breast-like, renal-like, ovary-like and colon-like CUP.

The topic experts said that these changes should be considered when the update of the NICE guideline is completed. All topic experts agreed that recommendations on managing specific presentations could be delayed until the molecular diagnostic tests evidence becomes available.

Systemic treatment

All topic experts agreed that the recommendations on systemic treatment should be updated when further results are available on molecular diagnostics and genomic medicine. It was detailed by 1 topic expert that no evidence exists at the moment for new systemic therapy but the CUPISCO study may provide practice changing evidence.

Views of stakeholders

We did not consult with stakeholders. Although we are not updating the guideline, we will be actively monitoring evidence as it publishes on molecular diagnostics, PET/CT, immunohistochemistry and MRI techniques and the impact of new evidence will be evaluated as it publishes.

Equalities

An equalities and health inequalities assessment was completed during this surveillance review. See appendix A for details.

Overall decision

After considering all evidence and other intelligence and the impact on current recommendations, we decided that an update is not appropriate at this time because suitable evidence on molecular diagnostic testing for the diagnosis of CUP and for informing treatment decisions is not currently available. The available evidence for MRI and

PET/CT scans is also of low quality. We will therefore monitor the evidence base on molecular diagnostic testing, MRI and PET/CT for CUP and propose an update when sufficient evidence to inform recommendation development is available. During this period of monitoring, the recommendation on gene-expression-based profiling for the identification of primary tumours will be reworded and the recommendation on gene-expression-based profiling for treatment decisions will be removed.

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