NICE National Institute for Health and Care Excellence

July 2025 exceptional surveillance of metastatic malignant disease of unknown primary origin in adults: diagnosis and management (NICE guideline CG104)

Surveillance report
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Topic area: cancer diagnosis and treatment

We will not update the diagnostic capabilities of comprehensive genomic profiling for patients presenting with cancer of unknown primary. The population affected is relatively small, and the budget impact is likely to be substantial. There are already capacity challenges in the provision of genomic testing which updated guidance in this area could exacerbate.

We will monitor the ongoing studies in this area and review the topic when these studies are completed.

Context

The guideline on metastatic malignant disease of unknown primary origin in adults was developed in 2010. A do not use recommendation for gene-expression-based profiling during diagnosis was recommended in 2010, 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. This recommendation was removed following a surveillance review in 2023 with no further recommendation being made but a link was provided to the NHS Genomic Medicine Service. The conclusion of the surveillance review was to monitor ongoing trials, with CUPISCO being the key trial which could trigger a review of the evidence upon publication.

Trigger for the exceptional review

The CUPISCO trial is a multicenter randomised controlled trial which has been monitored since the surveillance review in 2023. It randomised patients to receive either molecular guided therapy or a standard treatment of chemotherapy. Results were published in August 2024 and may lead to a change in current recommendations.

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence from the CUPISCO trial and other studies identified during the surveillance review of 2023.
- Considering the evidence used to develop the guideline in the 2010 update.
- Feedback from topic experts that was gathered during the previous surveillance review.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether or not to update sections of the guideline, or

the whole guideline.

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.

New published evidence considered in this exceptional surveillance review

CUPISCO – was an open-label randomised controlled trial (RCT) conducted in 34 countries including 10 UK centres. It recruited people aged over 18 years with unfavourable cancer of unknown primary; defined as histologically confirmed, metastatic malignancies with a primary tumour site that cannot be identified. They were required to have reached disease control after 3 cycles of standard first line platinum-based chemotherapy, and were then randomised to receive comprehensive genomic profiling, followed by molecularly guided therapy or at least 3 further cycles of standard platinum-based chemotherapy. A total of 1,505 patients were screened, 636 where eligible and 439 were randomised, 75 of these were based in the UK. Patients in the experimental arm received comprehensive genomic profiling using tumour or liquid biopsies, or both. The results were discussed by a virtual molecular tumour board to determine the optimal treatment. The randomisation was allocated 3:1 in favour of the experimental arm to account for the estimation that only a third of patients would be eligible for an actionable molecular guided therapy.

Median follow up was 24.1 months and results were presented on an intention to treat basis. Median progression free survival (PFS) was 6.1 months (95% confidence interval [CI] 4.7 to 6.5) in the molecularly guided therapy group (n=326) and 4.4 months (4.1 to 5.6) in the chemotherapy group (n=110), HR 0.72 (95% CI 0.56 to 0.92; p=0.0079). For a subgroup of 99 patients in the experimental arm, with an actionable molecular profile who received treatment guided by the molecular profiling, the median progression free survival was 8.1 months (95% CI 4.6 to 8.7). The trial has not reported results on overall survival, this is anticipated at 4 year follow up. However the current PFS data shows the potential for patients that have treatment guided by molecular profiling.

The incidence rate of adverse events in the molecularly guided therapy group was comparable to or lower than that in the chemotherapy group, except for serious adverse events that led to treatment discontinuation and those with fatal outcomes. Data is also presented on the use of tissue and liquid biopsies for comprehensive genomic profiling, exploring the potential for using liquid biopsies. The comparative accuracy of these methods is not reported, but the potential to use liquid biopsies where tissue biopsies are difficult to obtain is identified. This may be of particular use as sometimes, tissue material for people with carcinoma of unknown primary (CUP) is limited.

This is a good quality, well conducted RCT, with 17% of the participants being recruited in the UK. It was funded and sponsored by F Hoffmann-La Roche and their Foundations Medicine test was used in this trial for biopsy and genomic sequencing. There are several other commercially available tissue and liquid-based tests but head-to-head comparisons have not been reported in this patient population. This would need consideration during an update of the guideline. It is not currently clear whether the results reported here would be generalisable to other available tests and how these would fit with the Genomic Test directory.

The results are reported as statistically significant, whether these are clinically significant is difficult to ascertain, but given the poor prognosis of patients with CUP and the increasing availability of genomic profiling, molecular testing and molecularly guided treatments, it would be worthwhile to consider updating the recommendations in diagnosis and treatment planning.

Further published relevant evidence

There were 2 trials cited within the CUPISCO report which explored a similar hypothesis, but with a key difference that the testing in use was gene-expression-based profiling rather than comprehensive genomic profiling. The difference being that while gene-expression-based profiling focuses on the activity levels of genes to understand cellular behaviour, comprehensive genomic profiling provides a broader view of genetic alterations to guide personalised treatment strategies.

GEFCAPI 04 – recruited 243 patients with confirmed CUP who were treatment naive and randomised to receive empiric chemotherapy (n=120) or gene-expression testing followed by tailored treatment according to the suspect primary site (n=123). Median PFS was 5.3 months in the chemotherapy arm and 4.6 months in the tailored treatment arm (hazard ratio [HR] 0.95 [95% CI 0.72 to 1.25]; p=0.7). The trial was located in 4 EU countries and results published in 2019.

Hayashi et al. 2019 – this Japanese trial recruited 120 patients with CUP and randomised them to receive site-specific therapy or empirical chemotherapy. The primary end point was survival at 12 months. This was reported as 44.0% for site-specific treatment and 54.9% for empirical chemotherapy. PFS was 5.1 months for site-specific treatment and 4.8 months for empirical chemotherapy. For those tumours identified as more responsive there was an increase in PFS to 5.5 months, whereas less response reported a PFS of 3.9 months.

These 2 trials did not provide positive results for the use of gene-expression-based profiling. They also failed to be adequately powered to detect a response and there was potential for an overlap in treatments in the site-specific arm when compared with the standard-of-care arm.

A further 2 studies were identified during this surveillance review:

CUPCOMP – was a UK based study across 7 sites which made a comparison of tissue and liquid biomarkers for patients with a histologically confirmed diagnosis of favourable/unfavourable CUP. In 49 of the included 117 patients both tissue and blood profiling were performed, 77% agreement was observed between the liquid (circulating tumour DNA) and tumour tissue (FoundationOne CDX or whole genome sequencing). The study described the difficulty in obtaining tissue-based biopsies in this population, it was achieved in 59% of patients. This offers potential for the adoption of liquid biopsies to compliment tissues biopsies.

SUPER study – an Australian study of CUP patients which aimed to develop a biobank and determine the impact on diagnosis of tumour molecular profiling. The study recruited 449 patients and molecular tests were centrally performed and included comprehensive panel sequencing, gene-expression based profiling and whole genome sequencing. This study ran from 2013 to 2022 and was grouped into 3 time-phases. A retrospective analysis assessed where molecular tests agreed with clinical observations or caused a change in treatment decisions. These were reported across the 3 phases and molecular profiling improved over the time frame of the study. The results show an improvement in the clinical impact of molecular testing during this period but the retrospective design of the study and lack of a comparator which confirmed the diagnosis means we cannot truly assess the success of the diagnostic accuracy.

Ongoing studies

Two large cohort studies of participants with cancer which both include CUP subgroups were identified during the 2023 surveillance review. These have not published yet and will continue to be monitored:

- OCTANE is a Canadian 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 based in the United States, 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.

No further studies are currently on the NICE event tracker, which was last populated during the surveillance review of 2023.

Relevant NICE guidelines

The NICE portfolio was searched to identify examples of other cancer guidelines that currently recommend the use of molecular or genomic diagnoses to inform treatment.

NICE's guideline on brain tumours and brain metastases is an example of another NICE guideline which recommends the use of molecular markers to guide treatment. The committee stated that there are 3 main benefits to establishing a molecular diagnosis. These were: to identify the type of tumour, to help inform prognosis and to help guide treatment. They also commented that there are no meaningful harms to establishing a molecular diagnosis from an existing sample other than cost. Recommendations 1.1.4 to 1.1.6 detail the set of molecular markers to use in order to determine prognosis or guide treatment for glioma.

Genetic testing is recommended in NICE's guideline on ovarian cancer: identifying and managing familial risk, section 1.5 directs users to the NHSE national genomic test directory. The NICE prioritisation board also approved a proposal to incorporate similar recommendations in NICE's guideline on familial breast cancer.

This shows there is precedent for the use of molecular guided treatment and to recommend the use of the national genomic test directory. This could be adopted in the guideline for metastatic malignant disease of unknown primary origin in adults.

Other relevant guidance

Six of the 14 topic experts consulted during the 2023 surveillance review agreed that the recommendations in the diagnostics section of NICE's guideline on metastatic malignant

disease of unknown primary origin in adults needed updating. They identified 2 guideline sources that currently provide recommendations on the use of genomic and molecular profiling.

ESMO guideline for diagnosis, treatment and follow-up of CUP, published in 2022, stated that 'next-generation-sequencing' can be used for diagnostic purposes, but this is based on low-quality evidence from retrospective or case series studies.

Royal College of Pathologists published a dataset for histopathological reporting of CUP. This was updated in September 2024 and discusses current practice around molecular testing and highlights the potential for molecular profiling to play a role in the future. Also suggesting that genomic profiling could play a key role for patients with CUP.

Previous surveillance reviews

An exceptional surveillance review was completed in 2017, which investigated the use of gene-expression-based profiling for the diagnosis of CUP. The evidence base was assessed as not being sufficient to confirm a benefit of gene-expression-based profiling over immunohistochemistry techniques.

A surveillance review was completed in 2023. This was triggered by a clinician who stated that the guidelines were out of date and that emerging evidence existed on the use of molecular guided therapy for diagnosis and treatment planning for patients with CUP. Topic experts were consulted and searches for ongoing studies were executed. The topic experts highlighted additional immunohistochemical markers that could be adopted and discussed the potential use of molecular profiling noting the availability of the NHS Genomic Medicine Service in England. Topic experts also encouraged a review of available treatments to manage CUP.

The 2023 surveillance review concluded that while the guideline needed updating, it was not timely given then lack of evidence from high quality studies on molecular guided therapies. Ongoing studies were identified in the 2023 surveillance that could impact the recommendations so it was agreed that an update should be reconsidered when trial results of molecular profiling and the impact on treatment became available.

Budget impact and economic considerations

The budget impact of molecular guided therapy has not currently been assessed. It is likely that this would be required during the guideline update.

There is potentially a cost implication to the adoption of genomic testing and molecularly guided therapy. This will be incurred for genetic/molecular testing, and there is the potential high cost of targeted therapies which would be required to follow the molecular guided treatment pathway. These will have a higher cost burden than the current commonly used treatments of platinum-based or taxane chemotherapy regimens, such as carboplatin, paclitaxel or cisplatin. The use of more tumour agnostic approaches may impact on the NICE Technology Appraisal programme for targeted treatments.

It is likely that the way diagnostic tests and imaging, such as CT and MRI scans, are used will change as a result of the introduction of genetic profiling. These tests could be used in a more targeted way following the results of genetic profiling, but will still be needed and potentially used for a longer period to monitor treatment response.

System impact

The NHS genomic test directory is established and specifies the genomic tests commissioned by the NHS in England for cancer, the technology by which they are available, and the patients who will be eligible to access to a test. The tests are available for cancer of unknown primary in the directory. This would lead to an increase in genetic testing and may impact on the numbers of CT and MRI scans. Any updates would require discussion with the NHS genomic test directory team.

The opinion of topic experts during the surveillance review of 2023 highlighted the desire for earlier diagnosis to allow for more appropriate treatments to be provided with the potential for improved outcomes for patients. A report from Future Health detailed that the NHS genomic medicine service has increased its testing capacity, with a 22% increase in cancer tests being delivered in the 6 month period to June 2024. This report also described regional variations in availability and turnaround times and there is potential for the system to face capacity pressures in the future. The North West genomic laboratory states a turnaround time of 14 days for mutation specific molecular pathology tests.

Population impact

In the UK there were 8,575 new cases of CUP per year during the period from 2017 to 2019 making CUP the fifteenth most common cancer. The 1-year survival rates are low at around 16% often due to the difficulty in treating and the use of empirical chemotherapy rather than targeted treatment. Site specific therapies based on molecular profiling has the potential to impact on this population of patients who currently have poor outcomes. The results of the CUPISCO trial show that PFS can improve and as more targeted treatments become available and methods for sampling improved (tissue or liquid-based). It is likely that these outcomes will advance further.

Environmental sustainability

A potential reduction of unnecessary CT and MRI scanning during the diagnostic phase would offer a benefit in terms of environmental sustainability. By replacing generic chemotherapy treatments, the patient would receive treatment that is likely to be more effective. This would be a more efficient use of available medication and an opportunity to limit wasted treatment and resources, in addition to a reduction of side effects and an improvement in quality of life.

Health inequalities

A regional variation in the availability of genomic testing may lead to health inequalities. During the previous surveillance review there were inequalities raised by topic experts around CUP being more common in areas of socio-economic deprivation and ethnic minorities. It was suggested that this was partly due to lack of access to diagnostics, healthcare professionals and late presentation of cancer, and that more work in this area is needed.

Impact of new evidence and intelligence

The new evidence from the CUPSICO trial suggests that the use of comprehensive genomic profiling to provide targeted therapy can have an effect on rates of progression-free survival. It is still unknown what effect this has on overall survival. Taking into consideration the input from topic experts in the previous surveillance review from 2023 there is need to update this guidance. The ESMO guideline already recommends the use of molecularly guided therapy and the NHS Genomic Medicine Service already provides

instruction on the testing procedures to conduct the genetic testing. Now with the availability of clinical effectiveness evidence there is a need to reconsider the update of this guideline.

The early diagnosis of cancer has been identified as a priority for NICE. In a disease area where diagnosis is problematic, due to the difficulties in tracing the primary tumour site, this approach of molecularly guided therapy fits this remit by allowing early diagnosis and guiding therapy.

Overall proposal

We will not update the diagnostic capabilities of comprehensive genomic profiling for patients presenting with cancer of unknown primary. Despite the recent additions to the evidence base, the population affected is relatively small and the budget impact is likely to be substantial. There are already capacity challenges in the provision of genomic testing which updated guidance in this area could exacerbate.

The ongoing studies will continue to be monitored and the topic reviewed when these studies are completed.

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