MSAC Application 1809

Genomic testing in cancer of unknown primary (CUP)

Applicant: The Royal College of Pathologists of Australasia & The Peter MacCallum Cancer Centre

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1: PICO for genomic testing in patients diagnosed with Cancer of Unknown Primary (CUP) and cascade testing of biological relatives of patients with a confirmed CUP in whom a pathogenic or likely pathogenic germline variant associated with cancer has been identified

Component	Description
Population	Population 1: (PICO set 1) Patients with CUP Population 2: (PICO set 2) Biological relatives of patients with a confirmed CUP in whom a pathogenic or likely pathogenic germline variant associated with cancer has been identified
Prior tests	Population 1: Standard investigations/SOC for patients with CUP: • Blood tests • Imaging (CT, +/-MRI, US, PET-CT) • Histopathology review of biopsy material Population 2: N/A
Intervention	Population 1: Next-generation sequencing diagnostic genomic testing: • Matched WGTS and tissue of origin algorithm • CGP Population 2: Characterisation of specific (known) familial pathogenic or likely pathogenic variant(s) associated with cancer
Comparator/s	Population 1: No WGTS or CGP testing (SOC) Population 2: No cascade testing
Reference standard	Population 1 & 2: N/A
Outcomes	Population 1: *Clinical effectiveness outcomes* • Change in patient health outcomes: survival, response, mortality, morbidity, HRQoL • Proportion of cases with a TOO identified • Proportion of cases with an unidentified TOO • Cumulative somatic diagnostic yield of WGTS (informative result) • Cumulative somatic diagnostic yield of CGP (informative result) • Cumulative germline diagnostic yield of WGTS (informative result) • Cumulative germline diagnostic yield of CGP (informative result) • Cumulative prognostic yield of WGTS (from those with an informative result)

Component	Description
	• Cumulative prognostic yield of CGP (from those with an informative result) • Proportion of patients tested identified with a cancer predisposition syndrome • Change in management/treatment resulting in change in patient outcomes: survival, response, mortality, morbidity, HRQoL • Proportion of patients gaining access to PBS-listed site-specific treatments, including chemotherapy, immunotherapy and/or targeted therapy • Reduced toxicity (associated with empirical and inappropriate therapy) *Safety outcomes* • Test-related AEs • AEs from treatment • AEs from change in patient management • Harms related to over investigation (e.g. repeat biopsy, radiation exposure) • Misclassification of cancers, particularly rare cancers *Test-related outcomes* • Rate of repeat biopsy (as a result of test failure from inadequate quality/quantity of specimen) *Health system resources* • Total cost of genetic tests for the intervention (including any confirmatory germline testing required) and the comparator • Cost of PBS-funded site-specific treatments, immunotherapy and/or targeted therapies • Cost per quality-adjusted life year and/or cost-effectiveness • Total Australian Government healthcare costs *Other relevant considerations* • Value of knowing (e.g. psychosocial impact from not having a primary diagnosis) Population 2: • Uptake of cascade testing per germline pathogenic variant identified • Diagnostic yield • Impact on change in management • Value of knowing • Cost per pathogenic/likely pathogenic germline variant identified
Assessment questions	Population 1: What is the safety, effectiveness and cost-effectiveness of WGTS or CGP testing versus no WGTS or CGP testing in patients with CUP? Population 2: What is the safety, effectiveness and cost-effectiveness of cascade testing versus no cascade testing in biological relatives of patients with a confirmed CUP in whom a pathogenic or likely pathogenic germline variant associated with cancer has been identified?

AE=adverse event; CGP=comprehensive genomic profiling; CT=computed tomography; CUP=cancer of unknown primary; HRQoL=health-related quality of life; MRI=magnetic resonance imaging; PBS=Pharmaceutical Benefits Scheme; PET-CT=positron emission tomography–computed tomography; PICO=population, intervention, comparison, outcome; SOC=standard of care; TOO=tissue of origin; US=ultrasound; WGTS=whole genome and transcriptome sequencing.

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of genomic testing to identify a primary cancer site or tissue of origin (TOO) in patients with cancer of unknown primary (CUP) and diagnostically challenging cancers was received from the Royal College of Pathologists of Australasia (RCPA) & The Peter MacCallum Cancer Centre by the Department of Health, Disability and Ageing.

PICO criteria

Population

The application initially proposed testing in patients with CUP and patients with diagnostically challenging cancers.

PASC noted that diagnostically challenging cancers are a heterogeneous group of cancers . PASC noted that most of the information presented in the application related to patients with CUP. Therefore, PASC advised that the diagnostically challenging cancer population be removed. This was supported by the applicant.

Cancer of unknown primary (CUP)

CUP is a metastatic malignancy in which tumour cells originate from an unidentified primary site and disseminate to regional or distant secondary anatomical locations (Kato et al. 2021). Patients typically present with disease manifestations at these secondary sites and undergo a standardised sequence of clinical and pathological investigations (e.g. imaging studies and conventional pathological review of tumour tissue, including a second pathology opinion) to identify the primary cancer site or TOO (Kato et al. 2021; Kramer et al. 2023). A diagnosis of CUP is established when these investigations fail to determine a primary cancer site.

CUP incorporates ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) cancer codes:

- Incidence C80 (malignant neoplasm without specification of site)
- Mortality C77–C80
    - C77 (secondary and unspecified malignant neoplasm of lymph nodes)
    - C78 (secondary malignant neoplasm of respiratory and digestive organs)
    - C79 (secondary malignant neoplasm of other and unspecified sites)
    - C80 (malignant neoplasm without specification of site)
- C97 (malignant neoplasms of independent [primary] multiple sites)

Many CUPs are believed to metastasise early in their course, demonstrate aggressive biological behaviour and exhibit an unpredictable pattern of metastatic spread (Lee & Sanoff 2020). Because CUP is a highly clinically and biologically heterogeneous disease, patients may present with diverse symptoms that reflect the sites of metastatic involvement (Lee & Sanoff 2020). Metastatic sites often include multiple organs, with the liver being most frequently affected, followed by the respiratory system, lymph nodes, abdominal cavity, bones and brain (Kramer et al. 2023).

CUP typically presents as advanced disease, with distant metastases requiring systemic therapy. It generally carries a poor prognosis (Rassy et al. 2020). Patients with CUP are classified into 2 prognostic subgroups—unfavourable and favourable CUP—based on specific clinicopathologic features (Rassy et al. 2020). Around 80–85% of patients fall into the unfavourable CUP subgroup, showing limited response to platinum-based chemotherapy and median survival of 6–10 months (Rassy et al. 2020). The remaining

15–20% (favourable subgroup) have clinicopathologic features resembling known cancers and respond better to standard treatments, yet may still be ineligible for site-specific treatments, immunotherapy and targeted therapies due to their CUP diagnosis (Rassy et al. 2020). At the pre-PASC teleconference the applicant's clinical expert stated that testing in the favourable CUP population may be beneficial and should be performed at the clinician's discretion.

PASC noted that the European Society for Medical Oncology (ESMO) clinical practice guidelines recommend that patients with favourable CUP receive site-specific treatment tailored to the presumed primary site (Kramer et al. 2023). PASC queried whether patients in the favourable CUP subgroup currently undergo genetic testing in Australian clinical practice. PASC noted from the applicant that testing in this subpopulation is currently at clinician discretion, and that the proportion of patients undergoing this testing is unknown. PASC therefore considered that testing should include patients both with favourable and unfavourable CUP.

PASC emphasised the population should be a population of patients that are considered amenable to ongoing therapy, so should be restricted to patients with good Eastern Cooperative Oncology Group performance status (ECOG PS 0–1, in alignment with the CUPISCO trial and the majority of participants in the SUPER studies) and a life expectancy ≥12 weeks (in alignment with the CUPISCO trial).

Subtypes within the favourable CUP subgroup may include:

- single metastatic deposit or oligometastatic disease amenable to local ablative treatment (single-site or oligometastatic CUP)
- isolated axillary lymph node metastases (breast-like CUP in women)
- peritoneal carcinomatosis of a serous papillary adenocarcinoma (ovary-like CUP in women)
- squamous-cell carcinoma involving non-supraclavicular cervical lymph nodes (head and neck-like CUP)
- blastic bone metastases and/or immunohistochemistry (IHC) or serum prostate specific antigen expression (prostate-like CUP in men)
- adenocarcinoma with colorectal IHC (CK7-negative, CK20-positive, CDX2-positive) or molecular profile (colon-like CUP)
- carcinoma with renal-cell histological and IHC profile (renal-like CUP).

Regardless of the prognostic subgroup of CUP, in the absence of an identified TOO, patients with CUP are generally managed with empirical chemotherapy treatment and are ineligible for site-specific treatment, immunotherapy or targeted therapies that require a confirmed primary diagnosis. Molecular characterisation of tumour tissue may improve diagnostic accuracy and clinical outcomes by providing precision therapies, disease-specific clinical trials, supportive care pathways and multidisciplinary care. According to the 2023 revision of the ESMO clinical practice guidelines for CUP, next generation sequencing (NGS) may be considered as a diagnostic pathway for CUP where standard diagnostic procedures do not reveal the primary TOO (Kramer et al. 2023).

In some cases, the molecular profile discovered via NGS can help identify or suggest the likely primary tumour site. For example, anaplastic lymphoma kinase (*ALK*), ROS proto-oncogene 1 (*ROS1*) fusions seen in non-small cell lung cancer, transmembrane serine protease 2 (*TMPRSS2*) rearrangements in prostate cancer, or NUT midline carcinoma family member 1 (*NUTM1*) rearrangements in nuclear protein in testis (NUT) carcinoma, as well as genomic signatures linked to ultraviolet light or tobacco exposure can provide important diagnostic clues. A list of genomic aberrations associated with specific primary tumour types is provided in ***Appendix Table 1,*** as published in the ESMO CUP clinical practice guidelines (Kramer et al. 2023). As illustrated by ESMO, these genomic aberrations may be used alongside the differential diagnostic

algorithms. The differential diagnostic algorithm to discriminate between CUP and transcription termination factor 1 (TTF1)-negative non-small cell lung cancer is provided in ***Appendix Figure 1*** as an exemplar (Kramer et al. 2023). The ESMO differential diagnostic algorithms can supplement the current and proposed clinical management algorithms (***Figure 2*** and ***Figure 3***) that cover CUP more generally, without reference to a specific suspected primary site.

In Australia, it is estimated there will be 2,633 new CUP cases in 2025, with an age-standardised rate of 6.9 per 100,000 population (Australian Institute of Health and Welfare 2025a). Based on Australian Institute of Health and Welfare (AIHW) 2025 data, CUP is projected to be the 15th most common cancer diagnosis and the 8th most common cause of cancer-related death (***Table 2***) (Australian Institute of Health and Welfare 2025b). In 2021, CUP was the 5th most prevalent cause of cancer death among females and the 6th most prevalent cause of cancer death among males in Australia (Australian Institute of Health and Welfare 2021). Males in Australia have slightly greater incidence and mortality rates from CUP compared to females (Australian Institute of Health and Welfare 2021). The 5-year survival rate (2017–2021) for patients with CUP was 13.2%, being 15.4% for males (all ages) and 10.6% for females (all ages) (Australian Institute of Health and Welfare 2025a).

Age-standardised incidence rates of CUP were highest in remote and very remote areas, and were more than twice as high for Indigenous Australians living in very remote locations (28 cases per 100,000 people) as for those in major cities (13 per 100,000 people) (Australian Institute of Health and Welfare 2021). Moreover, compared to non-Indigenous Australians, Indigenous Australians had substantially lower 5-year relative survival rates (5% vs 13%) (Australian Institute of Health and Welfare 2021).

The global median age of CUP diagnosis is 65 years (Kato et al. 2021), with incidence and mortality rates generally increasing with age (Australian Institute of Health and Welfare 2025a).

Table 2: Estimated incidence and mortality rates of CUP in Australia by sex, 2025

Rate	Cancer type (ICD-10 code)	Male		Female		Total	
		Cases/deaths	ASR (per 100,000)	Cases/deaths	ASR (per 100,000)	Cases/deaths	ASR (per 100,000)
Incidence	CUP (C80)	1,423	8.3	1,210	5.8	2,633	6.9
Mortality	CUP (C77–C80, C97)	1,645	9.5	1,288	6.1	2,933	7.6

ASR=Age standardised rate (using 2001 Australian Standard Population); CUP=cancer of unknown primary; ICD= International Classification of Diseases

Source: Australian Institute of Health and Welfare (AIHW) National Mortality Database 2025 (Australian Institute of Health and Welfare 2025a).

Biological relatives at risk (cascade testing)

CUP may have a familial component, with several studies identifying that CUP patients were more likely to have a sibling with CUP; patients who had a diagnosis of lung, liver, kidney, pancreatic, ovarian or colorectal cancer were more likely to have a family member diagnosed with CUP; and family members of CUP patients had an increased CUP risk, as well as increased risk of lung and pancreatic cancer, myeloma and non-Hodgkin lymphoma (Hemminki et al. 2012; Hemminki et al. 2011; Hemminki, Kari et al. 2016; Samadder et al. 2016). Whole genome sequencing (WGS) and whole transcriptome sequencing (WTS) can identify a primary TOO. WGS analyses germline DNA from blood and can detect germline predispositions when used on tumour tissue (Droogers et al. 2025). Comprehensive genomic profiling (CGP) may detect potential germline pathogenic variants as a secondary finding. Alternatively, CUP patients with diagnosed TOO are likely to be treated in line with clinical guidelines for the diagnosed cancer, including additional testing for themselves or for germline variants in at-risk family members.

PASC advised adding a cascade testing population to align with other similar items. In the pre-PASC response, the applicant stated that patients are currently referred to a familial cancer centre (FCC) for follow-up when somatic testing is suggestive of a potential germline variant. The applicant further stated that many patients with CUP have already been referred to an FCC or have separate germline testing requested based on family history or clinical suspicion of the likely primary site before any somatic genomic test results are received. PASC noted that approximately 10% of patients with cancer are found to carry a pathogenic/likely pathogenic germline variant associated with cancer (DeBortoli et al. 2025), which accounts for approximately 158 patients in Year 1.

For relatives found to carry the variant, this is expected to lead to increased clinical surveillance, and/or referral to appropriate specialist services early, consistent with current cancer-specific clinical guidelines.

Standard investigations for CUP (prior tests)

Per clinical practice guidelines, essential clinical work-ups for CUP include a comprehensive patient history, physical examination, basic blood tests, and computed tomography (CT) scans or magnetic resonance imaging (MRI) of the neck, thorax, abdomen and pelvis for all patients, plus additional mammography for females (Cancer Council 2020; Kramer et al. 2023). Based on the pathological and clinical findings, further procedures may also be necessary, such as fluorodeoxyglucose (FDG)-positron emission tomography (PET), gastroscopy and colonoscopy (Cancer Council 2020; Kramer et al. 2023). A complete clinical and diagnostic work-up includes a second opinion pathology review (Kramer et al. 2023).

Current standard pathology evaluation of CUP involves histology and IHC of formalin-fixed paraffin-embedded (FFPE) biopsy sections. CUP can be classified according to histological subtype. Approximately 50% of cases are well- to moderately-differentiated adenocarcinomas, 30% are poorly- or undifferentiated adenocarcinomas, 15% are squamous cell carcinomas and 5% are undifferentiated neoplasms (Cancer Council 2020; Kramer et al. 2023).

According to Cancer Australia's optimal care pathways and ESMO's clinical practice guidelines, standard investigations for CUP are a prerequisite for genomic testing (Cancer Council 2020; Kramer et al. 2023). If a CUP diagnosis is confirmed via standard investigations, genomic testing may be performed (Kramer et al. 2023).

Intervention

The proposed investigative technology is genomic testing of the tumour and matched blood of patients with CUP using whole genome and transcriptome sequencing (WGTS) or tumour-only comprehensive genomic profiling (CGP) to identify genomic variants, the results of which can be analysed in conjunction with existing clinicopathological information and patient history to identify the TOO (MSAC 1809 PICO Set p.10). Both WGTS and CGP are based on NGS methodology that can detect large numbers of genetic alterations simultaneously in one test (Satam et al. 2023; Tjota, Segal & Wang 2024).

Whole genome and transcriptome sequencing

WGTS is a broad NGS approach that provides a comprehensive analysis of a patient's entire genetic and gene expression profile, potentially providing information on many pathologic variants (Jobanputra et al. 2022; Pleasance et al. 2022).

WGTS combines whole-genome DNA sequencing (WGS) with whole-transcriptome RNA sequencing (WTS) to capture structural genomic changes, functional gene expression patterns and gene fusions. WGS can detect variants, copy number variations and genome signatures across the genome and has the potential to detect a broader spectrum of actionable molecular variants (Pleasance et al. 2022).

A small number of studies describing the use of WGTS for CUP were identified during the PICO process. The Australian SUPER study (2025) combining WGTS (plus CUPPA) with centralised clinicopathology review informed the TOO in 71% of cases otherwise undiagnosed by clinicopathology review and informed SOC treatment in 71% of patients (Rebello et al. 2025). Similarly, a Dutch study using WGS with CUPPA achieved a 68% primary site diagnosis (Schipper et al. 2022). Around one-third of patients with rare and advanced cancers in 2 oncology programs were informed treatment by WGTS; integrated DNA and RNA profiling identified additional molecular features beyond the targeted panels (Cuppen et al. 2022; Pleasance et al. 2022). Across these studies, WGTS with TOO algorithmic interpretation refined the diagnosis and guided more appropriate chemotherapy and other SOC treatments. Clinical benefit to the patient was not reported.

Cancer of unknown primary prediction algorithm

The cancer of unknown primary prediction algorithm (CUPPA)—developed by the Hartwig Medical Foundation—can be applied to WGS/WGTS data to predict the most likely tumour origin by analysing characteristic DNA variants, RNA expression patterns and cancer type-specific mutational signatures (Schipper et al. 2022). CUPPA is a statistical model that weighs multiple genomic features to find resemblance of a sample compared with different cohorts of samples based on their primary tumour origin (reference cohorts) (Schipper et al. 2022). CUPPA generates a prediction likelihood from 0 to 1 that the tumour belongs to each cancer class, providing high-confidence (≥ 0.8) and low-confidence (<0.8) calls depending on the likelihood threshold (Schipper et al. 2022). WGS-based CUPPA was developed and validated on a pan-cancer database, achieving a precision/positive predictive value of 95% at the prediction likelihood score of ≥ 0.8 in the internal validation cohort. The true-positive rate and false-positive rate was 0.961 and 0.0013, respectively, in the internal validated cohort at the 0.8 cut-off (Schipper et al. 2022). A later study that extended CUPPA to use WGTS-based data also found that all high-confidence predictions (≥0.8) matched the tumour type determined by an expert pathology review, indicating the CUPPA algorithm has high specificity. In this particular study, the expert pathology review used as the reference standard was the pathologist's favoured TOO, based on an independent centralised clinical and genomics-informed pathology review in the absence of CUPPA (Rebello et al. 2025). Further detail on the independent review is not provided.

Based on preliminary scoping, CUPPA is currently the only predictive algorithm publicly available and clinically applied that combines both DNA and RNA data in a single model to identify molecular signatures to inform cancer diagnosis in CUP. Other algorithms (not exhaustive), such as CancerTYPE ID (Thomas et al. 2018), Tempus Tumor Origin (TO) (Michuda et al. 2023) and CUP-AI-Dx (Zhao et al. 2020), predominately rely on RNA-based data, while EPICUP (Moran et al. 2016), Supervised Cancer Origin Prediction Using Expression (SCOPE) (Grewal et al. 2019), and Cancer of Unknown Primary Location Resolver (CUPLR) (Nguyen, Van Hoeck & Cuppen 2022) rely on DNA-based data. In the near future, other predictive algorithms combining both DNA and RNA data will likely become available. The application provided no information if algorithms other than CUPPA would be considered.

The application is for the use of WGTS in association with CUPPA or other clinically validated prediction algorithms.

Comprehensive genomic profiling

CGP is a NGS approach that assesses 11 to 596 genes using a single assay. RNA is typically not included in CGP assays (Huang et al. 2025).

CGP is able to identify 4 main types of genomic variants: base substitutions, insertions and deletions, copy number alterations and rearrangements/fusions. Findings of a CGP test include somatic variants that can

inform eligibility and the potential effectiveness of immunotherapies and molecularly-guided therapies, as well as predictive, prognostic and diagnostic biomarkers (Pankiw, Brezden-Masley & Charames 2023). CGP via NGS is able to detect genetic changes in hundreds of genes and multiple molecular biomarkers simultaneously in a single test, which preserves limited specimens and provides a complete molecular description of cancers for personalised medicine and care (Tjota, Segal & Wang 2024).

During the PICO Confirmation process, a study was identified that examined the use of CGP for the diagnosis of CUP TOO. A 2023 retrospective Australian study conducted by the Peter MacCallum Cancer Institute (SUPER study) using CGP in 201 patients, identified a likely TOO in 31% of cases unresolved by clinicopathology (Posner et al. 2023). While another study (CUPISCO trial; NCT03498521) provides information relating to guiding treatment post CGP testing in patients with CUP, CGP was not used in this study to identify the primary tumour (Krämer et al. 2024).

Overall, studies indicated that CGP can clarify the TOO in about one-third of CUP cases, while WGS/WGTS plus CUPPA improves resolution to around two-thirds (Posner et al. 2023; Rebello et al. 2025).

Currently, no tissue of origin algorithm is currently in use for CGP. Algorithms for CGP may potentially be used in the future.

Choice of genomic test and sample preparation

According to the application, the choice between CGP and WGTS is primarily determined by the quality and quantity of available tissue or nucleic acid sample. CGP generally requires a smaller amount of material and demonstrates greater tolerance for FFPE tissue, making it appropriate for samples with limited material or suboptimal preservation. WGTS requires higher quality RNA and DNA and larger input volumes to provide accurate and complete sequencing over the entire genome and transcriptome. Fresh tissue specimen from a second biopsy is preferable for WGTS, although this is not mandatory, as WGTS can also be performed on FFPE tissue. Fresh samples typically yield superior quality DNA and RNA, resulting in improved sequencing accuracy and reliability.

Tissue specimens are typically obtained by needle biopsy or tissue resection, snap frozen (−20°C) in a cutting compound for pathologist examination, and then used to create and sequence nucleic acid libraries (Pleasance et al. 2022; Versmessen et al. 2024). Quantification of DNA and RNA yield is typically performed using methods such as the Qubit™ Fluorometer, which provides sensitive and accurate concentration measurements. Sample purity is commonly assessed via ultraviolet spectrophotometry using instruments such as NanoDrop™. Nanodrop™ measures absorbance ratios at 260/280 nm and 260/230 nm. DNA is generally regarded as pure when A260/280 ratio is 1.7–2.0 or A260/230 is 2.0–2.2 (Versmessen et al. 2024). Comprehensive sample assessment is critical to determining the most appropriate genomic testing approach.

Matched whole blood samples are typically obtained via peripheral blood in EDTA tubes or Streck DNA blood collection tubes to provide high-quality germline DNA to reliably distinguish somatic tumour variants from germline variants (Rebello et al. 2025). Alternative options for patients unable to provide a whole blood sample may include saliva or buccal (cheek) swab, only after documented clinical justification (Genomics England 2023). Saliva samples often contain a substantial fraction of microbial/oral DNA, which reduces effective human coverage, often resulting in higher sample failure rates (Genomics England 2023).

PASC noted from the applicant that archival samples will be used for testing where possible, with re-biopsy as needed depending on the quality and quantity of available samples. PASC noted that the proportion of patients requiring a second biopsy needs to be taken into consideration in the assessment report.

PASC considered that circulating tumour DNA (ctDNA) is not an appropriate sample type as the majority available evidence relates to testing in tumour tissue.

PASC discussed the selection of testing method for each genomic test. The applicant confirmed that WGTS is preferred to CGP and would be used where possible, due to the ability of WGTS to identify a greater number of biomarkers resulting in a greater number of resolved diagnoses. Compared with CGP, WGTS requires a higher quality and quantity of tumour sample to allow analysis of DNA and RNA. PASC noted that the proportion of use of each test was uncertain, advising that this should be examined in the assessment report. PASC noted that despite this preference for WGTS, it is not available currently in Australia outside the research setting and no labs have NATA accreditation for this. CGP is available via a commercial provider.

Clinical use of genomic testing in CUP

Genomic testing via NGS is recognised in the 2023 ESMO guidelines as a diagnostic pathway for CUP where standard diagnostic procedures fail to reveal the primary site or TOO, to be performed using a pan-cancer panel covering relevant molecular targets across different entities (Kramer et al. 2023). The ESMO guidelines do not indicate a preferred NGS methodology (e.g. CGP or WGTS). A list of genomic aberrations associated with specific primary tumour types is provided in ***Appendix Table 1,*** as published in the ESMO CUP clinical practice guidelines (Kramer et al. 2023). According to the ESMO guidelines, the clinical utility of gene expression profiling to elucidate the likely primary tumour in CUP is not currently supported by high-level evidence (Kramer et al. 2023). Two randomised trials failed to demonstrate the superiority of gene expression profiling-based site-specific therapy over standard empirical chemotherapy (Kramer et al. 2023). Therefore, currently the ESMO guidelines do not recommend the use of gene expression profiling based 'site-directed' therapy. Nevertheless, the ESMO guidelines recommend molecular targeted therapies if they have received cancer-type agnostic approval. Targeted therapies are also recommended for patients with tumours harbouring a genetic alteration suggestive of a primary for which molecular guided therapies are licensed and are the SOC.

National Comprehensive Cancer Network (NCCN) guidelines recommend biomarker testing as part of the diagnostic workup of patients with CUP (National Comprehensive Cancer Network 2025). This may be conducted using NGS or other techniques that may identify the gene alterations or mutational burden of the cancer. Molecular profiling is attained using gene expression profiling assays to determine the TOO, and NGS to identify genomic aberrations for targeted therapy (National Comprehensive Cancer Network 2025). Nevertheless, the clinical benefit of molecular profiling in guiding treatment decisions remains to be determined. Where the primary is found, treatment is recommended based on disease-specific guidelines. Where a primary is not identified, management will be based on the workup findings, where biomarker-driven therapy may be considered in certain circumstances. Currently, there is no evidence of improved outcomes with the use of site-specific therapy guided by molecular testing results in patients with CUP (National Comprehensive Cancer Network 2025).

The results of genomic tests may be applied according to the WHO Classification of Tumours list. The WHO documents that guide the classification of various cancers are not specific to CUP but may play a role in defining tumour type, lineage and molecular features that help infer the TOO. Examples include the presence of succinate dehydrogenase-deficient patterns that are characteristic of familial paraganglioma (Agarwal et al. 2024), *BRD3* or *NSD3* fusions with *NUTM1* or *NUTM2B* for NUT carcinoma (Goldman-Lévy et al. 2026), and *CDC73* gene variants in parathyroid carcinomas (Juhlin 2024). The presence of these variants may aid in tumour classification and guide treatment selection. A review of WHO classification of skin tumours state that molecular investigations may be performed for CUP that may occur in the skin to help guide targeted therapy, however the review also emphasises that no superiority of 'site-specific' therapy

based on gene expression profiling over standard empiric chemotherapy has been demonstrated so far (Goldman-Lévy et al. 2026). The genomic profile may also indicate an underlying hereditary cancer syndrome, identifying instances where family members should also undergo genomic testing and counselling, such as mismatch repair deficiency associated with Lynch syndrome in endometrial and/or colon cancer, *BRCA1/2* pathogenic variants predisposing to breast and ovarian cancers, and *RET* variants underlying medullary thyroid carcinomas (Jaber, Zhang & Godley 2025).

Incorporation of WGS into the CUP care pathway was found to be of significant value for diagnosing a primary TOO, and a germline predisposition can be found when this is applied to tumour tissue (P<0.001) (Droogers et al. 2025). WGTS is claimed to be a comprehensive precision diagnostic test for many tumour types and may guide the selection of a site-specific treatment, immunotherapy or targeted therapy over a more generalised empiric chemotherapy treatment, especially for rare cancers and CUP (Cuppen et al. 2022).

The CUPISCO trial (2024) reported an improvement in progression-free survival (PFS) for patients with unfavourable CUP harbouring actionable genomic variants (Krämer et al. 2024). The study reported that those treated with molecularly-guided treatment strategies experienced a median PFS of 6.1 months versus 4.4 months for those receiving standard chemotherapy (hazard ratio 0.72; 95% confidence interval 0.56–0.92; p = 0.0079) (Krämer et al. 2024). Based on the results of the CUPISCO trial, the ESMO Precision Medicine Working Group recommended tumour NGS for all patients with unfavourable CUP (Krämer et al. 2024; Mosele et al. 2024).

The clinical trials identified during completion of the PICO did not report clinical outcomes of CUP patients who received cancer-specific therapies following genomic testing with WGTS or CGP; therefore, the claim of clinical superiority in this clinical use is not directly supported by published trial evidence.

At the PASC meeting, the applicant noted that the purpose of testing is as a diagnostic test, with the primary intent to identify the TOO. PASC noted that PBS-listed treatments are predominantly specific to the tumour TOO, therefore identification of the TOO could allow patients to access tumour site-specific cancer therapies listed on the PBS.

PASC noted from the applicant that genomic test results would be analysed in combination with all other clinicopathological information and patient history. Multidisciplinary team input would be used to confirm and document any diagnosis, together with follow-up with the pathologist to amend previous CUP reports.

PASC noted applicant advice that genomic approaches to identifying the TOO (using CGP or WGTS) are not included in the WHO classification of tumours and it was not known when these may be included.

Subsequent therapy

The vast majority of PBS-listed therapies for cancers are tumour site specific, such as osimertinib for the treatment of non-small cell lung cancer, trastuzumab for HER2-positive breast cancer, or tebentafusp for the treatment of uveal melanoma. Therefore, identifying a gene variant without a TOO diagnosis may not lead to patients being eligible for PBS listed therapies. However, some medicines, such as larotrectinib for NTRK fusion-positive cancers, have a tumour-agnostic PBS listing (i.e. patients with the relevant gene variant may be eligible to access these treatments even without a TOO diagnosis) Access to non-PBS listed treatments is out of scope for the MSAC assessment and would require a codependent application to both the PBAC and MSAC for consideration.

PASC considered that while it may be biologically plausible that site-specific PBS subsidised therapies could lead to better clinical outcome, there was no evidence identified in the PICO process to support this claim. PASC noted from the applicant that results from the SUPER NEXT trial (soon to be published) may provide

data on the outcomes of treatment with PBS-listed drugs following testing. The applicant further noted that most cases in the SUPER-NEXT trial led to identification of the TOO and subsequent use of PBS-listed treatments.

PASC noted the use of PBS therapies for patients identified to have a TOO via genomic testing. PASC queried whether these patients who, by definition have metastatic stage of disease, experience the same effectiveness of the drug when these patients were unlikely to have been included in the clinical trials for the drug. PASC noted from the applicant that the available evidence on health outcomes is generalised rather than specific to each cancer type and that it would be challenging to match to each cancer type due to limited patient numbers and the presence of confounding variables.

PASC considered that it was not established that a diagnosis of the TOO based on CGP or WGTS was equivalent to a diagnosis based on current guidelines including histopathology. PASC considered that advice from the PBAC Executive is required as to whether diagnosing a primary site based on the genomic signature found in CGP or WGTS and without histology is appropriate for eligibility for PBS-subsidised tumour site-specific cancer therapies.

The applicant reiterated that the application was for diagnosis, and should not be considered to be a codependent application. However, PASC recognised that use of the genomic tests would likely have downstream impacts, including cost impacts due to utilisation of PBS-listed treatments. PASC sought advice from the PBAC Executive on whether a codependent application is required.

PASC noted that, for some cases, the proposed tests could identify genetic variants without identifying a TOO. However, as the vast majority of PBS-listed treatments are restricted to people with a diagnosed tissue of origin, people with a genetic variant alone detected would not have access to PBS funded therapies as currently listed.

PASC considered that the proposed testing to infer the TOO using WGTS or CGP was novel, and not a fully established approach explicitly supported by clinical guidelines at the time of PASC consideration. Furthermore, the PICO development process did not identify evidence showing that patients with CUP who have a TOO diagnosis from testing have better health outcomes as a result of treatment with tumour site-specific cancer therapies listed on the PBS. Taking this into consideration, PASC requested that the department seek advice from the PBAC Executive on eligibility for PBS-subsidised tumour site-specific therapies for patients with the TOO diagnosed based on WGTS or CGP.

Cascade testing

In some circumstances, genetic testing of CUP may identify germline variants, that is, an inheritable genetic change that can increase cancer risk and predisposition. Examples include mismatch repair deficiency associated with Lynch syndrome in patients with endometrial and/or colon cancer, BRCA1/2 pathogenic variants predisposing to breast and ovarian cancers, and RET mutations underlying medullary thyroid carcinomas (Jaber et al., 2025). As identified by eviQ, these germline-associated changes can be detected through a range of diagnostic modalities including IHC, polymerase chain reaction (PCR) and NGS (eviQ Cancer Genetics Reference Committee 2023). A recent study estimated that approximately 10% of adults with cancer, and 13–18% with rare cancers are found to carry germline pathogenic/likely pathogenic variants (DeBortoli et al. 2025). A first of its kind, genome-wide association study on CUP provided preliminary evidence that non-coding germline single nucleotide polymorphisms associated with inflammation (*LTA4H*), metastatic promotion (*TIAM1*) and lipid metabolic disturbance (chromosome 11 cluster) may contribute to the germline risk of CUP (Hemminki, K et al. 2016).

Separately, the diagnosis of a specific cancer in a CUP patient would lead to site-specific treatment, including any additional tests. Germline variants and familial risk would likely be considered at this stage, with access to genetic tests and genetic counselling in line with relevant guidelines. Cascade testing is not a CUP-specific issue.

ESMO guidelines recommend that when family history or molecular findings suggest the possibility of a germline cancer-predisposing variant, patients should be offered genetic counselling and testing (Kramer et al. 2023). If a germline variant is confirmed, additional screening is recommended (Kramer et al. 2023). In Australia, eviQ publish a list of genes associated with familial cancer risk for which there is consensus by the majority of Australian family cancer and genetics services that pathogenic variants are clinically actionable for diagnostic and/or predictive gene testing. For example, BRCA1 and BRCA2 in any tumour type warrant referral for germline testing and specialist genetic assessment (eviQ Cancer Genetics Reference Committee 2023).

A cascade testing population has been added based on PASC advice. The use of additional tests, including genomic tests, following identification of TOO in CUP patients, including for germline variants in the patient and in family members, should be investigated in the assessment.

Comparator(s)

The nominated comparator is no WGTS or CGP (MSAC 1809 PICO Set p.12).

The nominated comparator reflects the current standard of care (SOC) for patients diagnosed with CUP. This includes standard investigations and diagnostic work-up such as blood tests, imaging and histopathology review of biopsy material. These standard investigations are all covered under the MBS (***Appendix Table 2***).

Genomic testing via WGTS or CGP to identify the TOO in CUP would be an addition to the current SOC.

PASC agreed that the comparator was no WGTS or CGP testing (SOC) for Population 1 (patients with CUP).

PASC considered no cascade testing to be the appropriate comparator for Population 2 (cascade testing population).

Reference standard (for investigative technologies only)

The reference standard is a test used to determine the presence or absence of the target condition or clinical information of interest. Ideally, the reference standard is the best available clinically accepted, error-free procedure to do so.

PASC discussed possible reference standards applicable for CUP testing in order to understand the false positive and negative rates and test accuracy. PASC noted the applicant's pre-PASC response that the currently best available test is current SOC, which is clinical/pathological diagnostic work-up for CUP. However, PASC noted that the current SOC performance is sub-optimal, with only approximately 20% of CUP cases having a resolved diagnosis via this method (Rebello et al. 2025). Therefore, PASC considered that the accuracy of the proposed test will need to be demonstrated by direct from test to health outcomes evidence showing a health benefit resulting from the use of the test (in alignment with the MSAC guidelines).

Outcomes

The application provides a list of outcomes for assessment, covered under: clinical effectiveness, health system resources, value of knowing and health harms of genomic testing (MSAC 1809 PICO Set p.16–17). This list has been reviewed and updated based on published literature (Berglund et al. 2022; Cuppen et al. 2022; Droogers et al. 2025; Krämer et al. 2024; Posner et al. 2023; Rebello et al. 2025; Schipper et al. 2022; Wolyniec et al. 2022).

The application stated that integrating genomic testing into the routine diagnostic work-up of CUP patients will increase the proportion of patients receiving a resolved diagnosis, leading to changes in management and treatment decisions, and improvements in outcomes such as mortality, morbidity and health-related quality of life (HRQoL). Furthermore, the application stated that testing would enable more patients to access site-specific treatment, immunotherapy and/or targeted therapies. It may also facilitate enrolment in relevant clinical trials; however, this is not a primary driver of health benefits under public funding of genomic testing, therefore access to clinical trials is excluded for the purposes of this PICO Confirmation. In addition, resolving the TOO may enhance prognoses and potentially minimise further unnecessary investigations, offering substantial psychological benefits to improve overall quality of life (Wolyniec et al. 2022).

Population 1 (patients with CUP):

Clinical effectiveness

- Change in patient survival (PFS, overall survival [OS]), response (overall response rate [ORR], best overall response [BOR], duration of response [DOR]), mortality, morbidity and HRQoL
- Proportion of cases with a TOO identified
- Proportion of cases with an unidentified TOO
- Cumulative somatic diagnostic yield of WGTS (informative result)
- Cumulative somatic diagnostic yield of CGP (informative result)
- Cumulative germline diagnostic yield of WGTS (informative result)
- Cumulative germline diagnostic yield of CGP (informative result)
- Cumulative prognostic yield of WGTS (from those with an informative result)
- Cumulative prognostic yield of CGP (from those with an informative result)
- Proportion of patients tested identified with a cancer predisposition syndrome
- Change in management/treatment resulting in change in patient outcomes (PFS, OS, ORR, BOR, DOR, mortality, morbidity, HRQoL)
- Proportion of patients gaining access to PBS-listed site-specific treatments, including chemotherapy, immunotherapy and/or targeted therapy
- Reduced toxicity (associated with empirical and inappropriate therapy)

Safety outcomes

- Test-related adverse events (AEs)
- AEs from treatment
- AEs from change in patient management
- Harms related to over investigation (e.g. repeat biopsy, radiation exposure)
- Misclassification of cancers, particularly rare cancers

Test-related outcomes

- Rate of repeat biopsy (as a result of test failure from inadequate quality/quantity of specimen)

Health system resources

- Total cost of genetic tests for the intervention (including any confirmatory germline testing required) and the comparator Cost of PBS-funded site-specific treatments, immunotherapy and/or targeted therapies
- Cost per quality-adjusted life year and/or cost-effectiveness
- Total Australian Government healthcare costs

Other relevant considerations

- Value of knowing (e.g. psychosocial impact from not having a primary diagnosis)

Population 1 (patients with CUP):

PASC considered that only the 'psychosocial impact from not having a primary diagnosis' is actual value of knowing and suggested that 'identifying previously unknown germline findings' is a clinical utility outcome and should be moved to clinical effectiveness outcomes.

PASC noted from the application that the proposed testing would be additional to the currently MBS listed items used for the diagnostic work-up of patients with a malignant diagnosis of unknown origin and that the proposed testing would be performed after these existing tests. Therefore, PASC considered that 'shortening of the diagnostic odyssey' and 'reduced number of unnecessary imaging tests or other investigations seeking a primary site' are not relevant outcomes and considered that these should be removed.

PASC noted that patient access to clinical trials and off-label use of treatments as a result of genomic testing are outside the scope of the MBS and advised these to be removed as outcomes of the test for the purpose of the assessment.

PASC noted that patients tested with CGP (i.e. tumour only testing) will need to undergo additional testing to confirm the germline status of variants associated with cancer. PASC advised that the costs of these confirmatory tests should be factored into the cost of the CGP intervention. Therefore, PASC advised that the health system resources should capture the total cost of genetic tests for the intervention (including any confirmatory germline testing required) and the comparator. PASC advised for the removal of 'change in number of individual genetic tests' as an outcome as the required information on health resources use will be captured in the outcome for total cost of genetic tests in the intervention and comparator.

PASC advised to remove 'test turn-around time (TAT) of WGTS/CGP' as outcomes.

PASC queried the meaning of an 'actionable variant' and suggested the applicant explore clear evidence of the 'actionability' and how the changes in outcomes will be quantified for health economic modelling.

PASC proposed that safety outcomes also include misclassification of cancers, particularly rare cancers.

Population 2 (cascade testing population):

PASC considered the following to be the appropriate outcomes for Population 2:

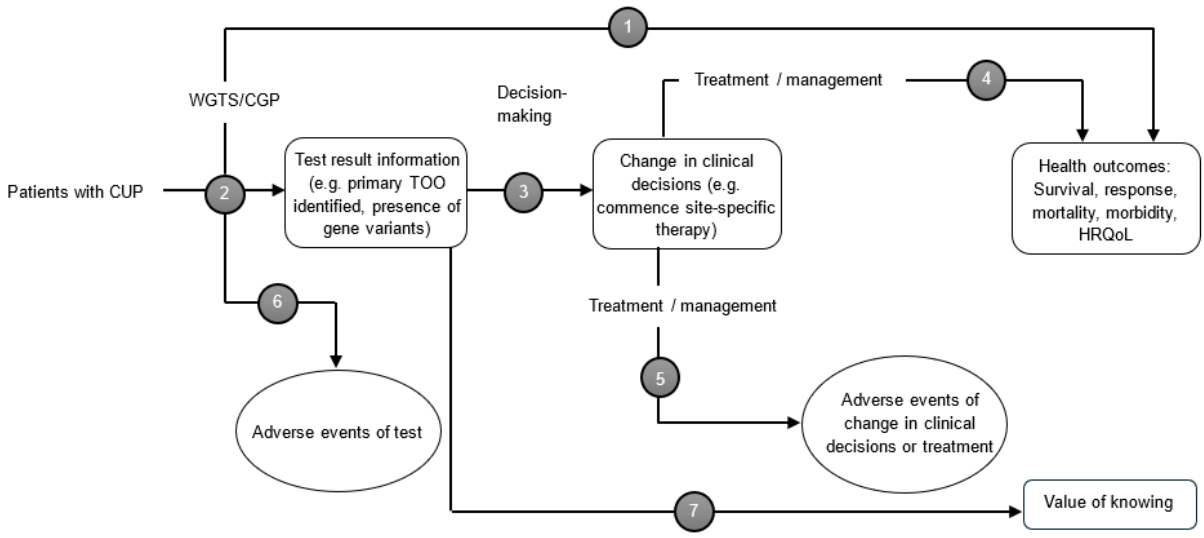
- *Uptake of cascade testing per germline pathogenic variant identified*

- *Diagnostic yield*
- *Impact on change in management*
- *Value of knowing*
- *Cost per pathogenic/likely pathogenic germline variant identified*

Assessment framework (for investigative technologies)

Figure 1 provides the assessment framework for genomic testing in CUP.

Figure 1: Assessment framework showing links from CUP test population to health outcomes



CGP=comprehensive genomic profiling; CUP=cancer of unknown primary; HRQoL=health-related quality of life; TOO= tissue of origin; WGTS=whole genome and transcriptome sequencing.

Notes: 1: direct from-test-to-health-outcomes evidence; 2: test performance; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: potential harm due to change in management; 6: adverse events due to testing; 7: value of knowing;

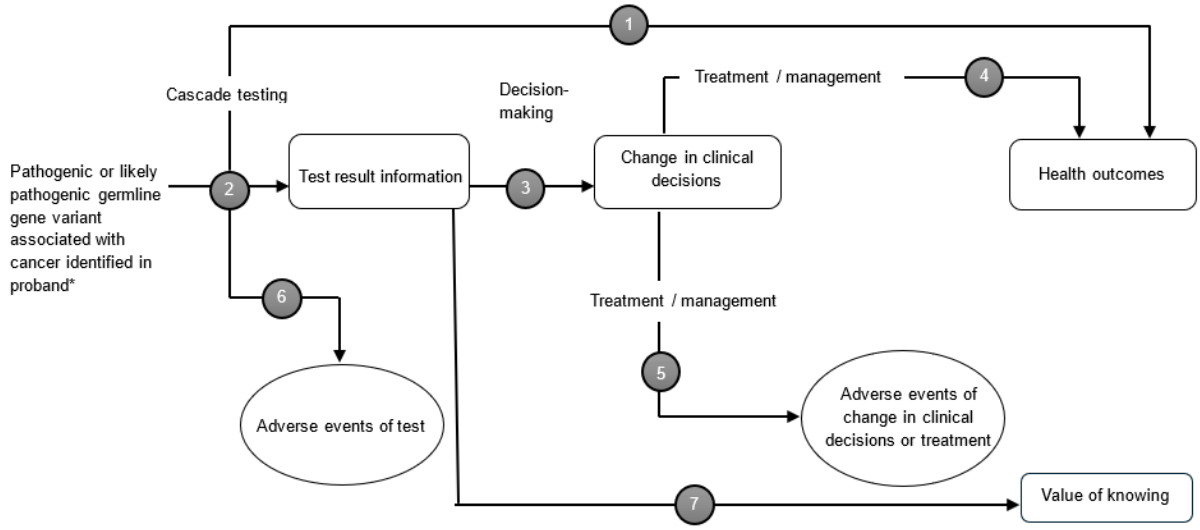
Assessment questions linked to the assessment framework:

1. What is the comparative effectiveness of WGTS or CGP testing versus no WGTS or CGP testing in patients with CUP, where direct evidence linking testing to health outcomes is available?
2. What is the diagnostic yield of genomic testing in patients with CUP?
3. How do the proposed genomic test results affect downstream clinical treatment/management and what is the evidence base of the impact?
4. What is the impact of the change in treatment/management versus no change in treatment/management on health outcomes such as survival, response, mortality, morbidity and HRQoL?
5. What is the impact of the change in treatment/management versus no change in treatment/management on safety outcomes (adverse events of treatment)?
6. What is the comparative safety (e.g. test-related adverse events) of WGTS or CGP testing (pre-treatment or at treatment commencement) versus no WGTS or CGP testing?
7. What beneficial outcomes does the availability of information from WGTS or CGP testing versus no WGTS or CGP testing have on outcomes related to value of knowing?

PASC recognised the need for cascade testing in biological relatives if pathogenic or likely pathogenic germline variants associated with cancer are identified in the proband during WGTS or CGP testing.

Figure 2 provides the assessment framework for cascade testing.

Figure 2: Assessment framework showing the links from the test population to clinical outcomes for cascade testing



Notes: 1: direct from-test-to-health-outcomes evidence; 2: test performance; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: potential harm due to change in management; 6: adverse events due to testing; 7: value of knowing

*proband is an individual in a family who is affected with a heritable disease or condition and has a relevant known pathogenic/likely pathogenic germline variant

Assessment questions for the cascade testing of biological relatives of patients with a confirmed CUP in whom a pathogenic or likely pathogenic germline variant associated with cancer has been identified:

1. What is the comparative safety, effectiveness and cost-effectiveness of cascade testing versus no testing?
2. What is the diagnostic yield of cascade testing in identifying cancer predisposition? What additional tests are needed to identify germline variants in at-risk biological relatives of a patient with an identified pathogenic/likely pathogenic variant?
3. Is there a change in management in individuals who undergo cascade testing?
4. Does change in management after cascade testing lead to a change in health outcomes?
5. What are the potential harms from change in management or treatment?
6. What are the potential harms associated with cascade testing?
7. What does the availability of information from cascade testing versus no testing have on outcomes related to value of knowing?

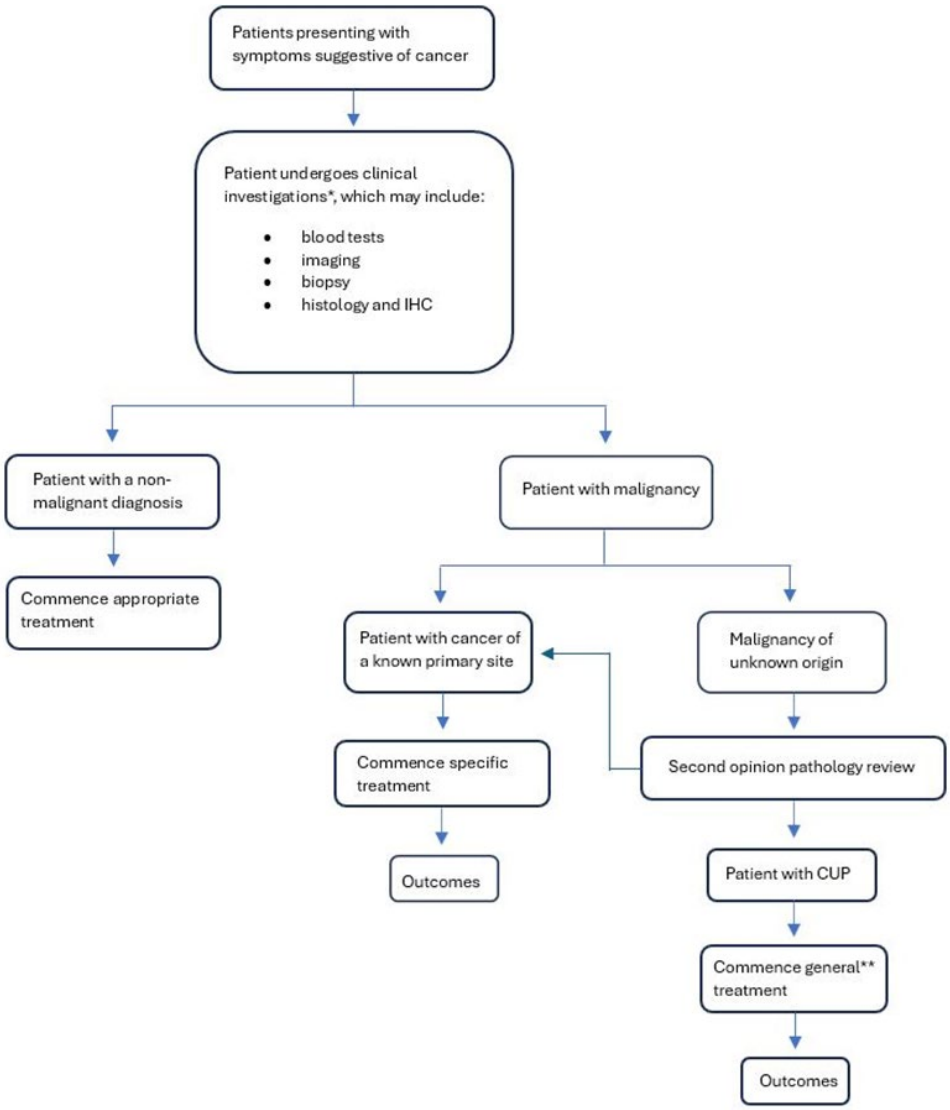
PASC noted that the overall claim of the application is that the proposed testing in patients with CUP results in superior health outcomes compared to no genomic testing. PASC noted that while the application included limited evidence of changes to health outcomes subsequent to testing, the application did not include any evidence of changes in health outcomes that resulted from patients accessing PBS-listed treatments post testing. PASC noted that if direct evidence from test to health outcomes is not available (or limited), a linked evidence approach would be needed. PASC discussed the available evidence, along with limitations of the current published studies in providing data to support outcome assessment. PASC and the

applicant discussed access to unpublished evidence from local and international trials which would be valuable to inform the assessment. However, PASC noted MSAC's strong preference for published, peer reviewed data for the evaluation and its decision-making purposes.

Clinical management algorithms

Two clinical management algorithms are presented: current clinical management for CUP patients in the absence of genomic testing (***Figure 3***) and the proposed clinical management for CUP patients with the addition of the proposed genomic testing (***Figure 4***).

Figure 3: Current clinical management algorithm for CUP



CUP=cancer of unknown primary; IHC=immunohistochemistry

Source: MSAC 1809 PICO Set, Figure 5, p.19.

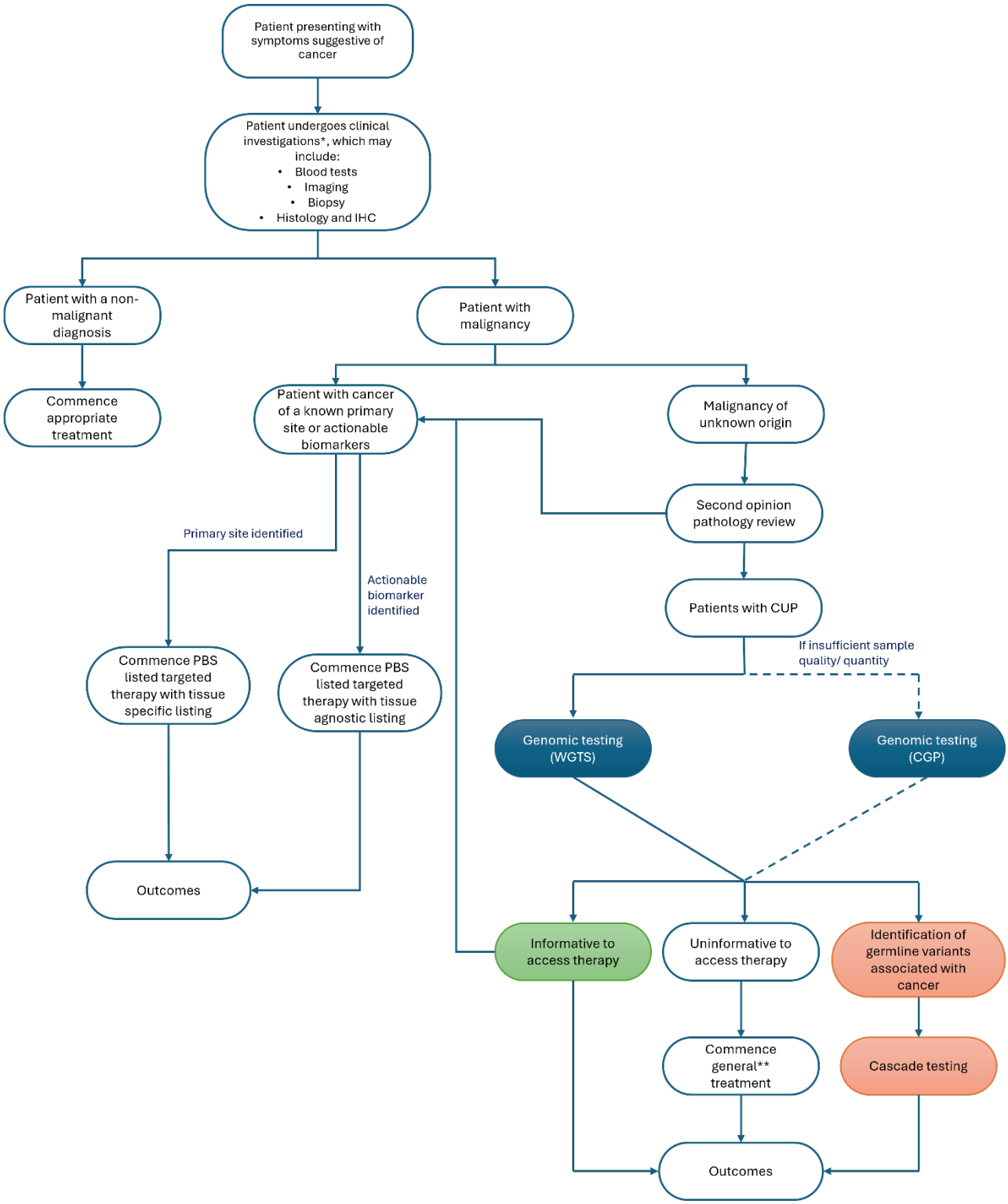
Figure notes:

*Investigations will depend on symptoms, clinical presentation and results of the investigations.

**Treatment for CUP patients will rely on empiric chemotherapy regimens.

In the current clinical management algorithm, patients with a diagnosis of CUP are directed to receive generalised treatment (i.e. chemotherapy). There is no difference in clinical management prior to genomic testing as complete clinical work-up (including second opinion pathology review) is required before a diagnosis of CUP can be given.

Figure 4: Proposed clinical management algorithm for CUP with genomic testing, including cascade testing of at-risk biological relatives



CGP=comprehensive genomic profiling; CUP=cancer of unknown primary; IHC=immunohistochemistry; PBS=Pharmaceutical Benefits Scheme; WGTS=whole genome and transcriptome sequencing.

Source: Adapted from MSAC 1809 PICO Set, Figure 6, p.21.

Figure notes:

*Investigations will depend on symptoms, clinical presentation and results of the investigations.

**Treatment for patients with CUP will rely on empiric chemotherapy regimens.

In the proposed clinical management algorithm, genomic testing via WGTS/CGP is an additional service provided to patients diagnosed with CUP after clinical investigation and second opinion pathology review.

Patients with resolved diagnosis may subsequently begin site-specific treatment, which may include chemotherapy, immunotherapy and/or targeted therapy. Patients with an unresolved CUP diagnosis following genomic testing will commence empirical chemotherapy regimens based on the current SOC.

PASC noted that WGTS is the preferred test, with CGP used if it is not possible to perform WGTS.

PASC acknowledged that in practice, testing may facilitate patient participation in clinical trials. However, PASC noted that MBS services cannot be used solely for this purpose (though it may be an incidental outcome), and therefore recommended removing clinical trial participation as a result of testing from the assessment of this application.

Proposed economic evaluation

The overall claim is that the proposed technology results in superior health outcomes compared to the comparator/SOC. Neither the application nor the PICO set document provided a claim about relevant safety (harms) for testing versus no testing.

The application claims that genomic testing via WGTS or CGP to achieve a resolved diagnosis in patients with CUP has superior health outcomes compared to no WGTS or CGP testing. Specifically, it is claimed that access to genomic testing will allow more patients to obtain a resolved diagnosis, access tissue-specific PBS-funded treatment, and receive prognostic information resulting in improved management and outcomes.

The clinical claim in the application leads to a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) for the economic evaluation (***Table 3***).

Table 3: Classification of comparative effectiveness and safety of the proposed intervention and guide to suitable economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflects uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost–consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detection of clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or comparative safety considerations.

[b] An adequate assessment of noninferiority is the preferred basis for demonstrating equivalence.

PASC advised that, based on the current application, a cost-effectiveness analysis using a cohort approach may be the most appropriate for the economic evaluation due to high levels of heterogeneity in the patient population. PASC noted the proposed testing is anticipated to have multiple purposes including informing diagnosis, prognostic utility, identification of a therapeutic option and direct therapy, and identification of hereditary cancer predisposition. PASC acknowledged it may not be feasible to quantify all the utilities and to obtain evidence across the different cancers and treatments.

Proposal for public funding

The application proposed 2 new MBS items for genomic testing via WGTS (***Table 4***) and CGP (***Table 5***) of CUP for funding under the MBS. An additional MBS item for cascade testing of biological relatives (***Table 6***) was added based on PASC advice.

Table 4: Proposed MBS item for WGTS in CUP (updated to incorporate PASC advice)

Category 6 – Pathology Services – P7 Genetics
MBS item AAAAA Characterisation of gene variants and tissue of origin on tumour tissue and blood (excluding circulating tumour DNA) by whole genome and transcriptome sequencing, requested by a specialist or consultant physician, if the service is: a. for a patient diagnosed with cancer of unknown primary where a diagnostic work-up is unable to determine a primary site or tissue of origin, and b. the patient: i. has not previously received a service to which item BBBBB applies within the same diagnostic episode, or ii. has received a service to which item BBBBB applies within the same diagnostic episode, for which the results were non-informative Applicable once per diagnostic episode at diagnosis or relapse.
Fee: $5,500 Benefit: 75% = $4125, 85% = $5395.50*

CUP=cancer of unknown primary; DNA=deoxyribonucleic acid; MBS=Medicare Benefits Schedule; WGTS=whole genome and transcriptome sequencing.

* Reflects the 1 November 2025 greatest permissible gap (GPG) of $104.50. All out-of-hospital Medicare services with an MBS fee of $697.00 or more will attract a benefit >85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the consumer price index (CPI) (June quarter).

Table 5: Proposed MBS item for CGP in CUP (updated to incorporate PASC advice)

Category 6 – Pathology Services – P7 Genetics
MBS item BBBBB Characterisation of gene variants and tissue of origin on tumour tissue by a comprehensive gene panel, requested by a specialist or consultant physician, if the service is: a. for a patient diagnosed with cancer of unknown primary where a diagnostic work-up is unable to determine a primary site or tissue of origin, and b. the patient has not previously received a service to which item AAAAA applies within the same diagnostic episode. Applicable once per diagnostic episode at diagnosis or relapse.
Fee: $3,300 Benefit: 75% = $2,475, 85% = $3195.50*

CGP=comprehensive genomic profiling; CUP=cancer of unknown primary; MBS=Medicare Benefits Schedule.

Source: MSAC 1809 PICO Set, p.18.

* Reflects the 1 November 2025 greatest permissible gap (GPG) of $104.50. All out-of-hospital Medicare services with an MBS fee of $697.00 or more will attract a benefit >85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the consumer price index (CPI) (June quarter).

Table 6: Proposed MBS item for cascade testing in CUP (added based on PASC advice)

Category 6 – Pathology Services – P7 Genetics
MBS item CCCCC Characterisation of one or more pathogenic or likely pathogenic germline gene variants associated with cancer, if the service is: a. requested by a specialist or consultant physician; and b. for a person (the person tested) who is a biological relative of a patient in whom a pathogenic or likely pathogenic germline variant associated with cancer has been identified following a service provided under item AAAAA; and c. the person tested has not previously received a service to which item AAAAA, BBBBB, 73296 or 73297 applies. Once per gene per lifetime.
Fee: $400 Benefit: 75% = $300 85% = $340

CUP=cancer of unknown primary; MBS=Medicare Benefits Schedule.

Currently, there are no MBS item numbers that cover genomic testing (WGTS or CGP) for CUP. Testing is being performed at patients' expense or covered by research funding or not performed at all. Public funding of these genomic tests would align Australian clinical practice with ESMO recommendations (Kramer et al. 2023; Mosele et al. 2024), and with publicly funded WGS services offered by the UK National Health Service (NHS) and the Netherlands Cancer Institute (NKI) (Karthikeyan, McKee & McKay 2024; Schipper et al. 2022).

As noted in the pre-PASC meeting, the applicant's clinical experts stated that WGTS is the preferred testing method. However, where requirements are not met for conducting WGTS (e.g. test failure typically due to poor quality input data or low tumour fraction), CGP may be performed instead. At the pre-PASC teleconference, the applicant's clinical expert stated that if a sample does not meet the requirements for WGTS, a second test request is not required by the ordering physician, as it will be the laboratory's responsibility to assess the sample quality/quantity and perform the appropriate test. If a second biopsy/specimen is obtained from a patient to allow for WGTS testing, a test will only be performed if the first test had objectively failed, meaning if information had been obtained via CGP a subsequent WGTS test would not be performed.

Importantly, if either test becomes MBS-listed and fails due to insufficient or low-quality sample and no valid test result can be reported, then no MBS rebate is payable for that test. The pathology provider or laboratory cannot claim reimbursement from Medicare for the failed test. The cost of the failed test is typically absorbed by the pathology provider or laboratory, or may be billed privately if agreed with the patient or provider.

During the pre-PASC teleconference, the applicant's clinical experts stated that CGP testing typically has a faster turnaround time than WGTS. It was noted that WGTS generally takes about three weeks but can be expedited if clinically urgent. The clinical experts stated that the choice between CGP and WGTS should remain at the clinician's discretion. The experts also highlighted that CGP is currently more widely used and, if WGTS is supported as proposed, appropriate education would be necessary.

Through correspondence with the Department, the applicant stated that both University of Melbourne Centre for Cancer Research and the Peter MacCallum Cancer Centre hold NATA accreditation for CGP. Furthermore, the applicant stated that University of Melbourne Centre for Cancer Research is in the process of applying for NATA accreditation for WGTS. The applicant is requested to provide relevant regulatory/accreditation information relevant to CUPPA and any other algorithms that are proposed to be considered as part of this MSAC application.

The application provided a cost breakdown for WGTS (***Table 7***) and CGP (***Table 8***). The proposed estimated cost per CUP patient for a single WGTS in a NATA-accredited laboratory is $5,500 (proposed MBS fee $4,125 at 75% benefit; $5,395.50 at 85% benefit subject to greatest permissible gap). Total proposed estimated cost per sample for a single CGP in a NATA-accredited laboratory is $3,300 (proposed MBS fee $2,475 at 75% benefit; $3,195.50 at 85% benefit subject to greatest permissible gap).

As per the pre-PASC meeting, the cost for sourcing and sending specimens is covered by a separate previously established MBS item number and has not been included in the cost breakdown. This reflects the current pathway for sample procurement and transfer.

Table 7: Estimated cost per patient for WGTS in a NATA-accredited laboratory

Component	Description	Justification	Estimated cost*
Sample preparation and extraction	Tissue sectioning, DNA/RNA extraction from tumour and matched normal (e.g. blood), quality control checks (Qubit), pathology oversight.	Dual sample extraction (tumour/normal), QC metrics, pathologist review, tissue handling requirements.	$500
Library preparation and sequencing	Library prep using clinical-grade kits (e.g. TruSeq DNA PCR-Free), sequencing on NovaSeq S4 (30x germline, ~90x tumour), QA/QC under NATA protocols.	High coverage depth (~90x tumour), use of validated clinical-grade reagents, overhead of NATA accreditation (method validation, SOPs, audits, documentation, QA).	$2,400
Bioinformatics and variant calling	Alignment, variant calling (SNVs, CNVs, SVs), tumour-normal subtraction, quality checks, pipeline validation under accreditation standards.	Complex tumour-normal comparison, computational resources, validated pipelines, clinical-grade annotation.	$1,200
Clinical interpretation and reporting	Interpretation by molecular pathologist/geneticist, variant annotation, reporting of actionable variants, MDT discussion, report generation.	Input from certified molecular pathologist/geneticist (oversight mandated), MDT involvement, compliance documentation.	$1,000
Data storage and compliance	Secure long-term storage of genomic data (~200–300 GB per patient), compliance with ISO 27001, record retention, audit trail maintenance.	Genomic data is large, requires long-term secure storage under health data governance and legal compliance.	$400
Total estimated cost per sample			**$5,500**

CNV=copy number variant; DNA=deoxyribonucleic acid; MDT=multidisciplinary team; NATA=National Association of Testing Authorities; PCR = polymerase chain reaction; QA=quality assurance; QC=quality control; RNA=ribonucleic acid; SNV=single nucleotide variant; SOP=standard operating procedure; SV=structural variant; WGTS=whole genome and transcriptome sequencing.

* Estimated cost in Australian dollars.

Source: MSAC 1809 CUP Cost Breakdown Attachment, Table 1, p.1.

Table 8: Estimated cost per patient for CGP in a NATA-accredited laboratory

Component	Description	Justification	Estimated cost*
Pre-analytical (sample handling and QC)	FFPE retrieval, pathology review, macrodissection, nucleic acid extraction, QC.	Covers pathology review for tumour content and QC assessments to ensure sample suitability for downstream testing.	$200
Sequencing (NGS reagent costs)	Illumina-based platforms using hybrid capture technology.	Includes reagents (DNA library prep kits, target enrichment probes, sequencing reagents, flow cells) and consumable costs for hybrid capture-based NGS (e.g. Illumina NovaSeq or NextSeq), which may span 500+ genes.	$2,000
Bioinformatics pipeline	Alignment to human reference genome, variant calling, CNV/structural analysis, annotation.	Encompasses computational analysis and annotation using clinical databases. Includes licensing costs, software, infrastructure, bioinformatics personnel time.	$400
Clinical interpretation and reporting	Curation by clinical scientists and pathologists.	Involves manual curation by accredited clinical scientists or molecular pathologists. Includes assessing variant pathogenicity, therapeutic relevance, clinical trial matches. MDT discussion and report generation.	$300
Data storage and compliance	Storage of datasets and compliance with privacy regulations.	Secure digital storage of genomic data in line with Australian regulations. Costs include cloud or on-premise infrastructure, backups, access control systems, documentation for audit and reanalysis.	$400
Total estimated cost per sample			**$3,300**

CGP=comprehensive genomic profiling; CNV=copy number variant; DNA=deoxyribonucleic acid; FFPE=formalin-fixed paraffin-embedded; MDT=multidisciplinary team; NATA=National Association of Testing Authorities; NGS=next-generation sequencing; QC=quality control.

* Estimated cost in Australian dollars.

Source: MSAC 1809 CUP Cost Breakdown Attachment, Table 2, p.2.

According to the application, up to two genomic tests may be required within 1 to 5 years for a patient diagnosed with CUP. As CUP is considered a rare cancer with poor survival rates, most patients will only require testing once per lifetime. However, with the introduction of improved diagnostic information provided by WGTS/CGP, and increasing access to site-specific treatments, immunotherapy and/or targeted therapies, the applicant at the pre-PASC teleconference considered that a minority of patients without an identified TOO from the initial testing should be eligible for repeat testing subsequent to relapse.

Limited evidence is currently available for the implementation and impact on patient outcomes/clinical management of repeat WGTS/CGP at relapse. However, evidence shows that repeat genomic testing via alternative NGS methods can identify new actionable drivers or resistance variants at relapse or progression, which is able to alter clinical management—though not specific to CUP (Herberts et al. 2022; Kuang et al. 2024; Lenz et al. 2025).

The applicant assumes that 60% of the proposed population will be expected to undergo genomic testing in year 1 or year 2, increasing to 70% in year 3 or year 4.The application noted that not all incident cases will be suitable for genomic testing and experience from the Peter MacCallum Cancer Centre's dedicated

CUP clinic from 2014–2020 reported that of 361 patients booked to attend the clinic, only 60% had a genomic test (van Mourik et al. 2023). Funding limitations may play a role in limiting historical rates of testing, but these figures highlight that the estimated number of patients likely to be tested in practice could be significantly below the incidence rate. According to the application, an uptake of 60% in year 1 is likely to overestimate short-term utilisation as there are currently only a limited number of specialist centres with experience in genomic testing in patients with CUP.

It is estimated that 1,580 patients will utilise the proposed genomic tests in the first year (based on the uptake rate estimated in the application), with the cost of testing ranging from approximately $5,214,000 to $8,690,000.

PASC considered that ctDNA should be excluded from item AAAAA. PASC noted that the frequency restriction is broadly consistent with other similar items (MBS 73445, genetic testing in haematological malignancy of myeloid origin). In the pre-PASC response, the applicant stated that some patients may require more than one test per lifetime, particularly where there is evidence of a second primary CUP. The department confirmed that such testing would be considered a new diagnostic episode not a repeat test. The applicant further noted that, in practice, the likelihood of claiming more than one test per patient is low due to the poor median survival of patients with CUP. PASC considered that the explanatory notes of the AAAAA MBS item descriptor should describe the nature of the prediction algorithm and any reporting standards for TOO diagnosis. Further to this, PASC advised that wording should be agnostic of any specific TOO prediction algorithm, to future-proof the MBS item for any novel validated algorithms. PASC noted from the applicant that similar algorithms for TOO diagnosis are being developed for CGP and considered that this should be included in the explanatory note for future-proofing. PASC considered that the explanatory note of item BBBBB should also specify the minimum standards for the comprehensive gene panel, for example, including the gene panel size (e.g. >500) and the use of both DNA and RNA to ensure effective TOO diagnostic yields.

PASC considered that the items should be restricted to patients with a life expectancy ≥12 weeks (in alignment with the CUPSICO trial) and an ECOG performance status of 0–1 (in alignment with the CUPISCO trial and the majority of patients in the SUPER studies). PASC advised for this information to be included in the explanatory note of the items.

PASC noted that the application proposed that items AAAAA and BBBBB be requested by a specialist, consultant physician or pathologist, in effect making both items pathologist-determinable. The applicant considered that making the tests pathologist-determinable would allow the tests to be performed without delay. PASC queried the appropriateness of making the items pathologist-determinable, given that the testing identifies hereditary cancer predisposition in a proportion of patients. PASC noted that the 'triggering' or preceding service to allow the pathologist to perform this test without a request form from the treating practitioner is unclear. PASC noted department advice that a 'triggering' service must be specified in the legislation for the item to be implementable. Post-PASC meeting, PASC considered the legislative need for a request to arise from a treating practitioner and advised against the proposed service being pathologist-determinable, since the 'triggering' or preceding service to allow a pathologist to perform the test without a request form from the treating practitioner would be unclear and poorly defined.

PASC noted the additional item descriptor proposed by the department for cascade testing for germline genetic variants, worded to be consistent with other cascade testing available via the MBS (items 73296 and 73297: Characterising germline gene variants in breast, ovarian, fallopian tube or primary peritoneal cancer).

PASC discussed the proposed item fees and cost inputs. PASC noted advice from the department that some components, such as sample preparation, are already partially funded under other existing MBS items (e.g. various examination of tissue pathology items under MBS items 72813–72838). Furthermore, PASC noted that clinical interpretation and reporting is partially funded by existing multidisciplinary items (MBS items 243/244/871/872). PASC noted departmental advice that data storage and compliance cannot be funded by the MBS as these are costs for infrastructure, not directly for the professional service funded under the MBS. PASC noted that similar WGS tests currently available via the MBS were at a lower cost (e.g. $2,900–3,300 for MBS 73457, 73359). The applicant stated that compared to WGS, WGTS also sequences RNA, introducing an additional level of complexity in the interpretation of the test result from a bioinformatics perspective. At the time of consideration, PASC noted that CGP was available at a lower cost via a commercial provider in Australia (LifeStrands[1], $2,300 for CGP assay). PASC requested the applicant to provide further supporting information and justification for the higher fee requested for both items, otherwise fees in line with commercial providers could provide a benchmark

Post-PASC meeting, PASC queried whether the BBBBB item should include verification of germline status of variants associated with cancer, and if so, for the applicant to provide further information on the proposed fee and justification for any additional cost components.

PASC noted that several labs in Australia hold NATA accreditation for CGP testing, while no laboratories are currently NATA-accredited for WGTS. The applicant stated that the University of Melbourne Centre for Cancer Research is intending to submit an application for NATA accreditation of WGTS in early 2026. PASC noted departmental advice that a laboratory is able to use the CUPPA algorithm once it receives NATA accreditation for the testing, including for the use of the algorithm.

Summary of public consultation input

PASC noted and welcomed consultation input from 8 organisations and no individuals. The organisations that submitted input were:

- Cancer Council Australia (CCA)
- Rare Cancers Australia (RCA)
- Public Pathology Australia (PPA)
- Human Genetics Society of Australasia Limited (HGSA)
- Inherited Cancers Australia (ICA)
- Lung Foundation Australia (LFA)
- Omico
- Australian Pathology (AP).

Consultation input was predominantly supportive of public funding for genomic testing in CUP and diagnostically challenging cancers.

Consumer Experience

Consumer organisations highlighted the psychological burden and uncertainty faced by patients with CUP, and the benefit that knowing the TOO, accessing targeted therapies, and reducing diagnostic delays brings to patients and their families. CCA stated that individuals with CUP will likely undergo multiple diagnostic investigations with associated financial, travel and time burdens.

[1] https://www.lifestrandsgx.com.au/wp-content/uploads/Test-Request-Form_v17.pdf

Benefits and Disadvantages

Consultation input included several key benefits of public funding for genomic testing in CUP and diagnostically challenging cancers. Organisations noted that improved diagnostic accuracy enables identification of the TOO, allowing patients to access targeted therapies and more personalised treatment options. Genomic testing can reduce diagnostic delays and unnecessary investigations, resulting in better patient management and outcomes. In addition to clinical advantages, consultation input described the psychological benefits of genomic testing for patients and families, including reduced uncertainty and distress that is associated with a CUP diagnosis. Genomic testing for patients with CUP was seen as aligning Australian practice with international guidelines and standards, such as those from the European Society for Medical Oncology and the National Health Service.

No significant disadvantages were identified in the consultation input received. However, some organisations advised that careful implementation would be required to ensure appropriate consent and genetic counselling processes are in place. Consultation input recognized the need to address workforce and laboratory capacity for genomic testing, and to monitor costs and utilisation to ensure the sustainability of the service. In particular, HGSA noted that no diagnostic laboratories in Australia offer NATA-accredited WGTS.

Population, Comparator (Current Management), and Delivery

Consultation input was supportive of the proposed population for genomic testing, which includes patients diagnosed with CUP and diagnostically challenging cancers. There was broad consensus that the eligibility criteria outlined in the application are appropriate.

Consultation input agreed with the nominated comparator, current management without genomic testing. Respondents acknowledged that standard investigations, such as blood tests, imaging, and histopathology, are essential but often insufficient for determining the primary site in CUP cases.

Ensuring equity of access was also emphasised, particularly for patients in regional and remote areas who may currently face barriers to advanced testing. There was recognition of the need for multidisciplinary collaboration, including coordination between pathology, oncology, and genetics services, to optimise patient care and support the integration of new technologies into routine clinical practice.

MBS Item Descriptor and Fee

Consultation input from health professionals and health organisations was supportive of the proposed MBS item descriptors for genomic testing in CUP and diagnostically challenging cancers. Organisations agreed that the item descriptors accurately reflect the nature of the service, including the use of WGTS or CGP to characterise gene variants and determine TOO. RCA stated that emerging methodologies, such as liquid biopsies, are becoming increasingly validated and could substantially address some current barriers to access, and that inclusion in the proposed item descriptor should be considered.

Consultation input agreed with the proposed fees and noted they aligned with the costs of delivering these advanced molecular diagnostic services. Input noted that public funding would remove financial barriers for patients and ensure equitable access to genomic testing, which is currently limited to those able to self-fund or participate in research programs.

Additional Comments

Input from Omico noted the broader underlying policy issue regarding equitable access to treatments for patients with CUP who undergo CGP and have an actionable variant identified as being likely to benefit from targeted or tumor-agnostic therapies. Consultation input also noted the value of ongoing research and data collection to monitor outcomes, inform best practice, and guide future updates to service delivery models.

ICA highlighted a consideration that was not adequately addressed in the application, the potential for somatic genomic investigations to identify variants suggestive of germline pathogenic variants. ICA stated that these findings may reveal an underlying hereditary cancer predisposition, and that genomic testing for patients with CUP needs to include pathways that ensure appropriate identification, referral, and support for families affected by inherited cancer syndromes.

PASC noted that 7 organisations (CCA, RCA, PPA, HGSA, ICA, LFA and Omico) were supportive of the application.

PASC noted from the consultation input and the applicant that access to testing is currently inequitable, as it depends on the ability to financially afford the test or the opportunity to participate in research trials. The consultation input and the applicant indicated that MBS listing of the proposed test would help to address these inequities.

Regarding access to testing for patients living in regional and rural areas, PASC noted from the applicant that their SUPER study included sites throughout Australia, including Darwin. PASC noted from the applicant that only the biological material (not the patients themselves) may require travel to other locations for testing. Furthermore, the applicant noted that archival tissue can be used for testing, noting that this would minimise the burden on patients by avoiding the need for re-biopsy, with a re-biopsy only needed if the archival sample is unsuitable for testing.

PASC noted the importance of access to genetic counselling services for patients who undergo the proposed testing and their families.

Next steps

PASC noted from the application that the assessment report would not be developed by the applicant, and that a Department contracted assessment report (DCAR) has been requested. For the DCAR development, the applicant is requested to provide further supporting information and justification for the higher fee requested for both items, otherwise fees in line with commercial providers could provide a benchmark.

PASC requested advice from the PBAC Executive to inform whether PBAC requires additional information to address issues relating to access to PBS-listed treatments following the proposed testing. PASC advised that any PBAC input should be considered prior to commencing an assessment report.

Applicant Comments on Ratified PICO

We thank PASC for their detailed review and comments, and would like to emphasise that this proposal is for molecular testing to diagnose the tissue of origin (TOO) in patients with CUP. Regarding the downstream impacts of testing on health outcomes, we will soon be submitting a paper for publication from our SUPER-NEXT cohort that will demonstrate improvements in survival for CUP patients, and are

happy to share this with the evaluators when appropriate. We also note the recent PBAC recommendations to broaden access to pembrolizumab and nivolumab/ipilimumab for advanced and metastatic cancers, which may mitigate concerns around access to PBS-funded therapies, noting immunotherapy is commonly recommended for tumour types identified following genomic testing in CUP.

We do not share PASC's view that genomic testing will not reduce the diagnostic odyssey in CUP. In our experience, many patients undergo investigations beyond those recommended in ESMO guidelines in search of a TOO, and face extended wait times in the public system (e.g., for endoscopy). Consistent with this, healthcare costs both prior to a final CUP diagnosis and in the first six months after diagnosis remain higher than for other cancers (e.g., ovarian) (Gordan et al 2023).

Finally, while we agree that the WHO Classification of Tumours does not specifically recommend using genomic sequencing to diagnose the tissue of origin in CUP, it clearly endorses a molecularly integrated diagnostic framework and indicates that modern tumour classification is increasingly based on molecular information.

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Appendices

Appendix Table 1: Genomic aberrations as tools to discriminate between CUP and defined primary tumour entities*

Tumour entity	Genomic aberration	Histology
Non-small cell lung cancer	*ALK* fusions	*ROS1* fusions
Intrahepatic cholangiocarcinoma	*FGFR2* fusions	
Salivary gland carcinoma	*ETV6-NTRK3* *MYB* fusions *MYBL2* fusions *EWSR1-ATF1* *MAML2* fusions *PLAG1* fusions *HMGA2* fusions *PRKD1* mutations	Secretory carcinoma Adenoid cystic carcinoma Adenoid cystic carcinoma Hyalinising clear-cell carcinoma Mucoepidermoid carcinoma Pleomorphic adenoma and ex PA-carcinoma Polymorphous adenocarcinoma
NUT carcinoma	*NUTM1* fusions	
Prostate cancer	*TMPRSS2-ERG*	
Sarcoma and other mesenchymal tumours	*EWSR1-FLI1* *EWSR1-ERG* *EWSR1-WT1* *ETV6-NTRK3* *EWSR1-POU5F1* *TFE3* fusions *NAB2-STAT6* *NR4A3* fusions *SMARCB1* alterations, *BCOR* alterations *SS18(SYT)* fusions *COL1A1-PDGFB* *KIT* mutations *FUS-CREB3L2/CREB3L1* *DDIT3* fusions *HEY1-NCOA2*	Ewing sarcoma Ewing sarcoma Desmoplastic small round-cell tumour Infantile fibrosarcoma Myoepithelioma/myoepithelial carcinoma Alveolar soft part sarcoma, epithelioid hemangioendothelioma, pecoma Solitary fibrous tumour Extraskeletal myxoid chondrosarcoma Malignant rhabdoid tumour Epithelioid sarcoma Synovial sarcoma Dermatofibrosarcoma protuberans GIST Low grade fibromyoid sarcoma/sclerosing epitheloid fibrosarcoma Myxoid liposarcoma Mesenchymal chondrosarcoma
Hepatocellular carcinoma	*PRKACA* fusions	Fibrolamellar hepatocellular carcinoma
Renal cell carcinoma	*TFE3* fusions *TFEB* fusions *VHL* alterations	Translocation-associated *RCC* Clear-cell carcinoma
Breast	*ETV3* fusions	Secretory carcinoma

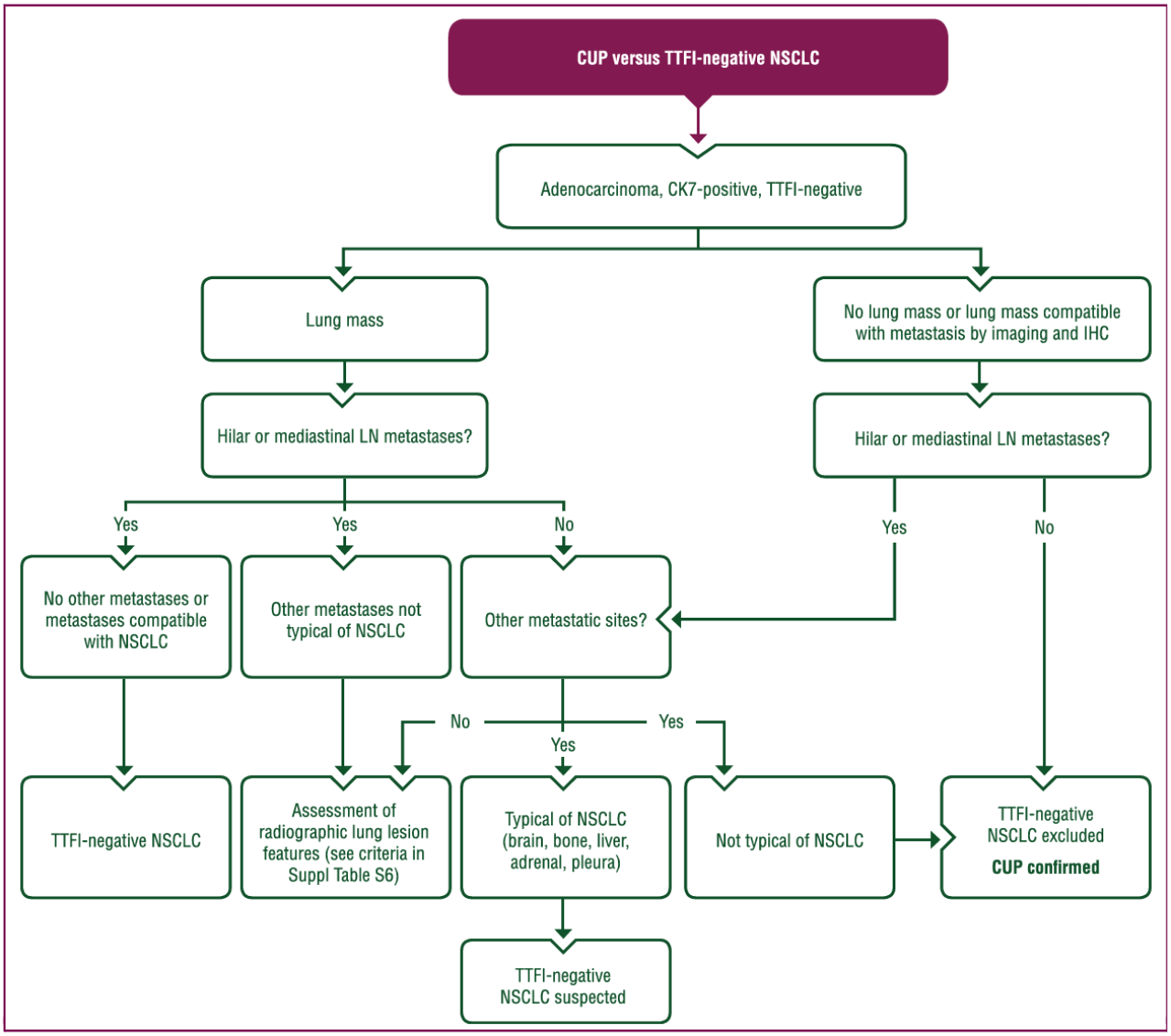
ALK=ALK receptor tyrosine kinase; ATF1=activating transcription factor 1; BCOR=BCL6 corepressor; COL1A1=collagen type1 alpha 1 chain; CREB3L1=cAMP responsive element binding protein 3 like 1; CREB3L2=cAMP responsive element binding protein 3 like 2; CUP=cancer of unknown primary; DDIT3=DNA damage inducible transcript 3; ERG= ETS transcription factor ERG; ETV3= ETS variant transcription factor 3; ETV6=ETS variant transcription factor 6; EWSR1=EWS RNA binding protein 1; FGFR2=fibroblast growth factor receptor 2; FLI1= Fli-1 proto-oncogene, ETS transcription factor; FUS= FUS RNA binding protein; GIST=gastrointestinal stromal tumour; HEY1=hes-related family bHLH transcription factor with YRPW motif 1; HMGA2=high-mobility group AT-hook 2; KIT=KIT proto-oncogene, receptor tyrosine kinase; MAML2=mastermind like transcriptional coactivator 2; MYB= MYB proto-oncogene, transcription factor; MYBL2=MYB proto-oncogene like 2; NAB2=NGFI-A binding protein 2; NCOA2=nuclear receptor coactivator 2; NR4A3=nuclear receptor subfamily 4 group A member 3; NTRK3=neurotrophic tyrosine receptor kinase type 3; NUT=nuclear protein in testis; NUTM1=NUT midline carcinoma family member 1; PDGFB=platelet derived growth factor subunit B; PLAG1= PLAG1 zinc finger; POU5F1= POU class 5 homeobox 1; PRKACA=protein kinase cAMP-activated catalytic subunit alpha; PRKD1=protein kinase D1; RCC=regulator of chromosome condensation; ROS1=ROS proto-oncogene 1, receptor tyrosine kinase; SMARCB1= SWI/SNF related BAF chromatin remodeling complex subunit B1; SS18(SYT)= SS18 subunit of BAF chromatin remodeling complex; STAT6=signal transducer and activator of transcription 6; TFE3=transcription factor binding to IGHM enhancer 3;

TFEB=transcription factor EB; TMPRSS2=transmembrane serine protease 2; VHL=von Hippel-Lindau tumor suppressor; WT1= WT1 transcription factor.

* incomplete list; haematological malignancies not included

Source: ESMO 2023 CGP, Supplementary Table S5 (Kramer et al. 2023).

Appendix 1: Exemplar differential diagnostic algorithm to discriminate between CUP and TTFI-negative NSCLC



CK=cytokeratin; CUP=cancer of unknown primary; IHC=immunohistochemistry; LN=lymph node; NSCLC=non-small cell lung cancer; TTFI=thyroid transcription factor 1.

Note: Brain, bone, liver, adrenal glands and pleura are the most common sites of metastatic disease in NSCLC.

Purple = general categories or stratification; white = other aspects of management.

Source: ESMO 2023 CGP, Table 1, p.231 (Kramer et al. 2023).

Appendix Table 2: Existing MBS items for investigations and diagnostic tests to identify primary site in CUP

Investigative technology	Item number	Description and fee
Blood examination	65070 (Group P1 – Haematology)	Erythrocyte count, haematocrit, haemoglobin, calculation or measurement of red cell index or indices, platelet count, leucocyte count and manual or instrument generated differential count – not being a service where haemoglobin only is requested – one or more instrument generated sets of results from a single sample; and (if performed) (a) a morphological assessment of a blood film (b) any service in item 65060 or 65072 Fee: $16.95 Benefit: 75% = $12.75, 85% = $14.45
	66650 (Group P2 – Chemical)	Alpha-fetoprotein, CA-15.3 antigen (CA15.3), CA-125 antigen (CA125), CA-19.9 antigen (CA19.9), cancer associated serum antigen (CASA), carcinoembryonic antigen (CEA), human chorionic gonadotrophin (HCG), neuron specific enolase (NSE), thyroglobulin in serum or other body fluid, in the monitoring of malignancy or in the detection or monitoring of hepatic tumours, gestational trophoblastic disease or germ cell tumour – quantitation – 1 test (Item is subject to rule 6) Fee: $24.35 Benefit: 75% = $18.30, 85% = $20.70
Diagnostic imaging	56807 (Group I2 – Computed Tomography, Subgroup 8 – Chest, abdomen, pelvis and neck)	Computed tomography scan of chest, abdomen and pelvis with or without scans of soft tissues of neck with intravenous contrast medium and with any scans of chest, abdomen and pelvis with or without scans of soft tissue of neck before intravenous contrast injection, when performed, not including a study performed to exclude coronary artery calcification or image the coronary arteries (R) (Anaes.) Fee: $615.40 Benefit: 75% = $461.55, 85% = $523.10
	63001 (Group I5 – Magnetic Resonance Imaging, Subgroup 1 – Scan of Head – for specified conditions)	MRI-scan of head (including MRA, if performed) for tumour of the brain or meninges (R) (Anaes.) (Contrast) Fee: $441.45 Benefit: 75% = $331.10, 85% = $375.25
	63271 (Group I5 – Magnetic Resonance Imaging, Subgroup 10 – Scan of Cervical Spine and Brachial Plexus – For Specified Conditions	MRI—scan of cervical spine and brachial plexus for tumour (R) (Anaes.) (Contrast) Fee: $539.60 Benefit: 75% = $404.70, 85% = $458.70
	61612 (Group I4 – Nuclear Medicine Imaging, Subgroup 2 – PET)	Whole body FDG PET study for the initial staging of eligible cancer types, for a patient who is considered suitable for active therapy, if: (a) the eligible cancer type is: (i) a rare or uncommon cancer (less than 12 cases per 100,000 persons per year); and (ii) a typically FDG-avid cancer; and (b) there is at least a 10% likelihood that the PET study result will inform a significant change in management for the patient Applicable once per cancer diagnosis (R) Fee: $953.00 Benefit: 75% = $714.75, 85% = $850.60
	55036 (Group I1 – Ultrasound, Subgroup 1 – General)	Abdomen, ultrasound scan of (including scan of urinary tract when performed), for morphological assessment, if: (a) the service is not solely a transrectal ultrasonic examination of any of the following: (i) prostate gland; (ii) bladder base; (iii) urethra; and

Investigative technology	Item number	Description and fee
		(b) within 24 hours of the service, a service mentioned in item 55038 is not performed on the same patient by the providing practitioner (R) Fee: $124.70 Benefit: 75% = $93.55, 85% = $106.00
	55065 (Group I1 – Ultrasound, Subgroup 1 – General)	Pelvis, ultrasound scan of, by any or all approaches, if: (a) the service is not solely a service to which an item (other than item 55736 or 55739) in Subgroup 5 of this Group applies or a transrectal ultrasonic examination of any of the following: (i) prostate gland; (ii) bladder base; (iii) urethra; and (b) within 24 hours of the service, a service mentioned in item 55038 is not performed on the same patient by the providing practitioner (R) Fee: $110.20 Benefit: 75% = $82.65, 85% = $93.70
	30473 (Group T8 – Surgical Operations, Subgroup 1 – General)	Oesophagoscopy (not being a service associated with a service to which item 41822 applies), gastroscopy, duodenoscopy or panendoscopy (1 or more such procedures), with or without biopsy, not being a service associated with a service to which item 30478 or 30479 applies. (Anaes.) Fee: $201.75 Benefit: 75% = $151.35, 85% = $171.50
	32222 (Group T8 – Surgical Operations, Subgroup 2 – Colorectal)	Endoscopic examination of the colon to the caecum by colonoscopy, for a patient: (a) following a positive faecal occult blood test; or (b) who has symptoms consistent with pathology of the colonic mucosa; or (c) who has anaemia or iron deficiency; or (d) for whom diagnostic imaging has shown an abnormality of the colon; or (e) who is undergoing the first examination following surgery for colorectal cancer; or (f) who is undergoing pre-operative evaluation; or (g) for whom a repeat colonoscopy is required due to inadequate bowel preparation for the patient's previous colonoscopy; or (h) for the management of inflammatory bowel disease; other than a service associated with a service to which item 32230 applies Applicable once on a day under a single episode of anaesthesia or other sedation (H) (Anaes.) Fee: $380.90 Benefit: 75% = $285.70
	59300 (Group I3 – Diagnostic Radiology, Subgroup 10 – Radiographic Examination of Breasts)	Mammography of both breasts if there is reason to suspect the presence of malignancy because of: (a) the past occurrence of breast malignancy in the patient; or (b) significant history of breast or ovarian malignancy in the patient's family; or (c) symptoms or indications of breast disease found on examination of the patient by a medical practitioner (R) Fee: $100.35 Benefit: 75% = $75.30, 85% = $85.30
Biopsy	30071 (Group T8 – Surgical Operations, Subgroup 1 – General)	Diagnostic biopsy of skin, as an independent procedure, if the biopsy specimen is sent for pathological examination (Anaes.) Fee: $59.50 Benefit: 75% = $44.65, 85% = $50.60
	30072 (Group T8 – Surgical Operations, Subgroup 1 – General)	Diagnostic biopsy of mucous membrane, as an independent procedure, if the biopsy specimen is sent for pathological examination (Anaes.) Fee: $59.50 Benefit: 75% = $44.65, 85% = $50.60

Investigative technology	Item number	Description and fee
	30075 (Group T8 – Surgical Operations, Subgroup 1 – General)	Diagnostic biopsy of lymph node, muscle or other deep tissue or organ, as an independent procedure, if the biopsy specimen is sent for pathological examination (Anaes.) Fee: $170.60 Benefit: 75% = $127.95, 85% = $145.05
	30078 (Group T8 – Surgical Operations, Subgroup 1 – General)	Diagnostic drill biopsy of lymph node, deep tissue or organ, as an independent procedure, where the biopsy specimen is sent for pathological examination (Anaes.) Fee: $55.20 Benefit: 75% = $41.40, 85% = $46.95
Histology	72849 (Group P5 – Tissue Pathology)	Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen – 7-10 antibodies Fee: $104.30 Benefit: 75% = $78.25, 85% = $88.70
	72859 (Group P5 – Tissue Pathology)	A second opinion, provided in a written report, where the opinion and report together require more than 30 minutes to complete, on a patient specimen, requested by a treating practitioner, where further information is needed for accurate diagnosis and appropriate patient management. Fee: $370.00 Benefit: 75% = $277.50, 85% = $314.50

Source: MSAC 1809 PICO Set, Table 4, pp. 12-15.