MSAC application 1809

Genomic testing in cancer of unknown primary (CUP) and diagnostically challenging cancers

Application for MBS eligible service or health technology

HPP Application number:

HPP200326

Application title:

Genomic testing in cancer of unknown primary (CUP) and diagnostically challenging cancers

Submitting organisation:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Submitting organisation ABN:

52000173231

Application description

Succinct description of the medical condition/s:

Cancer of unknown primary (CUP) is a metastatic cancer where tumour cells detach from a primary tumour site and disseminate to surrounding tissues and distant secondary anatomical locations. A patient presenting with symptoms of disease at these secondary sites will undergo standardised clinical and pathological investigations to determine the site of the primary cancer. When these investigations fail to detect the primary cancer, the patient receives a diagnosis of CUP. CUP usually presents as advanced disease when the cancer has spread to distant anatomical locations requiring systemic treatment and typically has a poor prognosis.

Succinct description of the service or health technology:

Genomic testing is a modern tool that looks at a cancer's DNA to find clues about its origin and the specific genetic changes driving its growth. By analysing the tumour's gene patterns, doctors can predict the tissue it came from or identify mutations that may respond to targeted therapies. While genomic testing doesn't always provide a clear answer, it has improved the chances of finding more personalised and effective treatment options for many people with CUP.

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?

Applicant

Are you applying on behalf of an organisation, or as an individual?

Organisation

Applicant organisation name:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Application details

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prescribed List?

No

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?

New

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology:

Molecular diagnostic tests

Please select the type of molecular diagnostics health technology:

Whole exome/genome sequencing

PICO sets

Application PICO sets:

Genomic testing for CUP and diagnostically challenging cancers

State the purpose(s) of the health technology for this PICO set and provide a rationale:

Purpose category:
Diagnosis / sub-classification

Purpose description:
To establish a diagnosis or disease (sub)classification in symptomatic or affected patients

What additional purpose(s) could the health technology be used for, other than the purposes listed above for this PICO set?

Purpose category:
Predictive

Purpose description:
To provide predictive information to support selection of a specific therapy or intervention

Rationale:
Certain genetic markers can predict response to targeted therapies regardless of the tumour's tissue of origin. NTRK rearrangements predict response to NTRK inhibitors. High tumour mutational burden (TMB) and microsatellite instability (MSI) are reliable indicators for likely benefit from immunotherapy. In CUP, high programmed death-ligand 1 (PD-L1) expression and TMB have been associated with better treatment response and longer survival in patients receiving nivolumab. In a prospective phase II study, nivolumab plus ipilimumab demonstrated antitumor activity in patients who had progressed after platinum-based chemotherapy. Notably, patients with TMB-high tumours had a significantly higher objective response rate of 60% (95% CI 15–95) compared to 7.7% (95% CI 1–25) in the TMB-low group. TMB-high status was also associated with better median progression-free survival (HR 0.32; 95% CI 0.09–1.10; P = 0.056) and overall survival (HR 0.32; 95% CI 0.09–1.09; P = 0.056) (21). Comprehensive genomic testing at diagnosis can determine MSI, PD-L1 and TMB status which is recommended when immune checkpoint inhibitor treatment is considered, in alignment with the ESMO guidelines

Purpose category:
Prognosis

Purpose description:
To provide information about prognosis (staging/re-staging)

Rationale:
Certain genetic alterations can provide insight into prognosis for CUP patients. Mutations in KRAS or NRAS, as well as loss of the CDKN2A gene, are associated with poorer outcomes. Likewise, TP53 mutations, chromosomal copy number losses, or deletion of chromosome 17p are linked to worse prognosis, particularly in patients with limited metastatic disease who may be eligible for localised treatment.

Purpose category:
Value of knowing

Purpose description:
Tests may also provide additional non-health value to patients or to their family members and carers, and discussion of these outcomes could supplement an assessment of the clinical utility of the technology.

Rationale:
CUP patients are impacted by higher levels of psychological distress and lower quality of life compared to patients with metastatic cancer of known origin. In CUP the existential dread of receiving a cancer diagnosis is compounded by the uncertainty regarding the diagnosis, treatment options and prognosis. A large national study of cancer patients in the UK found that CUP patients were less likely to have understood explanations of their illness compared to non-CUP patients. Furthermore, higher levels of anxiety and depression were found to be positively correlated with greater illness uncertainty. A better understanding of a patient's cancer diagnosis could provide a sense of empowerment and lessen uncertainty and psychological distress. Confirming a primary tissue of origin through genomic testing ends the diagnostic odyssey, thereby minimising further unnecessary investigations and offering substantial psychological benefits that enhance overall quality of life.

Population

Describe the population in which the proposed health technology is intended to be used:
The proposed testing population are patients diagnosed with cancer of unknown primary (CUP) where a diagnostic work-up, including imaging studies and conventional pathological review of tumour tissue (including a second pathology opinion), are unable to determine a primary site or tissue of origin. Without identification of a tissue of origin, patients with CUP are limited to empiric chemotherapy treatment and cannot access site-specific or targeted

treatments that are only available to patients with a specific known cancer diagnosis.
CUP incorporates ICD-10 cancer codes:

- incidence C80 (malignant neoplasm without specification of site);
- mortality C77-C80;
- C97 (malignant neoplasms of independent primary multiple sites).

Select the most applicable Medical condition terminology (SNOMED CT):
Malignant neoplasm of unknown origin

Intervention

Name of the proposed health technology:
Diagnostic genomic testing for CUP or diagnostically challenging cancer

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:
The nominated comparator is no genomic testing. The pre-requisite for testing is standard investigations for CUP, including blood tests, imaging (CT, +/-MRI, US, PET-CT), and histopathology review of biopsy material.

The introduction of genomic testing for CUP patients using WGTS or CGP would be additional to the currently listed MBS funded items used for the diagnostic work-up of patients with a malignant diagnosis of unknown origin. These MBS items for diagnostic tests are performed to provide initial characterisation of a malignancy and uncover a primary site of origin.

Outcomes

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:
Implementing genomic testing in the routine diagnostic work-up for CUP patients will increase the number of patients with a resolved diagnosis resulting in a change in management from empiric chemotherapy treatment to targeted therapies, leading to improvements in health outcomes (mortality, morbidity, HRQoL). In addition,

resolving primary tissue of origin (TOO) will provide information on prognosis, and reduce the diagnostic odyssey, thereby minimising further unnecessary investigations and offering substantial psychological benefits that enhance overall quality of life.

Proposed MBS items

Proposed item:
AAAAA

Category number:
Category 6: Pathology Services

Category description:
Group P7: Genetics

Proposed item descriptor:
Characterisation of gene variants and tissue of origin algorithm by whole genome and transcriptome sequencing, requested by a specialist or consultant physician or pathologist in a patient diagnosed with cancer of unknown primary.
Applicable once per diagnostic episode at initial diagnosis or at disease relapse.

Proposed MBS fee:
$5,500.00

Indicate the overall cost per patient of providing the proposed health technology:
$5,500.00

Please specify any anticipated out of pocket expenses:
$0.00

Proposed item:
BBBBB

Category number:
Category 6: Pathology Services

Category description:
Group P7: Genetics

Proposed item descriptor:
Characterisation of gene variants by a comprehensive gene panel, tissue of origin algorithm requested by a specialist or consultant physician or pathologist in a patient diagnosed with cancer of unknown primary.
Applicable once per diagnostic episode at initial diagnosis or at disease relapse.

Proposed MBS fee:
$3,300.00

Indicate the overall cost per patient of providing the proposed health technology:
$3,300.00

Please specify any anticipated out of pocket expenses:
$0.00

How is the technology / service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):

Currently genomic testing for CUP patients is funded by research funding or self-funded by the patient.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

The overall claim is that genomic testing in patients with CUP results in superior health outcomes compared to no genomic testing. Currently, there are no MBS item numbers that cover this testing, testing is either being performed at cost to the patient, covered by research funding, or not performed. Public funding of these molecular tests would align Australian clinical practice with ESMO's precision medicine working group recommendations for patients with a CUP diagnosis, as well as the ESMO guidelines for CUP management, and with publicly funded WGS available under the National Health Service (NHS) in the UK as well as in the Netherlands. Access to genomic testing will allow more patients to resolve a diagnosis, access site-specific treatment and clinical trials, provide prognostic information, resulting in better patient management and improved outcomes.

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:

CUP is considered a rare or less common cancer, constituting 1.6% of all new cancer cases diagnosed in Australia in 2021, or 2,353 new cases (see PICO Set, Table 1). Prevalence is lower due to poor survival rates, with an estimated 936 people living with CUP in 2017 (AIHW, 2025).

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%):
60
Year 2 estimated uptake (%):
60
Year 3 estimated uptake (%):
70
Year 4 estimated uptake (%):
70

Estimate the number of patients who will utilise the proposed technology for the first full year:
1,411

Optionally, provide details:

Between 2016-2020, 20.7% of persons diagnosed with CUP (all ages) survived one year after diagnosis, after adjusting for general mortality (AIHW, 2024). Based on prognostic indicators, not all incident cases will be suitable candidates for genomic testing. Experience from the Peter MacCallum Cancer Centre's dedicated CUP clinic from 2014-2020 reported that of 361 patients booked to the clinic, only 60% had a genomic test (van Mourik 2023). Funding limitations may play a role in limiting historical rates of testing, but these figures highlight that the estimated number of patients that are likely to be tested in practice is likely to be significantly below the incidence rate.
Using 60% of incident cases to estimate uptake in year 1 is likely to overestimate short-term utilisation due to access to services. There are currently only a limited number of specialist centres with experience in genomic testing for CUP, limiting the numbers of patients that are likely to be tested. For example, the SUPER-ED trial, which spans 15 metropolitan sites across the country, is expected to enrol just 240 patients over 25 months (Ugalde 2025). Similarly, the Peter MacCallum Cancer Centre treated 361 CUP patients between 2014–2020. Given these figures, the projection of 1,411 genomic tests in year 1 is likely to be an overestimate.
Further evidence from a retrospective cohort study of 252 DVA patients with CUP between 2004-2007 found only 30% received any cancer treatment, primarily due to poor prognosis (Schaffer 2015); in this cohort, 94.7% of patients were above the age of 75, and had a median survival rate of 37 days from diagnosis.

Will the technology be needed more than once per patient?

Yes, multiple times

Over what duration will the health technology or service be provided for a patient? (preferably a number of years):

1-5 years

Optionally, provide details:

CUP has a 5-year survival rate of 15% (16% for males and 10% for females), one of the lowest among all cancers in Australia during 2014-2018 (See PICO Set, Figure 1). As such, it is anticipated that the majority of patients will only require testing once per lifetime. However, with the advent of improved diagnostic information provided by WGTS/CGP, and increasing access to immunotherapy and targeted therapies, a minority of patients may be eligible for repeat testing due to relapse. As such, the current item descriptors are limited to once per diagnostic episode at initial diagnosis or disease relapse.

What frequency will the health technology or service be required by the patient over the duration? (range, preferably on an annual basis):

1-2 per lifetime

Consultation

List all entities that are relevant to the proposed service / health technology. The list can include professional bodies / organisations who provide, request, may be impacted by the service/health technology; sponsor(s) and / or manufacturer(s) who produce similar products; patient and consumer advocacy organisations or individuals relevant to the proposed service/health technology.

Entities who provide the health technology/service:

PATHOLOGY AUSTRALIA LIMITED

PUBLIC PATHOLOGY AUSTRALIA

THE HUMAN GENETICS SOCIETY OF AUSTRALASIA LIMITED

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Entities who request the health technology/service:

CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA LIMITED

MEDICAL ONCOLOGY GROUP OF AUSTRALIA

Private Cancer Physicians of Australia Limited

Entity who may be impacted by the health technology/service:

AUSTRALIAN GENOMIC CANCER MEDICINE CENTRE LTD

THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

Patient and consumer advocacy organisations relevant to the proposed service/health technology:

Rare Voices Australia Ltd

Consumers Health Forum of Australia Ltd

Cancer Voices Australia

RARE CANCERS AUSTRALIA LTD

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?
Yes

Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?
No

Is the therapeutic good classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?
Class III

Is the therapeutic good to be used in the service exempt from the regulatory requirements of the Therapeutic Goods Act 1989?
No

Is the therapeutic good classified by the TGA as for Research Use Only (RUO)?
No