MSAC application 1820

In situ hybridisation (ISH) testing of tumour tissue to detect viral genomes (EBV and HPV)

Application for MBS eligible service or health technology

HPP Application number:

HPP200374

Application title:

In Situ Hybridisation (ISH) for Viral Genomes (EBV and HPV)

Submitting organisation:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Submitting organisation ABN:

52000173231

Application description

Succinct description of the medical condition/s:
Human papillomavirus (HPV) and Epstein–Barr virus (EBV) play an important role in the development and behaviour of many cancer types. For example, HPV is associated with cancers of the middle throat (especially the tonsil and base of tongue) and anogenital areas, while EBV is associated with cancers of the upper throat behind the nose, as well as some lymphomas and post-transplant disorders. For these conditions, identifying the virus within the tumour is important because it helps confirm the diagnosis and provides clinically useful prognostic information.

Succinct description of the service or health technology:
In situ hybridisation (ISH) is a laboratory test that looks for HPV or EBV genetic material directly inside tumour cells in a tissue sample. It helps confirm whether a cancer is truly related to one of these viruses by showing that the virus is present in the cancer itself, rather than elsewhere in the body, or from a prior infection. This information helps pathologists classify the cancer more accurately, provides information about the likely prognosis of the cancer, and helps guide management decisions.

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:

Other genetic test

PICO sets

Application PICO sets:

PICO set name
In situ hybridisation (ISH) testing for viral genomes (EBV and HPV)

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

Purpose category:
Prognosis

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

Population

Describe the population in which the proposed health technology is intended to be used:

The proposed health technology, in situ hybridisation (ISH) testing for viral genomes, is intended for use in patients with malignancies in which the detection of Epstein–Barr virus (EBV) or human papillomavirus (HPV) within tumour cells is clinically indicated to support accurate tumour classification and downstream management. These viral targets have been included within the scope of the eligible population with the intent of aligning Australian clinical practice with the essential and desirable diagnostic criteria specified in the most recent editions of the World Health Organization (WHO) Classification of Tumours (aka Blue Books Online).

EBV is causally associated with several malignancies, most notably non-keratinising nasopharyngeal carcinoma, a range of lymphoid neoplasms including post-transplant lymphoproliferative disorders (PTLD), extranodal natural killer (NK)/T-cell

lymphoma, classic Hodgkin lymphoma, and EBV-associated subtypes of diffuse large B-cell lymphoma (DLBCL), and selected gastric carcinomas. In these settings, EBV-encoded RNA (EBER) ISH is used on tumour tissue to demonstrate latent EBV infection within malignant cells, to distinguish EBV-driven cancers from morphologic mimics, where management and prognosis may differ.

Similarly, HPV is associated with oropharyngeal squamous cell carcinoma (OPSCC), and a spectrum of anogenital squamous cell carcinomas of the cervix, vagina, vulva, penis, and anus. HPV ISH (commonly E6/E7 mRNA ISH) is used on tumour tissue to confirm HPV within tumour cells in contexts where HPV status is diagnostically informative, or where surrogate markers (such as p16) are insufficiently specific, thereby supporting accurate tumour classification, prognostic stratification, and appropriate multidisciplinary management.

Select the most applicable Medical condition terminology (SNOMED CT):
Human papilloma virus infection

Intervention

Name of the proposed health technology:
In situ hybridisation (ISH) testing for viral genomes (HPV and EBV).

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 proposed comparator for both EBV and HPV ISH is no molecular profiling.

EBER ISH is currently the reference standard for classifying EBV-associated tumours, as guided by the WHO tumour classification. Other molecular assays, such as EBV DNA PCR (usually performed on blood/plasma, sometimes on tissue), can support risk assessment and monitoring for certain cancers (e.g. PTLD), but it does not localise EBV to tumour cells and therefore cannot distinguish tumour-driven infection from bystander viraemia, limiting its utility for confirming EBV-associated tumours according to WHO guidelines; it is also not funded or routinely conducted in

Australia. LMP1 IHC may be used in some settings, but is not a reliable substitute for demonstrating EBV within tumour cells.

For HPV-associated cancers (particularly OPSCC), the usual comparator pathway includes p16 IHC as the primary surrogate test to confirm HPV status, with HPV-specific nucleic acid testing (i.e. ISH, or PCR-based methods) used selectively where confirmation is required or where results are discordant. While DNA-PCR is a sensitive modality for the detection of HPV in tissues, this modality cannot localise the infection to malignant cells and therefore may result in false positives in instances of non-pathogenic "passenger" HPV that is not driving cancer development. Whilst it remains a valid technique for establishing the diagnosis of HPV-related neoplasia, it must be used in conjunction with p16 IHC and is considered inferior to HPV RNA ISH. RT-PCR is technically challenging and unsuitable for general clinical use. Consensus guidelines recommend against the use of DNA-ISH.

Imaging techniques are primarily used guide initial biopsy (where necessary), inform staging, and provide functional information. As ISH is primarily associated with pathological classification of tumours based on viral status, imaging techniques are not considered to be relevant comparators for this application.

Outcomes

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

EBER and HPV ISH testing achieves intended patient outcomes by enabling more accurate tumour classification, through direct demonstration of viral nucleic acid within tumour cells, consistent with WHO diagnostic criteria. This reduces diagnostic uncertainty and misclassification, which in turn supports appropriate risk stratification and prognostic assessment in viral-associated cancers. By providing a definitive virologic attribution where clinically relevant, the test helps clinicians select the most appropriate management pathway (including avoiding unnecessary or ineffective treatments, and tailoring therapy to the correct tumour entity), and can reduce downstream harms associated with delayed or incorrect diagnosis, repeat biopsies, or prolonged diagnostic work-up.

Proposed MBS items

Proposed item: AAAAA

MBS item number (where used as a template for the proposed item):
NA

Category number:
P7

Category description:
Genetics

Proposed item descriptor:
An in situ hybridisation (ISH) test of tumour tissue from a patient with a tumour type in which high-risk human papillomavirus (HR-HPV) status is clinically relevant, where:
- the test includes at least subtypes 16/18, and
- HR-HPV status is unknown
Requested by a specialist or consultant physician practising as an oncologist or haematologist.
Applicable once per diagnostic episode.
(See para PN.1.2 of explanatory notes to this Category)

Proposed MBS fee:
$315.74

Indicate the overall cost per patient of providing the proposed health technology:
$315.74

Please specify any anticipated out of pocket expenses:
$0.00

Provide any further details and explain:
The costs associated with HPV ISH are heavily impacted by the number of probes used for testing. Given the large number of possible HPV markers available for testing, the proposed MBS items have been structured as two separate items to ensure the highest yield in the first instance (captured by item AAAA), while allowing follow-up testing for rarer types where needed (BBBB).
Approximately 90% of HPV-associated head and neck cancers are associated with HPV 16/18, and as such these are proposed as the main indications for initial

testing for suspected HPV-associated tumours.24
For the rarer subset of cancers, additional follow-up testing will be required to identify the relevant strain of HPV (service BBBB).

Relevant practice notes:
PN 1.2 indicates a pathologist determinable service

Proposed item: BBBBB

MBS item number (where used as a template for the proposed item):
NA

Category number:
P7

Category description:
Genetics

Proposed item descriptor:
An in situ hybridisation (ISH) test of tumour tissue from a patient with a tumour type in which human papillomavirus (HPV) status is clinically relevant, and
- the results from item AAAA or 73072 are negative or equivocal, and
- testing for additional HPV types, not including 16 and 18, is required due to ongoing suspicion of an HPV-associated cancer.
Requested by a specialist or consultant physician practising as an oncologist or haematologist.
Applicable once per diagnostic episode.
(See para PN.1.2 of explanatory notes to this Category)

Proposed MBS fee:
$315.74

Indicate the overall cost per patient of providing the proposed health technology:
$315.74

Please specify any anticipated out of pocket expenses:
$0.00

Provide any further details and explain:
This item is intended to allow follow-up testing for additional HPV types in patients with confirmed negative or equivocal HPV 16/18 results, in whom there is an

ongoing suspicion of an HPV-associated tumour.

Relevant practice notes:
PN 1.2 indicates a pathologist determinable service.

Proposed item: CCCCC

MBS item number (where used as a template for the proposed item):
NA

Category number:
P7

Category description:
Genetics

Proposed item descriptor:
An in situ hybridisation (ISH) test of tumour tissue from a patient with a tumour type in which Epstein–Barr virus (EBV) status is unknown and clinically relevant, requested by a specialist or consultant physician practising as an oncologist or haematologist.
Applicable once per diagnostic episode.
(See para PN.1.2 of explanatory notes to this Category)

Proposed MBS fee:
$142.93

Indicate the overall cost per patient of providing the proposed health technology:
$142.93

Please specify any anticipated out of pocket expenses:
$0.00

Provide any further details and explain:
EBER probes are comparatively cheaper than HPV probes, and there is no need for multiple probes per diagnostic episode as there is only one viral target for EBV. Therefore, there is only one proposed item for EBER ISH, with a lower fee than the HPV items.

Relevant practice notes:
PN 1.2 indicates a pathologist determinable service.

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

Currently, there is no dedicated public funding for HPV or EBER ISH. When performed in practice, costs are typically absorbed by laboratories as an unfunded component of diagnostic work-up, paid out-of-pocket by patients, or captured through state-based hospital funding. As these tests are crucial for accurate diagnosis, pathologists do not forgo testing, and costs are most often absorbed by laboratories, a practice that is not sustainable. A proportion of use is expected in rare/orphan indications, including rare lymphoma subtypes, where access and funding pathways are particularly variable.

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:

EBER and HPV ISH are superior to no molecular profiling, and are required to meet WHO tumour classification criteria for viral-associated cancers. Improved diagnostic classification translates into clinically meaningful downstream benefits by supporting the most appropriate management pathway and avoiding misclassification-driven overtreatment or undertreatment. For example, confirming EBV association in relevant lymphoid proliferations (including in post-transplant settings) can materially alter management, such as prioritising reduction of immunosuppression and targeted therapies over empiric, toxic chemotherapy when appropriate. More generally, viral status can inform prognosis and treatment selection, thereby improving patient-level outcomes.

Estimated utilisation

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

Prevalence data is not relevant for this application because this test is proposed for diagnostic purposes rather than disease monitoring or treatment response. Table 1 in

the attached file outlines the estimated incidence and number of new cases of eligible cancer types, sourced primarily from the AIHW.

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

Year 1 estimated uptake (%):
75

Year 2 estimated uptake (%):
85

Year 3 estimated uptake (%):
90

Year 4 estimated uptake (%):
95

Estimate the number of patients who will utilise the proposed technology for the first full year:
2902

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):
0 years

Optionally, provide details:
HPV and EBER ISH are required at initial diagnosis, so the duration of service delivery is cross-sectional rather than longitudinal.

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

Optionally, provide details:

The majority of patients will only require one test per lifetime; however, additional testing may occur in a minority of patients to characterise a subsequent biopsy (e.g. for a different suspected primary cancer). For this reason, a limitation of once per diagnostic episode is appropriate, as opposed to once 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 ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Entities who request the health technology/service:

HAEMATOLOGY SOCIETY OF AUSTRALIA AND NEW ZEALAND

Private Cancer Physicians of Australia Limited

MEDICAL ONCOLOGY GROUP OF AUSTRALIA

CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA LIMITED

HEAD AND NECK CANCER AUSTRALIA LTD

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

THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP

Entity who produces similar products:

ROCHE DIAGNOSTICS AUSTRALIA PTY LIMITED

LEICA BIOSYSTEMS MELBOURNE PTY LTD

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

RARE CANCERS AUSTRALIA LTD

CANCER VOICES AUSTRALIA

Consumers Health Forum of Australia Ltd

Cancer Council Australia

Cancer Australia

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

Is the therapeutic good in the process of being considered by the TGA?

No

Please provide details of when you intend to lodge an ARTG inclusion application, or provide a rationale if you do not intend to lodge an ARTG inclusion application:

EBER and HPV ISH assays are currently regulated as Class III in-house IVDs, provided by laboratories that are NATA accredited within the scope of this application, for example, SA Pathology, and St Vincent's Pathology (SydPath). These are searchable via the NATA website, and are examples of accredited services, but please note this does not constitute an exhaustive list.