MSAC Application 1820

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

PICO Set

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).[1-5]

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.[6-10] 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.[11-14] 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.[15-18]

We acknowledge the inherent complexity associated with the scope of viral-associated cancers eligible for the proposed services, as well as the heterogeneity of downstream management; however, we emphasise that the majority of these indications for testing are rare, with expected numbers of cases for many indications ranging from 10 to 100 patients per year (See Estimated Utilisation section). To enable a feasible assessment, the application therefore highlights exemplar populations where viral status is most clearly linked to classification and clinical decision-making, noting that specific parts of the application (including the diagnostic algorithm) have been structured around an exemplar pathway of HPV-related disease in head and neck cancer (i.e. OPSCC), where viral attribution is a key determinant of multidisciplinary management.[15]

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

Patients proposed to be eligible for ISH are those with confirmed (or strongly suspected) malignancies in which EBV or high-risk HPV status is clinically relevant to classify the cancer based on WHO criteria.[1-5]

Clinical presentation is heterogeneous across the eligible cancer types. The pathway to ISH testing in the Australian healthcare system generally begins with presentation to primary care, emergency, or specialist outpatient services, followed by targeted referral based on the suspected tumour site and clinical urgency. Patients with suspected head and neck malignancy are usually referred to ENT/head and neck services, suspected lymphomas to haematology, and other site-specific malignancies to the relevant oncology or surgical specialty, with most patients entering either a public hospital outpatient stream or a private specialist pathway. Staging and extent-of-disease assessment typically involves cross-sectional imaging (e.g., CT) and, where clinically indicated and accessible, functional imaging (e.g. PET-CT) to inform biopsy site selection and subsequent management planning.

In practice, eligibility for ISH would typically be triggered once a relevant tumour type/site is suspected on clinical and radiologic grounds, and an appropriate specimen is obtained for anatomical pathology assessment. A pathologist would triage ancillary testing (including EBER-ISH or HPV-ISH where required) after standard histologic confirmation, and in some cases immunohistochemistry (IHC). The requirement for standard histologic confirmation ± IHC helps to contain the utilisation to a limited subset of cancers rather than relying on symptom-based testing.

Provide a rationale for the specifics of the eligible population:

For both EBV- and HPV-associated cancers, eligibility is limited to tumours where localising viral nucleic acid within malignant cells is essential or desirable based on WHO classification criteria.[1-5]

For EBV, this includes non-keratinising nasopharyngeal carcinoma (where EBER-ISH is described as the gold standard for latent EBV detection in tissue), as well as EBV-driven lymphoproliferative disorders where EBER is requisite/mandatory for diagnosis, including extranodal NK/T-cell lymphoma, immune-associated lymphoma, classic Hodgkin lymphoma, EBV-positive DLBCL, and PTLD.

For HPV-associated cancers, the eligible population is restricted to settings where HPV-specific testing is required in addition to, or as a replacement for, surrogate markers such as p16 IHC, that may be insufficiently specific in certain anatomic sites. This includes HPV-related multiphenotypic sinonasal carcinoma and other selected head and neck tumours where HPV-specific assays are used selectively; conversely, the definition explicitly recognises that in many routine OPSCC cases p16 is commonly used and HPV-specific testing (including ISH) is reserved for selected scenarios (e.g. discordant findings), ensuring ISH is targeted to contexts with incremental diagnostic value.[15]

Are there any prerequisite tests?

Yes

ISH testing for EBV- and HPV-associated tumours is typically conducted as a pathologist-determinable reflex test. In this context, to determine the necessity/suitability of ISH, a pathologist will have first conducted histopathology on a biopsy specimen to confirm the tumour grade, and may also have conducted IHC for surrogate markers such as p16 (where relevant). These services may be claimed as part of the existing MBS services outlined in **Table 1**.

Table 1 MBS items for prerequisite tests for EBER and HPV ISH

Immunohistochemistry
72846 | P5 - Tissue Pathology Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 antibodies except those listed in 72848 (Item is subject to rule 13) **Fee:** $61.05 **Benefit:** 75% = $45.80 85% = $51.90
72847 | P5 - Tissue Pathology Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 4-6 antibodies (Item is subject to rule 13) **Fee:** $91.55 **Benefit:** 75% = $68.70 85% = $77.85
72848 | P5 - Tissue Pathology Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and c-erb-B2 (HER2) (Item is subject to rule 13) **Fee:** $76.30 **Benefit:** 75% = $57.25 85% = $64.90
72849 | 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 (Item is subject to rule 13) **Fee:** $106.80 **Benefit:** 75% = $80.10 85% = $90.80
72850 | P5 - Tissue Pathology

Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 11 or more antibodies (Item is subject to rule 13) **Fee:** $122.05 **Benefit:** 75% = $91.55 85% = $103.75
Histopathology
72828 | P5 - Tissue Pathology Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions - 18 or more separately identified specimens (Item is subject to Rule 13) **Fee:** $228.65 **Benefit:** 75% = $171.50 85% = $194.40 (See para PN.0.32 of explanatory notes to this Category)
72830 | P5 - Tissue Pathology Examination of complexity level 5 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions - 1 or more separately identified specimens (Item is subject to rule 13) **Fee:** $280.75 **Benefit:** 75% = $210.60 85% = $238.65 (See para PN.0.32 of explanatory notes to this Category)
72836 | P5 - Tissue Pathology Examination of complexity level 6 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions - 1 or more separately identified specimens (Item is subject to rule 13) **Fee:** $427.20 **Benefit:** 75% = $320.40 85% = $363.15 (See para PN.0.32 of explanatory notes to this Category)

Are the prerequisite tests MBS funded?

Yes

Provide details to fund the prerequisite tests:

N/A

Intervention

Name of the proposed health technology:

ISH testing for viral genomes (HPV and EBV).

Describe the key components and clinical steps involved in delivering the proposed health technology:

Within the Australian diagnostic pathway for suspected viral-associated cancers, ISH is typically an ancillary test ordered after initial clinical assessment, biopsy ± IHC ± imaging. Patients undergo routine evaluation, imaging where indicated, tissue sampling (commonly FNA/core biopsy for head and neck presentations) and histopathology with IHC triage; HPV status may be assessed initially by p16 for selected cancer such as OPSCC, with HPV-specific testing such as ISH used selectively, consistent with contemporary pathology guidance for head and neck specimens.[15]

For EBV-associated malignancies, EBER ISH is used on tumour tissue to confirm latent EBV infection within tumour cells, supporting WHO-aligned classification in entities such as nasopharyngeal carcinoma and selected lymphomas/PTLD, and is widely regarded as the gold standard method for tissue-based latent EBV detection.[1, 2] Results are incorporated into a pathology report and inform referral and MDT management (e.g. ENT/head and neck oncology teams; haematology for lymphomas).

Identify how the proposed technology achieves the intended patient outcomes:

EBER and HPV ISH improve outcomes for patients with viral-associated cancers by providing precise diagnostic and prognostic information that guides management. *Examples* highlighting the utility of ISH for selected cancer types are listed below.

For EBV-associated cancers:

- Nasopharyngeal carcinoma: EBER ISH is the reference standard for detecting latent EBV infection, which is crucial for accurate diagnosis and prognosis. Identifying EBV involvement helps in stratifying patients for appropriate therapies and monitoring response to treatment.[19]
- Lymphoproliferative disorders (e.g. Hodgkin lymphoma, PTLD): EBER ISH is essential in confirming EBV association, which provides prognostic information that may guide treatment decisions. EBV-positive lymphomas often have distinct prognostic profiles.[19, 20]

For HPV-associated cancers:

- OPSCC: High-risk HPV (HR-HPV) E6/E7 mRNA ISH is more sensitive and specific than DNA ISH, providing accurate detection of transcriptionally active HPV.[21] This correlates strongly with better overall survival, disease-specific survival, and disease-free survival, guiding less aggressive treatment protocols and improving prognosis.[21] Treatment may be de-escalated for HPV-associated OPSCC.
- Cervical cancer: HR-HPV testing, including E6/E7 mRNA ISH, confirms the presence of active HPV infection, which is essential for diagnosis, treatment planning, and

prognosis. HPV-positive cervical cancers generally have a better response to treatment and prognosis.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

Provide details and explain:

The majority of patients will only require one test per lifetime; however, a minority of patients may require more than one test in their lifetime to characterise a subsequent biopsy of a new primary cancer. For this reason, a limitation of *once per diagnostic episode* is appropriate.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Testing will be provided by Approved Pathology Practitioners (APPs) in line with other tests on the MBS Pathology Services Table.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

EBER-ISH and HPV-ISH are generally accessed through specialist cancer care pathways, and may be requested by specialist or consultant physicians practicing as oncologists or haematologists. In practice, these assays are most commonly conducted as pathologist-determined ancillary tests on an available biopsy specimen, to resolve a diagnostic or WHO classification question, with results incorporated into the pathology report.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

Testing will be delivered only by APPs with appropriate scope of practice in NATA Accredited Pathology Laboratories by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Services Table.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

☐ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☒ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

EBER-ISH and HPV-ISH are delivered predominantly in the outpatient setting, as most eligible patients are investigated and managed through outpatient specialist pathways (e.g. ENT/head and neck clinics, haematology, oncology). A smaller proportion of testing will occur for private and public hospital inpatients, typically where patients are admitted for diagnostic work-up, management of complications, urgent staging, or when biopsies are performed during an inpatient episode.

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

N/A

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 healthcare system). This includes identifying healthcare 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),[22] 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;[1] it is also not funded or routinely conducted in Australia. LMP1 IHC may be used in some settings,[23] 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.[15, 17] 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.[15]

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.

List any existing MBS item numbers that are relevant for the nominated comparators:

Immunohistochemistry
72846 | P5 - Tissue Pathology Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 antibodies except those listed in 72848 (Item is subject to rule 13) **Fee:** $61.05 **Benefit:** 75% = $45.80 85% = $51.90

(See para PN.1.2 of explanatory notes to this Category)

72847 | P5 - Tissue Pathology

Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 4-6 antibodies

(Item is subject to rule 13)

Fee: $91.55 **Benefit:** 75% = $68.70 85% = $77.85

(See para PN.1.2 of explanatory notes to this Category)

72849 | 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

(Item is subject to rule 13)

Fee: $106.80 **Benefit:** 75% = $80.10 85% = $90.80

(See para PN.1.2 of explanatory notes to this Category)

72850 | P5 - Tissue Pathology

Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 11 or more antibodies

(Item is subject to rule 13)

Fee: $122.05 **Benefit:** 75% = $91.55 85% = $103.75

(See para PN.1.2 of explanatory notes to this Category)

Histopathology

72828 | P5 - Tissue Pathology

Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions - 18 or more separately identified specimens

(Item is subject to Rule 13)

Fee: $228.65 **Benefit:** 75% = $171.50 85% = $194.40

(See para PN.0.32 of explanatory notes to this Category)

72830 | P5 - Tissue Pathology

Examination of complexity level 5 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions - 1 or more separately identified specimens

(Item is subject to rule 13)

Fee: $280.75 **Benefit:** 75% = $210.60 85% = $238.65 (See para PN.0.32 of explanatory notes to this Category)
72836 | P5 - Tissue Pathology Examination of complexity level 6 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions - 1 or more separately identified specimens (Item is subject to rule 13) **Fee:** $427.20 **Benefit:** 75% = $320.40 85% = $363.15 (See para PN.0.32 of explanatory notes to this Category)

Provide a rationale for why this is a comparator:

These services are appropriate comparators because they represent the current, accessible, standard-of-care diagnostic approach in Australia when EBER or HPV ISH are not available. They are the tests clinicians and pathologists use to answer the same (or closely related) clinical questions.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☐ None (used with the comparator)
☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☒ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☐ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

The comparators are expected to be partially substituted, primarily for tumours where ISH provides decisive incremental value over current surrogate IHC tests. In practice, ISH will not replace core comparator components such as biopsy, routine histopathology, or imaging.

For EBV-associated disease, EBER-ISH is the current reference standard for classification in Australian practice, and is therefore not expected to substitute other tests. Proxy approaches that do not localise EBV in tumour cells (e.g. EBV DNA PCR or EBV-related IHC markers such as LMP1) are not relied on for tumour classification in Australian practice, and thus are not expected to be substituted with ISH.

For HPV-associated disease, HPV ISH is expected to replace (or reduce reliance on) p16 IHC in selected scenarios, in accordance with the WHO Classification of Tumours. These include squamous cell carcinoma of the vulva, adenocarcinoma or adenocarcinoma in situ of the cervix, and penile squamous cell carcinoma.[3, 4]

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☐ Health harms
☒ Resources
☐ Value of knowing

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

Health benefits

ISH-derived viral status impacts management decisions by classifying tumours with distinct prognoses and treatment pathways. For example, in OPSCC, HPV-associated disease has a consistently more favourable prognosis than HPV-negative OPSCC,[24] and contemporary clinical practice guidelines recommend routine HR-HPV assessment in newly diagnosed OPSCC (commonly via p16 IHC on tissue, with HPV-specific testing used selectively), supporting prognostic counselling and consideration of treatment de-intensification in appropriate patients.[24]

In EBV-associated lymphoproliferative disorders, identifying EBV within tumour cells (via EBER-ISH) is essential diagnostic criteria per the WHO Classification of Tumours.[1] EBER ISH testing achieves intended patient outcomes by enabling more accurate tumour classification, through direct demonstration of viral nucleic acid within tumour cells. 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.[10, 23]

Health resourcing

Due to complexity in the downstream treatment pathways, modelling quality-adjusted life years (QALY) for all indications will be impractical. Further, as the primary indication for testing is diagnosis, for the purpose of meeting minimum essential WHO diagnostic criteria, and that the majority of the indications are expected to account for fewer than 100 tested patients per year, we also argue that it is not necessary. In these cases, cost per diagnosis may be suitable alternative to a QALY-based modelling approach. Although modelling downstream impacts on treatment will no doubt be required by MSAC, we suggest this be targeted to OPSCC.

Proposed MBS items

How is the technology/service funded at present? (e.g., 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.

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

Draft item AAAAA

MBS item number (where used as a template for the proposed item)	73342
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	**Fee:** $315.74 **Benefit:** 75%=$236.81 85%=$268.38
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 AAAAA), while allowing follow-up testing for rarer types where needed (BBBBB). 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.[25] For the rarer subset of cancers, additional follow-up testing will be required to identify the relevant strain of HPV (service BBBBB). **Relevant practice notes** PN 1.2 indicates a pathologist determinable service

Draft item BBBBB

MBS item number (where used as a template for the proposed item)	73342
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 AAAAA 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	**Fee:** $315.74 **Benefit:** 75%=$236.81 85%=$268.38
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.

Draft item CCCCC

MBS item number (where used as a template for the proposed item)	73342
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	**Fee:** $142.93 **Benefit:** 75%=$107.20 85%=$121.49
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.

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

Across the various indications for HPV and EBV ISH, clinicians first establish the anatomical site and tumour type from a biopsy or resection specimen, supported by routine pathology review, localisation via imaging, and IHC where appropriate. In practice, patients become eligible for HPV or EBV ISH only once this preceding work-up has been completed, and further confirmation of viral association is needed to inform the diagnosis and downstream management. Relevant MBS items for prior tests have been documented in this application, previously.

Using OPSCC as an exemplar scenario, clinicians must first decide whether the case is an OPSCC, sinonasal SCC, non-oropharyngeal/non-sinonasal SCC, or a cervical nodal metastasis with a known or unknown primary.[15] Once OPSCC is identified, there is a clear stepwise testing pathway: clinicians confirm invasive SCC, assess the oropharynx clinically and with imaging, and then use p16 IHC as the main triage test on tissue.[15] HPV-specific testing using ISH is indicated when p16 is equivocal (50–70% staining or weak diffuse staining), when morphology and p16 disagree, when the tumour overlaps multiple sites, or when it arises outside the tonsil/base of tongue. Routine HPV testing is generally not indicated for other non-oropharyngeal, non-sinonasal primaries.[15]

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

Yes, in some circumstances.

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

The pre-test clinical algorithm is mostly the same whether ISH or a comparator such as p16 IHC, or other non-ISH surrogate, is used. The main difference is that in selected indications HPV ISH can replace surrogate markers. For example, in sinonasal SCC, RNA ISH can replace p16 in the testing pathway, given that false-positive p16 results are too common to support a "p16-only" approach.[15] For EBV indications, the pre-test pathway is not expected to change, and there are no proposed offsets.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

None. ISH can be conducted on formalin-fixed paraffin-embedded (FFPE) tissue collected from the initial biopsy. Re-biopsy may be required if the initial tissue sample is of insufficient quality or quantity for ISH testing, but this is expected to be uncommon. As

the service is proposed to be pathologist determinable, additional patient consultations with specialists will not be required.

Explain what other healthcare resources are used in conjunction with the comparator health technology:

As the comparator is "no molecular profiling", see the previous section for relevant resources used in the pre-ISH testing pathway.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

N/A

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the proposed health technology:

After HPV or EBV ISH, treatment is managed ideally by an MDT; the ISH result refines the diagnosis and prognostic profile, and therefore informs treatment selection. The extent to which classification leads to differences in management pathways is, however, different for each cancer type.

In OPSCC, HPV ISH mainly distinguishes truly HPV-driven tumours from p16-discordant disease: p16+/HPV+ patients proceed down the favourable-risk HPV-associated pathway, whereas p16+/HPV- patients should generally be managed more like HPV-unrelated disease and should not be considered for treatment de-intensification on the basis of p16 alone.[26]

In NPC, EBER-positive tumours proceed down the EBV-associated pathway, followed by plasma EBV DNA testing to determine baseline prognostication, selection of more intensive systemic therapy in higher-risk curative cases, response assessment, and long-term surveillance.[27] DNA amplification alone is inadequate to prove localisation of the infection to malignant cells, and as such EBER ISH is a necessary prior test.[28] EBER-negative tumours are managed as biologically distinct, generally poorer-prognosis disease, and EBV DNA testing is not routinely useful in that setting.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

Where ISH is unavailable, patients proceed through a conventional cancer treatment pathways based on routine pathology, imaging, staging, and multidisciplinary review.

In OPSCC, p16 IHC generally directs patients into p16-positive or p16-negative treatment pathways, though this will misclassify some discordant tumours in the absence of HPV specific testing.

In NPC, treatment proceeds according to histology and anatomical stage, with radiotherapy-based treatment, plasma EBV DNA, and standard staging investigations used to guide prognosis and treatment intensity, but without the same confidence in tumour viral classification that EBER ISH provides.[27]

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

Compared with the comparator pathway, the proposed technology introduces the additional laboratory resource of HR-HPV or EBER ISH and associated specialist interpretation, but provides more definitive tumour classification that better targets subsequent healthcare use.

In OPSCC, this is would reduce the reliance on the interpretation of surrogate markers alone, such as 16; this is likely to lead to safe deescalation from radiotherapy in P16 positive HPV ISH negative patients.[26]

In NPC, EBER ISH more clearly identifies the subgroup in whom plasma EBV DNA testing is clinically useful for prognostication, response assessment, and surveillance, while avoiding routine EBV-directed monitoring in EBV-negative disease.[27]

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Figure 1 provides an exemplar pathway illustrating how HPV ISH is used in the investigation of invasive head and neck cancer by differentiating HPV positive and negative cancers. In the absence of HPV ISH, management decisions would often be based on p16 IHC results alone, that may be equivocal, leading to suboptimal management decisions.

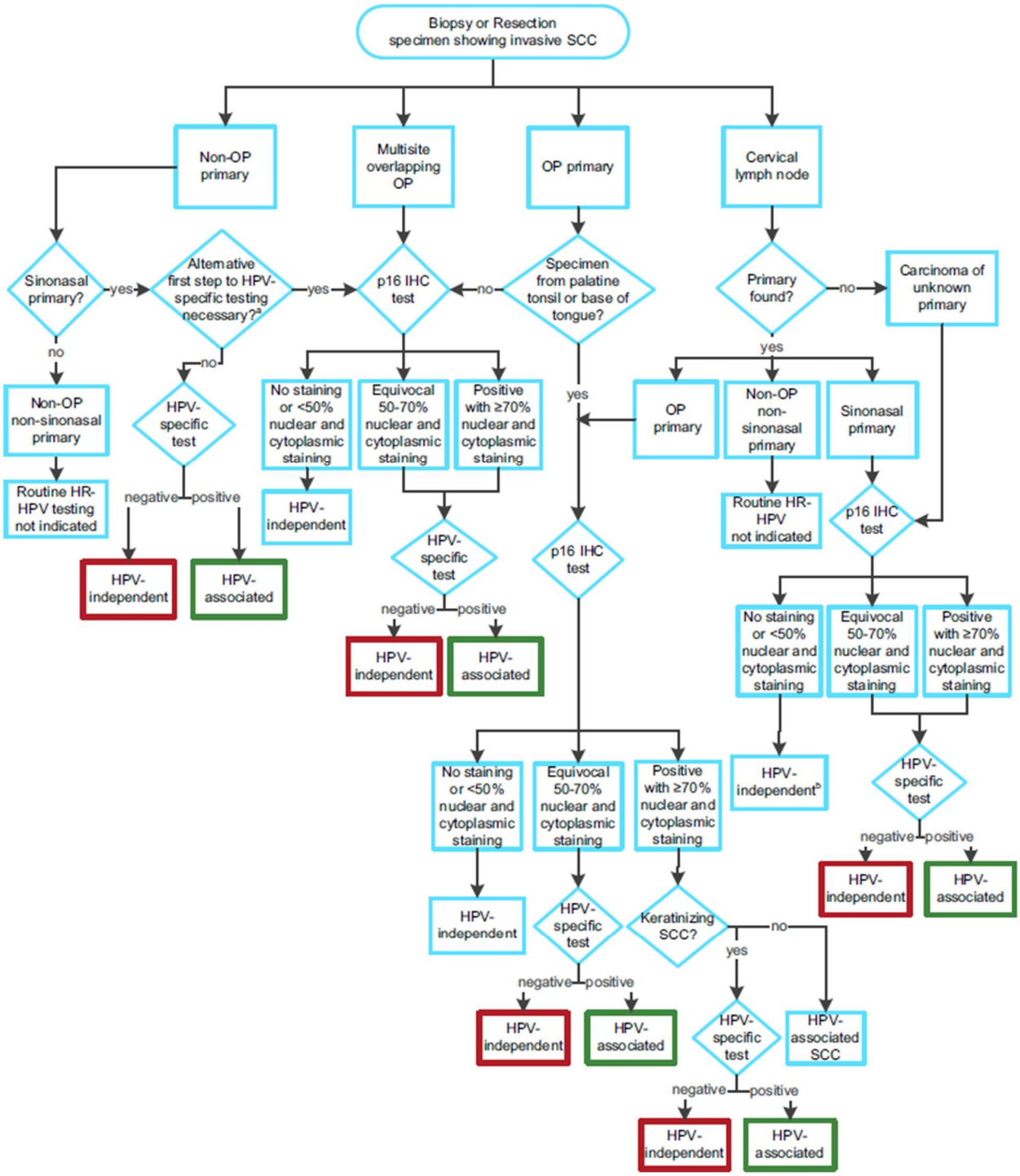

Figure 1 HR-HPV testing in head and neck SCC algorithm.

Source: Lewis et al. 2025[15]

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
☐ Non-inferior
☐ Inferior

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

EBER and HPV ISH is superior to comparators that do not directly demonstrate EBV or HPV infection within tumour cells, and is required to meet WHO tumour classification criteria for viral-associated cancers. Improved diagnostic accuracy 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.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

A requestor would use EBER or HPV ISH in addition to, and in selected cases instead of, the comparators because it directly demonstrates viral nucleic acid within tumour cells, which is the key question in many WHO diagnostic scenarios.[1-5] In contrast, common comparators (routine histopathology, IHC alone, or non-localising molecular tests) can be indirect, less specific, or non-definitive.

In practice, ISH is sought to: (1) meet essential/desirable WHO criteria for tumour classification based on viral status; (2) resolve diagnostic uncertainty when morphology and immunophenotype overlap between entities (e.g. distinguishing EBV-driven lymphoid proliferations from mimics, or confirming HPV-driven disease in settings where p16 is non-specific); (3) produce an integrated pathology report that is sufficiently certain to guide management decisions and avoid inappropriate escalation or de-escalation of therapy; and (4) provide a robust, reproducible result that is interpretable across laboratories and MDTs, supporting consistent staging, prognostication, and care pathways.

Identify how the proposed technology achieves the intended patient outcomes:

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.[1-5] 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.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? Yes

Please provide a rationale, and information on other benefits if relevant:

At a population level, more accurate attribution of cancers to EBV/HPV strengthens surveillance and epidemiologic estimates, which can inform preventive strategies and policy (e.g. reinforcing the value of HPV vaccination across sexes). While we acknowledge that these outcomes are outside the scope of an MSAC application, they are nonetheless tangible benefits of ISH testing to the health system.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

EBER and HPV ISH would typically be used as an additional investigation beyond standard histopathology and routine IHC, requiring specialised reagents/probes, dedicated technical staff time, and pathologist reporting. In most cases it would be performed as an adjunct test rather than an alternative, increasing per-specimen costs relative to comparators that rely on morphology with or without IHC. While ISH is likely to avert downstream costs by reducing diagnostic uncertainty and inappropriate management, the immediate testing cost will be higher than the comparator pathway.

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

N/A

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

#	Study	Title	Abstract	Link	Date
	EBV				
1	Bourbon et al, 2021 [29]	Clinicopathological features and survival in EBV-positive diffuse large B-cell lymphoma not otherwise specified	**Retrospective cohort study** of diffuse large B-cell lymphoma (DLBCL-NOS) diagnosed 2006–2019 (n=1,696). EBV positivity by EBER in situ hybridisation identified 70 EBV+ cases (4.1% prevalence). EBV+ tumours showed mainly latency II (88%). EBV positivity was linked to worse 5-year overall survival in patients >50 years (53% vs 60.8%).	PMID 34427583	Aug 2021
2	Lu et al, 2015[30]	Epstein-Barr virus positive diffuse large B-cell lymphoma predict poor outcome, regardless of the age	**Retrospective cohort study** of DLBCL patients (n=250) stratified by age and EBV status using EBER in situ hybridisation cut-offs of 20% and 50%. EBV+ prevalence was 14.0% (35/250) at 20% and 10.4% (26/250) at 50%. Across ages, EBV+ cases had adverse prognostic features and significantly worse overall and progression-free survival versus EBV−, with no outcome differences between young and elderly EBV+ groups.	PMID 26202875	July 2015

#	Study	Title	Abstract	Link	Date
3	Malpica et al, 2024[20]	EBV-positive diffuse large B-cell lymphoma, not otherwise specified: 2024 update on the diagnosis, risk-stratification, and management	**Narrative review** summarising EBV+ DLBCL, NOS. Diagnosis relies on EBER in situ hybridisation (ISH): ICC 2022 requires >80% EBER-positive malignant cells, while WHO-HAEM5 requires EBER positivity in the majority without a fixed cut-off. EBER-ISH also supports differential diagnosis from other EBV-associated lymphomas. EBV+ DLBCL, NOS, might have a worse prognosis than EBV-negative DLBCL in the era of chemoimmunotherapy	PMID 38957951	2024
4	Chen et al, 2024[31]	The efficacy of adjuvant chemotherapy in patients with different midpoint-radiotherapy Epstein-Barr virus DNA plasma loads	**Retrospective consecutive cohort** of locoregionally advanced NPC (stage III–IVa; n=675) assessing adjuvant chemotherapy (AC) benefit by mid-radiotherapy plasma EBV DNA status (***follow-up test that is gated by a positive EBER ISH result***). Detectable mid-RT EBV DNA (149/675, 22.1%) predicted worse 5-year PFS (74.8% vs 81.9%). In detectable cases, AC improved 5-year PFS (82.8% vs 66.8%; HR 0.48), but no benefit with undetectable EBV DNA (HR 0.87).	PMID 38970970	Sep 2024
5	Dupuis et al, 2006[32]	Prognostic significance of Epstein-Barr virus in nodal peripheral T-cell lymphoma, unspecified: A Groupe d'Etude des Lymphomes de l'Adulte (GELA) study	**Retrospective cohort study of** peripheral T-cell lymphoma, unspecified patients from LNH87/LNH93 trials (n=110) using EBER in situ hybridisation (EBER-ISH) for EBV status. EBER-ISH was positive in 45/110 (41%). EBER-ISH positivity predicted poorer outcomes: it was the only factor linked to worse 5-year event-free survival (11% in EBER-ISH+), and was associated with worse overall survival in older patients, with the adverse impact mainly within the first 2 years.	PMID 16902151	Dec 2006

#	Study	Title	Abstract	Link	Date
	HPV				
1	Jiromaru et al, 2021 [33]	p16 overexpression and Rb loss correlate with high-risk HPV infection in oropharyngeal squamous cell carcinoma	**Retrospective cohort study** of OPSCC patients (n=177), transcriptionally active high-risk HPV was determined by mRNA in situ hybridisation (ISH) and was present in 105 cases (59.3%). Eight tumours were p16-positive but HPV mRNA-ISH negative (4.5%). Compared with the HPV mRNA-ISH–positive group, HPV mRNA-ISH–negative cases (including p16-negative tumours) had worse overall survival (significant for p16−/ISH−; P=0.0004).	PMID 33450095	Sep 2021
2	Craig et al, 2020[34]	Comparison of Molecular Assays for HPV Testing in Oropharyngeal Squamous Cell Carcinomas: A Population-Based Study in Northern Ireland	**Retrospective cohort study** of Northern Ireland OPSCC cases diagnosed 2000–2011 (sample size not stated) evaluating second-line HPV assays alongside p16 IHC. Tissue-based HPV RNA-ISH and DNA-ISH were more specific than DNA-PCR (RNA-ISH 100%, DNA-ISH 95% vs PCR 67%) and less affected by block age; pooled-genotype RNA-ISH showed highest accuracy (95%) compared to p16.	PMID 31666283	Jan 2020
3	Mehanna et al, 2023 [26]	Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG-EPIC-OPC): a multicentre, multinational, individual patient data analysis	**Multicentre, multinational individual patient data analysis** (13 cohorts; n=7,654 curatively treated OPSCC) comparing p16 with HPV testing (including DNA/RNA tissue assays such as ISH). Discordance was common: 415/3,805 (10.9%) p16+ were HPV−. Discordant groups had intermediate outcomes; 5-year OS was 54.7% for p16+/HPV− vs 81.1% for p16+/HPV+.	PMID 36796393	Mar 2023

#	Study	Title	Abstract	Link	Date
4	Hongo et al, 2021[35]	Clinicopathologic Significance of EGFR Mutation and HPV Infection in Sinonasal Squamous Cell Carcinoma	**Retrospective cohort study** of sinonasal squamous cell carcinoma (SNSCC; n=146, including 14 ISP-SCC) using HPV RNA in situ hybridisation to detect transcriptionally active HR-HPV and chromogenic in situ hybridisation for EGFR copy-number gain. HR-HPV was found in 11/146 (7.5%) and was associated with better prognosis; HPV-positive cases had significantly better outcomes than HPV-negative molecular subgroups.	PMID 32868526	Jan 2021
5	Shinn et al, 2021[36]	Oropharyngeal Squamous Cell Carcinoma With Discordant p16 and HPV mRNA Results: Incidence and Characterization in a Large, Contemporary United States Cohort	**Multi-institutional retrospective cohort** of OPSCC (n=467) assessing transcriptionally active HPV using HPV mRNA testing (RT-PCR). Most were HPV mRNA positive (84%) and p16 positive (82%); 4.9% were discordant (3.4% p16−/HPV mRNA+, 1.5% p16+/HPV mRNA−). Outcomes for discordant groups were intermediate between concordant groups; selective HPV mRNA testing improved prognostication modestly.	PMID 33739785	Jul 2021
6	Ward et al, 2014[37]	Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer	**Retrospective multicentre cohort** of consecutively treated OPSCC (n=270) evaluating prognostic factors within HPV-positive disease. HPV status was positive vs negative. HPV-positive tumours had better survival (HR 0.33). Among HPV-positive cases, tumour-infiltrating lymphocytes stratified risk (3-year survival 96% with high TILs vs 59% with low TILs); a model using TILs, smoking, and T-stage validated well.	PMID 24169344	Jan 2014

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

#	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1	Phase 1 case series	An early phase, open label, multicentre, trial study to assess safety and efficacy of front-line therapy for EBV-associated Lymphomas 2 (TREBL-2) - ALLG NHL36	The study involves four stages over 83 weeks: 1) Induction with Tislelizumab and Rituximab for 9 weeks, 2) Combination with Tislelizumab, Rituximab, chemotherapy (cyclophosphamide, doxorubicin, vincristine), and prednisolone for 18 weeks, 3) Cell Therapy with EBV-specific T-cells and evaluation for response, and 4) Maintenance with Tislelizumab for 48 weeks if cancer has disappeared. Regular blood tests, bone marrow assessments, and ECHO scans are required.	ACTRN12622001189718	Estimated completion April 2031

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