

MSAC Application 1820

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

Applicant: The Royal College of Pathologists of Australasia

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 HPV ISH in HPV-associated cancers: PICO Set 1

Component	Description
Population	Patients with confirmed HNSCC and genitourinary or anal cancers* in which hr-HPV status is clinically relevant based on WHO Classification of Tumours criteria. Eligibility is limited to HNSCC and instances of genitourinary and anal malignancies where localising viral nucleic acid within malignant cells is essential or desirable based on WHO classification criteria or to guide clinical treatment and when p16 IHC results are unreliable, equivocal or discordant. Circumstances where HPV ISH is indicated based on WHO classification criteria include: • Equivocal p16 IHC results (50–70% staining) • Unreliable p16 IHC (p16 positive is a poor HPV surrogate in some populations e.g. SCC in neck lymph node where no primary site is identified in the oropharynx in a patient with sun damaged skin) • Certain specific tumours (e.g. HPV related multiphenotypic sinonasal carcinoma) • Discordance between morphology and p16 expression.
Prior tests	Histopathology on a biopsy or excision specimen to confirm tumour type and grade, and testing for surrogate markers including p16 by IHC.
Intervention	DNA or RNA ISH testing for hr-HPV viral genomes
Comparator/s	No molecular profiling (i.e. standard of care is considered an appropriate comparator and includes p16 IHC and histopathology used in the diagnosis of relevant cancers).
Reference standard	There is no universally accepted reference standard. The reference is defined as the combination of diagnostic information used to establish the final diagnosis and guide clinical management, together with the resulting patient outcomes. This may include histopathological assessment, p16 IHC, HPV ISH, PCR testing and clinical evaluation, recognising that no single test is definitive in all circumstances and that diagnostic certainty is derived from the integration of multiple sources of evidence.
Outcomes	Test performance • Diagnostic accuracy: sensitivity, specificity, PPV, NPV • Concordance/discordance with surrogate markers (p16 IHC) • Resolution of equivocal or discordant p16 IHC results • Concordance with WHO Classification of Tumours diagnostic criteria • Proportion of tumours correctly classified as HPV-associated or HPV-independent • Incremental diagnostic yield compared with existing diagnostic pathways • Prognostic accuracy: association between HPV status and health outcomes, including prognostic utility of HPV ISH in p16 negative tumours Change in management • Change in tumour classification, staging, prognostic stratification • Change in treatment selection or treatment intensity • Number/proportion of patients with changes in treatment selection or intensity based on HPV status • Change to surveillance or follow-up • Downstream effects on patient outcomes (mortality, morbidity, quality of life, safety) • Time to diagnosis • Time to treatment initiation Clinical effectiveness outcomes • Patient health outcomes (e.g. mortality, morbidity, quality of life)

Component	Description
	Safety outcomes - Harms associated with false positive or false negative results - Harms resulting from inappropriate changes in treatment Healthcare resource use - Uptake and utilisation rates of HPV ISH - Costs associated with the intervention - Total Australian Government healthcare expenditure - Frequency of testing for HPV16/18 (proposed MBS item AAAAA) - Frequency of testing for other hr-HPV genotypes (proposed MBS item BBBBB)
Assessment questions	What is the safety, effectiveness, cost-effectiveness and total costs of HPV ISH versus no molecular profiling in identifying viral genomes in HPV-driven cancers?

Abbreviations: DNA = deoxyribonucleic acid; HNSCC = head and neck squamous cell carcinoma; (hr)-HPV = (high-risk)-human papillomavirus; IHC = immunohistochemistry; ISH = In situ hybridisation; NPV = negative predictive value; PCR = polymerase chain reaction; PPV = positive predictive value; RNA = ribonucleic acid; WHO = World Health Organization.

* Potentially relevant malignancies include cases where HPV ISH may have diagnostic value (e.g. where a patient had not undergone HPV screening or where a high-grade endometrial cancer is p16 positive and involves the cervix).

Table 2 PICO for EBER ISH in EBV-associated cancers: PICO Set 2

Component	Description
Population	Patients with tumours in which EBV status is clinically relevant based on WHO Classification of Tumours criteria. Eligibility is limited to tumours where localising viral nucleic acid within tumour cells is essential or desirable based on WHO classification criteria or because of clinical need.
Prior tests	Histopathology on a biopsy specimen to confirm tumour grade
Intervention	ISH testing for EBER
Comparator/s	No molecular profiling (i.e. standard of care is considered an appropriate comparator and includes IHC and histopathology used in the diagnosis of relevant cancers).
Reference standard	EBER ISH is the reference standard for classifying EBV-associated tumours, following WHO Classification of Tumours guidance.
Outcomes	Test performance - Diagnostic accuracy of EBER ISH including sensitivity, specificity, PPV, NPV Healthcare resource use - Costs associated with the intervention - Total Australian Government healthcare costs - Uptake and utilisation rates of EBER ISH
Assessment questions	What is the diagnostic accuracy and total financial costs of EBER ISH versus no molecular profiling in identifying viral genomes in EBV-driven cancers?

Abbreviations: EBER = Epstein Barr encoded RNAs; EBV = Epstein Barr virus; IHC = immunohistochemistry; ISH = In situ hybridisation; NPV = negative predictive value; PPV = positive predictive value; WHO = World Health Organization.

Purpose of Application

An application requesting Medicare Benefits Schedule (MBS) listing of in situ hybridisation (ISH) for the detection of viral genomes (human papillomavirus [HPV] and Epstein Barr virus [EBV]) in HPV- and EBV-driven cancers was received from The Royal College of Pathologists of Australasia by the Department of Health, Disability and Ageing.

Although both indications involve the use of ISH to detect viral nucleic acids in tumour cells, they relate to different diseases, are used at different points in the diagnostic pathway and are intended to inform different clinical decisions.

For HPV-associated malignancies, ISH may be used as an adjunct test to confirm transcriptionally relevant HPV infection in selected tumour types where HPV status provides diagnostic information, as well as potentially providing prognostic or staging information.

In contrast, demonstration of EBV infection in tumour cells by Epstein Barr-encoded small RNA (EBER) ISH is primarily used to support the diagnosis and classification of a range of EBV-associated malignancies. EBER ISH is regarded as the reference standard for demonstrating EBV infection within tumour cells.

Both HPV and EBV infections are associated with multiple malignancies that have different diagnostic pathways, clinical roles for viral testing and treatment approaches. Therefore, assessment of the clinical evidence is likely to require the presentation of exemplar indications, noting there may be substantial heterogeneity between the different malignancies. This is especially so for EBER ISH, which is considered the reference standard for demonstrating EBV in tumour cells for the diagnosis of several EBV-associated malignancies, whereas for other malignancies, it is recommended only in specific circumstances as an adjunct diagnostic test. As the positioning and comparator tests are likely to differ between these indications, more than one exemplar may be required to adequately assess the use of EBER ISH.

The application nominated a single exemplar—oropharyngeal squamous cell carcinoma (OPSCC)— which relates to HPV-associated malignancies. However, OPSCC is not representative of EBV-associated malignancies. Exemplar indications for EBV-associated malignancies were requested from the applicant at the pre-PASC meeting and the applicant nominated post-transplant lymphoproliferative disorders (PTLD) as the exemplar indication.

Given the differences in clinical indications, patient populations, comparator tests and intended use, the PICO confirmation will present ISH for HPV and EBV separately.

PASC considered that p16 immunohistochemistry (IHC), which is widely available and already funded on the MBS as an IHC marker, is a very good surrogate of high risk HPV (hr-HPV) related infection in most cases, but may be unreliable in specific clinical circumstances. In contrast to HPV, there is no surrogate IHC marker that can be used for EBV infection.

PASC noted that advice was sought on whether the application should proceed to the assessment stage as a single application, or as 2 separate applications. PASC considered that the application encompassed 2 fundamentally different indications and that separating the application may provide clearer delineation of the populations, clinical indications, utility, evidence and expected utilisation. PASC considered the clinical and economic assessment requirements for HPV ISH and EBV ISH separately, noting these may proceed along different pathways depending on the scope of each assessment and whether a clinical assessment is required to inform an economic assessment. PASC noted the department would consider and advise on the logistics for managing the application as two applications going forward (e.g. whether separate application numbers are required).

PICO criteria (HPV-associated malignancies)

The proposed health technology—ISH testing for HPV viral genomes—is intended for patients with malignancies in which demonstration of HPV within tumour cells is clinically indicated to support accurate tumour classification according to the World Health Organisation (WHO) Classification of Tumours¹ and subsequent clinical management.

Disease background and natural history

HPV infection is common, with approximately 80% of Australians expected to acquire HPV during their lifetime.² Most infections are asymptomatic and resolve spontaneously within 1–2 years. However, persistent infection with hr-HPV genotypes can result in malignant transformation over many years or decades.

HPV comprises almost 200 genotypes, categorised as high- and low-risk according to their oncogenic potential (ACDC 2023). The WHO International Agency for Research on Cancer classifies HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 as carcinogenic to humans, HPV68 as probably carcinogenic and HPV66 as possibly carcinogenic (ACDC 2023). Persistent infection with hr-HPV is associated with the development of HPV-associated cancer, and continual expression of the viral oncogenic E6 and E7 proteins inhibits immune detection (Della Fera et al. 2021). HPV16 and HPV18 account for the majority of HPV-associated cancers, although several other hr-HPV genotypes also contribute (Anwer et al. 2026).

HPV is causally associated with cervical cancer and contributes to cancers arising in the oropharynx, anus, vulva, vagina and penis. The strength of this association varies according to tumour site and histological subtype. Australian incidence rates for HPV-related cancers are presented in Table 3. It is estimated that 90% of cervical and anal cancers, 70% of vulvar and vaginal cancers, 60% of penile cancers and 70% of oropharyngeal cancers are due to persistent hr-HPV infection (Jensen et al. 2024). HPV-related and HPV-independent carcinomas arising from these sites have different natural histories and, often, different treatment paradigms.

¹ <https://tumourclassification.iarc.who.int/>

² <https://www.cancer.nsw.gov.au/prevention-and-screening/screening-and-early-detection/cervical-screening/hpv-and-cervical-cancer>

Table 3 Annual crude incidence rate of HPV-related cancer in Australia (estimates for 2020)

Cancer site	Male (per 100,000)	Female (per 100,000)
Lip, oral cavity	14.7	7.23
Cervix uteri	–	7.19
Vulva	–	3.56
Anus	1.88	2.94
Oropharynx	6.26	1.2
Vagina	–	0.74
Larynx	3.89	0.5
Penis	1.03	–

Source: Adapted from Bruni et al. (2023), Figure 4 p 5.

Abbreviations: HPV = human papillomavirus

Australian epidemiology

Following implementation of the National HPV Vaccination Program in 2007³, the prevalence of vaccine-targeted HPV infection has declined substantially in Australia (Patel et al. 2018). Despite this success, HPV remains an important cause of cancer. Age standardised incidence rates for HPV-associated malignancies range from 0.4 to 3.7 cases per 100,000 population, depending on the tumour type (Table 4).

The application estimated the number of patients eligible for HPV ISH using Australian Institute of Health and Welfare (AIHW) incidence data (Table 4) and the applicant clarified during the pre-PASC meeting that all incident cases of OPSCC are potentially eligible for testing. For other HPV-associated malignancies, the application assumed that approximately 10% of cases would require HPV ISH confirmation. However, no supporting evidence was provided for these assumptions used to calculate the estimates of eligible cases for HPV ISH testing. However, p16 IHC suffices as a surrogate for hr-HPV related infection for the great majority of cases and therefore HPV ISH is very rarely required in genitourinary cancers, and only rarely required in OPSCC where p16 may be difficult to interpret. Therefore, the estimate of eligible OPSCC cases in the application is likely to be a significant over-estimate as only a minority of OPSCC cases would require HPV ISH (Badoual 2022; WHO 2023).

The applicant's pre-PASC response acknowledged that the estimated OPSCC population was an overestimate, and clarified that HPV ISH would be required only in select OPSCC cases where confirmatory testing is clinically indicated.

³ <https://ncirs.org.au/impact-evaluation-australian-national-hpv-vaccination-program> (Accessed 25 June 2026)

Table 4 Incidence and number of cases of eligible HPV cancer types

Cancer type	ICD-10 Code	Incidence rate per 100,000	Eligible cases
Oropharyngeal cancer	C09-C10	3.3*	863
Cervical cancer	C53	3.7*	95
Anal cancer	C21	2.2*	56
Vulvar cancer	C51	1.4*	34
Penile cancer	C60	0.5*	13
Vaginal cancer	C52	0.4*	10

Abbreviations: HPV = human papillomavirus

Note: *Age-standardised rate, 2025 population; data sourced from AIHW Cancer Data in Australia (AIHW 2026).

Target population and establishing an exemplar

HPV is associated with development of the following malignancies:

- OPSCC
- Cervical cancer
- Anal squamous cell carcinoma (SCC)
- Vulvar SCC
- Vaginal SCC
- Penile SCC.

Although these malignancies share an association with hr-HPV infection, the clinical role of HPV testing differs between tumour types (Table 5). In OPSCC, HPV status is routinely determined using p16 immunohistochemistry (IHC), as it informs tumour staging and subsequent treatment, whereas HPV ISH is primarily used as a confirmatory test in cases with equivocal or discordant p16 IHC results. For example, keratinising OPSCC is less likely to be HPV-associated than non-keratinising OPSCC. Therefore, a positive p16 IHC result in a keratinising tumour may be confirmed with HPV ISH to exclude a false positive p16 result and verify HPV association if no HPV related primary tumour is found in the oropharynx (Lewis et al. 2025). In cervical cancer, the NCCN guidelines recommend HPV ISH, molecular testing or p16 IHC for determining HPV association. In the adenocarcinoma subtype of uterine cervix carcinoma, HPV ISH is preferred over p16 IHC as p16 may be positive in non-HPV related adenocarcinomas, whereas HPV ISH is both sensitive and specific. Nevertheless, when HPV ISH is not available, p16 IHC is considered an acceptable surrogate test (NCCN 2025a). This differs from the WHO Classification of Tumours which recognises p16 IHC as an acceptable surrogate and lists it as an essential diagnostic test, whereas HPV specific testing is considered desirable only in selected cases where p16 results are equivocal or challenging to interpret (WHO 2020). Although HPV status does not guide treatment, HPV-associated cervical cancers generally have a more favourable prognosis than HPV-independent disease (Abu-Rustum et al. 2025; NCCN 2025a). In penile cancer, HPV status is assessed as part of the primary diagnostic evaluation using p16 IHC, while HPV-specific molecular testing including ISH or PCR, is performed in selected cases. HPV status may be considered in treatment decision-making, is generally associated with improved cancer-specific survival (CSS), and may prompt HPV screening of sexual partners (NCCN 2025c; Vandermaesen et al. 2025). In anal cancer, HPV testing is recommended but not required; HPV-associated tumours generally demonstrate greater responsiveness to chemoradiotherapy (NCCN 2026a). In vulvar and vaginal cancers, HPV testing is recommended but not mandatory, and treatment decisions are not routinely guided by HPV status (NCCN 2025d, 2026f).

The target population comprises patients undergoing diagnostic assessment of malignancies in which demonstration of HPV within tumour tissue influences tumour classification, prognostic stratification or clinical management. HPV ISH may be used either as a primary diagnostic test or as a confirmatory test following surrogate marker testing (e.g. p16 IHC) where results are equivocal or discordant. As such, the target population includes patients with malignancies for which direct localisation of HPV within tumour cells is essential or desirable by the WHO Classification of Tumours.⁴ The applicant's pre-PASC response acknowledged that except for use in head and neck SCC (particularly OPSCC), HPV ISH is expected to have limited use in gynaecological malignancies because p16 IHC is an adequate surrogate marker in most cases. The applicant's pre-PASC response also noted that HPV ISH may provide additional diagnostic value in rare circumstances such as when prior HPV screening information is unavailable or where a p16 positive high-grade endometrial carcinoma involves the cervix and the primary site of origin is uncertain.

PASC noted that in patients presenting with cervical nodes, the site of the primary tumour may be uncertain, particularly when distinguishing between oropharyngeal and cutaneous origin. In such cases, HPV ISH may be used more frequently to aid in tumour classification in specific circumstances (for example when no primary site is identified in the oropharynx or elsewhere). Given that HPV ISH is expected to have limited use outside of OPSCC, PASC advised that it may be appropriate to restrict the proposed population to patients with head and neck cancers, specifically OPSCC, with the possible inclusion of a very small number of clinically important cases among other tumour types.

PASC considered that in Australia virtually all screen detected uterine cervical carcinomas will already have had HPV molecular testing performed. PASC considered that testing of sexual partners is outside the scope of the application and is not clinically indicated given the widespread prevalence of HPV in the general population.

⁴ <https://tumourclassification.iarc.who.int/>

Table 5 HPV-associated malignancies

Malignancy	Diagnostic pathway⁵	Recommended treatment	Prognosis
OPSCC	Essential: SCC (usually non-keratinising); positivity for high-risk HPV as determined by surrogate marker p16 IHC alone (70% nuclear and cytoplasmic cut-off point) or by p16 IHC plus HPV-specific testing. Desirable: p40/p63 (positive) and neuroendocrine marker (negative) IHC (in selected cases).	Early-stage disease is treated with TORS or definitive radiotherapy. Locally advanced disease is treated with concurrent chemoradiotherapy or surgery followed by risk-adapted adjuvant therapy. Treatment according to TNM staging as per AJCC (8 th edition) staging system.	Patients with HPV-associated OPSCC have significantly better survival outcomes than those with HPV-independent OPSCC.
Cervical cancer	Essential: infiltrating, angulated, irregularly sized and shaped nests, anastomosing cords and solid sheets; nuclear pleomorphism and increased mitotic count; desmoplastic or inflammatory stroma; overexpression of p16 as an acceptable surrogate marker of HPV association. Desirable (in selected cases): HPV testing.	Management depends on stage and includes local excision for pre-invasive disease, surgery, radiotherapy and concurrent chemoradiotherapy for invasive disease, and systemic therapy or immunotherapy for recurrent or metastatic disease. HPV status does not guide primary treatment.	Histological patterns, HPV type and grading do not seem to have prognostic implications. HPV status has limited impact on treatment selection once invasive cancer is diagnosed.
Anal SCC	Essential: infiltrating squamous cell clusters and strands with malignant nuclei and eosinophilic cytoplasm; mitotic activity including atypical forms, intercellular bridges and variable keratin production.	Localised disease is treated with definitive concurrent chemoradiotherapy. Persistent or recurrent disease is generally treated with surgery.	Pathological stage is the most important prognostic factor.
Vulvar SCC	Essential: infiltrating, angulated, irregularly sized and shaped nests, anastomosing cords and solid sheets; nuclear pleomorphism and mitoses; desmoplastic or inflammatory stroma; p16 block-type immunoreactivity and/or positive molecular testing for HPV.	Surgery is the mainstay of treatment, with adjuvant radiotherapy or chemoradiotherapy according to pathological risk factors.	Prognosis in early-stage disease is good, with a reported 5-year survival rate of 80–90%. Stage and lymph node status are the most important prognostic factors for clinical outcome. Lymph node involvement decreases survival significantly. Depth of invasion is associated with lymph node involvement and is therefore included in clinical decision trees for groin surgery. HPV-associated vulvar SCCs are associated with better progression-free survival than are HPV-independent tumours.

⁵ <https://tumourclassification.iarc.who.int/home>

Vaginal SCC	Essential: no previous (≤ 5 years) or concomitant SCC of cervix or vulva; infiltrating, angulated, irregularly sized and shaped nests, anastomosing cords and solid sheets; nuclear pleomorphism and increased mitotic count; desmoplastic or inflammatory stroma; overexpression of p16 as an acceptable surrogate marker of HPV association. Desirable (in selected cases): HPV testing.	Radiotherapy with or without chemotherapy is commonly used. Surgery is reserved for selected early-stage tumours. Primary treatment with curative intent typically consists of radiotherapy, surgery, chemoradiotherapy or a combination of these, irrespective of HPV infection status.	Prognosis depends on patient age, tumour stage and tumour size (< 4 cm vs ≥ 4 cm). For high-stage disease, the prognosis is poor, with a 5-year overall survival rate of approximately 50% for all stages. In several studies, the presence of HPV DNA has been found to be an independent favourable prognostic factor for disease-free and overall survival. One study found HPV16-positive tumours to be associated with better survival.
Penile SCC	Essential: p16 block positivity or evidence of HPV on molecular testing; for basaloid SCC: invasive carcinoma with sheets and nests, solid tumour with scant cytoplasm, comedonecrosis and brisk mitoses; for warty carcinoma: tumour with surface papillary architecture and deeper infiltrative component composed of frankly atypical cells with koilocytic atypia; for clear cell SCC: invasive carcinoma with prominent cytoplasmic clear cell features; for lymphoepithelioma-like carcinoma: poorly differentiated to undifferentiated SCC with tumour cells arranged in syncytia and with prominent inflammatory (lymphoplasmacytic) infiltrate surrounding or obscuring neoplastic cells. Desirable: mixed patterns of HPV-associated carcinomas may be present.	Surgical excision is the primary treatment, with lymph node management according to nodal status. Radiotherapy, chemotherapy and immunotherapy are used in selected patients. HPV status may be considered in treatment decision-making.	HPV-associated tumours comprise approximately 45–80% of penile cancers and are generally associated with improved CSS compared with HPV-independent tumours. HPV status is primarily prognostic and assists tumour classification. It may also prompt screening for sexual partners

Source: NCCN (2026d); NCCN (2026f); NCCN (2025d); NCCN (2025a); Badoual (2022); Cree et al. (2020); Lewis et al. (2025); Machiels et al. (2020); Marth et al. (2017); Moch et al. (2022); Muneer et al. (2024); Rao et al. (2021)

Abbreviations: AJCC = American Joint Committee on Cancer; CSS = cancer-specific survival; HPV = human papillomavirus; IHC = immunohistochemistry; OPSCC = oropharyngeal squamous cell carcinoma; SCC = squamous cell carcinoma; TNM = tumour, node, metastasis; TORS = transoral robotic surgery.

PASC noted that HPV ISH has an established role in OPSCC but may have only limited utility in genitourinary and anal malignancies. In its response to PASC, the applicant described rare circumstances in which HPV ISH may be required in gynaecological pathology, including cases where prior HPV screening information is unavailable or where a p16 positive high-grade tumour involves the cervix and the primary site is uncertain. In such situations, HPV ISH may provide additional diagnostic value.

PASC noted that the application nominated OPSCC as the exemplar indication for evaluating HPV ISH, however, PASC did not support an exemplar approach. PASC noted that there is heterogeneity in the prognostic utility and clinical management for HPV-related cancers. PASC considered that while OPSCC was the primary indication, the assessment should present evidence on the clinical utility of HPV ISH testing in the entire population including the small number of clinically important circumstances among other genitourinary and anal tumour types. These circumstances include gynaecological malignancies where prior HPV screening information is unavailable or where a p16 positive high-grade endometrial carcinoma involves the cervix and the primary site of origin is uncertain.

Current international guidelines recommend p16 IHC as the initial surrogate marker for HPV-associated OPSCC. However, p16 overexpression is not specific for transcriptionally active HPV infection. In cases with equivocal p16 staining (50–70% staining), or discordance between morphology and p16 expression, HPV ISH directly demonstrates viral nucleic acids within tumour cells and confirms HPV-driven disease (Lewis et al. 2025).

The clinical evidence is strong for OPSCC, although clinical trials are largely conducted in HPV-associated OPSCC, with HPV association assessed by p16 IHC or direct HPV testing of biopsy or surgical tissue. However, direct evidence in a trial-based setting that randomises treatment allocation based on HPV status is unavailable. Thus, a linked evidence approach is likely to be required for the evaluation. A list of the clinical trials for OPSCC identified in a scoping search appears in Table 6. Importantly, it is simplistic to assume that OPSCC cases with discordant p16 and HPV ISH status behave in a manner predicted by the HPV ISH result. Evidence to date suggests that cases which are p16 negative but HPV ISH positive, or p16 positive but HPV ISH negative behave in an intermediate manner between definite HPV-related tumours (p16 positive/HPV ISH positive) and definite HPV-independent tumours (p16 negative/HPV ISH negative); and may behave more like HPV-independent tumours (Mehanna et al. 2023).

Table 6 Clinical trials of OPSCC

Study	Design	Population	Treatment	Key findings
RTOG 0129 (Ang et al. 2010)	Secondary analysis of Phase III RCT	Locally advanced OPSCC (~72% p16 positive)	Cisplatin + radiotherapy	Treatment did not improve outcome or increase late toxicity in locally advanced head and neck cancer.
De-ESCALaTE HPV (Mehanna et al. 2019)	RCT	Low-risk HPV-positive OPSCC	Radiotherapy + cisplatin vs radiotherapy + cetuximab	Compared with the cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity and showed significant detriment in terms of tumour control.
RTOG 1016 (Gillison et al. 2019)	RCT	HPV-positive OPSCC	Radiotherapy + cisplatin vs radiotherapy + cetuximab	Radiotherapy + cetuximab showed inferior OS and PFS compared with radiotherapy + cisplatin.

Study	Design	Population	Treatment	Key findings
E1308 (Marur et al. 2017)	Prospective Phase II	HPV-positive OPSCC	Response-adapted treatment with IMRT + cetuximab	Radiation dose reduction resulted in significantly improved swallowing and nutritional status.
ECOG 3311 (Ferris et al. 2022)	Randomised Phase II	Resected stage III/IVa HPV-positive OPSCC	TOS + radiotherapy	Primary TOS + reduced postoperative RT result in improved oncologic outcome and favourable functional outcomes in intermediate-risk HPV-positive OPSCC.
PATHOS (Owadally et al. 2015)	Ongoing RCT	HPV-positive OPSCC after surgery	Risk-stratified reduced intensity adjuvant therapy	Effect of risk-adapted adjuvant therapy on swallowing function.
Quarterback Trial (Lovett et al. 2026)	Phase II 2 sequential clinical trials	Poor risk HPV-positive OPSCC	Induction chemotherapy followed by reduced-dose chemoradiotherapy	Reduced-dose chemoradiotherapy following induction chemotherapy yields durable disease control in poor prognosis HPV-OPSCC, with outcomes comparable to historical benchmarks. Extended follow-up supports the safety and efficacy of de-escalation even in patients with aggressive disease characteristics, but underscores the need for careful patient selection, particularly in those with extracapsular extension.
OPTIMA (Seiwert et al. 2019)	Phase II non-randomised trial	HPV-positive OPSCC	Risk-adapted dose and volume de-escalation	Risk-stratified dose and volume de-escalated RT/chemo-RT for HPV-positive OPSCC is associated with favourable oncologic outcomes and reduced acute and chronic toxicity.
OPTIMA II (Rosenberg et al. 2024)	Phase II non-randomised trial	Stage III-IV HPV-positive OPSCC	Nivolumab + neoadjuvant nab-paclitaxel + carboplatin	Neoadjuvant nivolumab and chemotherapy followed by response-adapted locoregional therapy has favourable tolerability and improved OS and functional outcomes in HPV-positive OPSCC, including among patients with high-risk disease.
ORATOR (Nichols et al. 2024)	RCT	Early HPV-positive OPSCC	RT vs TORS	No differences in OS or PFS. Toxicity and QoL profiles differ in some domains between RT and TORS but oncologic outcomes were excellent in both arms.
ORATOR2* (Palma et al. 2022)	RCT	HPV-related OPSCC	RT vs TOS	For primary outcome of OS, 3 death events and 4 PFS events occurred in the TOS arm compared with none in the RT arm. Treatment-related adverse events were largely similar between treatment arms.

Abbreviations: HPV = human papillomavirus; OPSCC = oropharyngeal squamous cell carcinoma; OS = overall survival; PFS = progression-free survival; QoL = quality of life; RCT = randomised controlled trial; RT = radiotherapy; TORS = transoral robotic surgery; TOS = transoral surgery.

Note: * ORATOR2 trial was terminated early following deaths in the surgical arm; its findings should be interpreted with caution.

HPV plays a major role in the carcinogenesis of OPSCC, especially cancers arising from the tonsil and base of tongue (Anwer et al. 2026; Badoual 2022). The proportion of OPSCC attributable to HPV varies geographically, accounting for approximately 20–60% of cases worldwide, with the highest prevalence reported in North America and Northern Europe (60–80%) and a lower prevalence in Asia (10–20%) (Badoual 2022). HPV-associated OPSCC occurs predominantly in males (approximately 4:1 male:female), in

Caucasians, and in those of higher socioeconomic status. HPV16 accounts for approximately 90% of HPV-positive OPSCC (Badoual 2022).

Based on AIHW incidence data, the application estimated that approximately 863 Australian patients with OPSCC would require HPV ISH to confirm HPV association (Table 4). However, this may be an overestimation of the eligible population, as the surrogate biomarker p16 assessed via IHC is the first-line methodology used to establish HPV association. HPV ISH is generally reserved for selected cases with equivocal or discordant p16 IHC results, rather than being routinely performed in all patients with OPSCC.

Management of OPSCC involves a multidisciplinary approach including surgery, radiotherapy and systemic therapy. HPV status via p16 positivity or negativity forms the basis of the AJCC staging system for OPSCC (NCCN 2026d). Compared with HPV-independent tumours, HPV-associated OPSCC demonstrates greater radiosensitivity, improved treatment response and better overall survival (OS) and progression-free survival (PFS) (Cheung et al. 2026; Jiromaru et al. 2021; Shinn et al. 2021; Taylor et al. 2019).

The favourable prognosis of HPV-associated OPSCC has prompted evaluation of treatment de-escalation strategies aimed at reducing long-term treatment-related toxicity while maintaining oncological outcomes (Table 6). Therefore, HPV status has potential downstream implications for treatment selection in certain patients.

Prior tests

Patients with suspected HPV-associated malignancies undergo the standard diagnostic workup comprising clinical assessment, biopsy or surgical resection, routine histopathological examination, and imaging where appropriate. Histopathological assessment establishes the tumour site, histological subtype and grade, with p16 IHC performed routinely as a surrogate marker for HPV status. The prerequisite investigations may be claimed under existing MBS pathology items (Table 7).

HPV ISH is not a first-line investigation but is typically requested as a pathologist-determined reflex test following review of the biopsy or resection specimen. Across the proposed indications, patients become eligible for HPV ISH only after completion of the initial diagnostic workup when confirmation of HPV association is required to support tumour classification, diagnosis, prognostic assessment or subsequent clinical management.

The protein p16 is a cell cycle regulator and is encoded by the cyclin-dependent kinase inhibitor 2A gene (*CDKN2A*). In HPV-associated cancers, overexpression of p16 is a result of the HPV E7 oncoprotein that inactivates the tumour suppressor protein Retinoblastoma 1, encoded by the Retinoblastoma 1 gene (*RB1*). Overexpression of p16 may also be HPV-independent, due to genetic variants in *CDKN2A*, *RB1*, tumour protein p53 gene (*TP53*) or cyclin dependent kinase 6 gene (*CDK6*) (Berdugo et al. 2021).

For OPSCC, p16 IHC is the recommended initial surrogate marker for HPV status and is sufficient for tumour classification in most patients (Badoual 2022; NCCN 2026d). The WHO Classification of Tumours defines p16 positivity as strong, diffuse nuclear and cytoplasmic staining in at least 70% of tumour cells. Although p16 expression correlates closely with HPV status in populations where HPV-associated OPSCC is common, p16 overexpression is an indirect marker of transcriptionally active HPV infection and is not specific for HPV-driven carcinogenesis (Kuhn et al. 2021). Approximately 5–15% of p16 positive tumours are not HPV-associated (Gallus et al. 2023; Kuhn et al. 2021; Shinn et al. 2021).

Consistent with the NCCN guidelines, HPV ISH is recommended when there is discordance between tumour morphology and p16 positivity to confirm HPV association. Additional indications include equivocal p16 IHC results (50-70% staining) and multisite overlapping oropharyngeal tumours (e.g. involving non-tonsillar or non-base of tongue subsites) (NCCN 2026d). Therefore, HPV ISH is reserved for selected circumstances in OPSCC, including equivocal p16 staining, discordance between p16 expression and tumour morphology or clinical features, or where direct confirmation of HPV status is required for diagnosis or staging. In these situations, HPV ISH demonstrates the presence of hr-HPV nucleic acids within tumour cells, providing direct evidence of HPV-associated disease.

PASC noted that HPV ISH is indicated only for confirmed malignancy in which HPV status is relevant and p16 IHC is unreliable, equivocal or discordant with clinical features. As p16 positivity is determined by block positivity (at least 70% staining), only a subset of patients would require confirmatory HPV ISH. PASC considered that these circumstances should be explicitly reflected in the proposed population.

PASC considered whether p16 negative cancers should be included in the eligible population for HPV ISH testing and advised that the assessment report should look at the association between HPV status and health outcomes, including cancers with discordant p16 and HPV ISH results.

PASC noted that the frequency with which HPV ISH is required for confirmation is unclear, and uptake rates are not well characterised. The applicant did not provide data for how often p16 IHC fails to provide a definitive result, and this uncertainty limits the ability to estimate the size of the population requiring HPV ISH. Therefore, the number of patients eligible for HPV ISH is difficult to quantify and may be influenced by subjective clinical judgement.

Table 7 MBS items for prerequisite tests for 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)

Abbreviations: HPV = human papillomavirus; ISH = in situ hybridisation; MBS = Medicare Benefits Schedule.

HPV pathology services are currently funded via MBS items 73070–73076 as part of the National Cervical Screening Program. The implications are discussed in Proposal for public funding.

Intervention

Direct HPV detection methods include polymerase chain reaction (PCR), reverse transcriptase (RT)-PCR and deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) ISH. Although RT-PCR reliably identifies transcriptionally active HPV infection, its use in routine practice is limited by technical requirements and specimen quality (Kuhn et al. 2021). PCR-based assays are sensitive tests for HPV detection but do not localise viral nucleic acids and cannot distinguish oncogenic viral involvement versus incidental infection (Khan et al. 2025). Therefore, HPV ISH is the preferred methodology (Lewis et al. 2025). It is unclear if these alternative methods of HPV detection are currently used in Australian practice. The applicant's pre-PASC response advised that RT-PCR is typically performed on RNA from extracted tissue, which does not preserve cellular or spatial localisation. Therefore, while RT-PCR may detect transcriptionally active HPV, it cannot confirm that the viral transcripts arise from malignant cells. Thus, it is not clinically equivalent to HPV ISH.

HPV ISH is an investigative technology used in the diagnostic evaluation of select HPV-associated malignancies. Within the Australian diagnostic pathway, HPV ISH is performed after tissue diagnosis has been established, and is used to resolve specific diagnostic, classification or prognostic questions. The test is performed selectively rather than as a first-line investigation.

Patients with suspected malignancy undergo standard diagnostic assessments, including clinical evaluation, imaging where appropriate, tissue sampling and histopathological examination. In tumour types that may be HPV-associated, surrogate biomarkers such as p16 IHC may be used to initially assess HPV status. Unlike surrogate markers, HPV ISH directly demonstrates hr-HPV nucleic acids within malignant cells, providing evidence of viral involvement while preserving tissue morphology. This supports tumour classification in accordance with the WHO Classification of Tumours.⁶

Test procedure

HPV ISH is performed on formalin-fixed, paraffin-embedded (FFPE) tissue obtained from biopsy or surgical resection specimens (Khan et al. 2025). Labelled nucleic acid probes complementary to hr-HPV DNA or E6/E7 mRNA are hybridised to tissue sections following target retrieval. Probe–target complexes are subsequently detected using chromogenic or fluorescent methods and interpreted by a pathologist in conjunction with routine histopathological assessment. Preservation of tissue architecture enables direct correlation between HPV localisation and tumour morphology (Luk et al. 2019).

The application requests funding for both DNA and RNA HPV ISH. At the pre-PASC meeting, the applicant indicated that both methodologies are currently used in Australian pathology laboratories and restricting funding to a single methodology may create inequities in access.

A study comparing the performance of HPV DNA ISH versus HPV RNA ISH on hr-HPV demonstrated that RNA ISH had a significantly higher percentage of correct responses than did DNA ISH: 97.4% (450 of 462) versus 80.6% (650 of 806) ($p < 0.001$), respectively (Keung et al. 2020). Although RNA ISH has been reported to demonstrate greater analytical sensitivity than DNA ISH, especially in tumours with low or intermediate

⁶ <https://tumourclassification.iarc.who.int/>

viral copy numbers (Keung et al. 2020; Lewis et al. 2025), both methodologies are proposed as eligible technologies in the application.

RNA ISH has demonstrated high diagnostic performance for detecting transcriptionally active HPV infection. In a retrospective study of 122 OPSCC biopsy specimens, HPV RNA ISH demonstrated 100% sensitivity and 100% specificity relative to p16 IHC, with complete concordance between the two methods (Suresh et al. 2021). A literature review for the same study reported pooled sensitivities of 88–98% and specificities of 90–100% for RNA ISH across published studies (Suresh et al. 2021).

In most cases, sufficient material is available from the original biopsy or resection specimen and no additional invasive procedure is required. According to the application, re-biopsy may be necessary where tissue quantity or quality is inadequate for testing. However, re-biopsy undertaken solely to facilitate HPV ISH testing is expected to be uncommon as this testing only requires one slide containing the tumour sample. Should HPV ISH not be implemented as a pathologist-determinable service, additional specialist consultations may be required for the purpose of requesting the test.

Clinical utility

In OPSCC, HPV ISH is not performed routinely but is reserved for select circumstances where direct confirmation of HPV-driven disease is required.

Circumstances under which confirmation of HPV status by ISH is required to satisfy WHO Classification of Tumours diagnostic criteria for OPSCC include:

- equivocal p16 IHC results (e.g. staining involving 50–70% of tumour cells)
- discordance between p16 expression and tumour morphology or clinical features
- select tumour types or unusual presentations where p16 IHC alone is insufficient to establish HPV association (for example HPV related multiphenotypic sinonasal carcinoma).

HPV status via p16 expression is integral to AJCC tumour, node, metastasis (TNM) staging for OPSCC (NCCN 2026d). Where p16 IHC cannot reliably establish HPV association, HPV ISH may provide confirmatory evidence to support tumour classification, stage assignment and prognostic assessment. Treatment decisions are primarily determined by tumour stage, resectability and patient factors; however, accurate classification of HPV-associated disease may influence downstream management by ensuring appropriate staging and prognostic assessment (Table 5).

PASC considered that the clinical utility of HPV ISH testing beyond OPSCC is limited, and that the clinical utility of HPV ISH testing in other tumours should be evaluated as part of the assessment.

Service providers

HPV ISH is expected to be accessed via specialist cancer-care pathways. Referrals may originate from specialist clinicians involved in cancer diagnosis and management including surgeons, oncologists and haematologists. Should HPV ISH be implemented as a pathologist determinable test, it is expected to be requested predominantly as a pathologist-determined ancillary investigation following review of an existing tissue specimen.

Testing would be performed by approved pathology practitioners in pathology laboratories accredited by the National Association of Testing Authorities (NATA), consistent with other services listed in the MBS

Pathology Services Table.⁷ Results would be reported by appropriately qualified pathologists within their approved scope of practice.

The application states that most testing will occur in the outpatient setting, as most eligible patients are investigated and managed via outpatient specialist pathways. A smaller proportion of testing is expected to be performed during inpatient admissions for patients undergoing diagnostic investigations, staging procedures or management of complications.

PASC confirmed that the intervention should be method agnostic with respect to RNA or DNA probe-based ISH. While RNA ISH is generally considered more sensitive than DNA ISH for detecting transcriptionally active infection, PASC considered that the intervention should be defined as platform-agnostic and RNA ISH and DNA ISH do not require separate assessment. PASC noted that quality assurance for both RNA and DNA probes would be captured under an HPV ISH quality assurance program.

Comparator(s)

The proposed comparator for HPV ISH is no molecular profiling (i.e. current standard diagnostic assessment without molecular localisation of viral nucleic acids via ISH testing). This comprises routine diagnostic workup including clinical evaluation, biopsy, histopathological examination, IHC where appropriate and imaging. HPV ISH is intended to complement rather than replace the existing diagnostic pathway and is used selectively to confirm HPV association where clinically indicated. Thus, the diagnostic assessment may differ depending on tumour type. Nevertheless, HPV ISH is not expected to replace tissue sampling, routine histopathology or imaging, which remain essential components of diagnosis, staging and treatment planning.

In OPSCC, p16 IHC is the recommended initial surrogate marker for HPV status. HPV ISH is proposed as a confirmatory test in selected cases, including equivocal p16 IHC results or discordance between p16 expression and clinicopathological features.

Alternative direct HPV detection methods include HPV DNA PCR and RT-PCR. HPV DNA PCR is highly sensitive for HPV detection but cannot distinguish between transcriptionally active HPV driving carcinogenesis from incidental HPV infection because it does not localise viral nucleic acids to malignant cells.

Current international guidelines recognise HPV ISH as the preferred confirmatory method when direct demonstration of HPV within tumour tissue is required (Lewis et al. 2025).

Relevant MBS item numbers for services included in the comparator pathway are presented in Table 8. These services represent the current standard-of-care diagnostic approach in Australia when HPV ISH is unavailable. These are therefore appropriate comparators.

PASC confirmed that the comparator should be standard diagnostic assessment without HPV ISH (i.e. no molecular profiling). Standard diagnostic assessment would include routine histopathological evaluation including p16 IHC. PASC considered that the role of p16 IHC should be explicitly included in the description of prior testing within the diagnostic pathway.

⁷ [https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/B013E0789A07D708CA258B030013670A/\\$File/PDF%20Version%20-%201%20July%202024%20Category%206%20-%20Pathology%20Services.pdf](https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/B013E0789A07D708CA258B030013670A/$File/PDF%20Version%20-%201%20July%202024%20Category%206%20-%20Pathology%20Services.pdf) [Accessed 3 June 2026]

Table 8 Existing MBS item numbers 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)

Abbreviations: MBS = Medicare Benefits Schedule.

Reference standard (for investigative technologies only)

There is no universally accepted reference standard. P16 IHC is a good surrogate marker of HPV association. HPV DNA PCR may also enable direct detection of HPV and is highly sensitive (Khan et al. 2025). However, HPV positivity by PCR does not equate to the presence of transcriptionally active HPV (Khan et al. 2025). Therefore, the reference standard will be based on an integrated assessment incorporating histopathology, immunohistochemistry, molecular testing (where available), clinical findings and expert pathological review. In studies evaluating HPV ISH, comparators may include p16 IHC, HPV PCR or composite reference standards.

PASC advised that the reference standard should be defined as the combination of diagnostic information used to establish the final diagnosis and guide clinical management, together with the resulting patient outcomes. This may include histopathological assessment, p16 IHC, HPV ISH, PCR testing and clinical evaluation, recognising that no single test is definitive in all circumstances and a final diagnosis is derived from integrating multiple sources of evidence.

Outcomes

Test performance

- Diagnostic accuracy: sensitivity, specificity, positive predictive value, negative predictive value
- Concordance/discordance with surrogate markers (p16 IHC)
- Resolution of equivocal or discordant p16 IHC results
- Concordance with WHO Classification of Tumours diagnostic criteria
- Proportion of tumours correctly classified as HPV-associated or HPV-independent
- Incremental diagnostic yield compared with existing diagnostic pathways
- Prognostic accuracy: association between HPV status and health outcomes

Change in management

- Clinical utility of HPV ISH in p16 negative tumours, including the impact on tumour classification, prognosis and clinical management
- Change in tumour classification, staging, prognostic stratification
- Changes to treatment selection or treatment intensity
- Number/proportion of patients with changes in treatment selection or intensity based on HPV status
- Change to surveillance or follow-up
- Downstream effects on patient outcomes (mortality, morbidity, quality of life [QoL], safety)
- Time to diagnosis
- Time to treatment initiation

Patient health outcomes

Clinical effectiveness outcomes

- Patient health outcomes (e.g. mortality, morbidity, QoL)

Relevant patient health outcomes include mortality (OS, PFS, disease-free survival [DFS], CSS), treatment-related and disease-related morbidity, and health-related QoL.

A scoping search for evidence of change in management and health outcomes in OPSCC based on HPV-status was undertaken by the assessment group. The scoping review indicated that patients with HPV-associated OPSCC have better prognoses than those with HPV-independent disease, demonstrating greater responsiveness to radiotherapy and improved survival (Wang et al. 2015; Ward et al. 2014). This favourable prognosis has prompted investigation of treatment de-escalation strategies intended to reduce long-term treatment-related toxicity while maintaining oncological outcomes.

Several de-escalation approaches have been evaluated, including reduced-dose radiotherapy, reduced treatment volumes, response-adapted treatment following induction chemotherapy, transoral robotic surgery (TORS) followed by risk-adapted adjuvant therapy, and substitution of cisplatin with alternative systemic agents.

Randomised trials replacing cisplatin with cetuximab (DE-ESCALATE HPV and RTOG 1016) demonstrated inferior OS, poorer PFS and increased recurrence without reducing severe toxicity, indicating that this de-escalation strategy should not be adopted (Gillison et al. 2019; Mehanna et al. 2019).

Conversely, phase II studies evaluating surgery-based de-escalation have reported encouraging results. The ECOG-ACRIN E3311 trial demonstrated improved 2-year PFS (>94%) using TORS followed by reduced-dose adjuvant radiotherapy in select intermediate-risk patients (Ferris et al. 2022). Similarly, the MC1273 study reported high locoregional control (96%) and reduced swallowing toxicity following markedly reduced postoperative radiotherapy with concurrent docetaxel in carefully selected patients (Ma et al. 2019).

Overall, current evidence suggests that treatment de-escalation based on accurate identification of HPV-associated disease remains an evolving area of clinical practice. While some strategies have demonstrated promising functional outcomes without compromising disease control, others have resulted in inferior survival. As such, de-escalation strategies are not yet incorporated within management guidelines.

Safety outcomes

- Harm associated with false positive or false negative results
- Harms resulting from inappropriate changes in treatment

HPV ISH is performed on tissue obtained during routine diagnostic biopsy or surgical resection, thus introducing minimal additional procedural risk.

Healthcare resource use

- Uptake and utilisation rates of HPV ISH
- Costs associated with the intervention
- Total Australian Government healthcare expenditure
- Frequency of testing for HPV16/18 (proposed MBS item AAAAA)
- Frequency of testing for other hr-HPV genotypes (proposed MBS item BBBBB)

The application proposed that HPV ISH be funded once per diagnosis. However, discussion at the pre-PASC meeting noted that additional tests for hr-HPV genotypes other than HPV16/18 may occasionally be required, depending on tumour type and laboratory methodology (see Proposal for public funding).

Consequently, the proposed funding frequency may not reflect all clinical scenarios and will require consideration in the economic evaluation.

PASC noted that change to treatment selection or intensity based on HPV status is primarily relevant to OPSCC; the vast majority of genitourinary and anal cancers are HPV-associated, and treatment decisions are not typically guided by HPV status.

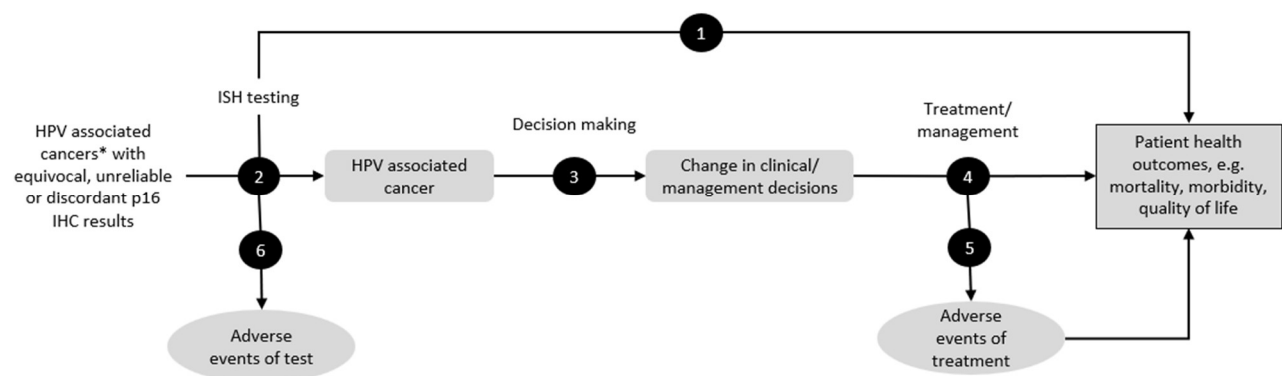
PASC noted that patients with discordant p16 IHC and HPV ISH results have an intermediate prognosis, distinct from those with concordant p16 IHC and HPV ISH results. PASC considered that while accurate classification has prognostic implications, the clinical benefit of HPV ISH testing of p16 negative cancers should be evaluated. In particular, PASC considered that OPSCC p16 negative/HPV ISH positive cancers behaved more like HPV-independent cancers and advised that the assessment report should look at evidence for changing treatment based on the HPV ISH result when it is discordant with the p16 result (rather than when p16 is uninterpretable).

PASC advised that additional outcomes could include time to diagnosis or time to treatment initiation, particularly where HPV ISH resolves diagnostic uncertainty and supports timely clinical decision-making. These outcomes may be relevant in cases where uncertainty regarding tumour classification delays treatment planning. The applicant stated that HPV ISH can typically be performed overnight, with results available the following day, potentially contributing to a timelier diagnosis.

PASC noted that HPV ISH testing is expected to be performed on existing FFPE tissue and re-biopsy for the sole purpose of HPV ISH testing is unlikely to occur. Therefore, PASC considered that re-biopsy solely to enable HPV ISH does not need to be captured as an outcome.

Assessment framework (for investigative technologies)

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



Abbreviations: HPV = human papillomavirus; IHC = immunohistochemistry; ISH = In situ hybridisation.

Notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: adverse events due to testing; 6: adverse events due to treatment

* Potentially relevant malignancies include OPSCC and clinically important cases of genitourinary and anal tumours where HPV ISH may have diagnostic value (e.g. where a patient has not undergone HPV screening or where a high-grade endometrial cancer is p16 positive and involves the cervix)

The questions to be addressed in the assessment report are:

1. What is the safety, effectiveness, cost-effectiveness and financial implications of ISH testing (for HPV in tumour cells) compared with no molecular profiling in patients with potential HPV-associated cancers, primarily confirmed HNSCC and clinically important cases of genitourinary and anal cancers in which hr-HPV status is clinically relevant?
2. What is the analytical and diagnostic accuracy of ISH testing (for HPV) compared with no molecular profiling?
3. How do the results from HPV ISH testing affect downstream clinical treatment/management and what is the evidence base of the impact?
4. What is the impact of the change in therapy versus no change in therapy on health outcomes such as mortality, morbidity and QoL?
5. What are the safety effects of changes in clinical management (e.g. de-escalation) on disease progression and treatment-related adverse events, and what impact do these have on patient health outcomes of mortality, morbidity and QoL?
6. What is the safety of HPV ISH testing versus no molecular profiling (e.g. impact of false negative or false positive results, inappropriate treatment recommendations)?

PASC advised that the assessment should consider the clinical circumstances in which HPV ISH would be used, incorporating the requirement for prior p16 IHC testing and the possible inclusion of a very small number of clinically important cases among tumour types other than OPSCC. PASC advised that concordance of DNA ISH and RNA ISH testing was not required.

Clinical management algorithms

Patients with suspected HPV-associated malignancies undergo evaluation through clinical assessment, imaging and histological examination. Following specialist referral and tissue biopsy, the diagnosis is established by routine histopathological assessment, with ancillary IHC and molecular testing performed where indicated to determine HPV status.

For OPSCC, p16 IHC is the recommended first-line biomarker because p16 overexpression is strongly associated with transcriptionally active HPV infection. However, p16 is a surrogate marker and does not directly demonstrate the presence of HPV within tumour cells. Therefore, p16 overexpression may occur in the absence of HPV-driven malignancy.

HPV ISH directly demonstrates HPV nucleic acid within tumour cells and is used as a confirmatory test of HPV association when this is required. Circumstances where HPV ISH may be needed include equivocal p16 staining (e.g. 50–70% staining), discordance between morphology and p16 expression, tumours involving multiple anatomical sites, or OPSCC arising outside the tonsil or base of tongue where HPV-driven disease is less common (WHO 2023).

The diagnostic workup for suspected OPSCC includes clinical examination, endoscopic assessment, cross-sectional imaging and PET/CT where indicated for staging. Histopathological confirmation is obtained from biopsy of the primary tumour or metastatic cervical lymph node. Following confirmation of SCC, HPV

testing is routinely performed for tumours arising in the oropharynx using p16 IHC as the initial surrogate marker, with HPV-specific testing performed when clinically indicated (Figure 2).

Treatment of OPSCC is determined by tumour stage, extent of nodal disease, patient performance status and HPV status. Standard treatment modalities include surgery, radiotherapy and concurrent chemoradiotherapy within a multidisciplinary care framework (NCCN 2026d). Early-stage disease is generally managed with either TORS or definitive radiotherapy, while locally advanced disease is treated with definitive concurrent cisplatin-based chemoradiotherapy or primary surgery followed by risk-adapted adjuvant radiotherapy or chemoradiotherapy based on pathological risk factors including positive surgical margins or extranodal extension.

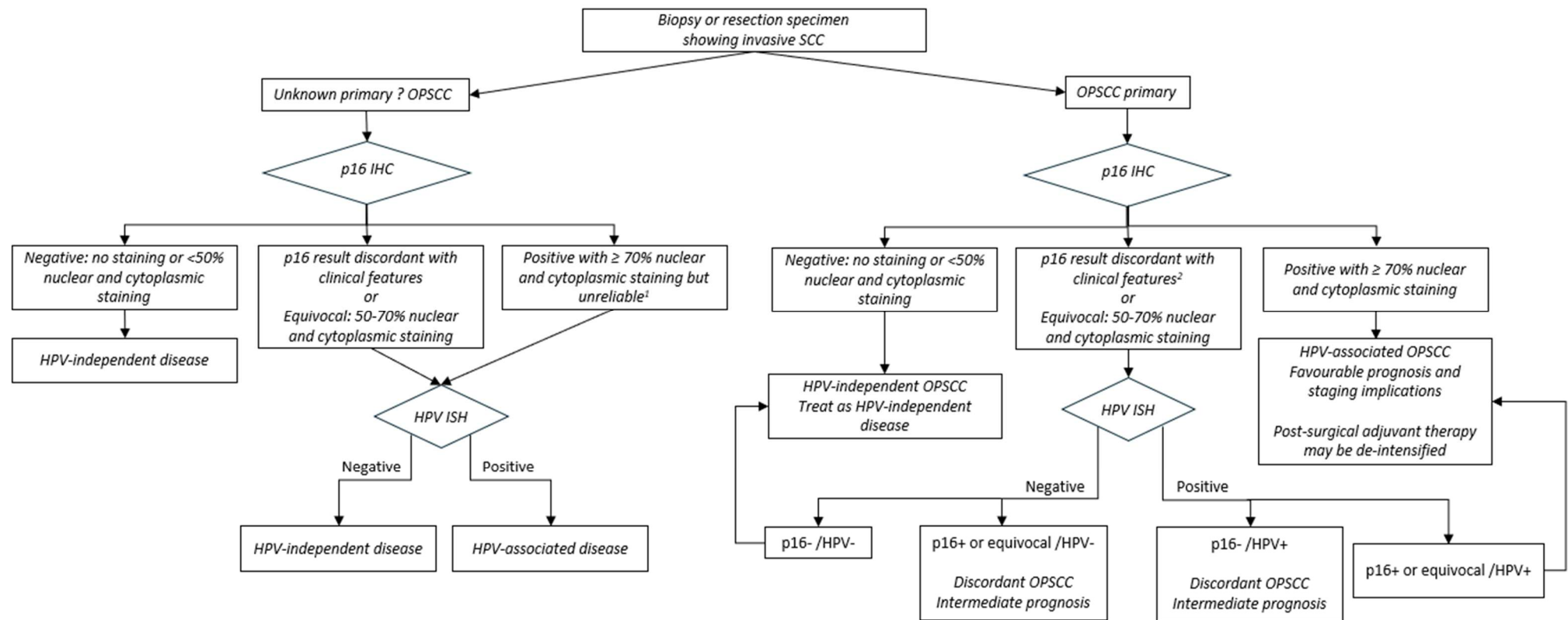
Although treatment modalities are broadly similar for HPV-associated and HPV-independent OPSCC, HPV status is an important prognostic factor. This distinction is recognised in the AJCC (8th edition) TNM staging system, which incorporates separate stage groupings for p16-positive and p16-negative OPSCC.

Patients with HPV-associated OPSCC generally have greater responsiveness to radiotherapy and chemotherapy, lower rates of recurrence, and improved OS and DSS compared with HPV-independent OPSCC. Therefore, treatment de-escalation strategies for select patients with HPV-associated OPSCC are being evaluated in clinical trials; however, these approaches are not currently considered standard of care (NCCN 2026d). In contrast, HPV-independent OPSCC is associated with poorer prognosis and is managed with standard intensity multimodality treatment. Thus, accurate determination of HPV status provides important prognostic information and informs TNM staging and subsequent treatment.

In the setting of OPSCC, p16 IHC is performed as a surrogate marker for HPV association. Where p16 IHC results are equivocal, unreliable or discordant with clinical features, HPV ISH may be performed as a confirmatory test. Cases identified as HPV negative—whether by p16 IHC alone or following HPV ISH testing—are managed as HPV-independent disease. In contrast, identification of HPV-associated OPSCC may have prognostic implications and may support consideration of treatment de-intensification, including post-surgical adjuvant therapy.

PASC advised that the clinical management algorithm should be simplified to focus on OPSCC as the primary condition. Considering that p16 IHC is usually sufficient to establish HPV association, the algorithm should identify the circumstances under which HPV ISH should be performed in relation to p16 IHC.

Figure 2 Clinical management algorithm for diagnostic workup for OPSCC with HPV ISH testing



Source: Adapted from Lewis et al. (2025); NCCN (2026d); eviQ (2024)

Abbreviations: HPV = human papillomavirus; IHC = immunohistochemistry; ISH = in situ hybridisation; OPSCC = oropharyngeal squamous cell carcinoma; SCC = squamous cell carcinoma.

¹ Unreliable p16 results are when p16 positive IHC results are a poor HPV surrogate in the tumour type.

²Example of a potentially discordant result includes a p16 positive IHC result in a keratinising tumour, which should be confirmed with HPV ISH to exclude a false positive p16 result and verify HPV association.

Proposed economic evaluation

The application claimed that HPV ISH testing was superior to the comparator (no molecular profiling) in effectiveness and non-inferior in safety. Therefore, a cost-effectiveness analysis (cost per patient with an HPV-driven malignancy correctly identified and/or cost per patient with a test-informed change in cancer management) or a cost-utility analysis (cost per quality-adjusted life year [QALY] gained) would be appropriate as per Table 9. However, incorporating multiple malignancies into a single economic model would be highly complex and likely to introduce substantial structural complexity and uncertainty due to heterogeneity in clinical management, treatment sequencing and health outcomes. It is potentially impractical to model QALYs for all indications.

Therefore, at the pre-PASC meeting, the applicant proposed using a cost-per-diagnosis approach for the economic evaluation. An alternative approach could be to develop a cost-utility analysis using OPSCC as an exemplar. However, due to the range of malignancies for which HPV ISH may be indicated, restricting the economic evaluation to the exemplar indication of OPSCC may not adequately capture the diversity of clinical pathways in which the test is used. Diagnostic work-up, treatment algorithms, prognosis and the impact of HPV status differ across tumour types, limiting generalisability of results from a single exemplar indication.

PASC noted that advice was sought on whether the HPV ISH testing assessment should progress as a 2-stage assessment. An assessment of the clinical evidence would be presented for ESC and MSAC to advise on the appropriate economic evaluation. Following ESC and MSAC advice, the economic and financial evaluation would be presented for ESC and MSAC consideration.

PASC considered that a 2-stage assessment process may be reasonable for HPV ISH if an exemplar (OPSCC) and CUA approach was undertaken. Given the uncertainty that the exemplar of OPSCC is representative of the clinical utility of HPV ISH in all HPV-related cancers, PASC considered an exemplar and CUA approach was unsuitable.

As noted earlier, PASC considered that assessment of the clinical utility of HPV ISH for OPSCC and other clinically important genitourinary and anal cancers is required to support the proposed clinical claim and subsequent economic evaluation. However, instead of undertaking a CUA, PASC advised that it may be appropriate for the economic evaluation to be truncated to a cost-per-diagnosis analysis. PASC noted that utilisation estimates may be difficult to substantiate with available evidence and the expected frequency of HPV ISH use may represent a source of uncertainty for the economic evaluation.

PASC considered the proposed assessment pathway for HPV ISH and advised that the assessment could proceed via a single stage assessment process to ESC and subsequently MSAC, for consideration of the clinical utility, economic and financial evaluation.

Table 9 Classification of comparative effectiveness and safety of the proposed intervention compared with its main comparator, and guide to suitable type of 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

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

Notes: ? = 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, detecting 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

Proposal for public funding

The application proposed a new MBS item for HPV ISH testing of tumour tissue to detect viral genomes to be funded under the MBS (Table 10 and Table 11).

No other in-progress MSAC applications for HPV ISH were identified. However, MSAC application 1752, currently under evaluation, proposes MBS funding for anal HPV genotyping and cytology testing in high-risk populations. The proposed indication for application 1752 is distinct from the current application. Application 1752 evaluates HPV testing as a screening and early detection strategy for anal cancer in asymptomatic individuals at increased risk, whereas the proposed HPV ISH service is intended for patients with established malignancy following histopathological diagnosis. In this setting, HPV ISH is used to confirm tumour-associated HPV infection to support tumour classification, staging and prognostic assessment. The only potential area of overlap is patients undergoing investigation for suspected anal SCC. If this population is ultimately included within the MBS listing arising from application 1752, consideration should be given to ensuring that the relevant MBS items are mutually exclusive to avoid duplicate funding for the same diagnostic episode.

HPV pathology services are also currently funded via MBS items 73070–73076 as part of the National Cervical Screening Program. These services support cervical screening, surveillance and management of HPV infection and precancerous disease rather than diagnostic evaluation of established invasive malignancies. The only potential overlap for cervical screening and HPV ISH is MBS item 73072, which may be used in patients with symptoms suggestive of cervical cancer. Exclusion of MBS item 73072 is included in proposed MBS item BBBBB (Table 11).

According to the application, most patients would require HPV ISH testing only once during a diagnostic episode. Repeat testing is expected to be uncommon and would generally be limited to patients with a new primary malignancy or where additional tissue becomes available or following an inconclusive initial result. Therefore, for proposed MBS item AAAAA, where the most common genotypes HPV16 and HPV18

are assayed, a restriction of once per diagnostic episode is proposed. The department advised that external references, such as the WHO Classification of Tumours diagnostic criteria, should be included in an explanatory note rather than referenced in the item descriptor.

Table 10 Proposed MBS item descriptor: hr-HPV for subtypes HPV16/18

Category 6-Pathology services	P7 – Genetics
MBS item AAAAA 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 service is requested by a specialist or consultant physician practising as an oncologist or haematologist; and - hr-HPV status is unknown; and p16 immunohistochemistry results were equivocal, unreliable, or discordant with clinical features; and - the test includes at least subtypes 16/18 Applicable once per diagnostic episode. (See para PN.1.2 of explanatory notes to this Category)	
Fee: \$315.74 Benefit: 75% = \$236.81 85% = \$268.38	

Note: Blue text represents changes suggested by the assessment group; bold text is changes suggested by PASC.

During the pre-PASC meeting, the applicant advised that hr-HPV genotypes are generally detected using single genotype-specific probes. Depending on the tumour type, assessment for up to 4 additional hr-HPV genotypes beyond HPV16 and HPV18 may be required to establish HPV association. Therefore, it is unclear whether a restriction of one service per diagnostic episode would be feasible for proposed MBS item BBBBB, as multiple probes may be required to achieve a definitive result.

PASC advised that the item descriptor should specify the circumstances in which HPV ISH may be performed, namely in people with a confirmed malignancy where HPV status is clinically relevant and p16 IHC results are unreliable, equivocal or discordant with clinical features. PASC considered that these qualification criteria should be explicitly incorporated into the descriptor to support appropriate use of HPV ISH.

PASC noted that the applicant suggested that restricting test requests to pathologists could ensure use remains within the intended population. The applicant also stated that allowing the MBS item to be pathologist determinable may facilitate more timely provision of test results to reduce delay in diagnosis. PASC considered that given patients with p16 negative and HPV ISH positive cancers have an intermediate prognosis, clinicians were best placed to consider the clinical benefit of HPV ISH testing and to request testing as appropriate. PASC considered that HPV ISH testing should not be pathologist determinable; but that both specialist clinician-initiated and pathologist-initiated testing pathways should remain open for further consideration as the application progresses.

Table 11 Proposed MBS item descriptor: other hr-HPV subtypes excluding HPV16/18

Category 6-Pathology services	P7 – Genetics
MBS item BBBBB 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 service is requested by a specialist or consultant physician ~~practising as an oncologist or haematologist~~; and p16 immunohistochemistry results were equivocal, unreliable, or discordant with clinical features; and - the results from item AAAAA or 73072 are negative or equivocal, and - testing for ~~additional~~ hr-HPV types, not including 16 and 18, is required due to ongoing suspicion of an HPV-associated cancer. Applicable once per diagnostic episode. ~~(See para PN.1.2 of explanatory notes to this Category)~~	
Fee: \$315.74 Benefit: 75% = \$236.81 85% = \$268.38	

Note: **Blue** text represents changes suggested by the assessment group; **bold** text is changes suggested by PASC.

Based on the application, the costs of current HPV ISH tests are typically absorbed by the laboratories as an unfunded component of diagnostic work-up, paid out-of-pocket by patients, or captured via state-based hospital funding. HPV ISH would typically be used as an additional investigation beyond standard histopathology and routine IHC, requiring specialised reagents/probes and 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.

The cost breakdown provided in the application for HPV ISH is presented in Table 12. It should be noted that overhead costs such as utilities (e.g. electricity and water) are not generally included in costings for MBS funding and would likely need to be removed.

At the pre-PASC meeting, the applicant also advised that although the submitted cost breakdown includes only those reagents and consumables required for HPV16/18 testing, the costs associated with single/individual probes for other hr-HPV genotypes are expected to be equivalent. Therefore, a separate cost breakdown for proposed MBS item BBBBB was not provided.

PASC noted that the item fee was benchmarked to the HER2 ISH fee and modelled as a stand-alone test. PASC considered that, in practice, HPV ISH testing would be performed alongside other markers and that unlike HER2 ISH testing, HPV ISH testing was determined by block positivity and did not require counting of individual cells. PASC advised that the proposed item fee should be considered by the department and confirmed following policy advice.

Table 12 Cost breakdown for HPV ISH

Item	Cost	Assumptions/inclusions	Cost per slide
HPV 16/18 reagents and consumables	\$14,039.13*	Includes HPV 16/18 2.5 LS Probe (16mL) ~370uL dispense (43T); BOND RNAScope (DS9815, 60T); Dewax, 1L; reaction buffer, 1L; enzyme (930T); epitope retrieval solution 2, 1L; DAB enhancer, 30mL (200T); coated slides (100/box); coverslip (1000/carton)	\$263.21
Scientist time	\$43/hr	8 min preparation and review time	\$5.73
Pathologist time	\$250/hr	11 min supervision, interpretation and reporting	\$45.80
Electricity, water etc	\$1/test		\$1.00
		Total	\$315.74

Abbreviations: HPV = human papillomavirus; hr = hour; ISH = in situ hybridisation; min = minute

Note: * Price for all materials purchased (bulk reagent and consumables)

PICO criteria (EBV-associated tumours)

Disease background and natural history

EBV infects more than 90% of the world's population and establishes lifelong latent infection, primarily within B lymphocytes (Shechter et al. 2022; Wong et al. 2022). Primary infection usually occurs during childhood and is asymptomatic, although infection during adolescence or early adulthood may present as infectious mononucleosis. Although latent infection is generally controlled by the host immune system, periodic viral reactivation may occur throughout life, usually without clinical symptoms.

EBV is classified by the WHO International Agency for Research on Cancer as a Group 1 carcinogen and is estimated to contribute to approximately 1% of cancers globally (Bakkalci et al. 2020). The oncogenic potential of EBV is related to the establishment of persistent latent infection and expression of viral proteins and non-coding RNAs that promotes cellular proliferation, inhibits apoptosis and evades immune surveillance (Esmaeili, Awasthi & Tabaei 2025). In susceptible patients, these mechanisms may contribute to malignant transformation after a prolonged latency period that may span several decades.

EBV is causally associated with a spectrum of epithelial and haematolymphoid malignancies, including non-keratinising nasopharyngeal cancer (NPC), extranodal NK/T-cell lymphoma (ENKTL), EBV-positive diffuse large B-cell lymphoma (DLBCL), PTLD, a proportion of classical Hodgkin lymphoma, and EBV-associated gastric carcinoma.⁸ The strength of the association between EBV and tumour development varies according to tumour type, geographic region, ethnicity and host immune status (Wong et al. 2022).

The natural history of EBV-associated malignancies differs according to tumour type. NPC is characterised by early cervical lymph node metastasis and progressive locoregional invasion. ENKTL is an aggressive lymphoma that typically presents with destructive midline lesions and rapidly progressive disease if untreated. EBV-positive DLBCL generally occurs in older adults and has been associated with poorer survival than EBV-negative disease (Sato et al. 2014), although more recent studies have reported no significant difference in survival by EBV status (Bourbon et al. 2021). In immunosuppressed transplant recipients, impaired immune surveillance may result in PTLD, which encompasses a spectrum ranging from benign lymphoid proliferations to aggressive lymphoma. Given the diverse clinical presentations and

⁸ <https://tumourclassification.iarc.who.int/>

prognoses, accurate demonstration of EBV within tumour cells is an important component of tumour classification and diagnosis (Low et al. 2023).

In several tumour entities recognised in the WHO Classification of Tumours,⁸ demonstration of EBV infection forms part of the diagnostic criteria or contributes to disease subclassification and prognostic assessment. EBER (EBER-1 and -2) are highly abundant non-coding RNAs expressed during latent infection and are considered reliable targets for identifying latent EBV in tissue specimens (Neparidze & Lacy 2014). Beyond their diagnostic utility, EBERs contribute to EBV-associated oncogenesis through modulation of innate immune responses (Shechter et al. 2022).

EBER ISH is an essential diagnostic investigation for several EBV-associated tumours, including ENKTL, PTLD and selected T-cell lymphomas, and is recommended in international diagnostic guidelines.⁹ In addition to its diagnostic role, EBV status has prognostic significance in several tumour types. A meta-analysis of 13 studies reported significantly poorer OS among patients with EBV-positive DLBCL compared with EBV-negative disease (Gao et al. 2018). In contrast, a meta-analysis of 57 studies found that patients with EBV-positive gastric carcinoma had improved OS compared with patients with EBV-negative tumours (Pyo, Kim & Kang 2023).

Australian epidemiology

EBV infects most of the Australian population, with primary infection typically occurring during childhood or early adulthood. Despite the high prevalence of latent infection, malignant transformation is uncommon and requires additional host, genetic and environmental factors (Lung et al. 2014; Nath et al. 2026; Umakanthan & Bukelo 2021).

EBV-associated malignancies comprise a heterogeneous group of cancers with varying incidence. Based on the application, the incidence of eligible EBV-associated cancers ranges from approximately 0.1 to 8.6 cases per 100,000 persons, depending on the tumour type (Table 13). PTLD in Australia is rare, with an estimated crude annual incidence of approximately 0.19 cases per 100,000 population (calculated by applicant). This estimate is based on 1,581 annual organ transplants in Australia in 2024 (Australian Organ and Tissue Donation and Transplantation Authority),¹⁰ multiplied by the cumulative incidence of PTLD in kidney transplant recipients of 3.3% (Francis et al. 2018), converted into a rate per Australian population 2026. This is a crude estimate that does not account for person-years at risk and is likely an overestimate.

Nevertheless, the estimates provided in the application are unlikely to have captured the full spectrum of EBV-associated malignancies. Other malignancies recognised in the NCCN guidelines, including peripheral T-cell lymphomas, primary cutaneous lymphomas, EBV-associated gastric carcinoma, EBV-positive inflammatory dendritic cell sarcoma and EBV-positive smooth muscle tumours (usually in the setting of immunosuppression) are not included in the estimated eligible population.¹¹

The application assumes that all incident cases of eligible EBV-associated cancers would undergo EBER ISH testing. This assumption is appropriate for tumour types in which EBER ISH is required to establish the diagnosis (e.g. T-cell lymphomas and PTLD). However, it is likely to overestimate test utilisation in tumour

⁹ https://www.nccn.org/guidelines/category_1

¹⁰ https://www.donatelife.gov.au/sites/default/files/2025-02/2024%20Australian%20Donation%20and%20Transplantation%20Activity%20Report.pdf?utm_source=UTM&utm_medium=download&utm_campaign=2024ActivityReport-webdownload&utm_id=2024ActivityReport-webdownload

¹¹ <https://tumourclassification.iarc.who.int/>

types where EBER ISH is a desirable test rather than one being essential for diagnosis, particularly where EBV status does not influence treatment decisions (NCCN 2026b). Therefore, the actual utilisation of EBER ISH in clinical practice is uncertain and likely to vary according to tumour type, diagnostic requirement and local practice. During the pre-PASC meeting, the applicant advised that EBER ISH may be performed even when not essential for diagnosis, taking into account that the WHO Classification of Tumours recommendations are intended to be used across a range of healthcare settings, including where ISH is not readily available.

Table 13 Incidence and number of cases of eligible EBV cancer types

Cancer type	ICD-10 Code	Incidence rate per 100,000	Cases
Diffuse large B-cell lymphoma	C83.3	8.6*	2,146
Classic Hodgkin lymphoma	C81	1.6*	412
Extranodal natural killer/T-cell lymphoma (nasal type)	C84	0.1*	27
Post-transplant lymphoproliferative disorders	D47.Z1	0.19 [^]	52
Nasopharyngeal cancer	C11	0.6*	162

Abbreviations: EBV = Epstein Barr virus

Notes:

*Age-standardised rate, 2025 population; data sourced from AIHW Cancer Data in Australia (AIHW 2026).

[^]Estimated from annual organ transplants in Australia 2024, multiplied by cumulative incidence of PTLD in kidney transplant recipients and converted to a rate per 2026 Australian population.

Target population and establishing an exemplar

The target population comprises patients with tumours for which demonstration of EBV infection within tumour cells is required for diagnosis or classification according to the WHO Classification of Tumours criteria.¹² Consistent with the application, eligibility is limited to tumours where localisation of viral nucleic acid within malignant cells is considered essential or desirable under the WHO Classification framework. A wide range of malignancies are associated with EBV and may require EBER ISH for diagnosis or classification. EBV-associated malignancies include T-cell lymphomas (e.g. ENKTL, ANKL), B-cell lymphomas (e.g. PTLD, DLBCL), cutaneous lymphomas, NPC and gastric carcinoma among others.¹²

EBER ISH is a pathologist-directed ancillary test performed after malignancy is suspected or established upon routine histopathological assessment. Thus, the target population includes patients undergoing histopathological assessment in whom an EBV-associated tumour is included in the differential diagnosis, and where demonstration of latent EBV infection by EBER ISH may influence pathological diagnosis, tumour classification or subsequent clinical management in accordance with WHO Classification of Tumours criteria.

For some tumours, demonstration of EBV within tumour cells is integral to diagnosis and classification. For example, EBER ISH is an essential component of the diagnostic work-up for PTLD and ENKTL and would, therefore, be expected to be performed routinely for all suspected cases. In contrast, for tumours in which EBER ISH is considered desirable not essential, testing is expected to be undertaken selectively when EBV status is likely to resolve diagnostic uncertainty, refine tumour classification, or inform downstream clinical

¹² <https://tumourclassification.iarc.who.int/>

management. The application does not specify the clinical or pathological criteria that would identify patients requiring testing.

Overall, for tumours in which EBER ISH is not mandatory for diagnosis, testing is expected to be reserved for cases in which the differential diagnosis includes EBV-associated tumour and there is sufficient clinical, morphological or immunophenotypic suspicion that determining EBV status will resolve diagnostic uncertainty or refine disease classification. In classic Hodgkin lymphoma, for example, diagnosis is established by the characteristic morphology and immunophenotype of Hodgkin/Reed-Sternberg cells (WHO 2024) and EBER ISH may be used to identify EBV-associated disease. In EBV-associated gastric carcinoma, EBER ISH identifies a distinct molecular subtype of gastric adenocarcinoma with unique pathological and biological characteristics (WHO 2019). In NPC, EBER ISH supports confirmation of EBV-associated non-keratinising carcinoma (WHO 2023).

Table 14 provides an overview of the EBV-associated malignancies included within the proposed population and the role of EBV status on diagnosis and treatment. Although these malignancies share an association with EBV infection, the contribution of EBV to tumour development varies across tumour types (Umakanthan & Bukelo 2021). Table 14 does not present an exhaustive list of EBV-associated tumours. Although EBV status may not directly influence treatment selection in many tumours, establishing EBV association is a required component of diagnosis. Therefore, appropriate treatment decisions cannot be made until the diagnosis, including EBV status, has been established.

PASC noted that EBER ISH is considered important for the identification and classification of a range of EBV-associated tumours. EBV is implicated in a diverse spectrum of malignancies, including lymphoproliferative disorders and non-haematological tumours, highlighting the broad diagnostic relevance of EBER ISH across multiple clinical settings.

Table 14 EBV-associated malignancies

EBV-associated malignancy	Diagnosis	Treatment implications of EBV status	Prognosis
PTLD	EBER ISH is essential for diagnosis. Plasma EBV DNA is used for surveillance in transplant recipients but is not diagnostic alone.	EBV-positive disease may respond to reduction of immunosuppression, rituximab, chemotherapy and EBV-specific cytotoxic T-cell therapy. Plasma EBV DNA guides monitoring.	Survival rate has been poor (30–60%), but recent data suggest improving outcomes. In general, non-destructive PTLDs regress after immunosuppression reduction, whereas EBV-negative M-PTLDs often require multiagent chemotherapy, immunotherapy and/or adoptive T-cell therapy. Poor prognostic factors include late onset, M-PTLD, CNS involvement, thoracic organ transplantation, elevated LDH and disseminated disease.
BL	Essential: medium-sized, monomorphic lymphoma cells with basophilic cytoplasm and multiple small nucleoli; CD20 and CD10 positivity, absence or (rarely) weak expression of BCL2, Ki-67 index >95%; usually strong expression of MYC (in >80% of cells) and/or demonstration of MYC breakage or IG:MYC translocation. Desirable: starry-sky pattern, cohesive growth pattern; BCL6 positivity, TdT negativity, CD38 positivity; exclusion of BCL2 and BCL6 rearrangements (mainly required in adult BL).	Standard intensive chemotherapy is the mainstay. EBV status has limited impact on standard treatment but is relevant for investigational EBV targeted therapies.	Prognosis is excellent for all patients with BL treated with contemporary immunochemotherapy regimens including rituximab in high-resource settings. Overall survival rate exceeds 90% in children and 80% in adults in contemporary multicentre clinical trials. The recently proposed BL-LPI subdivides patients into low-, intermediate- and high-risk groups, with overall survival rates of 96%, 76% and 59%, respectively. Patients with HIV-associated BL are currently successfully treated with similar immunochemotherapy regimens.
CHL	Essential: primary nodal or mediastinal presentation; HRS cells and variants in a reactive microenvironment composed of varying proportions of small lymphocytes, eosinophils, histiocytes, plasma cells and neutrophils; immunophenotype of HRS cells: CD30+, PAX5+ (weak to moderate), CD20–/weak/heterogeneous. Desirable: immunophenotype of HRS cells: CD15+, CD45–, decreased expression of OCT2 and BOB1; EBV positivity (~40% of cases); histological subtyping (if possible); exclusion of mimics of CHL by appropriate workup.	EBV status alone does not guide treatment decisions. EBV status is mainly prognostic.	>80% of patients with CHL can be cured with modern polychemotherapy selectively combined with radiotherapy. To reduce long-term organ dysfunction and increase efficacy, individual treatment is tailored to defined risk groups based on Ann Arbor stage (with or without FDG PET), bulky (mediastinal) disease, extranodal localisation, B symptoms and the IPS. Multiple studies have used gene expression profiling to identify signatures associated with treatment outcomes. In concordance, high numbers of macrophages and non-malignant B cells in the tumour microenvironment were validated as adverse and favourable prognostic factors, respectively. However, neither gene expression profiling nor enumeration of cells has found its way into clinical practice.

EBV-associated malignancy	Diagnosis	Treatment implications of EBV status	Prognosis
DLBCL	Essential: partial or total architectural effacement of affected tissue; atypical lymphoid infiltrate composed of either sheets of large malignant cells or many scattered large transformed cells of variable morphology (including HRS-like cells) in a richly cellular reactive background, often accompanied by necrosis; large cells confirmed to be of B-cell lineage (e.g. CD20, PAX5, CD79a); EBV present in the majority of large B cells; absence of inborn or acquired immunodeficiency or a history of lymphoma; exclusion of other EBV-related lymphomas and lymphoproliferative disorders. Desirable: EBV DNA detectable in serum or whole blood (in selected cases).	Standard treatment is R-CHOP-based chemoimmunotherapy. EBV status does not alter treatment.	Prognostic impact of EBV infection in DLBCL is variable according to Asian, European and US studies. Although most studies in Asian populations have demonstrated inferior outcomes after treatment including R-CHOP, several studies in European and US populations did not find any correlation between EBV positivity and prognosis, particularly in younger patients; however, some studies in European and US patients showed that EBV had a negative impact in elderly patients. An adverse impact of CD30 expression on both overall survival and progression-free survival has been observed. Some reported poor prognostic factors include type III EBV latency (EBNA2 expression) and the presence of secondary haemophagocytic lymphohistiocytosis at diagnosis or during treatment.
Extranodal NK/T-cell lymphoma	Essential: infiltration of extranodal tissues by lymphoma cells with variable morphology; NK or cytotoxic T-cell phenotype; majority of tumour cells positive for EBER. Desirable: angiocentric growth and necrosis.	EBV DNA is used for prognosis and disease monitoring. Treatment by clinical presentation (nasal/extranasal) and stage.	With concurrent or sequential chemoradiotherapy with non-anthracycline-containing regimens, 5-year overall survival rate is >70% in patients with early-stage disease. L-asparaginase-containing regimens yield an overall response rate of about 80% in patients with advanced-stage disease. On presentation, age >60 years, stage III/IV disease, distant nodal involvement, non-nasal clinical subtype disease and quantifiable plasma EBV, incorporated into the prognostic index of NK lymphoma-EBV (PINK-E) index, predict an unfavourable outcome with non-anthracycline-containing regimens or radiotherapy with curative intent. Two parameters that reflect dynamic tumour load and chemosensitivity are plasma EBV DNA level and the metabolic phenotype of the tumour by PET-CT. If interim or end-of-treatment plasma EBV DNA and/or PET-CT findings are still positive, the outcome is inferior. Immune checkpoint inhibitors targeting the PD1/PDL1 axis have shown promise in the treatment of relapsed/refractory ENKTL. It has been proposed that PDL1 expression (in both the tumour cells and tumour-associated macrophages), immune microenvironment subtypes (classified according to FOXP3, PDL1 and CD68 immunohistochemistry), or somatic structural rearrangements in the 3'-untranslated region of CD274 (PDL1) in tumour tissue may predict response to immune checkpoint inhibitors.

EBV-associated malignancy	Diagnosis	Treatment implications of EBV status	Prognosis
NPC	<u>Non-keratinising SCC</u> Essential: infiltrative poorly differentiated carcinoma; usually limited evidence of squamous differentiation; variable density of lymphocytes and plasma cells. Desirable: immunoreactivity for pancytokeratin and positive labelling for EBERs (in problematic biopsies). <u>Keratinising SCC</u> Essential: infiltrative SCC with overt keratinisation. <u>Basaloid SCC</u> Essential: invasive high-grade basaloid carcinoma with a nested growth pattern and frequent comedonecrosis; SCC component in the form of abrupt keratinisation in the basaloid nests, conventional invasive SCC or dysplasia/carcinoma in situ in surface epithelium. Desirable: variable myxoid to hyaline stroma.	NCCN treatment recommendations are based on clinical trial data for EBV-associated NPC and not stratified by EBV status. Plasma EBV DNA is a prognostic biomarker and may be useful for surveillance and early detection of disease relapse.	Stage of presentation is the most important prognostic factor. The validation study for the 8th-edition UICC/AJCC staging system showed that 5-year overall survival rate for stage I disease was 98%; stage II, 92%; stage III, 83%; and stage IVA, 71%. Prognosis depends on multiple tumour-, host-, and treatment-related factors. Significant tumour factors include histological type, gross tumour volume and EBV DNA. Incorporation of pretreatment plasma EBV DNA can refine TNM staging for NK-NPC, especially for identifying poor-risk subgroups among patients with early-stage disease; this may spare low-risk stage II patients from unnecessary chemotherapy. Significant host factors include age, sex, performance status, comorbidities (particularly for elderly patients), anaemia and LDH level. Treatment-related factors affect ultimate survival. Radiotherapy using the best available conformable technique to deliver the cancericidal dose with minimal late damage of adjacent normal structures is fundamental. Addition of the optimal sequence and dose of chemotherapy is needed for all stage III–IVA and high-risk stage II patients for the eradication of micrometastasis and the potentiation of locoregional control.

EBV-associated malignancy	Diagnosis	Treatment implications of EBV status	Prognosis
EBV-associated gastric carcinoma	Essential: For leiomyoma: fascicles of spindle cells with eosinophilic cytoplasm; lack of conspicuous mitotic activity and necrosis For leiomyosarcoma: cellular tumours with long intersecting fascicles of spindle cells; pleomorphic, enlarged nuclei; increased mitoses, sometimes with tumour necrosis For EBV-associated smooth muscle tumours: neoplasm with smooth muscle differentiation; positivity for EBER transcripts by ISH Desirable: Expression of SMA, desmin, and/or h-caldesmon; negativity for KIT (CD117) and DOG1 For EBV-associated smooth muscle tumours: clinical history of immunosuppression	Treatment by stage and generally not guided by EBV status. In gastric adenocarcinoma, MSI-H and EBV positivity are markers of good prognosis with potential therapeutic importance, namely for immunotherapy targeting the PD-1/PD-L1 axis (under investigation in clinical trials).	Leiomyomas are benign tumours; excision is curative. Due to the rarity of primary leiomyosarcoma of the GI tract, data regarding prognosis are limited, but most patients have an aggressive clinical course, with death from disease occurring in most patients. Accurate prognostication on the basis of histological features such as mitotic count and degree of atypia alone have not correlated well. Metastatic disease usually involves liver, lungs and peritoneal cavity. Prognosis for EBV-associated smooth muscle tumours is mainly dependent on the condition of the individual patient's immune system. Most of these tumours do not metastasise. Some posttransplant cases respond to reduced immunosuppression.

Source: WHO (2024); WHO (2023); WHO (2019); NCCN (2026b); NCCN (2025b); NCCN (2026e); NCCN (2026d); NCCN (2026c); Allen and Preiksaitis (2019); Shannon-Lowe, Rickinson and Bell (2017); Su et al. (2023); Styczynski et al. (2016); Crombie and LaCasce (2021); Young and Rickinson (2004); Hu et al. (2022); Kiliç Güneş et al. (2025); Nagtegaal et al. (2020)

Abbreviations: AJCC = American Joint Committee on Cancer; BL = Burkitt lymphoma; BL-IPI = Burkitt Lymphoma International Prognostic Index; CHL = classical Hodgkin lymphoma; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; EBER = Epstein Barr virus-encoded small RNA; EBV = Epstein-Barr virus; FDG = fluorodeoxyglucose; HRS = Hodgkin/Reed-Sternberg; IPS = international prognostic score; ISH = in situ hybridisation; LDH = lactate dehydrogenase; M-PTLD = monomorphic post-transplant lymphoproliferative disorder; MSI-H = microsatellite instability-high; NCCN = National Comprehensive Cancer Network; NK = natural killer; NPC = nasopharyngeal carcinoma; PD(L)-1 = programmed cell death (ligand) 1; PET = positron emission tomography; PLTD = post-transplant lymphoproliferative disorder; R-CHOP = rituximab, cyclophosphamide, hydroxydaunomycin, oncovin, prednisone/prednisolone (combination therapy); RNA = ribonucleic acid; SCC = squamous cell carcinoma; TdT = terminal deoxynucleotidyl transferase; TNM = tumour, node, metastasis; UICC = Union for International Cancer Control.

The application did not initially nominate an exemplar for EBV-associated tumours. During the pre-PASC meeting, it was requested that the applicant nominate an exemplar indication and provide the corresponding diagnostic and management algorithms. In response, the applicant nominated PTLD as the exemplar indication.

EBER ISH is already incorporated into established diagnostic pathways for the assessment of EBV-associated tumours. EBER ISH is routinely performed when the differential diagnosis includes an EBV-associated tumour, therefore its clinical utility is well established and generally accepted.

PASC noted that PTLD was nominated as the exemplar case. However, PASC considered that PTLD is not an ideal exemplar, as EBER ISH is used across a broad range of differential diagnoses that vary in natural history, clinical presentation and management. Among these, PTLD represents only a very small subpopulation of the broader spectrum of EBV-associated tumours. As such, PASC advised not to retain PTLD as an exemplar case. PASC queried if the population for which EBER ISH may be clinically relevant is broader than the 5 malignancy types included in the PICO, noting that the WHO Classification of Tumours recognises a broader range of EBV-associated tumours. PASC considered that the population should include all cases where the diagnostic criteria require the EBV status of tumour tissue to be known. PASC advised out of session that the population should be refined to patients with tumours in which EBV status is clinically relevant and where localising viral nucleic acid within tumour cells is essential or desirable based on the WHO Classification of Tumours criteria.

Prior tests

Based on the application, the diagnostic work-up for suspected EBV-associated malignancies typically includes imaging (usually CT), tissue biopsy, histopathological examination and IHC to establish a differential diagnosis. Where EBV association is suspected, EBER ISH is performed as a pathologist initiated ancillary test on the diagnostic biopsy specimen.

Initial diagnostic investigations for suspected EBV-associated tumours may include a complete blood count with white blood cell differential, together with other laboratory tests guided by clinical presentation (Allen & Preiksaitis 2019; NCCN 2026b, 2026d). Depending on the site and extent of disease, abnormalities in serum electrolytes, liver and/or renal function tests or serum immunoglobulin levels may be observed. Documenting the presence of EBV-specific nucleic acids in tissues is essential for the diagnosis of EBV-associated tumours (Allen & Preiksaitis 2019). IHC or histopathological tests required for diagnosis are presented in Table 15.

Table 15 MBS items for prerequisite tests for EBER 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)

Abbreviations: EBV = Epstein-Barr virus; ISH = In situ hybridisation; MBS = Medicare Benefits Schedule.

Intervention

EBER ISH is the preferred method for documenting the presence of EBV-specific nucleic acids in tissue specimens (Allen & Preiksaitis 2019). The assay detects EBER1 and EBER2 non-polyadenylated non-coding RNAs that are abundantly expressed during latent EBV infection directly within infected cells, while preserving tissue architecture and cellular morphology (AbuSalah et al. 2020; Gulley & Tang 2008). Therefore, EBER ISH is regarded as the reference standard for detecting latent EBV in tissue because it demonstrates viral infection specifically within tumour cells while maintaining histological context (AbuSalah et al. 2020; Gulley & Tang 2008; Neparidze & Lacy 2014). This enables distinction between EBV present in tumour cells and that present in surrounding non-neoplastic cells (Gulley & Tang 2008).

Alternative molecular assays for EBV have limitations. EBV may be detected in formalin-fixed tissue by IHC targeting EBNA-1, EBNA-2, LMP1 or BZLF1 (Allen & Preiksaitis 2019). However, these assays are less sensitive than EBER ISH and, the applicant advised at the pre-PASC meeting that these assays are not considered reliable surrogate markers of EBV infection and are not regularly used in Australia. Similarly, PCR-based detection of EBV DNA identified the presence of viral DNA in tissue extracts but did not determine its cellular localisation and, therefore, cannot distinguish EBV present within tumour cells from that present in surrounding non-neoplastic or passenger lymphocytes (Allen & Preiksaitis 2019; Gulley & Tang 2008). Given the high prevalence of latent EBV infection in healthy adults, assays without cellular localisation have limited specificity for establishing a causal association between EBV and tumour cells.

Although tissue PCR has limited diagnostic utility, circulating plasma EBV DNA measured by PCR does have a role in disease monitoring. NCCN guidelines identify plasma EBV DNA testing as an essential investigation to monitor treatment response in EBV-associated PTLD (NCCN 2026b). In Australia, plasma EBV DNA testing is eligible for MBS funding under item 69494, which covers the detection of virus or microbial antigen or microbial nucleic acid.

Test procedure

EBER ISH is usually performed on FFPE tumour tissue obtained from biopsy or surgical resection specimens. Following fixation and paraffin embedding, thin tissue sections are mounted onto microscope slides, deparaffinised and subjected to pretreatment to increase tissue permeability and facilitate probe penetration into cell nuclei (Gulley 2001). Labelled probes targeting EBER transcripts are then hybridised to tissue sections, after which unbound probe is removed by washing. Interpretation of EBER stains relies on microscopic visualisation of the nuclear EBER signal in latently infected cells (Gulley 2001).

The stained slides are interpreted by a pathologist in conjunction with routine histopathological findings. EBER ISH results are usually reported qualitatively as either positive or negative for EBV within tumour cells. A specific threshold for EBV positivity is not generally applied, although some studies have utilised thresholds ranging from 5–80% (Donzel et al. 2022; Hou et al. 2025).

PASC noted that, in practice, EBER ISH testing produced near binary results, with tumours reported as either EBER positive or EBER negative.

Clinical utility

Diagnostic utility

EBV status determined by EBER ISH is an essential component of the diagnosis of EBV-associated PTLD, and is recommended by both the WHO Classification of Tumours (2024) and NCCN (2026b) guidelines. In

patients with EBV-driven PTLD, quantitative PCR measurement of circulating EBV DNA is recommended for monitoring disease burden and treatment response (NCCN 2026b).

Prognostic utility

The prognostic significance of EBV varies according to tumour type. A meta-analysis of 13 studies of DLBCL found that EBV-positive disease was associated with significantly poorer OS and PFS than EBV-negative disease (Gao et al. 2018). In contrast, a meta-analysis of 57 studies of patients with gastric carcinoma reported that patients with EBV-associated gastric carcinoma had improved OS compared with those with EBV-negative gastric carcinoma (Pyo, Kim & Kang 2023). Similarly, EBV-positivity has been associated with favourable prognosis in NPC (Nakao et al. 2006).

In PTLD, however, EBV status appears to have no prognostic value. A retrospective cross-sectional study found no significant association between EBV status and either treatment response or survival outcome (Luskin et al. 2015).

Impact on clinical management

Determination of EBV status has important implications for the management of PTLD. While first-line treatment is often a reduction in immunosuppression (if tolerated), EBV status guides the selection of targeted second-line and salvage therapies including rituximab, chemoimmunotherapy and immunotherapy with EBV-specific cytotoxic T-lymphocytes (DeStefano et al. 2018; NCCN 2026b). EBV-specific cytotoxic T-lymphocyte immunotherapy may be accessed in Australia through the Special Access Scheme, with treatment costs borne by the patient (Neller et al. 2024). NCCN guidelines recommend that treatment is primarily guided by PTLD histological subtype, with reduction of immunosuppression (where feasible) as the initial management strategy, irrespective of subtype. For polymorphic PTLD and monomorphic B-cell PTLD, first-line treatment options also include rituximab monotherapy or rituximab-based chemotherapy. For monomorphic T-cell PTLD, no standard therapy has been established beyond reduction of immunosuppression, although chemotherapy may be considered. For primary CNS B-cell PTLD, high-dose methotrexate with rituximab is a suggested treatment regimen (NCCN 2026b).

Management for other EBV-associated tumours differ by type. In DLBCL, EBV status does not alter first-line therapy (NCCN 2026b). In classical Hodgkin lymphoma, EBV status is primarily prognostic and does not routinely alter treatment (NCCN 2025b).

Service providers

EBER ISH is expected to be accessed through specialist cancer-care pathways and may be requested by specialist or consultant physicians involved in the diagnosis and management of cancer, including oncologists and haematologists. In practice, testing is most commonly initiated by pathologists as an ancillary test following review of an existing tissue specimen.

Testing would be performed by approved pathology practitioners within NATA-accredited pathology laboratories, consistent with other services listed in the MBS Pathology Services Table.¹³ Services would be provided on referral from registered medical practitioners and reported by appropriately qualified pathologists operating within their approved scope of practice.

¹³

[https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/B013E0789A07D708CA258B030013670A/\\$File/PDF%20Version%20-%201%20July%202024%20Category%206%20-%20Pathology%20Services.pdf](https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/B013E0789A07D708CA258B030013670A/$File/PDF%20Version%20-%201%20July%202024%20Category%206%20-%20Pathology%20Services.pdf) [Accessed 3 June 2026]

The application states that most testing is expected to occur in the outpatient setting, as most eligible patients are investigated and managed via outpatient specialist pathways. A smaller proportion of testing will occur for public and private hospital inpatients undergoing diagnostic investigation, management of complications, urgent staging or biopsy procedures during an inpatient admission.

Comparator(s)

The proposed comparator for EBER ISH testing is no molecular profiling for EBV (the current standard diagnostic pathway without molecular localisation of viral nucleic acids i.e. no EBER ISH testing). This includes clinical assessment, imaging, routine histopathology, IHC and other laboratory investigations without specifically assessing latent EBV within tumour cells. EBER ISH is not expected to replace core components of the diagnostic pathway such as tissue sampling, routine histopathology or imaging.

Of note, in several tumours, EBER ISH is essential for diagnosis. In these cases, EBER ISH is already incorporated within the standard diagnostic pathway.

PASC considered the comparator to be no molecular profiling. However, PASC noted that EBER ISH is already embedded within the current diagnostic pathway for conditions in which EBV involvement is suspected and is routinely used to confirm the presence of EBV within tumour cells.

A list of existing MBS item numbers relevant to the nominated comparators is presented in Table 16.

Table 16 Existing MBS item numbers relevant to 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)

Abbreviations: MBS = Medicare Benefits Schedule

Reference standard (for investigative technologies only)

For EBV-associated tumours, EBER ISH is widely regarded as the reference standard for demonstrating latent EBV infection within tumour cells and this is incorporated into WHO diagnostic criteria for several tumour types. In practice, EBER ISH results are interpreted in conjunction with tumour morphology, immunophenotype, clinical findings and multidisciplinary review to establish the final diagnosis and classification. Alternative assays, such as EBV DNA PCR or EBV-related IHC markers, may provide supportive information but do not localise EBV infection to tumour cells.

PASC noted that there is no alternative test that provides equivalent demonstration of EBV RNA within tumour tissue and, as such, EBER ISH represents the established reference method for confirming EBV association. PASC acknowledged that conventional diagnostic accuracy evidence may be limited because the test is already embedded in routine clinical practice.

Outcomes

Test performance

- Diagnostic accuracy of EBER ISH including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)

EBER ISH is considered the reference standard for detecting EBV infection within tumour cells. Relevant measures of test performance such as sensitivity, specificity, PPV, NPV and overall diagnostic accuracy may not be available.

Healthcare resource use

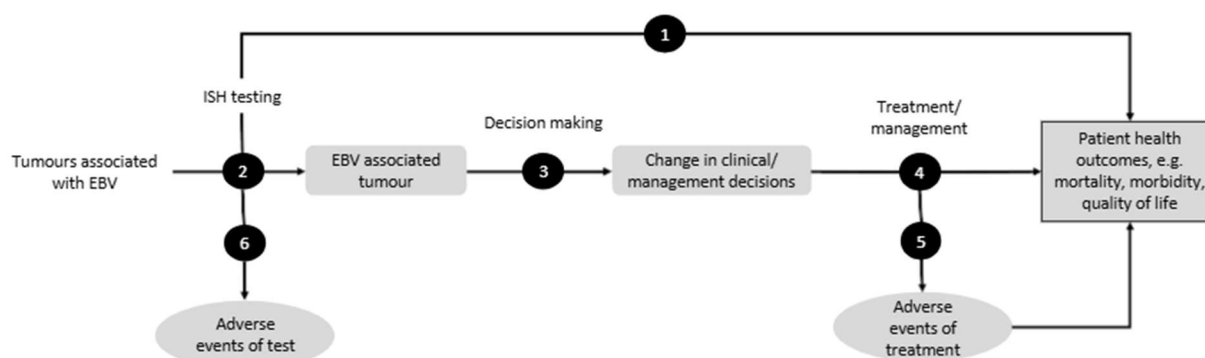
- Costs associated with the intervention
- Total Australian Government healthcare costs
- Uptake and utilisation rates of EBER ISH

Outcomes for healthcare resource use include uptake and utilisation rates of EBER ISH for diagnosis and classification of tumours in accordance with the WHO Classification of Tumours criteria. Ongoing disease monitoring, such as measurement of plasma EBV DNA levels, may also be recommended for selected EBV-associated tumours, resulting in downstream healthcare resource use and costs specific to the management of EBV-associated disease.

PASC noted the proposed outcomes for the assessment but advised that the assessment should focus on diagnostic accuracy and total financial costs. This reflects the view that EBER ISH is already embedded within routine clinical practice, although it is currently either unfunded or funded indirectly via broader pathology services. PASC accepted that EBER ISH is the established method for localising latent EBV within tumour cells and it is routinely used to resolve diagnostic uncertainty; its clinical utility is generally accepted. Consequently, the key question for assessment is not whether EBER ISH should be used, but rather the financial implications of introducing an MBS item for testing that is already part of standard care. PASC therefore considered that an economic analysis would not be informative and the assessment should be truncated to focus on outcomes for diagnostic accuracy and total financial costs.

PASC noted that repeat biopsy is exceptionally uncommon, generally occurring only when the original specimen is inadequate for diagnosis overall, not because additional tissue is required for EBER ISH testing. PASC considered that re-biopsy solely to enable EBER ISH does not need to be captured as an outcome.

Figure 3 Proposed assessment framework showing links from test population to health outcomes



Abbreviations: EBV = Epstein-Barr virus; ISH = in situ hybridisation

Notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of change in management on health outcomes; 5: adverse events due to testing; 6: adverse events due to treatment

PASC considered that the assessment should be limited to an evaluation of diagnostic accuracy and total financial costs.

The assessment framework diagram considered by PASC has been retained without modification for context; however, the assessment questions have been updated to reflect the outcomes of interest.

The questions to be addressed in the assessment report are:

1. What are the total costs of EBER ISH testing compared with no molecular profiling in patients with potential EBV-associated tumours?
2. What is the analytical and diagnostic accuracy of EBER ISH testing compared with no molecular profiling in patients with potential EBV-associated tumours?

Proposed clinical management algorithm considered by PASC

Given the broad range of tumours that may be associated with EBV, PTLD is used as the exemplar clinical scenario for the discussion of clinical management. It is acknowledged that the diagnostic and treatment pathway will vary for other EBV-associated tumours.

Patients with suspected PTLD typically present with constitutional symptoms, lymphadenopathy, extranodal disease or graft dysfunction (Allen & Preiksaitis 2019). Initial evaluation includes clinical assessment, laboratory investigations including plasma EBV DNA quantification where appropriate, cross-sectional imaging, and histopathological examination of an adequate tissue biopsy. Histopathological assessment, including morphology and immunophenotyping, is essential for establishing the diagnosis and classifying PTLD according to the WHO classification. EBER ISH is subsequently performed on biopsy tissue to determine the presence of latent EBV within tumour cells.

The results of EBER ISH are interpreted alongside histopathological findings, immunophenotype, clinical presentation, transplant type, time since transplantation and multidisciplinary team review. Confirmation of EBV-positive PTLD contributes to disease classification and may inform prognosis and therapeutic decision-making, although treatment is determined by the overall clinicopathological context rather than

EBV status alone. Initial management commonly includes reduction of immunosuppression where clinically feasible. For CD20-positive B-cell PTLD, rituximab-based therapy is the standard first-line systemic treatment, with escalation to chemoimmunotherapy (e.g. rituximab + CHOP chemotherapy) in patients with inadequate response or aggressive disease. Additional treatment options including surgery, radiotherapy, antiviral therapy or EBV-specific cytotoxic T-cell therapy may be considered depending on the PTLD subtype, disease extent, transplant type and patient factors (Allen & Preiksaitis 2019; Markouli et al. 2022). EBV-specific cytotoxic T-lymphocyte immunotherapy may be accessed in Australia through the Special Access Scheme, with treatment costs borne by the patient (Neller et al. 2024).

Following treatment, patients undergo clinical, radiological and laboratory follow-up to assess treatment response, monitor for relapse, evaluate graft function and detect treatment-related complications. In select populations, EBV DNA monitoring may complement clinical surveillance (Allen & Preiksaitis 2019; NCCN 2026b; Styczynski et al. 2016).

As EBER ISH is already embedded within the diagnostic pathway for EBV-associated tumours, PASC considered that an assessment of clinical utility and inclusion of an exemplar clinical management algorithm was unnecessary. PASC considered that the application should proceed as an assessment focusing on diagnostic accuracy and financial implications, with direct consideration by MSAC.

Proposed economic evaluation

Based on the application, the proposed clinical claim is that the addition of EBER ISH provides superior effectiveness and non-inferior safety. As such, a cost-effectiveness analysis (cost per patient with an EBV-driven tumour correctly identified and/or cost per patient with a test-informed change in tumour management) or a cost-utility analysis (cost per QALY gained) is proposed to evaluate the addition of EBER ISH to the management pathway for EBV-associated tumours (Table 17). However, incorporating multiple tumours into a single economic model would be highly complex and likely to introduce substantial structural complexity and uncertainty due to heterogeneity in clinical management, treatment sequencing and health outcomes. It is potentially impractical to model QALYs for all indications.

Therefore, at the pre-PASC meeting, the applicant proposed using a cost-per-diagnosis approach for the economic evaluation. An alternative approach could be to develop a cost utility analysis using PTLD as an exemplar. However, there are challenges with using PTLD as the sole exemplar. EBV-associated tumours encompass a heterogeneous group of tumours with differing disease biology, diagnostic pathways, treatment strategies and prognoses. Therefore, the costs and health outcomes associated with EBER ISH are likely to vary across tumour types. PTLD itself is also heterogeneous, comprising multiple histological subtypes that differ in clinical behaviour and management. As a result, the economic analysis is likely to remain complex regardless of whether an exemplar approach is adopted.

PASC considered whether EBER ISH testing should be assessed via a 2-stage evaluation process, where an assessment of the clinical evidence would be presented for ESC and MSAC to advise on the appropriate economic evaluation. PASC noted that a cost-utility analysis would be challenging for EBER ISH, given the broad range of EBV-associated tumours for which the test is used. As EBER ISH is primarily used to resolve diagnostic uncertainty and support tumour classification—rather than to directly guide treatment selection—PASC considered it unlikely that a cost-utility analysis would provide meaningful information. PASC noted that EBER ISH is already routinely performed in clinical practice and is not expected to generate additional demand if publicly funded. On this basis, PASC advised that a full economic evaluation may be unnecessary. PASC advised that a 2-stage evaluation process was not required and the application could

instead proceed as a truncated evaluation to MSAC, focusing on diagnostic accuracy and the financial implications to the MBS.

Table 17 Classification of comparative effectiveness and safety of proposed intervention compared with its main comparator 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

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

Notes: ? = 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, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or comparative safety considerations

^b Adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The application proposed a new MBS item for funding under the MBS for EBER ISH testing for tumour tissue to detect EBV viral genomes (Table 18).

In the application form, the proposed MBS item descriptors are for P7-Genetics. According to the application, most patients would require EBER ISH testing only once during a diagnostic episode. Repeat testing may be required in a small proportion of patients in cases of a new primary tumour or where additional tissue becomes available following an inconclusive initial result. Thus, a frequency of once per diagnostic episode is proposed. The department advised that external references, such as the WHO Classification of Tumours diagnostic criteria, should be included in an explanatory note rather than referenced in the item descriptor.

PASC considered whether EBER ISH should be implemented as a pathologist-determinable test. The decision to perform EBER ISH arises from the pathological differential diagnosis and the required integration of morphological findings, immunophenotypic results and other pathological investigations undertaken during tissue assessment. As such, PASC considered that pathologists are well placed to determine when EBER ISH testing is required to resolve diagnostic uncertainty, confirm an EBV-associated entity or support disease classification. PASC advised that the MBS item should enable pathologist-determinable testing.

Table 18 Proposed MBS item descriptor: for EBER ISH

Category 6 - Pathology services	P7 - Genetics
MBS item CCCCC 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)	
Fee: \$142.93 Benefit: 75% = \$107.20 85% = \$121.49	

Note: Blue text represents changes suggested by the assessment group.

Based on the application, the cost of current EBER ISH tests is typically absorbed by the laboratories as an unfunded component of diagnostic work-up, is paid out-of-pocket by patients, or captured via state-based hospital funding. EBER ISH, where not essential for diagnosis, 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. 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.

The cost breakdown provided in the application for EBER ISH is presented in Table 19. It should be noted that overhead costs such as utilities (e.g. electricity and water) are not generally included in the costing for MBS funding, so these would likely need to be removed.

PASC noted differing views regarding the proposed fee for EBER ISH, with some stakeholders considering it too high and others too low. PASC considered that EBER ISH would almost always be performed at the same time as IHC markers (and often concurrently and on the same platforms) and rarely as a standalone test. Therefore the pathologist and scientist time per test may be over-estimated. PASC advised that policy should provide guidance on an appropriate fee.

Table 19 Breakdown of costs for EBER ISH

Item	Cost	Assumptions/inclusions	Cost per slide
EBER reagents and consumables	\$1597 per 25 tests	Includes Ventana EBER probe; Ventana Magenta ISH DIG kit; ISH TSA ancillary kit (24ml); ISH peroxidase inhibitor; HybReady (250 drops); ISH protease 3; Haematoxylin II; bluing reagent; BMK ULTRA CC1; BMK ULTRA LCS; reaction buffer, 2L; SSC, 2L; kit pack, EBAR; slides	\$63.88
Scientist time	\$43/hr	45 min preparation and review time	\$32.25
Pathologist time	\$250/hr	11 min supervision, interpretation and reporting	\$45.80
Electricity, water etc	\$1/test		\$1.00
		Total	\$142.93

Abbreviations: EBER = Epstein-Barr virus; hr = hour; ISH = in situ hybridisation; min = minute

Summary of public consultation input

PASC noted and welcomed consultation input from 4 organisations and no individual input was received. The 4 organisations that submitted input were:

- Australasian Leukaemia & Lymphoma Group (ALLG)
- Public Pathology Australia (PPA)
- Rare Cancers Australia (RCA)
- Roche Diagnostics Australia.

Consultation input was uniformly supportive of public funding for ISH testing of tumour tissue to detect viral genomes (EBV and HPV).

Consumer Experience

RCA provided consultation input for HPV-related cancers. RCA input highlighted that patients living with HPV-related cancers experience significant physical, emotional, social and financial impacts throughout their care journey. Patients reported challenges associated with delayed diagnosis, particularly for cancers without established screening programs, with symptoms often attributed to other conditions before a diagnosis is confirmed. Treatment can be intensive and associated with substantial side effects including pain, radiation burns and long-term impacts on bowel, bladder and sexual function. RCA input stated that the physical side effects of treatment affected the daily life of patients, including disrupting activities such as sitting, driving and using the toilet. Financial pressures related to treatment, travel and ongoing care can create additional barriers, particularly for people living in regional areas or without access to reliable transport. RCA stated that stigma and misconceptions surrounding HPV-related cancers can lead to feelings of shame, self-blame and isolation. RCA input highlighted the importance of timely and accurate diagnostic testing, improved awareness of HPV-related cancers and equitable access to care to support earlier diagnosis and improve treatment experiences.

Benefits and Disadvantages

The main benefits of public funding reported in the consultation input included improved access to accurate diagnostic testing to support earlier diagnosis, more informed clinical decision-making and appropriate treatment selection. Consultation input also highlighted the potential to improve equity of access to specialised testing services and reduce delays in diagnosis. RCA stated that accurate viral status testing for all HPV-related cancers would reduce the inequity between cancers that have an organised screening pathway (e.g. cervical cancer) and those that do not have an organised screening pathway (e.g. anal and vulval cancer).

No significant disadvantages of public funding were identified in the consultation input.

Population, Comparator (current management) and Delivery

The consultation input was supportive of the proposed population. ALLG considered the proposed population should include patients with suspected Chronic Active EBV (CAEBV), a non-malignant haematological condition that is rare but frequently life-threatening. Roche Diagnostics also considered the population appropriate but noted that the proposed eligibility criteria should not unnecessarily restrict clinician discretion in determining when HPV ISH testing is appropriate.

The consultation input was generally supportive of the proposed comparator, no molecular profiling. RCA described the current diagnostic pathway for HPV-related cancers as including histopathology, IHC (such as p16) and, in some cases, PCR testing. ALLG stated that EBV testing is routine practice for lymphoma.

Other services identified in the consultation input as being needed to be delivered before or after the intervention included appropriate psychological support for patients diagnosed with HPV-related cancers, as well as timely access to specialised pathology services and multidisciplinary care.

MBS Item Descriptor and Fee

The consultation input was generally supportive of the proposed service descriptor. Roche Diagnostics suggested including an appropriate practice note for the HPV ISH item to require pathologists to consider or review known HPV test results (such as from the National Cervical Screening Program) prior to determining that an HPV ISH test is suitable. ALLG recommended expanding the descriptor for the EBV ISH item to include “testing of affected tissue in patients with suspected chronic active EBV where EBV status is unknown”.

The consultation input ranged from supportive to raising concerns regarding the proposed service fee. ALLG supported the proposed fee, while Roche Diagnostics considered the proposed fee for EBV ISH testing may be insufficient and suggested fees more closely reflect the costs of currently available ISH testing on the MBS.

PASC noted that public consultation input was broadly supportive of the proposed MBS listing for both HPV ISH and EBER ISH. PASC noted that Rare Cancers Australia supported the application for HPV ISH testing and highlighted the psychological impact of being diagnosed with an HPV-related cancer.

Next steps

PASC advised that the application should proceed as 2 separate Department Contracted Assessment Reports, with HPV ISH proceeding to ESC then MSAC and EBER ISH proceeding direct to MSAC. PASC noted that the department will manage the logistics of progressing the application as 2 separate assessments. PASC advised that policy should provide guidance on appropriate fees for HPV ISH and EBER ISH testing.

Applicant Comments on Ratified PICO

The RCPA thanks PASC for their thorough consideration of this application. The original application proposed HPV ISH as a pathologist-determinable service. Part of the indication for testing is established during examination of the tumour tissue, following assessment of morphology and p16 immunohistochemistry. The pathologist is well placed to identify when p16 is equivocal or unreliable and to initiate ISH before issuing the final diagnostic report. PASC’s concern about the prognostic and treatment implications of discordant results is also important, and those subsequent decisions remain with the treating team and are not excluded by enabling testing to be pathologist determinable. Requiring a separate clinician request for all tests will necessitate an additional consultation and delay tumour classification. The RCPA strongly supports retaining a specialist-initiated pathway alongside pathologist-determinable testing.

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