

## **MSAC Application 1752**

**Anal human papillomavirus (HPV) and cytology testing in high-risk populations to determine access to high-resolution anoscopy and ablative treatment to prevent anal cancer**

**Applicant: The Royal College of Pathologists of Australasia (RCPA) and St Vincent's Hospital, Sydney**

## **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 anal HPV testing, cytology testing and diagnostic HRA in populations at high-risk of anal cancer (caused by HPV)

Component	Description
Population	<p><b>Testing:</b> Populations at high-risk of developing anal cancer caused by HPV:</p> <ul style="list-style-type: none"> <li>• MSM and TW living with HIV age <math>\geq 35</math> years</li> <li>• MSM and TW living without HIV age <math>\geq 45</math> years</li> <li>• women and MSW living with HIV age <math>\geq 45</math> years</li> <li>• people with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis</li> <li>• SOTR, commencing 10 years post-transplant</li> <li>• patients being followed-up after treatment for anal cancer (i.e. chemoradiotherapy/surgery)</li> <li>• patients outside these above groups with incidental anal HSIL (e.g. lesions found at haemorrhoidectomy, colonoscopy or during diagnosis of other anal conditions) and patients presenting with symptoms suggestive of anal cancer</li> </ul> <p><b>Therapeutic intervention:</b> Populations described above with histologically confirmed anal HSIL .</p>
Prior tests	N/A
Intervention	<p><b>Tests:</b></p> <ul style="list-style-type: none"> <li>• anal HPV test (full HPV genotyping)</li> <li>• liquid-based cytology test if a high-risk HPV genotype is detected</li> <li>• immediate referral for diagnostic HRA when               <ol style="list-style-type: none"> <li>1. HSIL (or cancer [SCC]) is suspected/detected by liquid-based cytology (performed due to detection of non-16 HR-HPV)</li> </ol>               OR               <ol style="list-style-type: none"> <li>2. positive HPV-16 genotyping with any cytology result</li> </ol> </li> <li>• 12 months persistence of non-16 HR-HPV demonstrated, with any cytology result</li> </ul> <p><b>Therapeutic intervention:</b></p> <ul style="list-style-type: none"> <li>• HRA-guided anal HSIL ablation</li> </ul>
Comparator	<p><b>Test:</b></p> <ul style="list-style-type: none"> <li>• no testing</li> </ul> <p><b>Therapeutic intervention:</b></p> <ul style="list-style-type: none"> <li>• no intervention/ watchful waiting</li> </ul>
Reference standard	Histological testing (e.g. biopsy for HSIL) <sup>a</sup>
Outcomes	<p><b>Test:</b></p> <p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• harms arising from anal sampling and HRA investigation (e.g. physical discomfort, pain, bleeding)</li> <li>• harm associated with absence of testing</li> <li>• harm associated with false positive or false negative results</li> </ul> <p><b>Clinical effectiveness</b> Diagnostic accuracy</p>

Component	Description
	<ul style="list-style-type: none"> <li>• sensitivity, specificity</li> <li>• positive likelihood ratio, negative likelihood ratio</li> <li>• positive predictive value, negative predictive value</li> <li>• ROC curves</li> <li>• diagnostic yield</li> <li>• need for repeat tests (e.g. unsatisfactory sample)</li> </ul> <p>Patient management outcomes</p> <ul style="list-style-type: none"> <li>• change in patient clinical management</li> <li>• change in follow-up frequency</li> <li>• commencement of treatment</li> </ul> <p><b>Non-health outcome</b></p> <ul style="list-style-type: none"> <li>• value of knowing (i.e. clinical utility) of HPV and cytology testing <ul style="list-style-type: none"> <li>○ impact on patient behaviour (e.g. health, self-care practice, knowledge of diagnosis)</li> <li>○ impact on gender diverse populations (including HIV-positive people)</li> </ul> </li> </ul> <p><b>Healthcare resource use</b></p> <ul style="list-style-type: none"> <li>• costs associated with the intervention including cost of appointments, anal HPV and cytology tests; cost of test processing; out-of-pocket costs</li> <li>• cost-effectiveness of anal HPV and cytology testing</li> <li>• total Australian Government healthcare costs</li> <li>• uptake of HPV/LBC/diagnostic HRA</li> </ul> <p><b>Therapeutic intervention:</b></p> <p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• AE</li> <li>• all-cause mortality</li> <li>• hospitalisation</li> <li>• serious AE</li> <li>• bleeding</li> <li>• pain</li> <li>• infection</li> </ul> <p><b>Clinical effectiveness</b></p> <ul style="list-style-type: none"> <li>• general HRQoL</li> <li>• HSIL-free survival</li> <li>• local HSIL recurrence</li> <li>• metachronous HSIL lesions</li> <li>• progression to anal cancer</li> </ul> <p><b>Healthcare resource use</b></p> <ul style="list-style-type: none"> <li>• number of treatments and costs associated with treatment (e.g. cost of treatment, specialist visits, requirement for subsequent treatment, hospitalisation, out-of-pocket costs)</li> <li>• cost-effectiveness of treatment</li> <li>• total Australian Government healthcare costs</li> <li>• uptake of HRA/ablation</li> </ul>
Assessment question <sup>b</sup>	<p>In a population at high risk of developing anal cancer, what is the safety, effectiveness and cost-effectiveness of combined anal HPV testing, cytology testing and diagnostic HRA followed by HRA-guided ablation therapy of HSIL vs no testing and routine clinical care (i.e. no treatment)?</p> <p><u>Direct evidence</u></p>

Component	Description
	<p>1. In a population at high risk of developing anal cancer, does the use of anal HPV testing, cytology testing and diagnostic HRA instead of no testing result in a decrease in anal cancer?</p> <p><u>Indirect evidence</u></p> <p><i>Testing (i.e. diagnostic accuracy)</i></p> <p>2. In a symptomatic population, how does the information from anal HPV testing, cytology testing and diagnostic HRA differ from the information obtained from no testing?</p> <p>What is the accuracy of anal HPV testing, cytology testing and diagnostic HRA (against histological testing [biopsy])?</p> <p>3. Does the availability of new information from anal HPV testing, cytology testing and diagnostic HRA (compared to no test) lead to a change in patient management?</p> <p>5. Which AEs are associated with anal sampling (for HPV testing and cytology) compared to no test?</p> <p>6. Which AEs are associated with diagnostic HRA compared to no test?</p> <p>8. What are the benefits of receiving cytology testing results for pLSIL or LSIL vs what would happen in the absence of the test?</p> <p>9. What are the harms of receiving cytology testing results for pLSIL or LSIL vs what would happen in the absence of the test?</p> <p><i>Treatment (i.e. change in management)</i></p> <p>4. Does HRA-guided anal HSIL ablation (led from management decisions informed by anal HPV testing, cytology testing and diagnostic HRA) relative to routine clinical care (i.e. no treatment) result in a decrease in anal cancer?</p> <p>7. Which AEs are associated with HRA-guided anal HSIL ablation (led from management decisions informed by anal HPV testing, cytology testing and diagnostic HRA) relative to routine clinical care (i.e. no treatment)?</p> <p><i>Other considerations</i></p> <p>10. What are the organisational, ethical, social, environmental and legal considerations for implementing anal HPV testing, cytology testing and diagnostic HRA for anal cancer within the healthcare system?</p>

**Abbreviations**

**AE** = adverse event, **HIV** = human immunodeficiency virus, **HPV** = human papillomavirus, **HSIL** = high-grade squamous intraepithelial lesions, **HRA** = high-resolution anoscopy, **HR-HPV** = high-risk human papillomavirus, **HRQoL** = health-related quality of life, **LBC** = liquid-based cytology, **LSIL** = low-grade squamous intraepithelial lesions, **MSM** = men who have sex with men, **MSW** = men who have sex with women, **NA** = not applicable, **pLSIL** = possible low-grade squamous intraepithelial lesion, **ROC** = receiver operating characteristic curves, **SCC** = squamous cell carcinoma, **SOTR** = solid organ transplant recipient, **TW** = transgender women.

**Notes**

<sup>a</sup> Not every patient exposed to HPV testing will be subject to a biopsy (histological test).

<sup>b</sup> Assessment question numbers align with the stages of the assessment framework (Figure 1)

## Purpose of application

The application was received from the Royal College of Pathologists of Australasia (RCPA; Sydney, NSW) and St Vincent's Hospital (Sydney, NSW) by the Department of Health (MSAC 1752 PICO Set p. 1). The co-dependent application requested:

- Medicare Benefits Schedule (MBS) listing of anal human papillomavirus (HPV) testing, cytology testing and diagnostic high-resolution anoscopy (HRA) for the early identification of pre-cancerous high-grade squamous intraepithelial lesions (HSIL) in populations at high risk of anal cancer (caused by HPV)
- MBS listing of HRA-guided anal HSIL ablation for removal of HSIL lesions to prevent progression to anal cancer (i.e. treatment) in high-risk populations with anal HPV.

HSIL lesions are the main precursor of anal cancer (Berry et al. 2014). According to the applicant, there is currently no established regular testing regimen in Australia for populations at high risk of anal cancer caused by HPV (MSAC 1752 PICO Set p. 21-22, 26). The application stated that HRA-guided anal ablation of HSIL lesions would provide superior health outcomes compared to routine clinical care (i.e. no treatment) (MSAC 1752 PICO Set p. 32). In addition, the information provided by combined HPV testing, cytology testing and diagnostic HRA improves efficiency compared to routine clinical care (i.e. no testing). The clinical claim for superior information provided by the testing regimen is detailed in Appendix A (MSAC 1752 PICO Set p. 32). Regular testing will enable monitoring of patients at high risk of disease, and early identification of disease will allow patients to be treated early, reducing the invasive anal cancer progression rate (Palefsky, J. M. et al. 2022).

## PICO criteria

### **Population**

Given that this is a co-dependent application, there are 2 populations of interest (i.e. testing and treatment) (MSAC 1752 PICO Set p. 3). The testing population is people at high risk of developing anal cancer caused by HPV. This population is divided into 7 high-risk subgroups: men who have sex with men (MSM) and/or people who identify as transgender women (TW) who are positive for human immunodeficiency virus (HIV) and are age  $\geq 35$  years; MSM age  $\geq 45$  years and/or who identify as TW who are HIV negative; women and men who have sex with women (MSW) age  $\geq 45$  years who are HIV positive; women with previous vulval HPV-associated squamous cell carcinoma (SCC) and/or HSIL commencing within 1 year of diagnosis; solid organ transplant recipients (SOTR) commencing 10 years post-transplant; people being followed-up after treatment for anal cancer; and people with incidental HSIL (lesions found during diagnosis of anal conditions) (MSAC 1752 PICO Set p. 24). The treatment population is people with anal HSIL.

### *Definition of the condition*

#### *Testing population*

HPV is the most common sexually transmitted infection. It encompasses more than 150 genotypes, of which approximately 40 have anogenital tropism (Donà & Giuliani 2020). HPV genotypes are classified into 2 broad categories: non-carcinogenic (low-risk HPV) or carcinogenic (high-risk HPV). Low-risk HPV (LR-HPV) can induce benign lesions, whereas high-risk HPV (HR-HPV) can cause cancers such as anal cancer. Among

the anogenital tropism genotypes, 15 are considered as high-risk or oncogenic (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) (Kreuter et al. 2010; Wei et al. 2021), with HPV16 being the most frequently identified in anal cancer (73–80%) and its precancerous form: anal HSIL (60–75%) (Jin, F. et al. 2017; Lin, Franceschi & Clifford 2018; Machalek et al. 2012). HR-HPVs are responsible for approximately 90% of all anal cancers, also called anal SCC (De Vuyst et al. 2009; Machalek et al. 2012).

Subgroup 7 comprises patients who have been identified with incidental HSIL during investigation and management of anorectal disease (e.g. haemorrhoids) other than anal cancer (Mayo Clinic 2023; Pineda & Welton 2009). The disease can also be diagnosed through anal tissue samples taken to investigate other anal pathologies (Pineda & Welton 2009). Patients diagnosed with incidental HSIL are generally asymptomatic (Pineda & Welton 2009). However, patients have been known to experience nonspecific symptoms including anorectal pain, bleeding and pruritus (Pineda & Welton 2009). Regardless of whether HSIL is identified incidentally via treatment or screening, a diagnostic HRA (including biopsies) must be conducted to confirm the diagnosis, as most HSIL is invisible to the unassisted human eye (Pineda & Welton 2009). The applicant advised that, for patients who have been identified with incidental HSIL, HPV and cytology testing would be performed at the same time as HRA to allow a more accurate characterisation of anal cancer risk.

*PASC noted for background that rare rectal SCC is also usually HPV-related.*

#### Treatment population

HSIL is a precursor to invasive anal cancer (De Vuyst et al. 2009; Hoots et al. 2009). However, not all lesions will progress to anal cancer; some will clear spontaneously or persist uneventfully (Leber et al. 2020; Poynten, I. M. et al. 2021). HSIL consists of abnormal cells that cluster to form a lesion (The Bottom Line n.d.). These lesions can be divided into 2 types: peri-anal or intra-anal. Peri-anal lesions occur outside the anus and are located within 5 cm of the anal edges. Intra-anal lesions occur inside the anus and are located within 5 cm of the anal edges (St Vincent's Hospital 2024a). The anatomical characteristics of the anus (i.e. large surface area and anal columns) can make it challenging to diagnose precancerous and cancerous lesions (Clarke, M. A. & Wentzensen 2018). The associated underlying mechanism of HSIL progression is currently incompletely understood.

#### Burden of the disease

##### Testing population

It is estimated that at least 90% of the general population has been infected with at least one type of HPV (Chesson et al. 2014; HPV Information Centre 2023). Men and women are both infected by HPV. Initial anogenital infection usually coincides with first sexual activity (around 17 years of age) (Chesson et al. 2014; HPV Information Centre 2023; Richters et al. 2014). Over the past 10 years, the prevalence of oncogenic HPV among Australian women has decreased. This is due to the implementation of the National HPV Vaccination Program in 2007 (Patel, C et al. 2018). For example, the prevalence of HPV types included in the HPV vaccine in Australian women decreased from 28.7% (2005–2007) to 2.4% in vaccinated women (2010–2012) (Tabrizi et al. 2014). In 2014, HPV infection prevalence in vaccinated Australian women was significantly lower than in unvaccinated women (Tabrizi et al. 2014). This decrease in HPV infection prevalence has not been captured in Australian men, as school-aged males only became eligible for the national vaccination program in 2014 (Brill 2013; Patel, C et al. 2018). It is important to note that the

prevalence of HPV varies among Australian jurisdictions (HPV Information Centre 2023; Richters et al. 2014).

Regardless of the decrease in the prevalence of HPV infection among Australian women, 2012 data showed that in Australia, 90.8% of anal cancer in women was attributable to HPV infections (Patel, C et al. 2018). In addition, 74.9% of anal cancers in men was attributable to HPV infections (Patel, C et al. 2018). Furthermore, Australian women have a higher incidence of HPV-related anal cancer (crude incidence 2.94 per 100,000) than Australian men (crude incidence 1.88 per 100,000) (HPV Information Centre 2023). Anal cancer is rare in the general population, with an age-standardised incidence of 1 to 2 cases per 100,000 person-years. It is more prevalent among women than men and its incidence and mortality are rising worldwide (Clifford et al. 2021; International Agency for Research on Cancer 2020). In 2022, the Australian Institute of Health and Welfare (AIHW) estimated that 180 people died of anal cancer in Australia and 600 new cases would be diagnosed, equivalent to an age-standardised incidence rate of 1.9 cases per 100,000 people (Australian Institute of Health and Welfare 2022). The 5-year survival rate was 68.4% in 2014–2018. The survival rate is highly related to the extent of disease. Patients with localised disease have an 82% chance of 5-year survival, those with lymph node invasion have a 66% chance of 5-year survival, and those with metastasis to other body organs have a 34% chance of 5-year survival (Albuquerque, AC-A, E; Troche, J. 2019). While HPV infection is the main risk factor for anal cancer, other well-known factors may contribute to the development of anal cancer, including increasing age (>50 years), smoking tobacco, weakened immune system (medical condition and/or medication use), multiple sexual partners, and history of receptive anal sexual intercourse (American Cancer Society 2023).

Given the population characteristics and risk factors, the proposed population is further divided into the 7 subgroups listed in Table 1. The first 5 subgroups are included in Risk Category A of the consensus guidelines of the International Anal Neoplasia Society (IANS) (Stier, E. A. et al. 2024). Anal cancer incidence within these high-risk groups is  $\geq 10$ -fold compared to the general population (i.e.  $\geq 17$  per 100,000 person-years) (Stier, E. A. et al. 2024).

Regarding patients being followed-up after treatment for anal cancer, data from the United Kingdom (UK) indicates the detection of HSIL in 13% of patients after chemoradiation and 74% of patients after excision only, supporting the need for careful surveillance to detect and treat HSIL in this population, particularly following surgical excision (Benson et al. 2023; Cappello et al. 2020). A Swedish study reported locoregional recurrence in 14.1% of anal cancer patients treated with curative intent intensity-modulated radiotherapy (Nilsson et al. 2020).

Subgroup 7 comprises patients who have been identified with incidental HSIL. The incidence of anal cancer among this subgroup is not well documented. A Danish registry study reported an anal SCC incidence of 700/100,000 person-years among HIV-negative patients with anal intraepithelial neoplasia (AIN) 3 (Faber et al. 2022).

Testing population subgroups are detailed in Table 2.

### Treatment population

There is limited information regarding the prevalence and incidence of HSIL attributable to HPV in Australia (Bowel Cancer Australia 2022; St Vincent's Hospital 2024a; The Bottom Line n.d.). Table 2 details the

available published prevalences of HSIL attributable to HPV within the 7 subgroups (unavailable for some subgroups).

**Table 2 Testing population**

Subgroup	Testing population	Testing timepoint <sup>a</sup>	Proportion of testing population with anal HR-HPV	Proportion of HR-HPV population with anal HSIL attributable to HPV	Anal cancer per 100,000 person-years
1	MSM and TW living with HIV	age ≥35 years	70.5%	22.4%	>70 (age 30–44 years) >100 (age ≥45 years)
2	MSM and TW living without HIV	age ≥45 years	42.6%	11.3%	>18 (age 45–59 years) >34 (age ≥60 years)
3	Women and MSW living with HIV	age ≥45 years	76.0% (women) 48.0% (MSW)	1.0% (women) NR (MSW)	>25 (women) >40 (MSW)
4	People with previous vulval SCC/HSIL (HPV associated)	within 1 year of diagnosis	NR (HSIL) 47.5% (SCC)	35.7% (HSIL) 32.1% (SCC)	>40
5	SOTR	10 years post-transplant	3.6%	NR	>25
6	People being followed-up after treatment for anal cancer (i.e. chemoradiotherapy/surgery)	shared decision	NR	NR	NR
7	People with incidental HSIL (e.g. lesions found at haemorrhoidectomy, colonoscopy or during diagnosis of other anal conditions)	shared decision	NR	NR	700/100,000

**Abbreviations**

**HIV** = human immunodeficiency virus, **HPV** = human papillomavirus, **HSIL**= high-grade squamous intraepithelial lesions, **HR-HPV** = high-risk human papillomavirus, **MSM** = men who have sex with men, **MSW** = men who have sex with women, **NA** = not applicable, **NR** = not reported, **SCC** = squamous cell carcinoma, **SOTR** = solid organ transplant recipient, **TW** = transgender women.

**Notes**

Subgroups informed by International Anal Neoplasia Society consensus guidelines (Stier, E. A. et al. 2024).

<sup>a</sup> Harm is greater than benefit when HSIL is treated before ≥35 years of age.

**Source(s)**

(Albuquerque, A et al. 2020; Department of Health and Aged Care 2023; Gunbiyi et al. 1994; Patel, P et al. 2018; Stier, E. A. et al. 2024; Tatti et al. 2012).

*PASC raised concerns around the appropriateness of the subgroups included in the target population. The population, as it is currently defined by the applicant, includes subgroups with a 10-fold greater risk of anal cancer than the general population. The proposed population does not capture the population who account for the greatest number of anal cancer cases annually in Australia, namely women with HPV associated cervical/vaginal cancer or precursor lesions. The applicant acknowledged that the current population subgroups capture more men than women. This is due to the risk of anal cancer in the largest group of women at risk (women with cervical/vaginal cancer or precursor lesions) being lower (5–10-fold the risk of*



anal cancer compared to the general population) than that of men who are typically found in smaller defined groups at very high risk of anal cancer (more than 10-fold risk of anal cancer compared to the general population). While the applicant is amenable to including women with cervical/vaginal cancer or precursor lesions as a subpopulation group, if the population groups were to be expanded to include this subgroup, this would significantly increase the number of people being tested and will have cost implications. PASC noted that appropriate wording of the MBS item descriptors will be required to ensure that this group is not excluded from accessing HPV/liquid-based cytology (LBC) testing, diagnostic HRA and treatment if their referring practitioner thinks this is appropriate. This additional population group has been defined as **people with a possible history of cervical/vaginal cancer or precursor lesions**. Henceforth through the rest of this PICO this term is used when referring to the sub-group discussed above.

PASC asked if 6-monthly HPV/LBC/HRA for HSIL surveillance in patients previously treated for anal cancer would replace HRA-based surveillance (which is used in some other guidelines). In addition, PASC questioned if there is evidence to support the use of HPV/LBC/HRA in this subpopulation. The applicant indicated HPV/LBC testing should be performed in addition to HRA as these tests might detect recurrent/persistent HSIL not visible at HRA.

PASC enquired if groups representing the SOTR subgroup or clinicians treating this subgroup had supported the proposal for systematic anal HPV testing. The Department confirmed that neither the applicant nor the Department had been in contact with any transplant groups or experts. PASC requested feedback be sought from transplant groups. In addition, PASC requested that feedback should also be sought from gynaecological oncology experts.

PASC also sought feedback from radiation oncologists and other clinicians regarding the clinical utility of anal HPV/LBC testing and HRA in patients from subgroup 6 (patients being followed-up after anal cancer treatment) and subgroup 7 (patients found to have incidental HSIL or with signs and symptoms suggestive of anal cancer). PASC sought advice on whether clinicians think testing for anal HPV/LBC and HRA has a clinical place and is of clinical value for these patient subgroups.

#### *Natural history of the condition*

##### *Testing population*

Most HPV infections are asymptomatic and spontaneously clear within 1 or 2 years (The Royal Marsden 2017). Persistent HPV infections lead to cell abnormalities, which differ depending on the HPV genotype (Department of Health and Aged Care 2023). LR-HPV may present as benign lesions such as genital warts, which may remain unnoticed by the patient (Department of Health and Aged Care 2023). HPV6 and HPV11 are responsible for 90% of anal and genital warts (Department of Health and Aged Care 2023). Oncogenic HR-HPVs, for which the infection is usually subclinical, are strongly linked to anal HSIL and an elevated risk of developing cancers (Chowdhury et al. 2023). The most common genotype found in HSIL and anal SCC is HPV16, followed by HPV18 and HPV58, with frequencies varying geographically (Conde-Ferraz et al. 2023). These genotypes are commonly found in Australia (Machalek et al. 2016; Phillips et al. 2023). The HPV genotype influences the morphology of the lesion and the overall course of the disease, but the persistence of the virus in cells depends on the establishment of a viral reservoir in epithelial cells (Doorbar et al. 2020).

HPV has an affinity for the squamous stratified epithelium found in the transformation zone of the anal canal where the anal squamous epithelium transitions to rectal columnar epithelium (Donà & Giuliani 2020). The virus invades the cells of the basal layer of the anal transition zone, where a low viral copy number is maintained for months or years (International Agency for Research on Cancer 2007). When infected basal cells differentiate and move towards the upper layers of the epithelium, viral replication increases and a high number of viral particles is produced (International Agency for Research on Cancer 2007; Lupi et al. 2022). These viruses are then excreted to infect the surrounding cells, increasing the likelihood of developing precancerous lesions, known as dysplasia. These abnormal cellular changes within a tissue are classified as either low-grade squamous intraepithelial lesions (LSIL) or HSIL, according to the severity of the cellular abnormalities observed (Chen et al. 2010; Lupi et al. 2022). If left untreated, these dysplasias can progress to anal cancer over time (Stier, Elizabeth A & Chiao 2017).

#### Treatment population

Many uncertainties exist regarding the factors and mechanisms involved in the progression and regression of HSIL as the precursor to anal cancer (Barroso 2020; Lupi et al. 2022; Wentzensen & Clarke 2017). Progression of HSIL to anal cancer has been shown to be less frequent and slower when compared to cervical lesions, with an estimated rate of 10% over 5 years (Machalek et al. 2012). As in the cervix, not all HSIL will progress to anal cancer and in some lesions regress spontaneously (Tong et al. 2013).

HSIL is classified using the AIN classification system, used to categorise the severity of dysplastic changes in the anal epithelium (i.e. HSIL) observed under a microscope or colposcope (Siddharthan, Lanciault & Tsikitis 2019). AIN grade 1 is equivalent to LSIL: it results from persistent LR-HPV infection and is not generally associated with progression to invasive malignancy. HSIL, categorised as AIN2 (moderate dysplasia) or AIN3 (severe dysplasia), is the precursor of invasive anal SCC and is associated with HR-HPV infection (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) (Siddharthan, Lanciault & Tsikitis 2019). Compared to LR-HPV infection, HR-HPV genotypes—especially HPV16 and 18—are known to persist in the infected tissue, have an increased risk of disease progression and have mechanisms to escape the immune system (Department of Health and Aged Care 2023; Siddharthan, Lanciault & Tsikitis 2019).

#### Clinical presentation

##### Testing population

Currently, in selected locations, some HPV and cytology testing is available for HIV-positive asymptomatic patients; however, funding for this testing is ad-hoc through a mix of state and territory research and MBS sources and is rarely performed. The estimated uptake of the proposed investigative intervention (HPV and cytology testing) for high-risk testing over the next few years (i.e. 2022–2026) is presented in Table 3. If anorectal abnormalities are detected, the patient will undergo further investigations to assess any suspicious findings such as abnormal tissue, lesions or other potential indicators of anal dysplasia or cancer (Palefsky, Joel M et al. 2022; Stier, E. A. et al. 2024).

**Table 3 Estimated uptake of HPV and cytology testing in Australia 2023–2026**

	Prevalent population 2022	Estimated 2023	Expected 2024	Expected 2025	Expected 2026
<b>HPV testing</b>					
<i>People living with HIV, prevalent population includes:</i>	28,870 <sup>b</sup>				
MSM and TW living with HIV age ≥35 years (every 3-years)	21,320				
Women and MSW living with HIV age ≥45 years (every 3-years)	7,550				
78.4% of the prevalent population	22,634 <sup>c</sup>	7,544	7,544	7,544	7,544
MSM and TW living without HIV age ≥45 years * (every 5-years)	191,880*	38,376	38,376	38,376	38,376
People with vulval SCC/HSIL (HPV-associated) <sup>d</sup> (every 5 years)	2,400 cases <sup>d</sup> 800 HPV assoc	160	160	160	160
Organ transplant recipients** (every 3 years)	25,630**	8,543	8,543	8,543	8,543
People with previous anal cancer (every 6-months) <sup>e</sup>	1,900 <sup>e</sup>	3,800	3,800	3,800	3,800
People with incidental HSIL (every 5 years)	780	156	156	156	156
Number of patients undergoing HPV testing in any one year (excluding HIV incident population <sup>***</sup> )		58,579	58,579	58,579	58,579
<b>Reflex cytology testing</b>					
Number of HPV-positive patients undergoing cytology testing in any one year <sup>f</sup>		32,218	32,218	32,218	32,218
<b>Diagnostic HRA (± biopsy)</b>					
Number of HPV-positive patients undergoing HRA		12,887	12,887	12,887	12,887
<b>Treatment</b>					
Number of HSIL-positive patients undergoing HRA-guided ablation therapy		3,222	3,222	3,222	3,222

**Abbreviations**

**HIV** = human immunodeficiency virus, **HPV** = human papillomavirus, **HSIL**= high-grade squamous intraepithelial lesions, **HRA** = high-resolution anoscopy, **SCC** = squamous cell carcinoma, **SOTR** = solid organ transplant recipient

**Notes**

a Number tested in each subsequent year after 2022 is estimated to be the prevalent number divided by the frequency of testing (e.g. 1/3 of people living with HIV will be tested each year).

b <https://www.kirby.unsw.edu.au/research/reports/asr2023>

c Based on 78.4% of the incident HIV+ population being ≥30 years.

d Number of 10-year prevalent cases of vulvar cancer cases and 5-yearly testing.

e <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-prevalence> Number of surviving patients diagnosed with anal cancer, 5-year prevalence. Assume 60% 5-year survival, approximately 1,900 and twice-yearly testing.

f Although rates will vary greatly between the 6 groups, taken as a whole, approximately 55% of at-risk individuals tested for HPV would undergo cytology. Of these, approximately 40% would be referred on for diagnostic HRA and 25% of these would need treatment for persistent HSIL (expert advice).

\* Number of HIV-positive MSM has been subtracted from the total to avoid double counting (i.e. 213,320 MSM minus 21,320 (HIV+). The number of HIV+ MSM was sourced from King et al (2023). At the end of 2022, 21,320 people were living with HIV in who had acquired HIV through male-to-male sex (King et al. 2023), which was estimated to represent 10% of all MSM. This figure will overestimate the number of people to be tested as there is no way of knowing how many individuals are  $\geq 45$  years.

\*\* Number of surviving kidney transplant recipients has been used as a proxy for all organ transplant recipients. In 2019, there were a total of 12,815 people living in Australia with a functioning kidney transplant (Wyld, Wyburn & Chadban 2021), which was estimated to represent 50% of all solid organ transplants. \*\*\* Applicant proposed that the incident population be removed from estimates as they would already be covered by the estimates of the prevalent population tested. [Source](#)

Table provided by the applicant

*PASC noted inconsistencies in the reported follow-up testing intervals across the PICO. These have been reviewed by the applicant and a new Table has been provided to address these inconsistencies (Table 4). PASC asked if there is an evidence base to support the reported testing intervals, or if the items are solely based on expert opinions.*

### Treatment population

Currently, there is no nationally funded regular testing for anal HSIL in Australia. Thus, only patients presenting with anal symptoms—at an advanced stage of cancer with lesions usually  $>3$  cm—are seen by healthcare providers (Hillman 2023; Nyitray et al. 2020). The most common initial symptom of anal cancer is rectal bleeding (occurring in approximately 45% of patients) followed by anorectal pain or rectal lump sensation (30% of patients) (Walker, H & Palokas 2023).

## Intervention

### Testing

The proposed investigative technology is a targeted testing regimen for anal HPV and anal HSIL in people at high risk of anal cancer. At present, there are no clinical monitoring mechanisms or investigative technologies available for high-risk populations. When patients become symptomatic, their disease is likely to be at an advanced stage of anal cancer (usually lesions  $\geq 3$ cm). The proposed testing regimen involves an HPV test, a reflex LBC test if the prior HPV test is positive for HR-HPV, and a diagnostic HRA with biopsy (for lesion grading) if indicated according to the clinical algorithm. HPV and LBC tests represent potential new tests in the clinical management pathway of patients at high risk of anal cancer.

### HPV test

The application does not state a preferred HPV test (MSAC 1752 PICO Set p. 2). Within Australia, a variety of assays are used for the diagnosis of cervical HPV (Medical Services Advisory Committee 2014). HPV genotyping tests have been shown to improve specificity for detecting HSIL—information that may assist in patient risk stratification (Clarke, M. A. & Wentzensen 2018; Jin, F. et al. 2017; Lewitowicz et al. 2020).

HPV genotyping allows stratification of a person's risk of developing precancer or cancer according to the distinct risk levels associated with individual genotypes (Lewitowicz et al. 2020; Rokita et al. 2012; Wright et al. 2017). Full HPV genotyping is recommended for HIV-positive people because a larger proportion of cases is caused by a wide range of HPV types other than HPV16 (Lin, Franceschi & Clifford 2018). The applicant is requesting full genotyping for all listed subgroups, not just the HIV-positive subgroups.

*PASC noted that the National Cervical Screening Program (NCSP) involves partial genotyping. Partial genotyping includes an assessment for all 14 oncogenic HPV types; however, results are classified as HPV16, HPV18, or non-16/18 HR-HPV. PASC noted that most labs currently use the Roche 6800 HPV test*

*(partial genotyping) and the Hologic ThinPrep for cytology (a minority of labs use other platforms) for the NCSP.*

*PASC noted that very few laboratories are currently NATA-accredited for anal HPV testing, so even if currently available cervical assays were to be utilized (the most pragmatic approach), laboratories would need to conduct internal validation studies (as in-house in-vitro diagnostic [IVD] medical devices). However, the requirement for full genotyping for HPV, as requested by the applicant, would mean that this pragmatic approach would not be feasible, with implications for roll-out and accessibility. Additional assays would need to be registered with the Therapeutic Goods Administration (TGA) as no anal HPV assays have yet been approved by the TGA.*

*PASC noted that the only apparent reason for full genotyping in the algorithm is that patients with persistent infection with the same non-16 HR-HPV (but negative LBC) would be referred for diagnostic HRA. However, if the same patient had different non-16 HR-HPV infections, they would not be referred unless the cytology test was positive for HSIL. PASC questioned if it would be cost effective to implement full genotyping across all patients, simply to avoid HRA in this subgroup of patients. PASC emphasised that a full assessment of the costs/harms and benefits of partial vs full genotyping would be needed as part of any subsequent evaluation.*

*PASC noted that in some subgroups (e.g. MSM) it can be common for patients to have multiple HPV infections with different genotypes. PASC questioned how persistence (rather than reinfection) would be identified and whether a cumulative report (from the same laboratory) would be needed.*

The intervals for regular HPV testing are unclear, due to limited published evidence on this issue (Stier, E. A. et al. 2024). The application proposed different intervals for HPV testing based on the population-specific risks of anal cancer and on comparable screening intervals for cervical cancer (Table 4).

**Table 4 HPV testing frequencies for populations at high risk of anal cancer**

Population	Interval if previously HPV-negative	Triage test	HRA	HPV testing interval after negative HRA
1. MSM and TW living with HIV <sup>a</sup>	3 years	Cytology	<b>No HRA</b> <ul style="list-style-type: none"> <li>HPV negative + no clinical suspicion</li> </ul> <b>HRA regardless of cytology result</b> <ul style="list-style-type: none"> <li>HPV-16 positive (immediate HRA)</li> <li>HR-HPV (non-16) positive at baseline and 1 year (HRA at 12 months)</li> </ul> <b>HRA based on cytology result</b> <ul style="list-style-type: none"> <li>HR-HPV (non16) with cytology of pHSIL, HSIL or carcinoma</li> </ul>	1 years
2. MSM and TW living without HIV <sup>b</sup>	5 years			
3. Women and MSW living with HIV <sup>b</sup>	3 years			
4. Women with previous vulval SCC/HSIL – HPV associated <sup>c</sup>	5 years			
5. SOTR <sup>d</sup>	3 years			
6. Patients after treatment for anal cancer <sup>e</sup>	6 months			
7. Patients with incidental HSIL <sup>f</sup>	5 years			

**Abbreviations**

HIV = human immunodeficiency virus, HPV = human papillomavirus, HRA = high-resolution anoscopy, HSIL= high-grade squamous intraepithelial lesions, HR-HPV = high-risk human papillomavirus, LSIL = low-grade squamous intraepithelial lesions, MSM = men who have sex with men, MSW = men who have sex with women, pLSIL = possible low-grade squamous intraepithelial lesions, SCC = squamous cell carcinoma, SOTR = solid organ transplant recipient, TW = transgender women.

**Notes**

<sup>a</sup> Age ≥35 years

<sup>b</sup> Age ≥45 years

<sup>c</sup> Commencing within 1 year of diagnosis

<sup>d</sup> Commencing 10 years post-transplant

<sup>e</sup> Commencing 6 months after completion of treatment and lasting for 3 years or until any residual disease has been eradicated.

<sup>f</sup> Lesions found at colonoscopy and patients presenting with symptoms suggestive of cancer.

Harm is greater than benefit when HSIL is treated before ≥35 years of age.

**Source**

Table provided by the applicant.

*PASC expressed concern around the callback and follow-up requirements for testing (as per recommended intervals or if repeat testing required). The current recommendation assumes a stable medical practitioner and/or general practitioner (GP) relationship. However, not all patients will have this stable relationship in place, as some of the high-risk populations involved are vulnerable/stigmatised. In addition, PASC expressed concern around which entity would be responsible for monitoring testing intervals (12 months etc.). The applicant stated that many of the subgroups are currently engaged in health services, such as HIV services, which is likely to reduce the risk of loss to follow-up if repeat testing is required.*

*PASC noted that if the proposed anal HPV/HSIL surveillance program is to be pursued, it would likely have to utilise the infrastructure of the existing cervical screening program. However, PASC acknowledged that there are potential differences between LBC in cervical screening and the proposed intervention that must be considered, which could require local verification and/or criteria for additional training of cytology staff.*

### Cytology test

The application proposed that the HPV LBC test would be ordered after a positive HR-HPV test (including positive HPV-16). The cytology test can be performed on an aliquot of transport medium from the same anal sample or a second anal smear could be collected if required. The sample is processed to purify and concentrate the cells before being applied to a glass slide, which is stained to enhance visualisation under a microscope for identification of any cell abnormalities. An Australian modified Bethesda classification system (AMBS), as per cervical testing, is used to classify cell morphology. Cytology findings are reported as either negative for intraepithelial lesion or malignancy (NILM) or as showing squamous cell abnormalities, including LSIL or HSIL, PLSIL, PHSIL and SCC as per cervical screening in Australia. A finding of PHSIL, HSIL or SCC acts as a threshold for referring patients for a diagnostic HRA, if they tested positive for non16 HRHPV.

Anal cytology is a well-validated technique for identifying HSIL but some limitations exist (Clarke, Megan A et al. 2022). A systematic review and meta-analysis by Clarke et al (2022) found that the sensitivity (81.0%; 95% confidence interval [CI]: 72.0% to 87.0%) and specificity (62.4%; 95% CI: 54.0% to 70.0%) of anal cytology for identifying HSIL, when the threshold is PLSIL, varies considerably between studies (Clarke, Megan A et al. 2022). The interpretation of results is subject to considerable inter-observer variability and poor reproducibility (Gaisa, M. M. et al. 2021; McGovern, Fuller & Burris 2021; Rao et al. 2021). A lack of correlation between cytology results and histological grades has also been reported, leading to a higher likelihood of under-diagnosing lesions when interpretation is based solely on cytological findings (Albuquerque, A 2020; Gaisa, M. M. et al. 2021).

*PASC noted that dual immunohistochemistry for p16/Ki67 on the LBC sample is being investigated as a mechanism for assessing cases with persistent non-16/18 HR-HPV to determine the likelihood of significant disease and may assume greater relevance in this area.*

### Diagnostic HRA

In Australia, diagnostic HRAs are only undertaken either when there is concern that anal cancer may develop or in people participating in clinical trials (St Vincent's Hospital 2024c). The procedure is performed at a limited number of centres throughout the country. It is generally performed by a specialist (consultant) in a dedicated room during an hour-long appointment. The physical procedure generally takes 15 to 30 minutes (St Vincent's Hospital 2024c).

No specific bowel preparations are required prior to the appointment. Patients should not clean their anus (including douching and enemas) within 24 hours of the procedure (Johns Hopkins Medicine 2024; St Vincent's Hospital 2024c). Patients should also abstain from inserting objects (including medications) into their anus and avoid anal sex (Johns Hopkins Medicine 2024). This is to prevent the removal of potentially abnormal cells that are critical to a diagnosis (St Vincent's Hospital 2024c). The procedure includes both peri-anal and intra-anal examinations (Richel et al. 2013; St Vincent's Hospital 2024c).

### Intra-anal examination

The intra-anal examination starts with the insertion of an anoscope (small tube) into the anal canal with the assistance of a lubricant mixed with a local anaesthetic (Albuquerque, A 2015; St Vincent's Hospital 2024c). The colposcope (high-powered mobile microscope) is used to provide a magnified examination of the anal canal through the anoscope (Albuquerque, A 2015; Johns Hopkins Medicine 2024; St Vincent's



Hospital 2024c). Most of the colposcope investigation is conducted using x16 magnification; x25 magnification is used to examine specific areas of concern (Albuquerque, A 2015). Magnification x10 is used to examine the anal verge (Albuquerque, A 2015). The consultant may choose to temporarily insert a cotton swab or gauze containing dye (i.e. 5% acetic acid and/or Lugol's iodine) via the anoscope to assist with identification and characterisation of lesions (Albuquerque, A 2015; St Vincent's Hospital 2024c). Examination with and without dyes will generally be conducted (Albuquerque, A 2015).

The consultant may need to take biopsies from the anal canal using specialised biopsy forceps to assist in grading the lesion histologically (Albuquerque, A 2015; Johns Hopkins Medicine 2024; St Vincent's Hospital 2024c). The patient will be informed if this is necessary. Several biopsies may be required, resulting in several independent tissue samples (St Vincent's Hospital 2024c). The procedure is mostly painless and tissue samples are sent to a specialised laboratory for further investigation (Albuquerque, A 2015; Johns Hopkins Medicine 2024; St Vincent's Hospital 2024c).

#### *Peri-anal examination*

The peri-anal examination does not involve an anoscope. A colposcope is used to examine the outside edges of the anus following the application of 5% acetic acid (St Vincent's Hospital 2024c). Biopsies may be required. Unlike the intra-anal biopsy, the consultant may need to use local anaesthetics to perform the biopsy (St Vincent's Hospital 2024c). Sutures may or may not be necessary to improve post-procedure healing at the biopsy site(s) (St Vincent's Hospital 2024c). As with the intra-anal biopsy, tissue samples are sent to a specialised laboratory for further investigation (St Vincent's Hospital 2024c).

#### *Postoperative care following diagnostic HRA*

After the procedure, the patient will likely be provided with a pad to insert into their underwear (St Vincent's Hospital 2024c). Within the first week post-procedure, patients should avoid strenuous activities (heavy lifting etc.), inserting items into their anal canal (including medicine) and anal sex (Johns Hopkins Medicine 2024; St Vincent's Hospital 2024c). Patients will likely experience a little anal bleeding for the first 24 to 48 hours post-procedure. Complications within the first week after the procedure include scabs, infection, and bleeding during bowel movements (Johns Hopkins Medicine 2024; St Vincent's Hospital 2024c). Infections are rare after a diagnostic HRA (St Vincent's Hospital 2024c).

*PASC noted that there is currently a shortage of trained staff to perform diagnostic HRA and HRA/ablation. PASC also noted a lack of clarity around certification for clinicians enabling them to perform HRA/ablation. A recent international certification launched by IANS provides a potential process upon which local guidelines could be based. The applicant supported this possibility. The applicant stated that the creation of MBS item numbers for HRA may increase the number of clinicians willing to be trained in the procedure. The applicant noted there is some interest from clinicians who favour being trained in HRA, but are reluctant to commence training because they are concerned about the lack of rebates. The applicant noted that training in HRA is intensive due to the technical complexity of the procedure.*

#### **Treatment**

The treatment intervention is ablation of anal HSIL. Within the past few years, HRA-guided ablation has gained popularity for treating HSIL (Gaisa et al. 2020). The procedure is minimally invasive and requires minimal preparation (Cleveland Clinic 2019). It can be performed on an outpatient basis (i.e. day surgery) or in hospital, using either a local anaesthetic or sedation (Cleveland Clinic 2019; Gaisa et al. 2020; Mayo



Clinic 2024; Palefsky, Joel M et al. 2022). Evidence suggests that HRA-guided ablation of anal HSIL may not be beneficial for MSM patients <35 years of age as the harms of the treatment outweigh the benefit (Deshmukh et al. 2017; Stier, E. A. et al. 2024); however, the decision to ablate anal HSIL is patient-dependent and should be guided by the consultant (Stier, E. A. et al. 2024). With regards to anal low grade lesions, in Australia no active treatment is generally recommended unless symptoms exist (Cancer Council 2022).

The consultant will prepare the lesion-affected perianal area by disinfecting it and removing hair if needed (Cleveland Clinic 2019). HRA is used to identify the mapped intra and/or perianal HSIL, after which the ablation tool is used to remove the lesions by a variety of high-intensity energy (e.g. extreme temperature) modalities, such as laser, infrared coagulation and electrocautery (Cleveland Clinic 2019; Gaisa et al. 2020; Mayo Clinic 2024; Palefsky, Joel M et al. 2022). The lesion is fulgurated and debrided until only healthy tissue remains (Gaisa et al. 2020). Procedure time is patient-dependent but it can take up to 6 hours (Cleveland Clinic 2019).

*PASC noted that the application stated that ablation is only required for patients with persistent HSIL. However, the algorithms do not clarify how persistence is defined. The algorithms imply that ablation occurs whenever a diagnostic HRA confirms the presence of HSIL.*

#### *Postoperative care following treatment*

Postoperative care and recovery are guided by the consultant and are patient-dependent (Cleveland Clinic 2019). Patients may remain in hospital overnight or for a few hours. Those who receive local anaesthetic or sedation may suffer nausea and discomfort for a few days post-surgery (Cleveland Clinic 2019). Patients should avoid strenuous activities until it is safe to resume normal activities (Cleveland Clinic 2019). If excessive bleeding, pain or vomiting occurs, patients should seek immediate medical treatment (Cleveland Clinic 2019). In addition to any ablation-specific care, general postoperative care procedures such as those described following diagnostic HRA should be followed (see Postoperative care section).

#### *MBS item*

##### *Testing*

Existing MBS professional attendance items are available for clinicians to use when collecting an anal sample. Any appropriate attendance item contained within MBS Category 1, Group A1 (GP), A2 (other medical practitioner), A3 (specialist), A4 (consultant physician) or A32 (sexual health medicine) could be used.

There are 2 existing MBS items (MBS 69494, MBS 73043) that could cover HPV and cytology testing (Department of Health and Aged Care 2024a, 2024b). MBS item 69494 (schedule fee \$26.65) descriptor specifies the detection of a virus or microbial antigen or microbial nucleic acid (not elsewhere specified) to test high-risk patients when clinically indicated (Department of Health and Aged Care 2024a). MBS item 73043 (schedule fee \$22.85) descriptor specifies cytology testing of smears from the anus, nipple, skin, lip, mouth or nose for detection of precancerous or cancerous changes (Department of Health and Aged Care 2024b). Due to the broad nature of both MBS descriptors, it is unclear whether service claims have been made against either item for anal HPV testing and, if so, how many. The application indicated that these 2 items are not regularly used for HPV and cytology testing in high-risk populations.

*PASC noted that the proposed tests could theoretically be performed using existing generic MBS items for 'Detection of virus or microbial antigen or microbial nucleic acid not elsewhere specified' (MBS item 69494 = \$28.65) and 'Cytology smear from skin, lip, mouth, nose or anus for detection of precancerous or cancerous changes' (MBS item 73043 = \$22.85). However, PASC also noted that these MBS items are not currently used for anal HPV and cytology testing. PASC noted that the applicant is proposing the creation of new MBS items comparable to the cervical screening program and with a higher rebate than existing MBS items. The applicant noted that the increased rebate aims to support quality assurance and monitoring of the MBS item usage, and enables laboratory staff to be properly trained and install quality assurance methods for the proposed tests. The applicant noted that relative to the generic tests (MBS items 69494 and 73043), the proposed tests have an increased technical difficulty and specificity. The applicant also justified the higher fee for the cytology test by stating that nearly every anal cytology slide needs to be reviewed by a pathologist because the abnormality rate is much higher and interpretation more complex for anal samples (50% according to the Study of Prevention of Anal Cancer [SPANAC] study) than for cervical samples (20% abnormality rate as quoted by the applicant), which do not require pathologist review of every cytology sample. Furthermore, the applicant stated that pathology training and education would need to be concentrated in certain pathology centres to ensure a high quality of anal cytology interpretation.*

#### Treatment

No items on the MBS cover HRA-guided anal ablation (Department of Health and Aged Care 2024d). Existing MBS item 35645 (schedule fee \$363.10) covers cervical ablation with colposcopy in conjunction with ablative therapy of additional areas of HSIL of one or more sites of the vagina, vulva, urethra or anus. Item 35645 currently enables treatment of some patients who meet the restricted situation of the item descriptor.

#### Sample collection

##### Testing population

##### Anal Swabs

Anal HPV and cytology tests require the collection of an anal sample by a trained healthcare professional (St Vincent's Hospital 2024b). Once the patient is lying on their left side, a swab is inserted about 5 cm into the anal canal and a firm circular movement applied. Cells collected on the swab from the anal lining are mixed with a solution in a specific container and sent to a laboratory for testing (St Vincent's Hospital 2024b). This service can be performed in a consulting room or outpatient clinic by a sexual health practitioner, GP or specialist colorectal surgeon already involved in the patient's care (St Vincent's Hospital 2024b).

*PASC enquired if self-collection for anal HPV and HSIL testing could be a sustainable future option. PASC highlighted that for cervical screening tests, self-collection is offered to eligible people and the patient collects the specimen themselves. Self-collected vaginal swabs as part of the cervical screening program are sent to the laboratory dry and are not suitable for cytology as opposed to practitioner collected swabs which are immersed in a medium and can be used for reflex cytology. PASC noted that validation studies are currently underway to determine the utility of dry swabs for HPV testing. (Dry swabs have the potential to be collected at home and returned through the postal service.) However, PASC considered that dry swabs may be appropriate for HPV testing but would not be useful for cytology testing.*

### Diagnostic HRA biopsy

The specialist (consultant) may need to take a biopsy(s) of abnormal tissue identified during the diagnostic HRA (St Vincent's Hospital 2024c). Biopsies may be taken from either the anal canal or peri-anal area. Specialised tweezers are used to collect the biopsy samples (Albuquerque, A 2015; Johns Hopkins Medicine 2024; St Vincent's Hospital 2024c). To biopsy the peri-anal area, the consultant may need to use local anaesthetic to perform the biopsy (St Vincent's Hospital 2024c). Sutures may be necessary to improve post-procedure healing at the site(s) (St Vincent's Hospital 2024c). The biopsied tissue samples are sent to a specialised laboratory for further investigation (Albuquerque, A 2015; Johns Hopkins Medicine 2024; St Vincent's Hospital 2024c).

### Treatment

A biopsy sample may be collected during HRA-guided anal ablation.

### *Regulatory issues concerning HPV tests*

#### Testing

##### HPV testing and cytology

In Australia, human pathology testing, including for infectious diseases (e.g. HPV), is regulated by the National Association of Testing Authorities (NATA) (National Association of Testing Authorities 2024a). All laboratories (public or private) that conduct any human pathology testing must hold an ISO 15189 accredited by NATA (Dimech, Vincini & McEwan 2024; National Association of Testing Authorities 2024b). The ISO 15189 accreditation standard includes both management and technical standards (Dimech, Vincini & McEwan 2024; National Association of Testing Authorities 2024b). ISO 15189 accreditation enables specific information on human pathology to be collected, including haematology, microbiology, histopathology, immunopathology, cytopathology and chemical pathology (Dimech, Vincini & McEwan 2024; National Association of Testing Authorities 2024b).

#### HRA

Colposcopes and disposable anoscopes are regulated by the TGA (Therapeutic Goods Administration (TGA) 2023, 2024). Specific brands or models are not recommended or endorsed in the application (MSAC 1752 PICO Set p. 5-6). The application suggested that due to the complexity of the procedure, only accredited consultants be allowed to perform the procedure (MSAC 1752 PICO Set p. 25). However, there is currently no accreditation process for this in Australia, so currently any consultant with access to HRA equipment can perform the procedure.

### Treatment

#### HRA

See HRA section above.

#### Ablation system

Ablation systems are regulated by the TGA (Therapeutic Goods Administration (TGA) 2017). A specific brand or model is not recommended or endorsed in the application (MSAC 1752 PICO Set p. 5-6).

*PASC noted that ablation may be associated with multiple HRA appointments.*

## **Comparator(s)**

### Testing comparator

The application stated that no comparators for a targeted testing regimen for anal HPV and anal HSIL in people at high risk of anal cancer currently exist in Australia (MSAC 1752 PICO Set p. 26).

*PASC acknowledged that there is currently no targeted testing regimen for anal HPV and HSIL.*

*PASC noted that digital anorectal examination (DARE) should be conducted as part of investigative standard practice for patients symptomatic for anal cancer. However, the procedure is rarely conducted in this setting and it is not diagnostic.*

### Treatment comparator

The application stated that, in Australia there is no comparator to HRA-guided anal ablation (MSAC 1752 PICO Set p. 26). However, one published RCT compared HRA-guided ablative systems to topical ablative therapy (e.g. imiquimod and fluorouracil) to treat HPV-attributable anal HSIL in MSM living with HIV (Richel et al. 2013). An additional study combined HRA-guided ablation therapy with topical ablative therapy and excision under anaesthesia and compared it with active monitoring to treat HPV-attributable anal HSIL in asymptomatic persons living with HIV (Palefsky, Joel M et al. 2022). A clinical expert confirmed that topical ablative therapy and excision under anaesthesia are used in Australia to treat HPV-attributable anal HSIL (personal communication, 9 July 2024).

*PASC acknowledged that there currently are no funded MBS items for HRA-guided therapy or 'specific' ablative therapy for anal HSIL. There are existing MBS items linked to cervical HSIL ablation.*

*PASC noted that the assessment group highlighted topical ablative therapy and excision under anaesthesia as possible treatment comparators, although no specific MBS items are available for these procedures. The applicant noted that topical ablative therapy might be used for treatment of perianal HSIL, but is not routine care for intra-anal lesions.*

## **Reference standard (investigative technologies only)**

HRA has been described as the gold standard for the detection, targeted treatment and monitoring of HSIL (Spindler et al. 2024). Histological evaluation of HRA-guided biopsies is the gold standard for diagnosis of HSIL (Dias Gonçalves Lima et al. 2019; Rollo et al. 2021), and was proposed as the reference standard for this application.

The application proposed a combination of HR-HPV testing followed by cytology testing as a triage strategy if any non-16 HR-HPV genotype is detected (or direct referral to HRA if HPV16 is detected) to inform the decision to refer for HRA. IANS has indicated that use of HR-HPV genotyping—specifically for HPV16—may help identify patients at high risk of HSIL or cancer (Stier, E. A. et al. 2024). IANS further noted that triage of HR-HPV-positive results with cytology can improve specificity and reduce HRA referral, but that observational data on this approach is lacking (Stier, E. A. et al. 2024).

HRA and HRA-guided biopsy are not currently funded by the MBS. However, requests for listing were included in this application. Thus, the reference standard (histological evaluation of HRA-guided biopsy) is included in the proposed testing algorithm. In such cases, MSAC Guidelines state 'the accuracy of the

proposed test itself will need to be demonstrated by direct from test to health outcomes evidence showing a health benefit resulting from use of the test, or by comparison against a suitable clinical utility standard.'

While histological evaluation of HRA-guided biopsy may be an appropriate reference standard for the screening tests, to assess the accuracy of HRA and HRA-guided biopsy, evidence showing a health benefit resulting from use of the test is required.

The application cited the ANCHOR phase III RCT study (Palefsky, Joel M et al. 2022) in support of the clinical claim that patients treated for anal HSIL have improved outcomes relative to those who undergo active monitoring without treatment (MSAC 1752, PICO Set p.32). The ANCHOR study provides evidence on the effectiveness and safety of treating anal HSIL (relative to active monitoring) among persons  $\geq 35$  years of age living with HIV with HSIL confirmed via HRA-guided biopsy (Palefsky, Joel M et al. 2022). In the study, people age  $\geq 35$  years living with HIV were invited for anal HSIL screening. Screening included liquid-based anal cytology, a complete physical examination and HRA, with biopsies taken of lesions suspicious for HSIL or cancer. Participants with biopsy-confirmed HSIL were eligible for inclusion in the trial (Palefsky, Joel M et al. 2022).

### **Outcomes**

The application provided a list of outcomes for assessing the clinical safety and effectiveness of anal HPV and cytology testing in high-risk populations (MSAC 1752 PICO Set p. 32-33). The list has been reviewed and updated based on published literature (Albuquerque, A et al. 2018; Clarke, Megan A et al. 2019; Clarke, Megan A et al. 2022; D'Souza et al. 2016; Dias Gonçalves Lima et al. 2019; Donà et al. 2018; Gaisa et al. 2020; Goldstone, Stephen E, Enyinna & Davis 2009; Goldstone, Stephen E et al. 2019; Jin, Fengyi et al. 2016; Palefsky, Joel M et al. 2022; Poynten, I Mary et al. 2022; Santorelli et al. 2018; van der Zee et al. 2023; Vergara-Fernandez et al. 2021; Walker, RJ et al. 2024). The outcomes specified below are consistent across all 7 subgroups.

Non-health outcomes have been added, including the value of knowing and organisational considerations regarding HRA.

An MBS item(s) for regular anal HPV testing and anal ablative treatment for HSIL has potential ethical, organisational, legal, social and environmental considerations. Implementation of regular anal HPV testing may lead to an increase in the number of patients referred to HRA, which raises organisational issues such as an increase in consultant training for the procedure and the capacity of the workforce to meet the demand for services (i.e. number of consultants available for training). The purchase of relevant equipment by medical practices may be a further barrier to the implementation of anal HPV testing and HSIL treatment. An additional potential organisational issue is consideration of patient education regarding the procedure and what an LSIL or pLSIL result means, given there is no active treatment. Ethical considerations include identification of patients with a condition that has no clear treatment pathway, and the ability of often-stigmatised populations of MSM, TW and HIV-positive people to access the service. Legal issues around consultant training and accreditation for HRA need to be considered, due to the complexity of the procedure and the fact that currently there is no limitation or accreditation regarding who can perform the procedure in Australia. Accreditation may be needed to minimise patient harm and improve the quality of care provided. Social considerations must also be considered, specifically around

ensuring minority MSM, TW and HIV-positive populations are aware of the increased risk of anal cancer attributable to HPV (Charlton et al. 2017; Meites, Wilkin & Markowitz 2022; National LGBT Cancer Network n.d.; Piróg et al. 2022). Social considerations include patients feeling safe enough to disclose their sexual orientation and gender identity to their healthcare provider, as well as being willing to endure the social and physical discomfort associated with testing for sexual transmitted infections such as HPV (Charlton et al. 2017; Meites, Wilkin & Markowitz 2022; National LGBT Cancer Network n.d.; Piróg et al. 2022). Lastly, the environmental impact of medical waste associated with disposable anosscopes must be considered.

## Testing

### Safety

- Harms arising from anal sampling and HRA investigation (e.g. physical discomfort, pain, bleeding)
- Harms associated with the absence of testing
- Harms associated with false positive and false negative results

### Clinical effectiveness

#### Diagnostic accuracy

- Sensitivity, specificity
- Positive likelihood ratio, negative likelihood ratio
- Positive predictive value, negative predictive value
- ROC curves
- Diagnostic yield
- Need for repeat tests (e.g. unsatisfactory sample)

#### Patient management outcomes

- Change in patient clinical management
- Change in follow-up frequency
- Commencement of treatment

### Non-health outcome

- Value of knowing (i.e. clinical utility) of HPV and cytology testing
- Impact on patient behaviour (e.g. health, self-care practice, knowledge of diagnosis)
- Impact on gender diverse populations (including HIV-positive people)

### Healthcare resource use

- Costs associated with the intervention, including cost of appointments, anal HPV and cytology tests; cost of test processing; out-of-pocket costs
- Cost-effectiveness of anal HPV and cytology testing
- Total Australian Government healthcare costs
- Uptake of HPV/LBC/diagnostic HRA

*PASC noted that the comparability of assays needs to be considered when assessing diagnostic accuracy.*

*PASC acknowledged the change in clinical management that results from HPV/LBC testing and diagnostic HRA. PASC expressed concern around the lack of clarity around the frequency of follow-up testing and requested further information from the applicant. (see Table 4)*

*PASC noted that the value of knowing may impact patient behaviour.*

## Treatment

### Safety

- Adverse events (AE)
- All-cause mortality
- Hospitalisation
- Serious AE
- Bleeding
- Pain
- Infection

### Clinical effectiveness

- General health-related quality of life (HRQoL)
- HSIL-free survival
- Local HSIL recurrence
- Metachronous HSIL lesions
- Progression to anal cancer

### Healthcare resource use

- Number of treatments and costs associated with treatment (e.g. cost of treatment, specialist visits, requirement for subsequent treatment, hospitalisation, out-of-pocket costs)
- Cost-effectiveness of treatment
- Total Australian Government healthcare costs
- Uptake of HRA/ablation

*PASC acknowledged that harms associated with HPV/LBC/HRA included harms associated with false positive and/or false negative results.*

*PASC noted that expected uptake would be useful to assess as an outcome.*

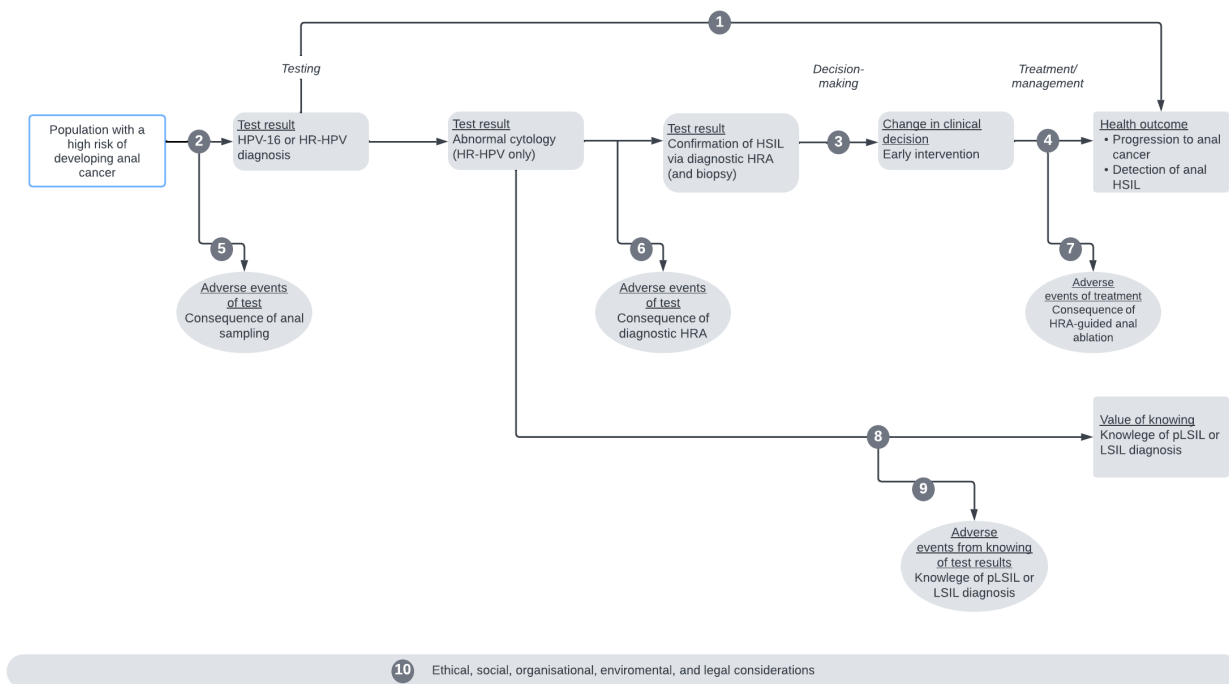
*PASC queried the out-of-pocket costs associated with HPV/LBC testing and diagnostic and treatment HRA/ablative treatment. PASC suggested these costs should be included as an outcome for assessment.*

## Assessment framework

The treatment regimen of anal HPV testing, cytology testing and diagnostic HRA is an investigative technology that may benefit a population at high risk of anal cancer by impacting subsequent management decisions. A single assessment framework (Figure 1) has been developed to illustrate pathways for the 7 subgroups.



**Figure 1 Assessment framework showing the links from people at high risk of developing anal cancer caused by HPV to HSIL lesions**



**Abbreviations**

**HIV** = human immunodeficiency virus, **HPV** = human papillomavirus, **HRA** = high-resolution anoscopy, **HSIL** = high-grade squamous intraepithelial lesions, **HR-HPV** = high-risk human papillomavirus, **LSIL** = low-grade squamous intraepithelial lesions, **pLSIL** = possible low-grade squamous intraepithelial lesions.

**Notes**

**1:** direct from test to health outcomes evidence; **2:** test accuracy; **3:** change in diagnosis/management; **4:** influence of the change in management on health outcomes; **5:** adverse events due to testing; **6:** adverse events due to subsequent tests; **7:** adverse events due to treatment; **8:** benefits associated with the value of knowing; **9:** harms associated with the value of knowing; **10:** ethical, social, organisational, legal and environmental considerations.

**Clinical management algorithms**

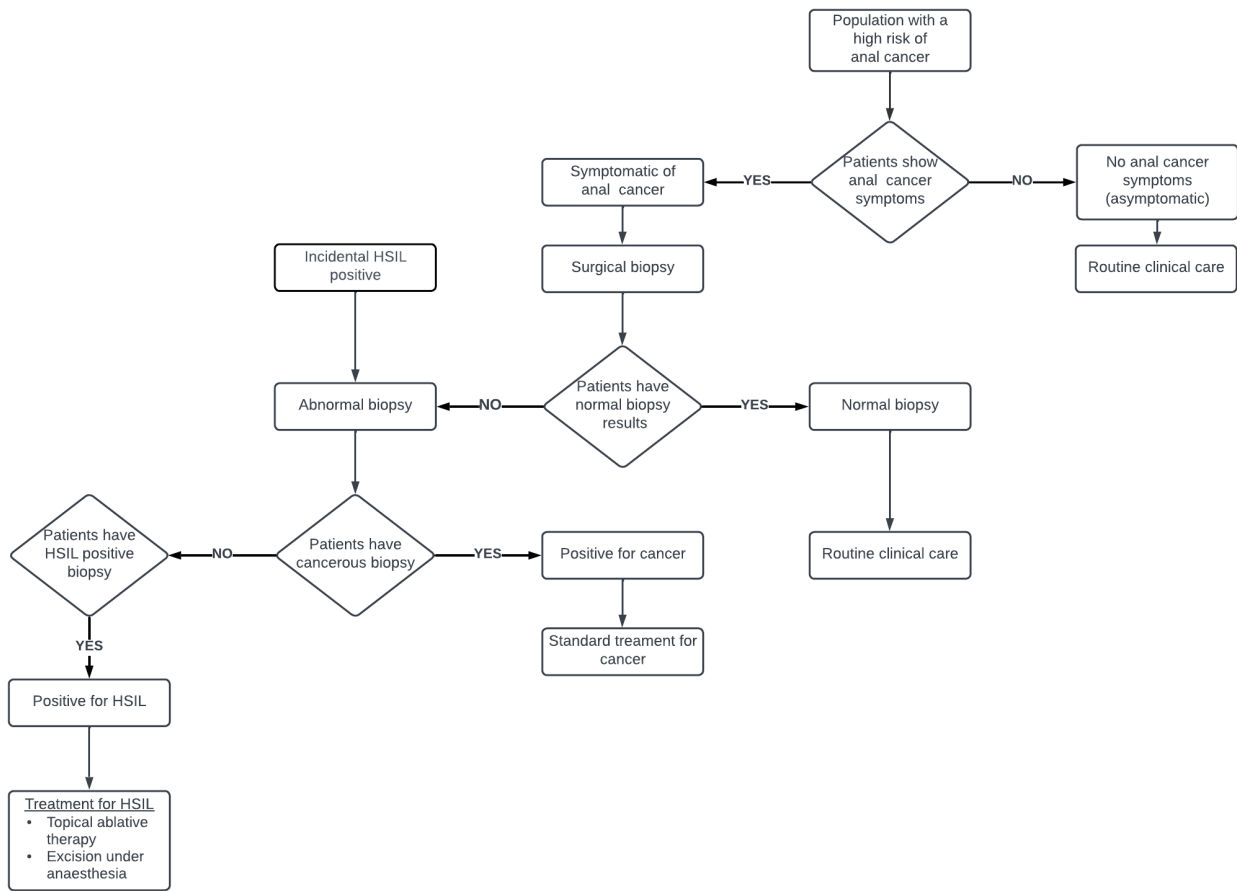
Two clinical management algorithms are presented below. The first, illustrates the current testing of patients symptomatic for anal cancer and the treatment of people who have HSIL (Figure 2). The second, shows the proposed testing protocol for asymptomatic populations at high risk of anal cancer, combined with the proposed treatment protocol for asymptomatic populations with HSIL (Figure 3).

*Current clinical management*

Currently, there are no national guidelines for anal cancer screening in Australia. Thus, only patients presenting with symptoms suggestive of anal cancer such as pruritus, bleeding, discharge, irritation and tenesmus are tested (Figure 2). If anal abnormalities are found during an examination, a surgical biopsy will be taken of any lesions suspected of being HSIL or anal cancer to confirm signs of dysplasia or cancer, and appropriate treatments will be initiated. The current test treatment in Australia for HSIL lesions includes topical ablation and surgical excision.



**Figure 2 Current clinical management algorithm**



**Abbreviations**

**HSIL**= high-grade squamous intraepithelial lesions

**Source**

Compiled by assessment group based on the proposed algorithm provided by the applicant (Figure 5, MSAC 1752 PICO Set, p. 22). Adjustments were made based on feedback from a clinical expert.

*Proposed clinical management*

The proposed clinical pathway (Figure 3) contains both the testing used to identify HSIL lesions in asymptomatic patients at high risk of anal cancer and the subsequent treatment of HSIL. The testing regimen includes HPV testing, cytology testing and diagnostic HRA.

All patients at high risk of anal cancer will be tested for HPV. If the HPV test is positive for HPV-16, the patient will be referred for a diagnostic HRA and biopsy. The HPV-16-positive sample will still undergo cytology testing; however, the results do not impact the testing pathway. If the HPV test is positive for other HR-HPV strains (non-HPV16), the samples will undergo cytology testing. A cytology test result indicating possible HSIL, HSIL or SCC will result in patients undergoing diagnostic HRA and biopsies. Patients being followed-up after treatment for anal cancer (subgroup 6) and patients with incidental HSIL (subgroup 7) would proceed directly to diagnostic HRA. Anal swabs for HPV and cytology testing would be taken at the appointment for the diagnostic HRA. In situations where the HPV test, cytology test or diagnostic HRA does not detect anal HPV and/or high-risk cell abnormalities, patients will undergo follow-up anal HPV tests at subgroup-dependent risk time intervals.

Confirmation of HSIL via diagnostic HRA and biopsy will result in patients undergoing HRA-guided ablation therapy. Depending on the extent and number of lesions present, additional HRA-guided ablation procedures may be necessary. Patients will have to undergo follow-up testing for anal HPV every 6 months for up to 2 years post-initial HRA-guided ablation treatment. At the completion of the 2-year follow-up period, HSIL-free patients will undergo follow-up anal HPV tests at subgroup-dependent risk time intervals.

*PASC highlighted that the 12-month follow-up testing for patients found to have LSIL requires further clarification. Clarity around the pathway for patients with negative LBC results is also needed. The proposed clinical management algorithm was updated to capture this. The proposed algorithm includes 12-month follow-up testing when the initial HPV test is positive for a non-16 HR-HPV strain to detect persistent non-16 HR-HPV infections.*

*PASC noted that LBC conducted after a positive HPV16 test result is informative only, as these patients will be referred directly for a diagnostic HRA.*

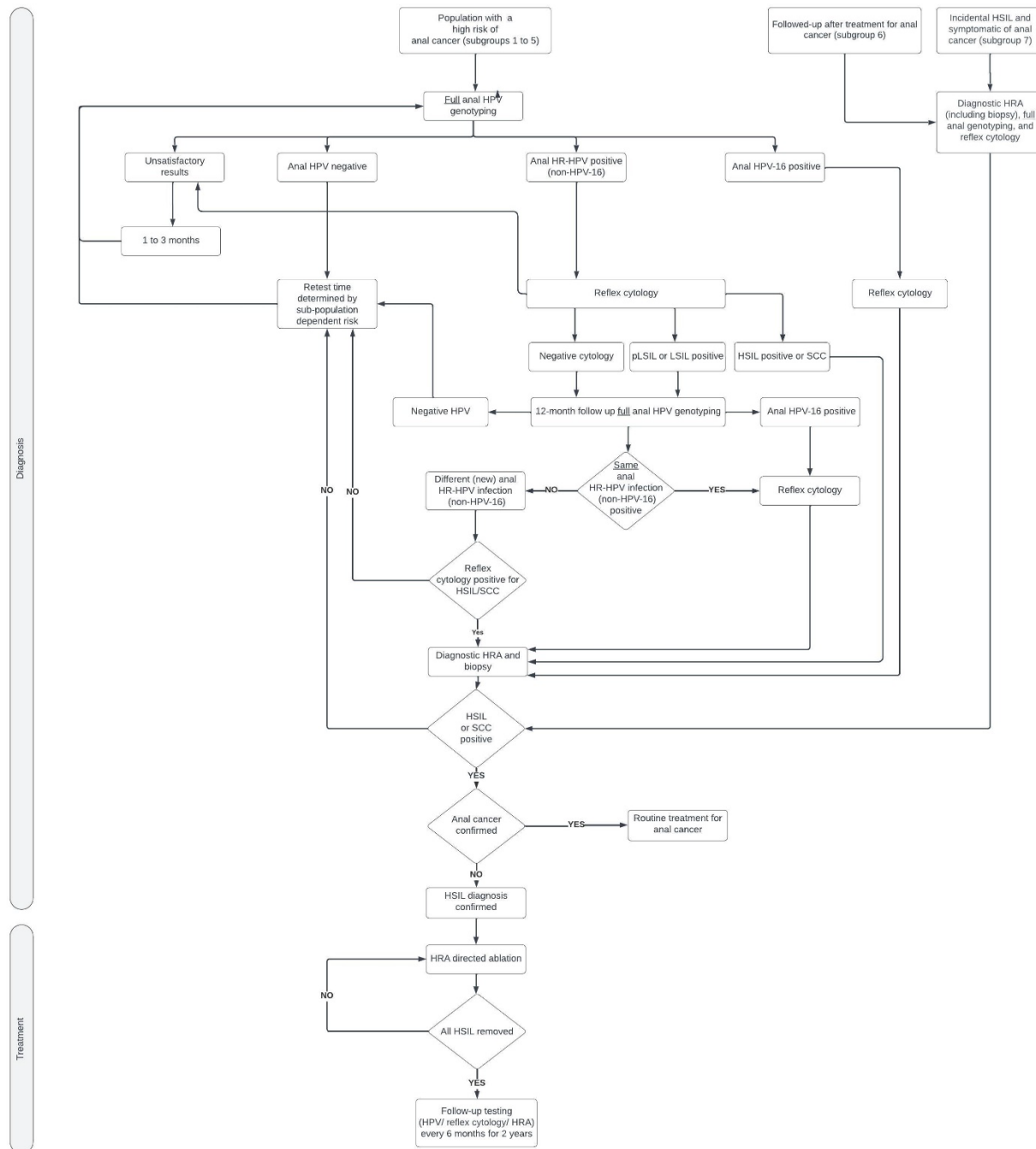
*PASC acknowledged that if persistent non-16 HR-HPV is identified, but LBC is negative, there is a need for a diagnostic HRA. PASC noted that this was not captured in the management algorithm. The proposed clinical management algorithm was updated to capture this.*

*PASC noted that the proposed management algorithm suggests that the follow-up post-HRA/ablation should occur every 6 months for a period of 2 years. The applicant noted that the follow-up testing should include HPV/LBC/HRA.*

*PASC sought clarification regarding the algorithm for patients in whom HSIL is identified incidentally or patients who have symptoms suggestive of anal cancer (subgroup 7). The clarification was to determine if these patients require HPV/LBC/HRA or whether they should progress directly to HRA/ablation. The applicant indicated that these patients would progress directly to HRA. The applicant stated that there is merit in also performing HPV genotyping and LBC at the time of HRA for added reassurance (as HRA is technically challenging) and for the quantification of future cancer risk (particularly in predicting recurrence and multifocality). The proposed clinical management algorithm was updated to capture this.*

*PASC accepted the proposed order of HPV testing followed by cytology, which mirrors the NCSP and is supported by SPANC study data. PASC noted results from a recent Australian study by the SPANC study group (not yet published), which assessed the value of reflex anal cytology testing after HPV testing and found the combined testing protocol improved test performance and reduced HRA referrals.*

**Figure 3 Post-PASC proposed clinical management algorithm**



**Abbreviations**

**HPV** = human papillomavirus, **HRA** = high-resolution anoscopy, **HSIL** = high-grade squamous intraepithelial lesions, **HR-HPV** = high-risk human papillomavirus, **LSIL** = low-grade squamous intraepithelial lesions, **pLSIL** = possible low-grade squamous intraepithelial lesions.

**Notes**

Unsatisfactory anal HPV genotyping results in repeat of anal swab, genotyping and cytology (if required).

Reflex cytology testing will be conducted on anal swabs positive for HPV-16. The testing results are informative only, they do not impact patient management.

Follow-up for HSIL patients after HRA-guided ablation is 6-monthly for 2 years. Follow-up after 2 years is based on subgroup-specific risk.

**Source**

Compiled by the assessment group based on the proposed algorithm provided by the applicant (Figure 6, MSAC 1752 PICO Set, p. 29). Adjustments were made based on feedback from a clinical expert.

## Proposed economic evaluation

The application claimed that anal HPV and cytology testing in asymptomatic populations at high risk of developing anal cancer to determine access to HRA and ablative treatment of HSIL is superior to routine clinical care (i.e. no testing and no treatment).

*PASC acknowledged that the clinical claim is that HPV/LBC testing in mainly asymptomatic patients at high risk of anal cancer to determine access to HRA/ablative treatment is superior to routine clinical care. The routine clinical care in this scenario is no testing and no treatment.*

The application highlighted that early detection of anal cancer precursor HSIL would enable patients to be treated more efficiently and would improve outcomes. It has been shown that the anal cancer progression rate of patients treated for anal HSIL is reduced by 60% compared to patients who undergo active monitoring without treatment (Palefsky, Joel M et al. 2022). The application further noted that if a cancer diagnosis (rather than HSIL) is established, early detection of cancer via testing will result in improved patient outcomes.

The clinical claim in the application leads to a cost-effectiveness analysis (CEA) or a cost-utility analysis (CUA) for the economic evaluation (Table 5).

*PASC noted that the clinical claim indicated a need for a CEA or CUA.*

*PASC considered that the effects of HPV vaccination should be incorporated into the economic evaluation, noting that although the full effects of vaccination may take decades to be seen, as vaccination takes effect in the population the risk of HPV will reduce over time. PASC also considered that the economic evaluation should incorporate the likely callback success rate and the behavioural change that may result once the tests and treatment become available.*

**Table 5 Classification of comparative effectiveness and safety of the proposed intervention compared with its main comparator, and guide to the suitable type of economic evaluation**

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain <sup>a</sup>	Noninferior <sup>b</sup>	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain <sup>a</sup>	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior <sup>b</sup>	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

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

### Notes

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

<sup>b</sup> An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

## Proposal for public funding

The application proposed new MBS items for the collection and testing of anal samples, diagnostic HRA and treatment of HSIL (HRA-guided ablation).

*PASC was concerned about a number of uncertainties associated with the proposal for public funding. The concerns are detailed below.*

- *PASC noted that the Department confirmed a new dedicated professional attendance item for sample collection would not be required. It was noted that specific training for clinicians to undertake sample collection is not required: a set of instructions for clinicians would be adequate. It was further noted that sampling conditions for the HPV genotyping item may either need to be specified in the item descriptor or described in an explanatory note.*
- *Both PASC and the Department noted a careful review of the proposed items was necessary to prevent unintended consequences, overuse and/or co-claiming. This includes potential co-claiming related to potential overlap with the cervical HSIL investigation and treatment items.*
- *Both PASC and the Department had concerns regarding how restrictions around patient eligibility criteria (e.g. issues of access and equity), follow-up testing (i.e. time intervals), responsible practitioners (e.g. test result monitoring, patient education, testing reminders), and practitioner training and awareness (e.g. training and HRA accreditation) could be integrated into the item descriptor.*
- *Both PASC and the Department questioned the relatively high rebates requested by the applicant for the proposed testing and treatment items, particularly when compared to the corresponding cervical HPV/HSIL-related items. The applicant stated the higher rebates were due to anal cytology assessment being more time intensive (compared to cervical cytology) and the increased complexity of anal anatomy compared to that of the cervix.*

### **Sample collection**

The application proposed a draft MBS item descriptor for a professional attendance item for sample collection (MSAC 1752 PICO Set p. 40) and suggested that costs associated with the collection of anal swab samples would be similar to those for cervical screening items. The application proposed a fee of \$17.90 for this item.

It was subsequently confirmed by the Department that a new dedicated professional attendance item for sample collection would not be required, as any appropriate existing attendance item contained within MBS Category 1, Group A1 (GP), A2 (other medical practitioner), A3 (specialist), A4 (consultant physician) or A32 (sexual health medicine) could be used for sample collection.

The application noted that the collection of anal samples would primarily be made by a GP or sexual health practitioner; specialists already involved in a patient's care may also conduct sampling (e.g. colorectal surgeon, transplant physician, gynaecologist) (MSAC 1752 PICO Set p. 25). The application stated that the sensitivity of the HPV testing technology, together with the use of internal controls, suggests that only instructions rather than specific training will be required for swab sample collection.

Research is underway to determine whether anal sample collection can be done by patients themselves (St Vincent’s Hospital 2024b); however, this option was not included in the application or proposed item descriptors (in contrast to cervical screening items, which include the option for self-collection).

**Pathology services**

Draft MBS item descriptors for the pathology service items proposed in the application are shown in Table 6 to Table 9. The application suggested that costs associated with the testing of anal samples would be similar to those for cervical screening items (MSAC 1752 PICO Set p.39). The application proposed fees of \$70.00 for genotyping and cytology tests. Fees for cervical screening MBS items 73070 to 73075 (partial genotyping test for oncogenic HPV) are \$35.00 and the fee for MBS item 73076 (cytology of a liquid-based cervical or vaginal vault specimen) is \$46.00.

The application provided a cost breakdown of relevant cost inputs for HPV genotyping (MSAC 1752 PICO Set p39), which includes costs for DNA extraction, PCR (reagents and consumables), controls and an estimated 5% repeat tests (subtotal of \$26.33). It also includes pre- and post-analytical costs (swab, transport, specimen and data handling, waste management; subtotal of \$20.00). However, the Department have advised that costs associated with collection, transport and storage of specimens are funded under existing patient episode initiation (PEI) items. Labour costs (subtotal of \$2.00) and costs for the pathologist’s time (subtotal of \$21.67) are also included.

HPV testing and cytology can be claimed under existing MBS items 69494 and 73043, respectively. The application indicated that these generic items are not regularly used for anal HPV and cytology testing in high-risk populations. The application proposed separate fit-for-purpose items.

**Table 6 Draft MBS item proposed in the application for HPV genotyping in asymptomatic patients**

Category 6 – PATHOLOGY SERVICES – P7 Genetics
MBS item BBBB Expanded genotyping of 14 oncogenic human papillomavirus genotypes (16, 18, 31, 33, 35, 39, 45 ,51, 52, 56, 58, 59, 66, 68) that may be associated with anal pre-cancer or cancer: (a) performed on a liquid based anal specimen; and (b) for an asymptomatic patient who is at least 35 years and has satisfied the conditions of sample collection using MBS item AAAAA
Fee: \$70.00

**Source**  
MSAC 1752 PICO Set, p.41

*PASC noted that proposed item BBBB covered expanded HPV genotyping in asymptomatic patients. PASC’s concerns with this item included a need to define what a ‘liquid-based’ anal sample is; consideration of whether partial genotyping (only testing for HPV16, 18, and non-16/18 HR-HPV) may be adequate rather than the proposed full genotyping, including its cost and implementation implications; and potential difficulties for pathology laboratories to know if ‘sample collection conditions’ have been fulfilled (PASC queried where these conditions would be stipulated). PASC noted it is appropriate that these items can be requested by any qualified medical practitioner. PASC noted that the recommended cost of \$70 is double*

*the NCSP fee of \$35. PASC accepted the Department-proposed amended fee of \$50 for full genotyping, which removes specimen costs (\$20) that are included as part of the patient episode initiation (PEI) item. However, PASC still emphasised that an assessment of full vs partial genotyping would need to be assessed as part of the assessment report. The Department suggested that the item does not require a frequency restriction as there is a low risk of leakage. However, PASC advised that this does not remove the necessity for an item note that details the relevant patient populations and recommended testing intervals.*

**Table 7 Draft MBS item proposed in the application for HPV genotyping for investigation of patients at higher risk or with symptoms, or for follow-up management**

Category 6 – PATHOLOGY SERVICES – P7 Genetics
MBS item CCCC
Expanded genotyping of 14 oncogenic human papillomavirus genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) performed on a liquid based anal specimen:
(a) for the investigation of a patient in a specific population that appears to have a higher risk of anal pre-cancer or cancer; or
(b) for the follow-up management of a patient with a previously detected oncogenic human papillomavirus infection or anal pre-cancer or cancer; or
(c) for the investigation of a patient with symptoms suggestive of anal cancer
Fee: \$70.00

**Source**

MSAC 1752 PICO Set, p.41

*PASC noted that proposed item CCCC covers genotyping for patients in a specific population that appears to have a higher risk of anal HSIL or cancer, patients requiring follow-up and patients with symptoms suggestive of anal cancer. PASC suggested that this descriptor could apply to many different patient populations. But PASC also noted that this may have benefits insofar as it means that access to testing would not be restricted only to the specific groups in the proposed population with a tenfold risk of anal cancer, but could be based on the clinical discretion of the referring practitioner. PASC questioned if symptomatic patients or those with incidental HSIL would require this HPV testing item, as these patients will proceed directly to HRA. PASC questioned if knowledge of the HPV genotype would impact management in these patients. The applicant stated that there is prognostic value (recurrence/multifocality) in the results of HPV/LBC in these patients.*

**Table 8 Draft MBS item proposed in the application for repeat HPV genotyping testing**

Category 6 – PATHOLOGY SERVICES – P7 Genetics
MBS item DDDD
Expanded genotyping of 14 oncogenic human papillomavirus genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) performed if:
(a) the test is a repeat of a test to which item BBBB, CCCC or this item applies; and
(b) the specimen collected for the previous test is unsatisfactory
Fee: \$70.00

**Source**

MSAC 1752 PICO Set, p.41

PASC noted that proposed item DDDD covers HPV follow-up testing and repeat testing after an unsatisfactory test. PASC noted the Department’s observation that proposed item DDDD may be redundant if no frequency restriction was placed on item BBBB. However, PASC noted that testing intervals would need to be noted in item BBBB, and that a separate item for repeat/unsatisfactory tests as per proposed item DDDD is useful (as in the NCSP) for identifying clinicians who repeatedly provide poor samples.

**Table 9 Draft MBS item proposed in the application for cytology testing of HPV-positive anal specimens**

Category 6 – PATHOLOGY SERVICES – P6 Cytology
<p>MBS item EEEE</p> <p>Cytology of a liquid based anal specimen found to be HPV positive by item numbers BBBB, CCCC or DDDD, where the stained cells are examined microscopically or by automated image analysis by or on behalf of a pathologist, if:</p> <p>(a) the cytology is associated with the detection of oncogenic human papillomavirus infection by:</p> <p>i. a test to which item BBBB applies; or</p> <p>ii. a test to which item CCCC applies for a patient mentioned in paragraph (a) or (b) of that item; or</p> <p>(b) the cytology is associated with a test to which item CCCC applies for a patient mentioned in paragraph of that item; or</p> <p>(c) the test is a repeat of a test to which this item applies, if the specimen collected for the previous test is unsatisfactory</p>
Fee: \$70.00

**Source**

MSAC 1752 PICO Set, p.42

The application noted that HPV testing and cytology testing would be delivered by trained scientists in an accredited laboratory, and that testing would be requested by the treating clinician and provided by approved practising pathologists in line with other tests on the MBS Pathology Table (MSAC 1752 PICO Set p.25). According to the application, testing would be delivered only by approved practising pathologists (appropriately qualified cytologists and histopathologists who are Fellows of the Royal College of Pathologists of Australasia [RCPA]) in NATA-accredited pathology laboratories (as defined in the MBS Pathology Table) by referral only by registered medical practitioners (in line with other tests in the MBS Pathology Table) (MSAC 1752 PICO Set p.25).

The practice note associated with cervical and vaginal screening items (PN.0.22) specifies that ‘unless a co-test is specifically requested...the pathology laboratory will by default perform an HPV test and then only undertake reflex LBC testing if oncogenic HPV (any type) is detected’ (Department of Health and Aged Care 2024c). This would also apply to the screening item proposed in this application.

The application proposed different intervals for HPV testing (6-monthly to 5-yearly) based on population-specific risks (see Table 4, Intervention section).

PASC noted that proposed item EEEE covers LBC (i.e. not the direct smear). PASC queried why the proposed fee (\$70) should be higher than the cervical LBC rebate (currently \$46). PASC acknowledged the current cervical LBC rebate may be inadequate, considering the compliance requirements. The applicant noted that 50% of anal cytology tests are abnormal, therefore nearly all LBC slides must be reviewed by a pathologist in addition to a cytologist. The proportion of abnormal cervical cytology slides is much lower



(approximately 20%, as quoted by the applicant), so pathologists do not need to review every cervical LBC slide. This is the justification for the increase in the requested rebate compared to reflex cervical LBC testing.

PASC noted that the wording of this item number must be simplified because the logic underlying conditions (a), (b) and (c), as specified in the item EEEE item descriptor, is unclear.

### Diagnostic HRA

The draft MBS item descriptor proposed in the application for diagnostic HRA is shown in Table 10. The application suggested that costs for diagnostic HRA and anal HSIL treatment are based on fees for the colposcopy and treatment MBS items listed for the cervical screening program (MSAC 1752 PICO Set p.40). The fee for MBS item 35614 ('Examination of the lower genital tract using a colposcope...') is currently \$72.75 (July 2024). The application justified its proposal of a higher fee (relative to MBS item 35614) for diagnostic HRA based on increased complexity and procedure length and the higher number of biopsies taken on average (MSAC 1752 PICO Set p.40).

**Table 10 Draft MBS item descriptor proposed in the application for diagnostic high resolution anoscopy**

Category 3 – THERAPEUTIC PROCEDURES
<p>MBS item FFFF</p> <p>Examination of the anal canal and perianus using a high resolution anoscope in a patient who:</p> <ul style="list-style-type: none"> <li>(a) has a human papilloma virus (HPV) related anal/perianal indication; or</li> <li>(b) has symptoms or signs suspicious of anal/perianal malignancy; or</li> <li>(c) is undergoing follow-up treatment for anal/perianal malignancy; or</li> <li>(d) is undergoing assessment or surveillance of an anal/perianal premalignant or malignant disease; or</li> <li>(e) is undergoing assessment or surveillance as part of an identified at-risk population.</li> </ul> <p><u>Explanatory notes:</u></p> <p>Benefit will not be paid except in the following circumstances:</p> <ul style="list-style-type: none"> <li>(a) where the patient has had an <b>abnormal</b> anal HPV test result <b>using MBS item AAAA</b>; or</li> <li>(b) where the patient has been referred by another medical practitioner with suspicion of anal cancer.</li> </ul> <p>Diagnostic HRA performed no more than four times per year.</p> <p>HRA must be performed by a suitably trained and qualified practitioner.</p>
Fee: \$140.60

**Note**

Red text added by the assessment group based on advice from the Department

**Source**

MSAC 1752 PICO Set, p.42

In discussion with the Department and the applicant, it was agreed that an additional MBS item specific to HRA-guided biopsy should be included in the application. A draft item descriptor for the additional MBS item (drafted by the assessment group) is included in Table 11.

PASC noted that proposed item FFFF covers HRA. PASC raised concerns with the proposed fee (\$140.60) being higher than the current rebate for colposcopy (\$72.75 – item number 35614). The applicant cited higher anatomical complexity of the anus as the reason for the higher rebate. The applicant had also cited the higher number of biopsies taken as a reason for the higher rebate; however, this no longer applies, as the applicant has since proposed a separate item for biopsy (proposed item HHHH) after discussions with the Department. PASC noted that the phrasing of point ‘e’ could potentially allow the use of HRA without patients having undergone HPV/LBC. PASC also questioned how a ‘suitably trained and qualified practitioner’ could be defined, as stipulated in the explanatory note.

**Table 11 Draft MBS item descriptor proposed by assessment group for high resolution anoscopy-guided biopsy**

Category 3 – THERAPEUTIC PROCEDURES
MBS item HHHH Anus, biopsy of, when performed in conjunction with a service to which item FFFF applies
Fee: \$80.20

**Note**

Draft descriptor based on MBS item 35615 for vulva or vaginal biopsy when performed in conjunction with 35614. An MBS fee equivalent to item 35615 has been suggested.

**Source**

Compiled by assessment group.

PASC noted that proposed item HHHH covers HRA-related biopsy. It is proposed to be separate from the HRA item above (proposed item FFFF). PASC stated that the proposed item needs a limit on the number of times it can be co-claimed with HRA. The relevant pathology items are ‘coned’ at 1 biopsy, 2–4 biopsies, 5–7 biopsies et cetera. PASC noted that MBS items 72823 (fee: \$97.15) and 72824 (fee: \$141.35) provide rebates for a single biopsy or for 2–4 biopsies in a single procedure, respectively.

**Ablative treatment**

The draft MBS item descriptor proposed in the application for anal HSIL treatment is shown in Table 12. The application suggested costs for diagnostic HRA and anal HSIL treatment based on fees for the colposcopy and treatment MBS items listed for the cervical screening program (MSAC 1752 PICO Set p.40).

The fee for MBS item 35644, which covers cervical treatment only (‘Cervix, ablation by electrocoagulation diathermy, laser or cryotherapy, with colposcopy...’) is currently \$232.00 (July 2024). The fee for MBS item 35645, which covers treatment at one or more sites of the vagina, vulva, urethra or anus (‘Cervix, ablation by electrocoagulation diathermy, laser or cryotherapy, with colposcopy...’) is \$363.10. This item, which allows for treatment at one or more sites including the anus, already allows for treatment of anal HSIL for women who are HPV positive at a lower fee than proposed in this application. The application justified its proposal of a higher fee (relative to MBS item 35645) based on the length of time required for the procedure due to the complex anatomy of the anus (MSAC 1752 PICO Set p.40).

**Table 12 Draft MBS item descriptor proposed in the application for treatment of HSIL (ablation with high resolution anoscopy)**

Category 3 – THERAPEUTIC PROCEDURES
<p>MBS item GGGG</p> <p>Anal HSIL ablation or cryotherapy, with high-resolution anoscopy guidance, including any local anaesthesia or biopsies, for previous biopsy confirmed HSIL <del>using item number FFFF*</del>;</p> <p>Up to a maximum of 6 ablative treatments per episode, until clearance of HSIL is achieved.</p> <p><u>Explanatory notes:</u></p> <p>Benefit will not be paid except in the following circumstances:</p> <p>(a) where the patient has histological confirmation of anal HSIL <del>using MBS item CCCC;* or</del></p> <p><del>(b) where the patient has been referred by another medical practitioner with suspicion of anal cancer. **HRA must be performed by a suitably trained and qualified practitioner.</del></p> <p><del>(Anaes.)</del></p>
Fee: \$701.60

**Notes**

Red text added by the assessment group based on advice from the Department  
References to item numbers removed as testing may occur outside the MBS system.  
Reference to suspicion of anal cancer removed as alternative treatment pathway more appropriate than ablation.

**Source**

MSAC 1752 PICO Set, p.423

The Department considered that the inclusion of restrictions based on specific item numbers may limit patient access. Therefore, references to items FFFF and CCCC have been removed from the proposed item descriptor. Additionally, the requirement of referral by another medical practitioner for suspicion of anal cancer has been removed, as the wording of the item descriptor makes it clear that the item is intended for use only for patients with previous biopsy-confirmed HSIL.

When ablative methods such as electrocautery, infra-red coagulation and laser are used to treat HSIL, repeated treatments are required (St Vincent’s Hospital 2024a). Therefore, individuals requiring ablative treatment will likely claim the proposed item GGGG multiple times within a year. The proposed item descriptor (Table 12) specifies a maximum of 6 ablative treatments per episode until clearance of HSIL is achieved.

The risk of HSIL recurrence after ablative treatment is high and repeat examinations are required (Goldstone, S. E., Johnstone & Moshier 2014; Spindler et al. 2024). The application suggested a limit on the number of diagnostic HRAs of no more than four times per year (Table 10).

HRA requires specialised training associated with a challenging learning curve (Lum et al. 2020; Sun et al. 2023). Compared to cervical colposcopy, performing an HRA is more challenging due to a higher prevalence of coexisting pathologies in the anal canal that may prevent correct visualisation, and the anal anatomy itself, whereby lesions can be missed in the folds of the anal mucosa (Clarke, M. A. & Wentzensen 2018).

The application noted that given the importance and difficulties of anal HSIL identification, consideration should be given to restricting diagnostic and treatment HRA to suitably trained and certificated practitioners (MSAC 1752 PICO Set p.40).

IANS has defined quality criteria for HRA, which recommend practitioners perform a minimum of 50 diagnostic HRAs per year and achieve a detection rate of 90% for HSIL in patients in whom cytological HSIL has been detected in the preceding 3 months (Hillman et al. 2016; Spindler et al. 2024). The application noted that IANS recently launched an international certification, upon which local guidelines could be based (MSAC 1752 PICO Set, p.25). No certification process is currently in place.

*PASC noted that proposed item GGGG covers ablative treatment for anal HSIL. PASC noted the procedure may be performed in an inpatient setting and require general anaesthetic. PASC questioned what defines an 'episode', due to the item descriptor stating 'a maximum of 6 ablative treatments per episode, until clearance of HSIL is achieved'. PASC also questioned whether the proposed HRA item (FFFF) could be routinely charged with the proposed ablative treatment item (GGGG).*

*PASC questioned whether the cervical ablation item with colposcopy (MBS item 35645) could be routinely co-claimed alongside the proposed ablative treatment item (GGGG). PASC noted that the proposed item fee of \$701.60 is considerably higher than that for comparable items for cervical ablation (MBS items 35644 and 35645), noting that the applicant suggested this is based on the time required due to the complex anatomy of the anus. PASC noted that careful thought would be required to assess potential interactions between items 35539 (colposcopically directed laser therapy for HSIL in vagina, vulva, urethra or anal canal, including biopsies), 35644 (cervical ablation with colposcopy for HSIL, including biopsies), 35645 (cervical ablation with colposcopy for HSIL, including biopsies, in conjunction with ablative treatment of additional areas of HSIL in vagina, vulva, urethra, or anus), 35648 (complete excision of the endocervical transformation zone, using large loop or laser therapy, including biopsies, in conjunction with ablation of additional areas of HSIL in one or more sites from vagina, vulva, urethra, or anus) and proposed item GGGG, including potential co-claiming.*

Diagnostic HRA and treatment can be performed in a variety of private and public settings, but usually occurs in an outpatient setting. Treatment may be conducted in an inpatient setting (including operating theatres and endoscopy suites) if the patient requires pain management and monitoring; however, this would be the minority of cases. Even among high-resource settings, limited availability of HRA infrastructure for referral of patients with abnormal results is a major challenge in the implementation of anal cancer screening (Stier, E. A. et al. 2024). Screening providers should have access to HRA clinics, and screening only be performed if referral for HRA is possible (Spindler et al. 2024; Stier, E. A. et al. 2024).

*PASC also requested additional consultation to justify the 2-fold increase in the fee relative to existing items. PASC noted targeted feedback from the Colorectal Surgical Society of Australia and New Zealand (CSSANZ) regarding the increased complexity involved in anal HSIL ablative therapy vs cervical HSIL. PASC suggested additional targeted consultations on this issue may be needed.*

## Summary of public consultation input

PASC noted and welcomed consultation input from 9 organisations and 2 individuals, 1 of whom is a consumer and 1 a health professional. These were provided in the lead-up to the August 2023 PASC meeting (from which the application was withdrawn), as well as part of the consultation conducted prior to the August 2024 PASC consideration. The 9 organisations that submitted input were:

- ACON
- Cancer Council Australia
- The Royal Australian College of General Practitioners (RACGP)
- Australian Pathology
- National Association of People with HIV Australia (NAPWHA)
- Rare Cancers Australia
- Colorectal Surgical Society of Australia and New Zealand (CSSANZ)
- Private Healthcare Australia (PHA)
- Positive Life NSW

The consultation feedback received all was supportive of public funding for the proposed testing and treatment interventions.

### Consumer Feedback

The individual consumer stated that a diagnosis of HPV 16 and/or 18 can be extremely difficult and cause anxiety about developing cancer. They said access to anal cytology was unavailable even when they requested this, other risk factors were present and the individual was willing to pay for testing.

Consultation feedback highlighted the negative impacts of anal cancer and the adverse effects of treatment. Rare Cancer Australia, Positive Life NSW, NAPWHA and CCSANZ highlighted the adverse impacts of pelvic organ dysfunction arising from anal cancer treatment. This included pain, fertility impacts, sexual dysfunction and negative effects on intimate relationships, urinary dysfunction, faecal incontinence, intestinal hurry and vaginal stenosis.

Positive Life NSW provided results of a survey of people with HIV and gay and bisexual men in NSW about their awareness of HPV-related anal cancer.

*PASC expressed concern around an equity issue raised by a consumer. Heterosexual women who are HIV-negative are scared about the possibility of anal cancer following a diagnosis of cervical HPV16/18. However, under the current proposal this population group may not be able to access anal HPV testing. PASC considered that anal HPV testing should be accessible to all people with HR-HPV.*

*PASC noted that patient advocacy groups were supportive of the proposed testing regimen and corresponding treatment. The NAPWHA and Positive life NSW noted that there is currently low health literacy around anal cancer and that the disease is stigmatised and the treatment can be painful. Rare Cancers Australia highlighted this application addresses an area of unmet need. Positive life NSW stated there is a clear economic benefit and that increased awareness among at-risk groups and clinicians is paramount. Positive life NSW also highlighted the limited number of anal dysplasia clinics and lack of specialists for HRA. The impact of the anal cancer prevention program is dependent on how accessible the testing and treatment is to those with the greatest need.*

## **Clinical need and public health significance**

The main benefits of public funding that were received in the consultation feedback included the potential to prevent anal cancer if HSIL is identified and treated. The feedback considered that avoiding cancer or earlier diagnosis would avoid deaths, morbidity and the adverse effects of treatment for more advanced anal cancer. This includes invasive surgery, colostomy, radiation therapy, associated adverse effects on pelvic organs and the negative impacts on quality of life. The feedback considered that there is an unmet need for subsidised testing and treatment, both medically and financially.

Other benefits included improved health equity and inclusion, especially for LGBTQ+ people (lesbian, gay, bisexual, transgender, queer or questioning and others) and people with HIV, improved health literacy and reduced costs to the health system.

The main disadvantage of public funding that was received in the consultation feedback was that the proposed testing may not identify and enable early diagnosis for women (implicitly women who may not be considered high risk) who otherwise form the bulk of the anal SCC cases to be diagnosed earlier.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included follow-up treatment (not included in the 2023 application) and an adequate workforce trained and able to provide HRA (Cancer Council, Positive Life NSW).

Several respondents considered improving health literacy, community engagement, educational campaigns and building on knowledge from cervical cancer screening as important for successful implementation. Several respondents considered that overcoming barriers and stigma and improving health literacy were important for successful implementation. Several respondents (Positive Life, ACON, NAPWHA) stated that stigmas (from both consumers and health professionals) around anal cancer, anal health and symptoms, sexual practices that increase risk of anal cancer, and HIV are barriers to testing.

### Comments on testing intervention

One respondent (a pathologist) provided an unpublished manuscript that evaluated different testing and referral algorithms using findings from the SPANC study. Two testing and referral algorithms had comparable sensitivity and specificity to high-risk HPV testing alone. These involved immediate referral of those with HPV16 infection and either immediate or delayed (for 12 months) referral for those with non-HPV16 infection depending on cytology result at baseline.

Cancer Council Australia (in response to the 2023 application) advised that hybrid capture to test for HPV has been superseded and is not widely available. It considered that modern PCR tests that separately identify HPV16 would be more appropriate.

*PASC noted feedback from CSSANZ. The professional body noted that late presentation can necessitate radical surgery (including colostomy and loss of pelvic organs).*

*PASC noted that CSSANZ noted recurrent anal SCC is more likely than a secondary cancer and questioned the benefit of 'screening-type' investigations in patients with prior anal SCC.*

*PASC acknowledged that CSSANZ noted the costs associated with the proposed anal HSIL treatment may require justification. CSSANZ also suggested that the fee for cervical HSIL treatment may need to be adjusted upwards.*

*PASC noted CSSANZ concerns regarding the proposed target population. CSSANZ were specifically concerned that women with a history of vaginal or cervical SCC/HSIL were not included in the population as they can experience 'field change', whereby epithelial changes are more broad-based and extend to involve the perineum and/or anus. PASC supported this concern, stating that there is uncertainty if the inclusion criteria would also enable women at high risk of anal cancer (who comprise the majority of anal SCC cases) to access early diagnosis.*

#### Comments on treatment intervention

CCSANZ advised that examination of the anal canal using HRA is fairly comparable to the examination of the lower genital tract using a colposcope in terms of time and complexity, stating that the procedure takes 15–30 minutes. However, ablation retraction and visualising the anal canal for ablative treatment is more challenging than it is for cervical lesions. In the experience of CCSANZ, HRA has been provided at the request of a gynaecologist/gynae-oncologist where a patient is typically in the operating theatre under a general anaesthetic and having the examination.

CCSANZ and NAPWHA both stated that the procedures are painful and may require anaesthesia. CCSANZ advised that bedside anoscopy and colposcopy are considered 'well tolerated' but considered unpleasant by patients who have had the procedure.

Australian Pathology considered there are already treatment modalities available in Australia in addition to a number of Australian trials of new and innovative treatment modalities.

#### **Indication(s) for the proposed medical service and clinical claim**

The consultation feedback mostly agreed with the proposed populations.

- ACON advised that the population in the 2023 application had the potential to exclude other at-risk people, as unprotected anal sex is a risk factor for developing HPV not limited to gay and bisexual men.
- ACON suggested that aligning eligibility for anal HPV testing and cytology with HPV testing for cervical cancer screening (from 25 years for cervical cancer, from 35 years for anal cancer) would remove barriers and create clear and effective health promotion messaging.
- CCSANZ (2024 application), RACGP (2023 application) and Cancer Council Australia (2023 application) commented on the subpopulation of 'women with other gynaecological HPV-associated lesions'. They considered that this subpopulation needed further clarification. The population was identified as being a large (and underestimated) group with different risks of developing anal cancer. CCSANZ considered this group often has a 'field change' in the perineum from exposure to HPV infection.

The consultation feedback generally agreed with the proposed comparator.

The consultation feedback generally agreed with the clinical claim, with Cancer Council Australia highlighting that the potential harms of testing and investigation should also be described.

## Cost information for the proposed medical service

The consultation feedback was mixed regarding the proposed service descriptor. Cancer Council Australia supported new MBS item numbers because adapting existing cervical screening items was considered cumbersome, hard to maintain and likely difficult for providers to understand.

The consultation feedback was mixed regarding the proposed service fee. The RACGP advised that the proposed rebate (\$17.90) for the consultation and swab was inadequate and advised it would be more appropriate to be equivalent to Level B (MBS item 23, \$42.85). CCSANZ advised the cost associated with the proposed HSIL treatment seemed a little high. Treatment of cervical HSIL under MBS item number 35645 attracts a lower fee and this may require some adjustment (upwards) to reflect an appropriate fee.

*PASC noted that the RACGP was supportive of the application, but indicated that the proposed Category 1 attendance fee of \$17.90 is too low to take a patient's history, perform a swab and provide associated counselling.*

*PASC noted that PHA stated management of anal cancer is expensive and challenging. The body stated that early detection could result in cost savings for the health system.*

*PASC noted that PHA mentioned the impact of the possible MSAC decision on health insurance premiums had not been considered.*

## Additional comments

Australian Pathology considered gender equity was important for the 2013 expansion of HPV vaccination to boys and, similarly, the prevention of HPV-related cancers should be equitable. Australian Pathology considered it would be unethical not to look for and treat HSILs, as the ANCHOR trial showed treating anal HSIL reduced anal cancer. Positive Life NSW stated that at-risk patients are either managed in private settings or in state-based sexual health clinics until symptomatic for anal cancer, which raises issues around equity and access.

## Next steps

*There are a number of issues that require consideration either during the assessment or implementation phase. The issues are listed below.*

### **Issues that require consideration during the assessment phase**

- **Consultation with transplant groups, gynaecological experts and colorectal surgeons:** *PASC requested feedback be sought from transplant groups regarding the clinical utility of anal HPV/LBC and diagnostic/treatment HRA in the SOTR subgroup. In addition, PASC requested that feedback should also be sought from gynaecological oncology experts regarding the clinical utility relative to current pathways of testing and HRA in the subgroup of people with cervical/vaginal cancer or precursor lesions and requested information (e.g. utilisation estimates) for the purposes of modelling the financial and economic impacts of adding this proposed subgroup. In the post-PASC phase the department noted that surgical excision under anaesthesia may be a potential treatment option and further consultation would be required from colorectal surgeons to understand when excision is required and billing circumstances.*



- **Additional population subgroup:** PASC raised concerns around the appropriateness of the target population, which does not capture the population with the largest incidence of anal cancer in Australia: people with cervical/vaginal cancer or precursor lesions. The applicant is amenable to including this subgroup. PASC considered that this subgroup should be examined in the assessment report as a potential additional population and the impact of including this could be considered as sensitivity analyses in the economic and financial evaluations. PASC noted that this would therefore also require consideration of the evidence for clinical safety and effectiveness in this subgroup.
- **Review of proposed MBS item descriptors:** Both PASC and the Department noted a careful review of the proposed items was necessary to prevent unintended consequences, overuse and/or co-claiming.
- **Review of proposed MBS item fees:** PASC sought justification for the cost differences between anal HPV/cytology testing against cervical HPV/cytology testing. PASC also requested additional consultation to justify the 2-fold increase in the fee for ablative treatment for anal HSIL relative to existing cervical items.
- **Assessment of the pros and cons of partial vs full genotyping:** PASC noted that an analysis of the costs/harms and benefits of partial genotyping vs full genotyping in all high-risk patients would be needed as part of any future assessment. Considerations for partial genotyping include the impact of additional patients presenting for HRA with 'pseudo-persistence' of different genotypes of non-16 HR-HPV. Considerations for full genotyping include the additional cost and associated issues regarding test validation, implementation, and patient access. PASC noted that data in the SPANC study could be used to undertake preliminary modelling to determine how many false positive patients would proceed to HRA/biopsy (with costs/harms) compared to the increased costs of full genotyping for all (but noting that the SPANC MSM population is not reflective of the whole population included in this application).
- **Clarification on repeat testing and monitoring requirements:** PASC expressed concern around the callback and follow-up requirements for testing (as per recommended intervals or if repeat testing required). The current recommendation assumes a stable medical practitioner and/or GP relationship, which may not be the case. In addition, PASC expressed concern around which entity would be responsible for monitoring testing intervals (12 months etc.)
- **Surgical excision as a potential treatment option:** In the Post-PASC phase the department noted that surgical excision of HSIL under anaesthesia may be a potential treatment option, either in addition to or as an alternative to ablation. Inclusion of surgical excision as a treatment option may require further exploration in the DCAR. In addition, further consultation is required from treating clinicians (e.g. colorectal surgeons) to understand under what circumstances excision of HSIL is required rather than ablation and how the procedure might be billed.

#### **Issues that require consideration during the implementation phase (Post-MSAC)**

- **Considerations around workforce capacity and certification:** PASC noted that there is currently a shortage of trained staff to perform diagnostic HRA and HRA/ablation. PASC also noted a lack of clarity around certification for clinicians to enable them to perform HRA/ablation.
- **Registration/validation of anal HPV assays:** PASC noted that very few laboratories are currently NATA-accredited for anal HPV testing, so even if currently available cervical assays (i.e. partial genotyping) were to be utilized (the most pragmatic approach,) laboratories would need to conduct internal validation studies (as in-house in-vitro diagnostic [IVD] medical devices). However, the

*requirement for full genotyping for HPV, as requested by the applicant, would mean that this pragmatic approach would not be feasible. Additional assays would need to be registered with the Therapeutic Goods Administration (TGA) as no anal HPV assays have yet been approved by the TGA.*

- **Clarity around validation, training and quality assurance of anal cytology:** *PASC noted that clarity is needed around the use of liquid based cytology on anal smears. PASC queried if local validation and training would be required in domestic laboratories, and queried if a local quality assurance plan (QAP) would need to be implemented.*
- **Considerations around patient access:** *PASC sought clarification around the ability of the often-stigmatised populations of MSM, TW and HIV-positive people to access the HPV/LBC/HRA and HRA/ablation services.*
- **Relevance of self-collection to the application:** *PASC enquired if self-collection for anal HPV and HSIL testing could be a sustainable future option. PASC noted that validation studies are currently underway to determine the utility of dry swabs for HPV testing.*

## Applicant Comments on Ratified PICO

Thank you for providing the opportunity for the Royal College of Pathologists of Australasia to provide feedback on the Ratified PICO document for application 1752, and to answer questions raised by PASC.

The College would like to clarify that the testing intervals were chosen to align with those used in the Australian cervical screening program guidelines that recommend testing of at-risk immunocompetent individuals every 5 years and immunocompromised every 3 years. These intervals reflect the natural history of genital HRHPV infections, which take years to develop into precancer.

Whilst the College agrees that the callback and follow-up requirements for testing require a stable therapeutic relationship, it should be noted that this model is used for HIV and other STI testing. The opportunity for marginalised populations to also potentially undergo opportunistic testing if they present in extremis should be offered.

The College advises that procedure time would be approximately 1-1.5 hours in the Australian practice (not 6 hours as stated based on a US source), inclusive of diagnostic HRA, with the duration of treatment depending on the size of the lesion. Quoting a USA source for procedure time is likely to be biased towards overuse of health system resources. In addition, it is unlikely that patients would be required to remain in hospital overnight or for a few hours, especially when treated in an outpatient setting with electrocautery.

The previously unpublished Australian study by the SPANC study group has now been published – see Jin et al 2024 PMID: 39279187

The College notes that equity of access is at the heart of this application, i.e. making testing and treatment available to a group of high-risk populations who currently have limited options available to them. The College is concerned about the potential harms outweighing benefits (i.e. unnecessary HRA) in making testing available to low-risk populations. Testing of women >45 years with persistent cervical HPV16 (>1 year) should be a shared decision with their healthcare provider. The College is supportive of the DCAR considering targeted testing in all Category B groups. However, at the initial implementation stage Category A groups need to be the focus for several years, until sufficient treatment resources are developed.

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## Appendix A

Table 63 Possible benefits of tests and suitable claims associated with these benefits

Comparative function	Possible benefits	Effect on management of patient	Health outcomes	Suitable clinical claims (health outcome gains)	Supportive evidence
Combined • anal HPV testing • cytology testing • diagnostic HRA To detect a new parameter (HSIL)	<ul style="list-style-type: none"> <li>confirms diagnosis</li> <li>provides prognostic information</li> <li>combined regimen replaces no testing</li> <li>detects pre-cancerous HSIL lesions to inform patient treatment</li> <li>identifies new diagnosis or disease</li> <li>removal of pre-cancerous HSIL prevents progression of lesions to anal cancer</li> </ul>	<b>No change in management</b>	<b>Progression to anal cancer</b>	Noninferior to comparator	(Goldstone, Stephen E, Enyinna & Davis 2009) (van der Zee et al. 2023) (Walker, RJ et al. 2024)
		<b>Change in management for at least some patients</b> <ul style="list-style-type: none"> <li>removal of HSIL lesions for positive patients</li> </ul>	<b>Decreased risk of anal cancer</b>	Superior to comparator	(Clarke, Megan A et al. 2019) (Clarke, Megan A et al. 2022) (Gaisa, Michael M et al. 2021) (Goldstone, Stephen E, Enyinna & Davis 2009) (Jin, Fengyi et al. 2016) (van der Zee et al. 2023) (Walker, RJ et al. 2024)

### Abbreviations

HPV = human papilloma virus, HRA = high-resolution anoscopy, HSIL = high-grade squamous intraepithelial lesions.

### Source

MSAC 1752 PICO Set p. 32