Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 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**

Date of MSAC consideration: **27 November 2025**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

The Department of Health, Disability and Ageing received a co-dependent application from The Royal College of Pathologists of Australasia (RCPA) and St Vincent's Hospital, Sydney, requesting:

- Medicare Benefits Schedule (MBS) listing of anal human papillomavirus (HPV) and cytology testing in high-risk populations; and
- Medicare Benefits Schedule (MBS) listing of high-resolution anoscopy and ablative treatment to prevent anal cancer.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its advice on the public funding of anal human papillomavirus (HPV) and cytology testing in high-risk populations to determine access to high-resolution anoscopy (HRA) and ablative treatment of high-grade squamous intraepithelial lesion (HSIL) to prevent anal cancer in eight high-risk populations. These populations are 1) men who have sex with men (MSM) and/or people who identify as transgender women (TW) who are positive for HIV and aged ≥ 35 years; 2) MSM aged ≥45 years and/or who identify as TW who are HIV negative; 3) women and men who have sex with women aged ≥45 years who are HIV positive; 4) women with previous vulval HPV-associated squamous cell carcinoma and/or HSIL commencing within one year of diagnosis; 5) solid organ transplant recipients (SOTR) commencing 10 years post-transplant; 6) people being followed up after treatment of anal cancer; 7) people with incidental HSIL and symptomatic patients, and 8) people with a history of cervical or vaginal cancer or precursor lesions.

MSAC considered that the proposed sequential testing and HSIL ablation appeared to have superior effectiveness in reducing anal cancer incidence in some high-risk groups. However, MSAC considered that the majority of the clinical evidence was from studies of MSM and people living with HIV who appear to have the highest risk of developing anal cancer, and that the other proposed populations have heterogeneous risks of developing anal cancer, although still much higher than the general population. Therefore, the evidence for testing and treatment may not be fully applicable across all the populations proposed. MSAC considered there were several limitations in the economic model and considered a different modelling approach is required to reliably estimate the cost-effectiveness of testing and treatment. MSAC also considered the financial impacts and utilisation were highly uncertain and should be revised.

MSAC advised further assessment is required for MSAC to provide advice on the safety, comparative effectiveness, cost-effectiveness and financial estimates. MSAC considered this updated assessment should also identify populations most likely to benefit by considering the different risks of developing anal cancer, assess the optimal screening intervals, starting and stopping ages for testing, and other relevant parameters through scenario analyses. MSAC considered the economic model should adopt a structure that is more aligned with existing cancer screening models. This model should incorporate benefits and harms of screening for anal cancer and include both cost-effectiveness analysis (e.g., cost per lesion detected and cancer case avoided) and cost-utility analysis (cost per quality-adjusted life year and cost per life-year gained).

MSAC advised that MBS fees, utilisation and costing assumptions need further investigation. Additional work is required to refine the item descriptors and explanatory notes, given that the proposed populations are mostly defined by HIV status, age, sex, and sexual behaviours. MSAC advised that the assessment report should be considered by ESC before returning to MSAC.

Consumer summary

This is an application from the Royal College of Pathologists of Australasia and St Vincent's Hospital, Sydney, requesting Medicare Benefits Schedule (MBS) listing of a series of services to test for different types of human papillomavirus (HPV). If HPV is detected, the application also requests public funding for a procedure called high-resolution anoscopy, to diagnose and treat such lesions to prevent them from turning into anal cancer. These tests and treatment are for people who are at high risk of anal cancer.

HPV is a common sexually transmissible infection. HPV can cause lesions. Some HPV lesions turn into cancers such as cervical cancer, anal cancer and other cancers. Certain HPV types are linked to types of lesions that carry a higher risk of cancer developing (pre-cancerous lesions). Australia has a vaccine to protect against HPV, which is provided free under the National Immunisation Program for adolescents and some other age groups. The HPV vaccine has been available in Australia since 2007 for girls and 2013 for boys. As HPV-related cancers take years to develop, they usually occur later in life. Currently, older people who are more likely to have anal cancer would not have received the HPV vaccine. It will take many years to see a drop in the rates of these cancers as a result of the vaccine. Australia also has a National Cervical Screening Program to detect cervical cancer early in women, but there is currently no approach to screening and early detection for anal cancer.

Current research on HPV-related cancer has found people in the following eight groups have a higher risk of anal cancer than the general population: people living with HIV, men who have sex with men, transgender women, people who have had vulval cancer or vulval pre-cancerous lesions, people who have had a solid organ transplant, people who have received treatment for anal cancer, people with pre-cancerous anal lesions found incidentally, people with symptoms of anal cancer, and people with previous cervical and vaginal cancer or precancerous lesions.

In this application, it is proposed that people at higher risk of anal cancer would have a sample taken from the anal region (anal swab) to test for HPV. If the test shows one of the HPV types that are associated with pre-cancerous lesions and anal cancer, the same sample will require a second test (called a cytology test) for cancer cells. If abnormal cells are found, the person would be referred to a specialist for a diagnostic high-resolution anoscopy (HRA). This involves having a tube with a camera inserted in the anus to check for any lesions in the anal canal. If a lesion is found during the HRA, the specialist will take a biopsy and send it to pathology for testing. If this shows cancer or pre-cancer, the specialist will undertake a second HRA to remove the lesion. This aims to prevent pre-cancerous lesions from developing into cancer. Patients whose anal swab test shows they have HPV16, a specific type of HPV that has a high risk of causing anal cancer, would be referred for a diagnostic HRA regardless of the cytology test results.

Consumer summary
The applicant was granted a hearing for this application to answer some of MSAC's questions. MSAC thought the HPV testing and treatment in this application were safe and most likely effective. There are some high-quality studies that support this testing and treatment approach in men who have sex with men and people living with HIV, who have the highest risk of developing anal cancer. MSAC thought that this evidence may not be fully relevant to people in the other population groups. MSAC did not think the economic model in the application was useful for decision making because it was insufficiently detailed to resolve a lot of uncertainties, making the cost-effectiveness estimates unreliable. For example, it was unclear what age people should start and stop testing, how often testing should occur, and which groups should be offered testing. Because of these issues, the financial estimates were also uncertain. MSAC advised that a revised economic model should be developed to address these questions and identify which groups would benefit most from testing. MSAC considered that a more detailed investigation of various costs and health benefits in the economic model, such as preventing cancer cases and improving quality of life, would be important for decision making. **MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing** MSAC deferred its decision on whether testing for different types of HPV accompanied by cytology testing and high-resolution anoscopy to diagnose and treat precancerous lesions should be publicly funded. MSAC requested a new economic model and updated financial estimates to help them to make better informed decisions about which high-risk groups should get publicly funded testing and treatment.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from the Royal College of Pathologists of Australasia and St Vincent's Hospital Sydney is requesting Medicare Benefits Schedule (MBS) listing of:

- anal human papillomavirus (HPV) testing and cytology testing in populations at high-risk for anal precursor lesions and anal cancer, and
- high-resolution anoscopy (HRA) and ablative treatment to prevent anal cancer.

The applicant was granted a hearing for this application and feedback from the hearing is incorporated into Section 3.

MSAC noted the consultation feedback received for this application. All consultation responses were supportive.

MSAC noted that high-risk (oncogenic) HPV genotypes are responsible for approximately 90% of all anal cancers. The proposed testing population in the original application comprised 7 subgroups at higher risk of developing anal cancer:

- men who have sex with men (MSM) and transgender women living with HIV
- MSM and transgender women not living with HIV
- women and men who have sex with women, living with HIV
- women with previous vulval squamous cell carcinoma or high-grade squamous intraepithelial lesions (HSIL) commencing within one year of diagnosis
- solid organ transplant recipients (SOTR) commencing 10 years post-transplant
- patients being followed up after treatment for anal cancer
- patients with incidental HSIL (found during diagnosis of anal conditions) or symptoms suggestive of anal cancer

MSAC noted that the proposed populations are those with a 10-fold or greater risk of HSIL, which, when treated, can reduce the risk of anal squamous cell carcinoma (ASCC) by approximately 60%. MSAC noted that the comparator was no HPV testing, which was appropriate.

MSAC noted that an additional population – people with a history of cervical or vaginal cancer or precursor lesions – had been added by PASC. MSAC noted ESC's advice that the size of this population is uncertain but potentially large, and within this additional population, the people with cervical lesions and precursor cervical lesions would require further examination of the available evidence given that the risk of anal cancer in this group is lower than the other proposed population groups. In its pre-MSAC response, the applicant agreed with ESC's advice and as a result supported the exclusion of this additional population group to maintain the focus of the application on higher-risk populations included in the original application.

The application proposes 7 MBS item numbers to implement targeted investigation, assessment and preventive treatment for anal cancer:

- item BBBB – HPV genotyping in asymptomatic patients
- item CCCC – HPV genotyping in higher-risk or symptomatic patients or follow-up management
- item DDDD – repeat of BBBB or CCCC
- item EEEE – cytology testing of HPV-positive anal specimens
- item FFFF – diagnostic high-resolution anoscopy (HRA)
- item HHHH – biopsy during HRA
- item GGGG – HRA-guided ablation.

MSAC noted the proposed MBS item descriptors and the need to prevent the use of discriminatory language when specifying the eligibility criteria for testing in people at higher risk. The department advised that any item descriptors supported for implementation should not reference populations using highly sensitive personal identifiers such as sexual behaviours.

MSAC noted and supported the revised MBS fees proposed by ESC, including an adjusted fee for expanded HPV genotyping (Items BBBB, CCCC and DDDD) of $35.85 (lower than applicant proposed fee of $50), benchmarked to the National Cervical Screening Program's HPV genotyping item (MBS item 73072). MSAC noted the applicant's pre-MSAC response. In the response, the applicant stated that the recommended $35.85 MBS fee was too low and did not agree with ESC's view that similar economies of scale to the National Cervical Screening Program (NCSP) could be achieved to make the lower fee feasible. The applicant's pre-MSAC response also stated the low fee could lead laboratories to use less comprehensive testing, which might result in more patients being unnecessarily referred for HRA and higher downstream costs. ESC suggested that the fee for item EEEE for liquid-based cytology (LBC) could be set at $47.10 to align with the fee for cervical cancer LBC rather than the $70 proposed fee by the applicant. The applicant's pre-MSAC response explained that anal cytology is significantly more labour intensive than cervical LBC and therefore requires a higher fee. MSAC noted the applicant's proposed fees of $140.60 for item FFFF (diagnostic HRA) and $80.20 for item HHHH (HRA guided biopsy). ESC did not recommend a particular fee, but noted that the biopsy fee should incorporate all biopsies as part of a complete medical service. MSAC considered that a fee of $140.60 is appropriate for item FFFF. The applicant's justification for the proposed fee for diagnostic HRA is that it reflects the time required to undertake the procedure and the associated costs for clinics. MSAC noted that ESC had proposed a fee for item GGGG (HRA guided ablation or cryotherapy of anal HSIL) of $371.80 to align with the existing MBS item 35645 for cervical ablation. This proposed fee is lower than the applicant's proposed fee of $701.60. The applicant did not comment on this proposed change. MSAC confirmed that there should be no co-claiming of items FFFF and GGGG.

MSAC confirmed that the HPV genotyping test could be requested by any medical practitioner, mirroring the NCSP. MSAC considered that HRA would likely be performed by surgeons and gastroenterologists, and noted concern from consumers about the current lack of availability of HRA across Australia.

MSAC noted that HPV testing in Australia's NCSP involves testing for 14 oncogenic HPV genotypes, including HPV16 and HPV18, and reports HPV test results as: oncogenic HPV 16/18 detected, oncogenic HPV (not 16/18) detected, oncogenic HPV not detected, or unsatisfactory HPV test.[1] MSAC noted that the reporting of the result "oncogenic HPV (not 16/18)" pools together several oncogenic HPV genotypes, and does not identify the HPV genotypes individually. This differs from this application (1752) which proposes separate reporting of each HPV genotype. MSAC agreed with ESC that the proposed expanded HPV genotyping, which covers the 14 oncogenic HPV genotypes and reporting of individual HPV genotypes should be adopted for anal HPV. MSAC noted that laboratories are likely to use the same test as for cervical screening for pragmatic purposes, and a minimum set of genotypes for testing could be described.

MSAC queried the rationale for permitting two diagnostic HRAs per person per year. The applicant confirmed in the hearing that each person with positive cytology or HPV16 may require up to two diagnostic HRAs – one for initial diagnosis and one for follow-up. If HSIL is not detected at the first HRA, a repeat HRA is recommended to ensure that no lesions have been missed. If HSIL is found during the initial diagnostic HRA, a second HRA is needed for HSIL treatment, which involves HRA guided ablation or cryotherapy.

MSAC noted that this application does not fit the definition of a population-based screening program, as it involves targeted testing of asymptomatic high-risk groups rather than the whole population and also includes testing of symptomatic patients. MSAC considered that including both symptomatic and asymptomatic people was appropriate to ensure that all people from high-risk groups are tested and subsequently have access to subsidised treatment. However, MSAC considered that the principles of screening were relevant for the asymptomatic group.

MSAC noted the proposed clinical management algorithm, including that all patients who receive HRA-guided ablation must go through the entire algorithm again every 6 months for a period of 2 years. The applicant confirmed in the hearing that this was based on a study from the Netherlands of people living with HIV, which found that HSIL recurrence following treatment is common and people may require multiple treatments for HSIL. An ongoing study at St Vincent's Hospital Sydney suggests better HSIL clearance rates compared with those reported in the Netherlands study. The applicant also stated in the hearing that although there is limited published data for anal cancer, evidence for cervical cancer screening shows that patients with persistent high-risk HPV infection are more likely to develop HSIL. The applicant commented that this is also likely to be the case for patients at high risk of anal cancer. Therefore, intensive follow-up is needed to ensure that any HSIL has been successfully treated.

MSAC agreed with ESC that it would be reasonable to allow self-collection of HPV anal swab samples. MSAC noted consumer feedback that expressed concern about false positive and false negative test results; however, MSAC considered that the risk of false positive results is reduced by the inclusion of the second-tier liquid-based cytology test. If the self-collected sample has insufficient cells for cytology assessment, these people may need to be recalled for a repeat clinician-collected sample for cytology.

MSAC also noted that stigma can be a significant barrier to accessing health care for MSM, transgender people and people living with HIV, but that MBS funding has the potential to destigmatise care and reduce these barriers.

MSAC noted there were no significant safety issues regarding the proposed tests and treatment.

MSAC agreed with ESC that there is limited or no direct evidence for some of the proposed populations in the application. MSAC considered that the majority of the clinical evidence was based on studies including MSM and people living with HIV who appear to have the highest risk of developing anal cancer, and that the other proposed populations have heterogeneous risks of developing anal cancer, although much higher than the general population. Anal cancer is overall more common in women than men. MSAC considered that the evidence provided for the testing

[1] Australian Institute of Health and Welfare. (2025). *National Cervical Screening Program monitoring report 2025: Screening pathway.* https://www.aihw.gov.au/reports/cancer-screening/ncsp-monitoring-report-2025/contents/national-cervical-screening-program/screening-pathway

regimen (i.e. the triaged combination of tests) may not be fully applicable across all the populations proposed. MSAC noted that there was an ongoing clinical trial (NCT03061435) which may provide further high-quality evidence to confirm whether screening offers a significant survival benefit for the proposed population of women with high-grade vulval lesions or vulval cancer.

MSAC noted that the highest quality evidence of clinical effectiveness demonstrating that treatment of anal HSIL reduces anal cancer incidence was from the ANCHOR trial.[2] MSAC noted that the study population comprised MSM and transgender women living with HIV. The trial demonstrated a 57% lower risk of progression to cancer in the group that received HSIL treatment from 402 per 100,000 person-years in the active monitoring group to 173 per 100,000 in the group where HSIL was treated The applicant noted in the hearing that this is an ongoing large and costly trial and is unlikely to be repeated for other high-risk groups. The applicant stated that it could be expected that HSIL treatment would lower the risk of anal cancer even further in people who are not immunocompromised. In addition, the applicant confirmed that HRA-guided ablation reduces the risk of anal cancer but does not completely eradicate the risk. The applicant explained this is because pre-cancerous lesions may have been present for many years and may have already spread into a different area from where the biopsy was taken.

MSAC noted the economic evaluation was a cost-utility analysis. MSAC agreed with ESC's significant concerns with the model structure, errors in model input variables and subsequent uncertainty in outputs. ESC did not consider the model was useful for MSAC decision making on the cost-effectiveness of the proposed testing. MSAC noted that published Australian models[3][4] are available and could have been adapted as the basis for the modelling, but the assessment group stated in the pre-MSAC response that the published models were unsuitable for the purpose of the application because they did not explore the impact of repeated testing.

The department had provided supplemental analysis using the revised MBS fees suggested by ESC. This resulted in a 23.4% reduction in the incremental cost-effectiveness ratio (ICER) for MSM living with HIV and a new ICER of $49,886 per quality adjusted life year (QALY) gained; and a 22.6% reduction in the weighted average ICER for all populations, resulting in an ICER of $100,659 per QALY gained. MSAC also noted the revised economic model provided by the assessment group in its post-ESC rejoinder used the MSM living with HIV as an exemplar and included testing every 3 years instead of annually (in line with current guidelines for people living with HIV), included test sensitivity and specificity to capture false positives and false negatives, and added outcomes of HPV positive result, HSIL positive result and cancer avoided. These updates resulted in revised ICERs of $164 per HPV positive test (for HPV genotyping test only), $1,805 per HPV positive test (for all sequential testing), $5,742 per HSIL positive case detected, $168,613 per cancer avoided, and $16,025 per QALY gained. However, MSAC noted that these updates were not yet verified, and other issues with the economic model remained unaddressed. MSAC considered that a revised approach to the economic modelling was required.

MSAC also noted the limitations of financial and budgetary impacts results. The department's supplemental analysis using the revised MBS fees suggested by ESC indicated that the first year of listing the new MBS items would have a net financial implication to whole of government through the MBS, PBS and state governments of almost $55.6 million, rising to $73.3 million in year 6. This equates to total financial implication of approximately $385.5 million over 6 years – a reduction of almost 23.4% compared to the previous financial estimates.

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[2] Palefsky, J. M., Lee, J. Y., Jay, N., Goldstone, S. E., Darragh, T. M., Dunlevy, H. A., Rosa-Cunha, I., Arons, A., Pugliese, J. C., & Vena, D. (2022). Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. New England Journal of Medicine, 386(24), 2273-2282.

[3] Cheng, Q., Poynten, I. M., Jin, F., Grulich, A., Ong, J. J., Hillman, R. J., Hruby, G., Howard, K., Newall, A., & Boettiger, D. C. (2023). Cost-effectiveness of screening and treating anal pre-cancerous lesions among gay, bisexual and other men who have sex with men living with HIV. The Lancet Regional Health – Western Pacific, 32. https://doi.org/10.1016/j.lanwpc.2022.100676.

[4] Ong JJ, Fairley CK, Carroll S, Walker S, Chen M, Read T, Grulich A, Bradshaw C, Kaldor J, Clarke P. Cost-effectiveness of screening for anal cancer using regular digital ano-rectal examinations in men who have sex with men living with HIV. J Int AIDS Soc. 2016 Mar 1;19(1):20514. doi: 10.7448/IAS.19.1.20514. PMID: 26942721; PMCID: PMC4778406

MSAC agreed with ESC that cancer incidence and testing uptake are key drivers for the economic and financial analyses, but both are uncertain in these high-risk populations. MSAC considered that the base case utilisation estimate of 56.7% of HPV genotyping (based on HIV testing uptake) as well as the number of services provided in each year at each step of the clinical management algorithm were highly uncertain. For instance, MSAC noted that amending the financial estimates to incorporate utilisation estimates based on data from the SPANC study[5] instead led to a significant reduction in the cost to the MBS of new items from $51.09 million to $22.45 million in the first year of listing. MSAC advised that revised financial analyses should explore the service utilisation estimates in sensitivity analyses.

MSAC noted a comparison of the proposed screening approach with existing screening programs in Australia for breast, cervical, bowel and lung cancers, recognising that this was for contextualisation purposes rather than a direct comparison. MSAC noted that the proposed anal cancer testing approach results in relatively fewer deaths prevented than other screening programs and most likely a higher ICER per QALY gained than all except the cervical screening program.

MSAC deferred providing its advice on this application. MSAC advised further assessment is required for MSAC to provide advice on the safety, comparative effectiveness, cost-effectiveness and financial estimates. MSAC advised that in addition to re-assessing the clinical evidence available for each of the proposed populations, a new economic model should be commissioned for this application, with the aim of identifying the population(s) who are most likely to benefit from the screening approach and for whom such an approach is cost-effective. The revised model should explore sensitivity analyses in the following areas:

- starting age for testing (e.g. 35, 40, 45, 50 years)
- stopping age for testing (e.g. 70, 75, 80 years)
- various thresholds of anal cancer risk in different populations (noting that the incidence rate of anal cancer in the general population is 2 per 100,000 person-years; e.g. thresholds could be low [<25 per 100,000 person-years], medium [25–75 per 100,000 person-years] and high [75+ per 100,000 person-years])
- frequency of testing (e.g. 1 year, 3 years, 5 years)
- uptake of testing in the proposed populations (e.g. 40%, 50%, 60%, 70%)
- number of patients at each step of the testing and treatment cascade

MSAC advised that the revised model should have a conceptual structure in line with other cancer screening models, which includes health states, benefits and harms that are relevant to anal cancer screening. It should include age- and gender-based estimates for each of the risk groups and the risk of anal cancer development and the risk of death in each group. It should show the benefits of early detection and the cost per diagnostic yield, the cost per lesion detected, and the cost per cancer avoided. Outputs should include life-years gained as well as QALYs. Sensitivity analyses should clearly show the effects of parameter changes on uncertainty.

MSAC advised that MBS fees, utilisation and costing assumptions need further investigation. Additional work is required to refine the item descriptors and explanatory notes, given that the proposed populations are defined by HIV status, age, sex, and sexual behaviours. MSAC advised that the assessment report should be considered by ESC before returning to MSAC.

[5] Poynten IM, Jin F, Garland SM, Hillman RJ, Molano M, Roberts JM, Templeton DJ, Phillips S, Law C, Fairley CK, Farnsworth A, Grulich AE. HIV, Immune Dysfunction, and the Natural History of Anal High-Risk Human Papillomavirus Infection in Gay and Bisexual Men. J Infect Dis. 2021 Jul 15;224(2):246-257. doi: 10.1093/infdis/jiaa723

4. Background

MSAC has not previously considered the co-dependent technologies: anal HPV testing, anal cytology testing, diagnostic high-resolution anoscopy (HRA) and HRA-guided ablation for high-grade squamous intraepithelial lesions (HSIL) for anal cancer prevention.

5. Prerequisites to implementation of any funding advice

The application for the proposed technology includes therapeutic goods that require Therapeutic Goods Administration (TGA) approval.

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). All laboratories (public or private) that conduct any human pathology testing must hold an ISO 15189 standard accredited by NATA. The ISO 15189 accreditation standard includes both management and technical standards. ISO 15189 accreditation enables specific information on human pathology to be collected, including haematology, microbiology, histopathology, immunopathology, cytopathology and chemical pathology.

PASC noted that very few laboratories are currently NATA-accredited for anal HPV testing, so even if currently available cervical assays were to be utilised (the most pragmatic approach), laboratories would need to conduct internal validation studies (as in-house in-vitro diagnostic [IVD] medical devices).

PASC also noted that 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 TGA as no anal HPV assays have yet been approved by the TGA.

While there are no assays that are specifically registered for anal HPV detection, there are a number that are anatomical site-agnostic, In addition, there are at least two TGA registered assays (The Aptima HPV assay and the Roche HPV test) that cover the full 14 oncogenic genotypes, so a pragmatic approach (using already available tests for cervical screening) may be possible, but requires further investigation. The most common oncogenic HPV genotype is different for cervical and anal cancers. Assays that are not restricted by sample source could be used on anal samples are listed in Table 1.

Table 1 HPV genotyping assays not restricted by sample location listed on the Australian Register of Therapeutic Goods (ARTG)

Company	System	ARTG ID
Abbott Australasia Pty Ltd	Abbott Australasia Pty Ltd Molecular Division - Human papilloma virus IVDs	324193 221520
Integrated Sciences Pty Ltd	Human papilloma virus IVDs	241313
ESL Biosciences Australia 2012 Pty Ltd	Human papilloma virus IVDs	252593
Roche Diagnostics Australia Pty Limited	Human papilloma virus IVDs	187190
Hologic (Australia & New Zealand) Pty Ltd	Human papilloma virus IVDs	230663

HRA

While no specific models of colposcopes and disposable anoscopes are registered, these devices are regulated by the TGA. Disposable anoscopes currently listed on the Australian Register of Therapeutic Goods (ARTG) are listed in Table 2.

Table 2 Disposable anoscopes listed on the Australian Register of Therapeutic Goods (ARTG)

Company	System	ARTG ID
Medical Specialties Australasia Pty Ltd	Anoscope, single-use (482747)	482747
Medical Specialties Australasia Pty Ltd	Anoscope, single-use (442154)	442154
Reveale Enterprises Pty Ltd	Anoscope, single-use (427026)	427026
Stark Medical	Anoscope, rigid (412136)	412136
Mediquip Pty Ltd	Anoscope, single-use (356988)	356988
Defries Industries Pty Ltd	Anoscope, single-use (320506)	320506
Vitramed Pty Ltd	Anoscope, single-use (282041)	282041
Medical Specialties Australasia Pty Ltd	Anoscope, single-use (288480)	288480
Rocket Medical Pty Ltd	Anoscope, single-use (222383)	222383
Welch Allyn Australia Pty Limited	Anoscope, single-use (237323)	237323
Innovative Medcare Technology Pty Ltd	Anoscope, single-use (220927)	220927
Medical Specialties Australasia Pty Ltd	Anoscope, single-use (180428)	180428
Ebos Group Australia Pty Ltd	Anoscope, rigid (181348)	181348
Medical Specialties Australasia Pty Ltd	Anoscope, single-use (159456)	159456
Heine Aust Pty Ltd	Anoscope, rigid (107118)	107118
Emergo Asia Pacific Pty Ltd T/a Emergo Australia	Anoscope, single-use (204913)	204913

The applicant suggested that due to the complexity of the procedure, only accredited clinicians be allowed to perform HRA. There is currently no accreditation process for this in Australia, so currently any specialists, consultant physicians, specialist general practitioners or medical practitioners with access to HRA equipment can perform the procedure.

Ablation system

Ablation systems are regulated by the TGA. Ablation systems listed on the ARTG with nonspecific indications are displayed in Table 3.; however, it is unclear whether they can be used in anal ablation. There are no electrocautery or infrared ablations systems on the ARTG that are specifically indicated for anal ablation therapy. In addition, some of the systems listed in Table 3 may need additional consumables (e.g. probes) to be registered before they can be used for anal ablation therapy.

Table 3 Ablation systems listed on the Australian Register of Therapeutic Goods (ARTG)

Company	System	ARTG ID
Medgyn	MTA Thermal Ablation System	460508
Varian Medical Systems Australasia Pty Ltd	Microwave ablation system	462199
GRC Surgical Pty Ltd	Radio-frequency ablation system generator	488286
Medtronic Australasia Pty Ltd	Microwave ablation system generator	411730
Medtronic Australasia Pty Ltd	Radio-frequency ablation system generator	317040
Surgical and Medical Supplies Pty Ltd	Microwave ablation system generator	431490
Asia Actual Australia	Intradermal radio-frequency ablation system	401231
Life Healthcare Pty Ltd	Radio-frequency ablation system generator	324842
Olympus Australia Pty Ltd	Radio-frequency ablation system generator	276869
Device Technologies Australia Pty Ltd	Radio-frequency ablation system generator	277760
Getz Healthcare Pty Ltd	Radio-frequency ablation system generator	260260
Medtronic Australasia Pty Ltd	Emprint™ Ablation System with Thermosphere™ Technology	226598

6. 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). The applicant proposed eight MBS item descriptors, one for HPV genotyping sample collection (which was removed during the PICO development process as PASC noted that a new professional attendance item for sample collection is unnecessary, and clinician instructions are sufficient in place of formal training, therefore current attendance items could be used), six for testing/testing procedure, and one for treatment.

In the ratified PICO, PASC and the Department questioned the relatively high MBS fees requested by the applicant for the proposed testing and treatment items compared to the corresponding cervical HPV/HSIL-related items. The applicant stated the higher fees were due to anal cytology assessment being more time and labour intensive (compared to cervical cytology) and anal anatomy being more complex than cervical anatomy.

Pathology services

The PICO presented four items for pathology services:

1. HPV genotyping in asymptomatic patients
2. HPV genotyping for patients at higher risk or with symptoms, or for follow-up management
3. HPV genotyping repeat testing
4. Cytology testing of HPV-positive anal specimens

HPV genotyping

The applicant's proposed fee for the HPV genotyping (Items BBBB, CCCC and DDDD) was $70. However, during the PASC process, it was noted that the fee should be $50, which is what has been used in the base case. It was assumed that an 85% benefit would apply, as the service would likely occur in the primary care setting.

PASC noted that the Department confirmed a new dedicated professional attendance item for sample collection would not be required and current attendance items could be used. It was noted that specific training for clinicians to undertake sample collection is not required: a set of instructions for clinicians to follow 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.

PASC and the Department noted 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.

In the PICO, PASC noted that the National Cervical Screening Program (NCSP) uses partial or limited HPV genotyping, with risk-stratified results reported as HPV16 and/or HPV18, non-HPV16/18 high-risk HPV (hrHPV) or no hrHPV detected. This aligns with NCSP guidelines recognising the following categories for HPV test results[6]:

- HPV 16/18 detected
- oncogenic HPV (not 16/18) detected
- oncogenic HPV not detected.

[6] Cancer Council Australia, 2022. Clinical Guidelines - HPV testing terminology. https://www.cancer.org.au/clinical-guidelines/cervical-cancer/cervical-cancer-screening/terminology/hpv-testing-terminology

However, partial genotyping for the purpose of this application is defined as HPV testing for HPV types 16 and 18, with or without HPV45, aligning with the definition used in the NCSP (MBS Item 73072).

Expanded genotyping (note that ESC preferred this terminology to full genotyping, as there are more than 100 recognised HPV genotypes, most of which are not recognised to be oncogenic) would include genotyping for 14 hrHPV subtypes with results reported for individual HPV subtypes (as specified in the PICO). In the current clinical management algorithm, the only reason for expanded genotyping is that patients with persistent infection with the same non-16 hrHPV would be referred for diagnostic HRA. Therefore, it is important to consider (1) the prevalence of non-16 hrHPV in each PICO-specified subpopulation; (2) the clearance of non-16 hrHPV in each PICO-specified subpopulation; and (3) the role of non-16 hrHPV genotypes in HSIL and anal cancer.

PASC noted that the proposed requirement for expanded HPV genotyping, as requested by the applicant, would mean that a pragmatic approach for roll-out and accessibility to expanded genotyping would be problematic if it was reliant on the NCSP laboratories, and that an assessment of partial vs expanded genotyping would be needed as part of the evaluation. However, PASC also noted most laboratories currently use the Roche 6800 HPV test, which covers all the expanded genotypes requested in the proposal for public funding (Table 4).

Table 4 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
Fee: $50.00 Benefit: 75%: $37.50 85%: $42.50

Table 5 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: $50.00 Benefit: 75%: $37.50 85%: $42.50

Table 6 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: $50.00 Benefit: 75%: $37.50 85%: $42.50

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.

PASC also noted the Department's observation that proposed item DDDD may be redundant if no frequency restriction was placed on item BBBB.

Reflex cytology testing

Table 7 Draft MBS item proposed in the application for cytology testing of HPV-positive anal specimens

Category 6 – PATHOLOGY SERVICES – P6 Cytology
MBS item EEEE 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: (a) the cytology is associated with the detection of oncogenic human papillomavirus infection by: i. a test to which item BBBB applies; or ii. a test to which item CCCC applies for a patient mentioned in paragraph (a) or (b) of that item; or (b) the cytology is associated with a test to which item CCCC applies; or (c) the test is a repeat of a test to which this item applies, if the specimen collected for the previous test is unsatisfactory
Fee: $70.00 Benefit: 75%: $52.50 85%: $59.50

Therapeutic procedures

The PICO presented two items for therapeutic procedures:

1. Diagnostic HRA
2. HRA guided HSIL ablation

Diagnostic HRA

Table 8 Draft MBS item descriptor proposed in the application for diagnostic high resolution anoscopy

Category 3 – THERAPEUTIC PROCEDURES
MBS item FFFF Examination of the anal canal and perianus using a high resolution anoscope in a patient who: (a) has a human papilloma virus (HPV) related anal/perianal indication; or (b) has symptoms or signs suspicious of anal/perianal malignancy; or (c) is undergoing follow-up treatment for anal/perianal malignancy; or (d) is undergoing assessment or surveillance of an anal/perianal premalignant or malignant disease; or (e) is undergoing assessment or surveillance as part of an identified at-risk population. Multiple Operation Rule (Anaes) Explanatory notes: Benefit will only be paid in the following circumstances: (a) where the patient has had an abnormal anal HPV test result; or (b) where the patient has been referred by another medical practitioner with suspicion of anal cancer. Diagnostic HRA performed no more than four times per year. HRA must be performed by a suitably trained and qualified practitioner.
Fee: $140.60 Benefit: 75%: $105.45 85%: $119.51

Table 9 Draft MBS item descriptor proposed by assessment group for high resolution anoscopy-guided biopsy biopsy

Category 3 – THERAPEUTIC PROCEDURES
MBS item HHHH Anus, biopsy of, when performed in conjunction with a service to which item FFFF applies Multiple Operation Rule (Anaes)
Fee: $80.20 Benefit: 75%: $60.15 85%: $68.17

Ablative treatment

Item GGGG does not explicitly state that it cannot be billed with item FFFF. For the purpose of the evaluation, it was assumed that they would not be billed together, i.e., Item GGGG covered both the HRA-guided procedure and the ablation procedure. However, MSAC may wish to consider if it needs to be stated in the item descriptor. In addition, PASC queried what was meant by an episode ("treatments per episode"), based on the clinical data an episode was assumed to be the treatment of a lesion(s) discovered during guided HRA until HSIL clearance was achieved. However, this may need to be clarified with the applicant.

Table 10 Draft MBS item descriptor proposed in the application for treatment of HSIL (ablation with high resolution anoscopy)

Category 3 – THERAPEUTIC PROCEDURES
MBS item GGGG Anal HSIL ablation or cryotherapy, with high-resolution anoscopy guidance, including any local anaesthesia or biopsies, for previous biopsy confirmed HSIL. Up to a maximum of 6 ablative treatments per episode, until clearance of HSIL is achieved. Multiple Operation Rule (Anaes) Explanatory notes: Benefit will not be paid except in the following circumstances: (a) where the patient has histological confirmation of anal HSIL (b) HRA must be performed by a suitably trained and qualified practitioner.
Fee: $701.60 75%: $526.20 85%: $596.36

Surgical excision

In the post-PASC phase, the Department noted that surgical excision under anaesthesia may be a potential treatment option (though noting it is not recommended by the ASHM guidelines). The Committee may wish to consider if surgical excision should be included as a treatment option, and if so, whether existing MBS items appropriately provide for such excision.

7. Population

There are two populations of interest given this is a co-dependent application (i.e., the treatment and testing populations).

Testing population

The testing population is people at high risk of developing anal cancer associated with HPV. The proposed technologies will be used to test asymptomatic patients considered at high risk of anal cancer, the comparator is no testing. Generally, in the proposed testing scenario, a patient would present to a doctor for a check-up, sexual health examination or other illness and the clinician would advise testing if they considered the patient at high risk of anal cancer.

The testing population is originally divided into 7 high-risk subgroups (and an additional eighth sub-group added by PASC), termed "PICO-specified subpopulations" henceforth:

1. 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 ≥35 years.
2. MSM age ≥45 years and/or who identify as TW who are HIV negative.
3. women and men who have sex with women (MSW) age ≥45 years who are HIV positive.
4. women with previous vulval HPV-associated squamous cell carcinoma (SCC) and/or HSIL commencing within 1 year of diagnosis.
5. solid organ transplant recipients (SOTR) commencing 10 years post-transplant.
6. people being followed up after treatment for anal cancer.
7. people with incidental HSIL (lesions found during diagnosis of anal conditions).
8. *people with history of cervical/vaginal cancer or precursor lesions (added by PASC).*

Risk of anal cancer in PICO-specified subpopulations

Anal cancer incidence by subpopulation as identified in the literature is reported in Table 11. Results are primarily taken from a meta-analysis conducted by Clifford et al. (2021)[7]. Estimates are from international data and may not be generalisable to the Australian population. Additionally, age restrictions were not applied, therefore the reported incidence rates likely underestimate the true rates for the older PICO-specified age ranges, as the meta-analysis found that the anal cancer incidence increases with age.

Incidence rates were highest in MSM LWH and people with previous vulval SCC/HSIL. Of note, Clifford et al. (2021) reported that for women diagnosed with cervical lesions (specifically cervical intraepithelial neoplasia [CIN]-3, the most severe form of CIN) incidence rates increased substantially with age (considering two large studies conducted in Sweden and the Netherlands). This may suggest a benefit of age-based criteria for testing for this subpopulation.

The applicant stated that the original selected subpopulations are those with a 10-fold greater risk of anal cancer than the general population. PASC noted that the proposed populations did 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. This is because the largest group of women at risk (people with history of cervical/vaginal cancer or precursor lesions) has lower anal cancer risk compared to other high-risk subgroups, although their risks remain about 5-10-fold higher than that of the general population. Inclusion of people with possible history of cervical/vaginal cancer or precursor lesions (added by PASC) would increase the number of people tested (representing approximately 8.8% of the total testing population).

[7] Clifford GM, Georges D, Shiels MS, Engels EA, Albuquerque A, Poynten IM, de Pokomandy A, Easson AM, Stier EA. A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. Int J Cancer. 2021 Jan 1;148(1):38-47.

Table 11 Anal cancer incidence by PICO-specified subpopulation

Population		Incidence rate per 100,000 person-years	Heterogeneity from meta-analysis	Source
MSM and TW LWH		85 (95% CI = 82-89)	I^2 = 93%, p < .01	Clifford 2021
MSM and TW not LWH		19 (95% CI = 10-36)	I^2 = 0%, p = .90	Clifford 2021
Women and MSW living with HIV*	Women LWH	22 (95% CI = 19-24)	I^2 = 76%, p < .01	Clifford 2021
	MSW LWH	32 (95% CI = 30-35)	I^2 = 63%, p = .03	Clifford 2021
People with previous vulval SCC/HSIL	Women diagnosed with vulvar cancer	48 (95% CI = 38-61)	I^2 = 0%, p = .45	Clifford 2021
	Women diagnosed with vulvar pre-cancerous lesions	42 (95% CI = 33-52)	NR	Clifford 2021
SOTR†	Males	49.6 (35.4-67.5)	NR	Clifford 2021
	Females	24.5 (16.3-35.4)	NR	Clifford 2021
Patients after treatment for anal cancer		4.2 (3.7–4.8)	NA	Faber 2020
Patients with incidental HSIL		NA‡	NA	-
People with possible history of cervical/vaginal cancer or precursor lesions (added by PASC)	*Women diagnosed with cervical cancer*	9 (95% CI = 8-12)	I^2 = 0%, p < .63	Clifford 2021
	Women diagnosed with cervical pre-cancerous lesions	6 (95% CI = 5-7)§	I^2 = 74%, p < .01	Clifford 2021
	Women diagnosed with vaginal cancer	10 (95% CI = 3-30)	I^2 = 0%, p < .81	Clifford 2021
	Women diagnosed with vaginal pre-cancerous cancer	19 (95% CI = 9-43)	NA	Clifford 2021

Source: Clifford 2021[7], Faber 2020[8]
Notes: *Incident ratios for this population were highest in a study from Switzerland, where incident ratios were restricted to persons aged 40 years or older only (supporting age-based cut-offs used in the proposed PICO population).
†Anal cancer incidence increased by age of transplant recipients, from 0.0 and 3.1 per 100 000 person-years in males and females aged <30 years, respectively, up to 14.3 and 25.9 per 100 000 person-years for those aged ≥60 years. However, years since transplant appeared to identify SOTRs at highest anal cancer risk better than age, with anal cancer IR for ≥10 years after transplant reaching 24.5 and 49.6 per 100 000 person-years for males and females, respectively. This aligns with the current PICO subpopulation time specification.
‡Not available. It would be assumed that methods to incidentally detect HSIL would also detect anal cancer if present. However, noting that anal HSIL progresses to anal cancer.
§Two of the largest studies in the meta-analysis, conducted in Sweden and the Netherlands, reported combined age-stratified incidence rates of anal cancer among women diagnosed with CIN3 as 1.3 per 100,000 person-years in women under 40, 8.1 per 100,000 person-years in those aged 40 to 59, and 15.0 per 100,000 person-years in women aged 60 and above. This may suggest a benefit of age-based criteria for this subpopulation to target those at highest risk.
Abbreviations: CIN = cervical intraepithelial neoplasia, HIV = human immunodeficiency virus, HSIL= high-grade squamous intraepithelial lesions, MSM = men who have sex with men, MSW = men who have sex with women, NA = not applicable, NR = not reported, PY = person-years, SCC = squamous cell carcinoma, SOTR = solid organ transplant recipients, TW = transgender women

Other risk groups examined in Clifford et al. (2021) included systemic lupus erythematosus, ulcerative colitis and Crohn's disease, which showed incidence rates of 10 (95% CI 5–19), 6 (95% CI 3–11) and 3 (95% CI 2–4) per 100,000 person-years, respectively. Another recent systematic review (Albuquerque et al. 2023) reported the incidence of anal cancer was 10.2 (95% CI 4.3–23.7) per 100,000 person-years in ulcerative colitis and 7.7 (95% CI 3.5–17.1) per

[8] Faber M, Frederiksen K, Palefsky J, Kjaer S; Risk of Anal Cancer Following Benign Anal Disease and Anal Cancer Precursor Lesions: A Danish Nationwide Cohort Study. *Cancer Epidemiol Biomarkers Prev* 1 January 2020; 29 (1): 185–192.

100 000 person-years in Crohn's disease.[9] These reported rates are similar to Clifford et al. (2021) in those people with possible history of cervical/vaginal cancer or precursor lesion (added by PASC).

Natural history of HPV, HSIL and anal cancer

HPV is a common sexually transmitted infection. While most HPV infections clear over time, some persist. Persistent high-risk HPV (oncogenic HPV; hrHPV) infections are strongly associated with anal intraepithelial neoplasia (AIN) which is a premalignant condition characterised by abnormal changes in the squamous cell lining of the anal canal and perianal skin. High grade AIN or HSIL lesions, if left untreated, may progress to invasive anal cancer. Prevalent infections are less likely to clear than incident infections as long-standing infections are unlikely to resolve, whereas new infections following a previously negative test are more likely to be transient and clear naturally within a short time.

HIV status and sexuality have been shown to impact the natural history of HPV. The prevalence of hrHPV infection by genotype for each PICO-specified subpopulation is presented in Table 12. Estimates are taken from Australian studies or the most relevant meta-analyses where possible. Of note, HPV vaccination (commenced in 2007 in Australia initially for school-aged girls and subsequently for boys in 2013) alters the natural history of HPV infection, anal HSIL and anal cancer. Further details are provided in the 'Other relevant information' section.

Incidence and clearance rates for anal hrHPV infection for key PICO-specified subpopulations is presented in Figure 1 which was taken from Wei et al. (2023), a pooled analysis of individual-level longitudinal data (from 34 studies).[10] Low clearance suggests that infections are more likely to persist, and greater persistence of HPV increases the likelihood of progression to HSIL or anal cancer.

There was limited evidence relevant to the Australian population on prevalence, incidence and clearance of different hrHPV types for some subpopulations:

- People with previous vulval SCC/HSIL
- SOTR
- Patients after treatment for anal cancer
- Patients with incidental HSIL
- *People with possible history of cervical/vaginal cancer or precursor lesions (added by PASC).*

HPV16 was the most carcinogenic hrHPV infection, evidenced by the highest incidence and lowest clearance rates and longest infection duration, most notably in MSM LWH and MSM not LWH.[8] Similar incidence-clearance ratios were reported in the two studies[8, 11] , indicating that anal HPV18 infection is less carcinogenic than HPV18 infection in the cervix. This supports the proposed clinical management algorithm whereby patients with HPV16 detected alone (not including HPV18 as per the NCSP) are referred for diagnostic HRA. The proposed clinical management algorithm is further supported by lower prevalence rates of HPV18 in key populations (shown in Table 12) than that of HPV16 and similar to other oncogenic HPV variants.

However, other hrHPV types in specific populations also had low clearance rates and high incidence-clearance ratios, namely MSM and TW LWH, MSM and TW not LWH, Women and MSW living with HIV where certain non-HPV16 genotypes may occasionally reach prevalence and

[9] Albuquerque A, Cappello C, Stirrup O, Selinger CP. Anal High-risk Human Papillomavirus Infection, Squamous Intraepithelial Lesions, and Anal Cancer in Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Crohns Colitis. 2023 Aug 21;17(8):1228-1234.

[10] Wei et al, Incidence and Clearance of Anal Human Papillomavirus Infection in 16 164 Individuals, According to Human Immunodeficiency Virus Status, Sex, and Male Sexuality: An International Pooled Analysis of 34 Longitudinal Studies, Clinical Infectious Diseases, 76(3): e692–e701, 2023

[11] de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 Feb;8(2):e180-e190. doi: 10.1016/S2214-109X(19)30488-7.

clearance levels similar to HPV16. This suggests the need for expanded genotyping to detect persistence of non-HPV16 genotypes in certain populations. However, HPV16 remains markedly higher than any other genotype.

Further, the Australian SPANC study of MSM found a higher prevalence and incidence, and reduced clearance of non-16 hrHPV types in MSM LWH, though no difference between HIV status in hrHPV clearance rates overall.[5] This indicates a more substantial role of non-HPV16 hrHPV types in anal cancer development for MSM LWH, supporting the potential need for expanded hrHPV genotyping in this cohort.

For subpopulations other than MSM and PLWH, the value of expanded genotyping to detect persistent non-HPV16 hrHPV is currently lacking in Australian context. Ongoing studies will provide prevalence estimates for (1) people with previous vulval SCC/HSIL and (2) people with possible history of cervical/vaginal cancer or precursor lesions (NCT05217940, NCT03061435; further details in Characteristics of the evidence base - Relevant ongoing trials).

Table 12 Prevalence of hrHPV genotypes by PICO-specified subpopulation

Population		HPV16	HPV18	HPV31	HPV33	HPV35	HPV39	HPV45	HPV51	HPV52	HPV56	HPV58	HPV59	HPV68	HPV16/18	hrHPV	Source
MSM and TW LWH		28.5%	15.2%	11.9%	10.5%	8.7%	10.6%	12.1%	13.6%	15.6%	7.9%	13.2%	11.9%	10.5%	37.4%	74.3%	Wei 2021[12]
		31.9%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	84.3%	Poynten 2021[5]; Jin 2025[13] (SPANC)
MSM and TW not LWH		13.7%	6.4%	4.2%	3.3%	2.7%	5.5%	5.1%	7.5%	6.6%	4.3%	5.0%	5.8%	4.7%	18.9%	41.2%	Wei 2021[12]
		35.8%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	73.8%	Poynten 2021[5]; Jin 2025[13] (SPANC)
Women and MSW living with HIV*	Women LWH	12.2%	6.2%	5.2%	3.9%	4.0%	3.6%	4.9%	6.1%	6.3%	4.6%	7.8%	4.1%	6.2%	16.6%	43.2%	Wei 2023[14]
	MSW LWH	8.7%	4.7%	2.1%	1.4%	1.4%	2.6%	3.6%	3.8%	3.4%	0.9%	3.6%	4.1%	1.9%	11.4%	26.9%	Wei 2021[12]
People with previous vulval SCC/HSIL	All	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	26.3%*	Proctor 2019[15]
	Vulval HSIL	71.8%	5.8%	2.6%	8.0%	1.5%	0.0%	1.5%	0.8%	0.8%	0.8%	0.8%	0.8%	0.0%	NR	85.3%**	De Vuyst 2009[16^]
	Vulval SCC	32.3%	4.6%	0.8%	4.9%	0.0%	0.0%	1.5%	0.8%	0.8%	0.0%	0.0%	0.0%	0.0%	NR	40.4%**	De Vuyst 2009[16^]
SOTR†		3.6%[18]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	9.0%[17]	Rosales 2021[17] Albuquerque 2020[18]
Patients after treatment for anal cancer		73.8%	4.9%	1.6%	4.3%	0.0%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	NR	84.3%**	De Vuyst 2009[16^]

[12] Wei F, Gaisa MM, D'Souza G, Xia N, Giuliano AR, Hawes SE, et al. Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies. Lancet HIV. 2021 Sep;8(9):e531-e543. doi: 10.1016/S2352-3018(21)00108-9. Epub 2021 Jul 30.

[13] Jin F, Poynten IM, Hillman RJ, Law C, Molano M, Fairley CK, Garland SM, Templeton DJ, Grulich AE, Roberts J; SPANC study team. Does use of anal cytology as a triage test improve the performance of high-risk human papillomavirus screening in gay and bisexual men for anal cancer prevention? Int J Cancer. 2025 Feb 1;156(3):575-586.

[14] Wei F, Xia N, Ocampo R, Goodman MT, Hessol NA, Grinsztejn B, Ortiz AP, et al. Age-Specific Prevalence of Anal and Cervical Human Papillomavirus Infection and High-Grade Lesions in 11 177 Women by Human Immunodeficiency Virus Status: A Collaborative Pooled Analysis of 26 Studies. J Infect Dis. 2023 Feb 14;227(4):488-497.

[15] Proctor, L., Grennan, T., Albert, A., Miller, D., Sadownik, L., & Lee, M. (2019). Screening for Anal Cancer in Women With a History of Vulvar High-Grade Squamous Intraepithelial Lesions. Journal of Lower Genital Tract Disease, 23(4).

[16] De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer. 2009

[17] Rosales BM, Langton-Lockton J, Hedley J, et al. Prevalence of anal cytological abnormalities and high-risk human papillomavirus prevalence in kidney transplant recipients: A cross-sectional study. Clin Transplant. 2021; 35:e14476.

[18] Albuquerque A, Stirrup O, Nathan M, Clifford GM. Burden of anal squamous cell carcinoma, squamous intraepithelial lesions and HPV16 infection in solid organ transplant recipients: A systematic review and meta-analysis. Am J Transplant. 2020; 20: 3520–3528.

Patients with incidental HSIL		59.7%	17.5%	8.0%	13.4%	4.8%	4.8%	8.8%	2.4%	3.9%	4.8%	12.6%	3.5%	0.5%	NR	93.9%**	De Vuyst 2009[16]^
People with possible history of cervical/vaginal cancer or precursor lesions (added by PASC)	All	8%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	17.3%*§	Hillman 2015[19]
	Vaginal HSIL	57.3%	7.0%	3.4%	6.1%	3.0%	0.0%	0.0%	3.4%	1.6%	5.5%	6.0%	1.5%	0.0%	NR	90.1%**	De Vuyst 2009[16]^
	Vaginal SCC	54.3%	7.6%	5.3%	3.8%	0.8%	0.8%	0.8%	0.0%	0.8%	0.0%	0.8%	0.0%	0.0%	NR	69.9%**	De Vuyst 2009[1616]^

Source: Study reports

Notes:

*Secondary outcome of the ongoing SWAN study (NCT05217940)[20] is prevalence of hrHPV types in women with a history of pathologically proven high-grade genital HPV-associated neoplastic disease (cervical intraepithelial neoplasia 2+, vulvar intraepithelial neoplasia 2+, or vaginal intraepithelial neoplasia 2+, or history of non-metastatic cervical, vaginal or vulvar cancer) (estimated enrolment: N=300); study completion date January 2027). Proctor 2019 is not an Australian study and only includes those with vulval HSIL (not cancer). Hillman 2015 is Australian, and includes women with a history of cervical, vaginal and vulval HPV-related disease (not HSIL). Estimates from the SWAN study will provide up-to-date estimates for both people with previous vulval SCC/HSIL and people with possible history of cervical/ vaginal cancer or precursor lesions in a comparable population to Australia (Canada). In addition, the ongoing Vulvar-AIN study (NCT03061435) [21] has a primary outcome of prevalence of hrHPV DNA in women with VIN 2/3 or vulvar cancer. This will provide prevalence estimates for this population directly in a comparable population to Australia (Canada); estimated study completion 2026-01-01).

**Includes all HPV types. However, stated in text of manuscripts that no other type than HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, 6 and 11 were found in more than 0.5% of any anogenital carcinomas. This indicates high cross-over with hrHPV.

§This is the lowest estimate in the identified literature. Meta-analysis by assessment group of prevalence studies identified in systematic review: 7 studies (n=1030) showed rate of 0.29 (95% CI 00.22 – 0.38; I2 = 86.4% – Figure F66 in Appendix F). De Vuyst 2009 reported HPV rates of 0.699–0.901 for people with vaginal HSIL/SCC.

^HPV subtype results estimated from graph using online plot digitiser as not provided numerically.

Abbreviations: HIV = human immunodeficiency virus, HSIL= high-grade squamous intraepithelial lesions, MSM = men who have sex with men, MSW = men who have sex with women, NA = not applicable, NR = not reported, PY = person-years, SCC = squamous cell carcinoma, SOTR = solid organ transplant recipients, TW = transgender women

[19] Hillman, R., Gunathilake, M., Roberts, J., Farnsworth, A., Tabrizi, S., Bellingham, R., Tahir, A., Jin, F., Poynten, I., & Grulich, A. (2015). Results from a screening pilot for anal HSIL in women with a history of cervical, vaginal and vulval hpv related disease (WHCVVHD). Sexual Health, 12, 82-82.

[20] NCT05217940. Screening Women With Prior HPV for Anal Neoplasia (SWAN). https://www.clinicaltrials.gov/study/NCT05217940

[21] NCT03061435. Screening for Anal Cancer in Women With High-grade Vulvar Dysplasia or Vulvar Cancer. (Vulvar-AIN). https://clinicaltrials.gov/study/NCT03061435

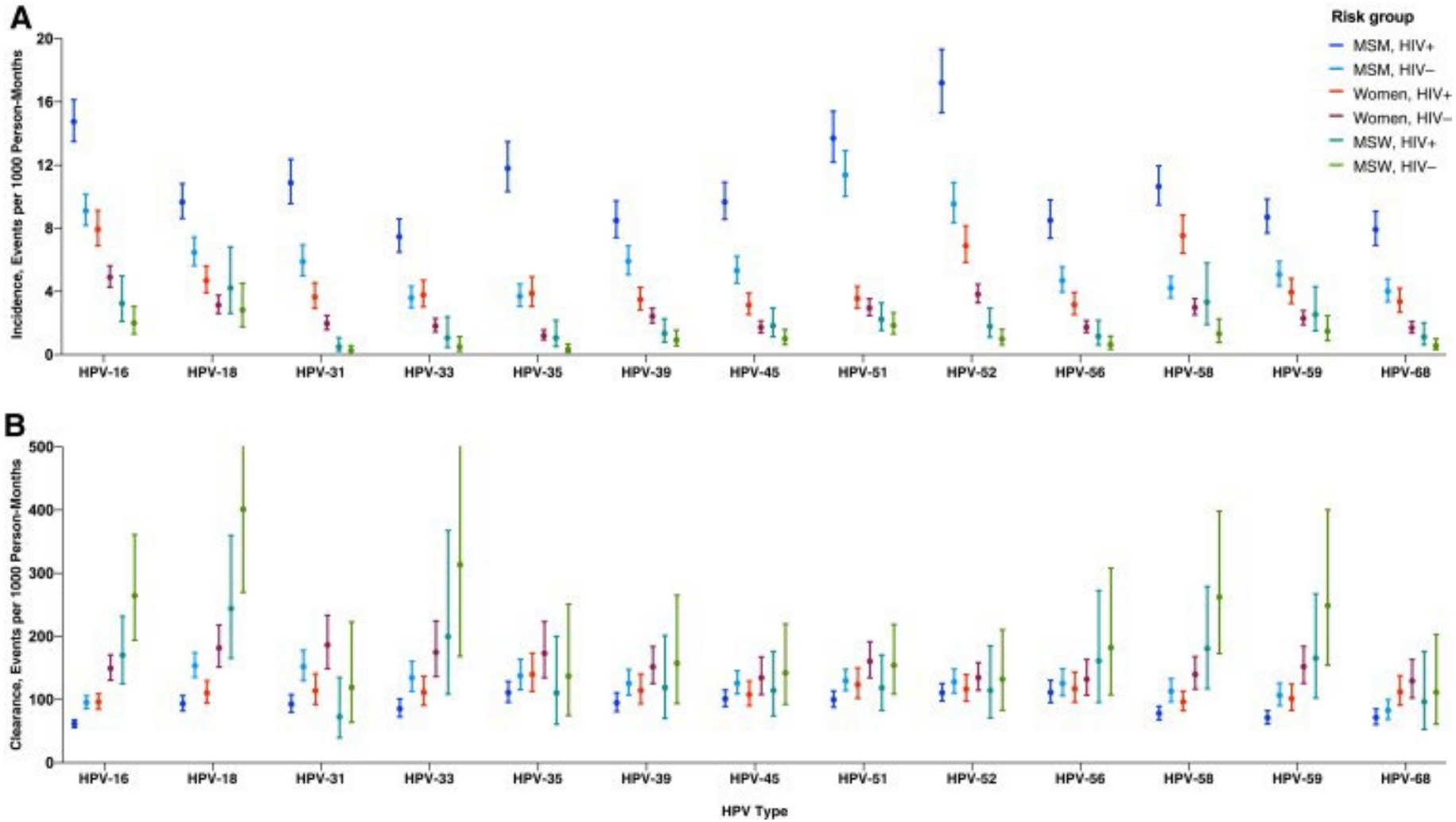

Figure 1 Incidence and clearance rates of anal hrHPV infection in 6 risk groups from Wei et al. 2023

Notes: Error bars represent 95% confidence intervals.
Abbreviations: HIV+ = with human immunodeficiency virus; HIV- = without human immunodeficiency virus; MSM = men who have sex with men; MSW = men who have sex with women.

Genotyping identifies virologic risk, but clinical management is guided by lesion grade. AIN is a premalignant condition characterised by abnormal changes in the squamous cells lining the anal canal and perianal skin. Development of AIN is strongly associated with persistent hrHPV infection. AIN is classified into: AIN1 for low-grade squamous intraepithelial lesion (LSIL), whereas AIN2 and AIN3 correspond to HSIL. Higher grades of AIN are more likely to lead to cancer. In a Danish cohort[8], the 5-year risk of anal cancer following diagnosis of AIN2 has been estimated at 1.57% (95% CI 0.65–2.48) and 3.7% (95% CI 2.6–4.7) for AIN3 (HSIL is considered AIN2/3). While there was no active follow-up or monitoring of this cohort, if identified, treatment may have been performed, supporting the need for earlier identification of lesions.

HPV testing frequencies for sub-populations

The applicant noted that the intervals for regular HPV testing are unclear, due to limited published evidence on this issue.[22] 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. As the eighth subpopulation was added by PASC, proposed retesting frequencies were not provided in the PICO. Given incidence rates in this subpopulation are some of the lowest reported, the longest re-testing interval may be most appropriate (5 years).

In the ASHM Australian Anal Cancer Screening Guidelines for people living with HIV the recommended testing interval if previously HPV negative is 6 years, not 6 months as proposed in the PICO. This may require review, as other testing frequencies either exactly aligned (MSM and TW LWH; Women and MSW LWH) or more closely aligned (Patients with incidental HSIL) with the ASHM guidelines. Though, acknowledging these guidelines include further criteria of PLWH only.

[22] Stier E, Clarke M, Deshmukh A, et al. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. International Journal of Cancer 2024;154:1694-702.

Table 13 Proposed HPV testing frequencies for PICO-specified subpopulations in the PICO

Population	Interval if previously HPV-negative		Triage test	HRA	HPV testing interval after negative HRA
	PICO proposed	ASHM guidelines			
1. MSM and TW living with HIV [a]	3 years	3 years	Cytology	**No HRA** • HPV negative + no clinical suspicion **HRA regardless of cytology result** • HPV16 positive (immediate HRA) • HR-HPV (non-16) positive at baseline and 1 year (HRA at 12 months) **HRA based on cytology result** • HR-HPV (non16) with cytology of pHSIL, HSIL or carcinoma	1 years
2. MSM and TW living without HIV [b]	5 years	-			
3. Women and MSW living with HIV [b]	3 years	3 years			
4. Women with previous vulval SCC/HSIL – HPV associated [c]	5 years	-			
5. SOTR [d]	3 years	-			
6. Patients after treatment for anal cancer	6 months [e]	6 years			
7. Patients with incidental HSIL [f]	5 years	3 years			
8. People with possible history of cervical*/vaginal cancer or precursor lesions (added by PASC)*	*5 years*	-			

Source: Table 4 in MSAC1752 ratified PICO (table provided by the applicant).
Abbreviations: HIV = human immunodeficiency virus, HPV = human papillomavirus, HRA = high-resolution anoscopy, 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, pHSIL = possible high-grade squamous intraepithelial lesions, SCC = squamous cell carcinoma, SOTR = solid organ transplant recipient, TW = transgender women.
Notes: a Age ≥35 years; b Age ≥45 years; c Commencing within 1 year of diagnosis; d Commencing 10 years post-transplant; e Commencing 6 months after completion of treatment and lasting for 3 years or until any residual disease has been eradicated; f 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.

The proposed clinical management algorithm includes follow-up testing for anal HPV every 6 months for 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.

Treatment population

The treatment population is people with anal HSIL.

There is limited information regarding the prevalence and incidence of HSIL attributable to HPV in Australia.

Estimates rates of HSIL investigation, treatment and outcomes

Based on evidence appraised, a summary of the anal HSIL investigation and treatment care cascade per 10,000 people for each PICO-specified subpopulation is presented in Table 14 (not considering uptake or referral rates, which are acknowledged to be less than 100%).

Table 14 Anal HSIL investigation and treatment care cascade as estimated from the evidence (per 10 000 people for each PICO-specified subpopulation)

Population	MSM and TW LWH	MSM and TW not LWH	Women and MSW living with HIV		People with previous vulval SCC/HSIL – HPV associated	SOTR	Patients after treatment for anal cancer	Patients with incidental HSIL	*People with possible history of cervical/ vaginal cancer or precursor lesions (added by PASC)*
			Women LWH	MSW LWH					
N	10000	10000	10000	10000	10000	10000	10000	10000	10000
Test positive for hrHPV	**8430**	**7380**	**4320**	**2690**	**2630**	**940**	**8430**	**9390**	**1730**
Input	0.843†	0.738‡‡	0.432	0.269	0.263*	0.094‡	0.843††	0.939††	0.173*§
Source	Jin 2025	Jin 2025	Wei 2023	Wei 2021	Proctor 2019	Rosales 2021	De Vuyst 2009	De Vuyst 2009	Hillman 2015
Test positive for cytology	There was no evidence for test positive rates for cytology in hrHPV positive PICO subpopulations.								
Referred for HRA	**6590**	**5530**	**3305**	**2058**	**2012**	**719**	**6449**	**7183**	**1323**
Input	0.659	0.553	0.765						
Source	Jin 2025 HRA referral rate for total tested population		Jin 2025 Average HRA referral rate for those who test positive for hrHPV (across both MSM populations) from Jin 2025 (referral rate for those who are hrHPV positive)						
Histologically confirmed HSIL¶	**1970**	**1653**	**988**	**615**	**602**	**215**	**1928**	**2148**	**396**
Input	0.299								
Source	Correspondence with author of Jin 2025								
Cured following ablation at 12 months	**1399**	**1174**	**702**	**437**	**427**	**153**	**1369**	**1525**	**281**
Input	0.71								
Source	Goldstone 2019** (cure rate at 12 months for PLWH)								
Recurrence following ablation at 12 months	**571**	**480**	**287**	**178**	**174**	**62**	**559**	**623**	**115**
Input	0.29								
Source	Goldstone 2019** (inverse of cure rate)								
Progression to anal cancer after 12 months	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**0**
Input	0.00173								
Source	173 per 100,000 person-years cases in the treatment group (median follow-up of 25.8 months); Palefsky 2022[100] (PLWH only)								

Source: Calculations by assessment group.
Notes: *Secondary outcome of the ongoing SWAN study (NCT05217940) is prevalence of hrHPV types in women with a history of pathologically proven high-grade genital HPV-associated neoplastic disease (cervical intraepithelial neoplasia 2+, vulvar intraepithelial neoplasia 2+, or vaginal intraepithelial neoplasia 2+, or history of non-metastatic cervical, vaginal or vulvar cancer) (estimated enrolment: N=300); study completion date January 2027). Proctor 2019 is not an Australian study and only includes those with vulval HSIL (not cancer). Hillman 2015 is Australian, and includes women with a history of cervical, vaginal and vulval HPV-related disease (not HSIL). Estimates from the SWAN study will provide up-to-date estimates for both people with previous vulval SCC/HSIL and people with possible history of cervical/ vaginal cancer or precursor lesions in a comparable population to Australia (Canada). In addition, the ongoing Vulvar-AIN study (NCT03061435) has a primary outcome of prevalence of hrHPV DNA in women with VIN 2/3 or vulvar cancer. This will provide prevalence estimates for this population directly in a comparable population to Australia (Canada); estimated study completion 2026-01-01).
††Includes all HPV types. However, stated in text of manuscripts that no other type than HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, 6 and 11 were found in more than 0.5% of any anogenital carcinomas. This indicates high cross-over with hrHPV
†Similar to Wei 2021 pooled analysis of 64 studies (n=29900) – 74.3%.
‡‡Lower estimate than Wei 2021 pooled analysis of 64 studies (n=29900) – 41.2%.
‡This is the lowest estimate in the identified literature. Meta-analysis by assessment group of prevalence studies identified in systematic review: 4 studies (n=566) showed rate of 0.17 (95% CI 0.12 – 0.23; I2 = 62.4% – Figure F65 in Appendix F).
§This is the lowest estimate in the identified literature. Meta-analysis by assessment group of prevalence studies identified in systematic review: 7 studies (n=1030) showed rate of 0.29 (95% CI 00.22 – 0.38; I2 = 86.4% – Figure F66 in Appendix F). De Vuyst 2009 reported HPV rates of 0.699–0.901 for people with vaginal HSIL/SCC.
¶Not considering attrition rates – HRA uptake and receipt of ablative treatment will not be 100% of those referred. Results for these outcomes (reported in change in management section) varied significantly.
**Goldstone 2019 was selected as the input as it was the only RCT/key evidence study assessing the relevant outcome with a moderate (rather than high) risk of bias. Notably, the study included only patients with small lesions, which are more likely to resolve with treatment or regress spontaneously. As a result, the observed cure rate may be lower, consistent with findings from single-arm studies, which estimate cure rates of 35–40% in MSM LWH and PLWH across three studies with average follow-up periods of 12.2–13.7 months]).
Abbreviations: HIV = human immunodeficiency virus; HPV= human papillomavirus; HRA = High Resolution Anoscopy; hrHPV = high risk HPV variants; HSIL= High-Grade Squamous Intraepithelial Lesion; LWH = living with HIV; MSM = men who have sex with men; MSW = men who have sex with women; SCC = squamous cell carcinoma; SOTR = solid organ transplant recipients; TW = transgender women

8. Comparator

Testing comparator

The comparator is the standard of care in Australia, which is no targeted testing regimen for anal HPV or anal HSIL in asymptomatic people at high risk of anal cancer. Investigation/testing is completed at the treating clinician's discretion, primarily when symptoms occur.

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 during standard investigative practice, and it is not diagnostic (as per ratified PICO).

Treatment comparator

The application stated that, in Australia, there is no comparator for HRA-guided anal ablation. For the DCAR, the comparator for treatment is based on patients not receiving prior risk-based testing for anal cancer when asymptomatic and hence being treated for anal HSIL or anal cancer opportunistically or when symptoms occur. When evaluating the clinical effectiveness and safety of HRA-guided ablation for HSIL, the comparator was no treatment/active monitoring.

The ratified PICO stated that the current treatment in Australia for HSIL lesions includes ablation and surgical excision. 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. Of note, the recently published Anal Cancer Screening Guidelines for PLWH from ASHM[23] lists recommended treatment modalities for anal HSIL as HRA-guided ablation and topical therapies only. Excision is specifically not recommended given its high risk of complications, including anal stenosis and faecal incontinence. However, given surgical excision

[23] ASHM Anal Cancer Screening Guidelines Committee. (2025). Targeted Australian Anal Cancer Screening Guidelines for people living with HIV. https://analcancerscreening.guidelines.org.au/

is still a treatment option considered appropriate by PASC and is identified in the literature, consideration of surgical excision as a treatment option is provided.

9. Summary of public consultation input

Consultation input was welcomed from:

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	No. of Inputs Received
Organisations (11)	
I am providing input on behalf of a consumer group or organisation. Consumer organisations are not-for-profit organisations representing the interests of healthcare consumers, their families and carers.	8
I am providing input on behalf of a medical, health, or other (non-consumer) organisation. For example, input on behalf of a group of clinicians, research organisation, professional college, or from an organisation that produces a similar service or technology.	6
Health Professionals (2)	
I am a health professional or health academic working in the area.	2
Consumers (1)	
I have the health condition that this health service or technology is for.	1
Grand Total	**17**

The organisations that submitted input were:

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

PASC TARGETED CONSULTATION:

Letters of support received from the National Association of People with HIV Australia.

Organisations approached for targeted consultation

All responses received from consultation on this application were supportive, for example:

- AIDS Council of NSW (ACON) support:
  - any intervention that seeks to increase HPV testing in high-risk populations in order to avoid preventable diseases including cervical and colon cancer
  - standardisation of test intervals between cervical and anal HPV testing

  - self-collect and testing by a broader range of health professionals including sexual health nurses.

- Australian Pathology strongly support:
  - Anal HPV testing for the detection of anal precancer and cancer particularly in HIV positive men who have sex with men because the risk of anal cancer is greater than the risk of cervical cancer.

- Cancer Council Australia state:
  - The proposed population should be focussed on those at highest risk
  - Patients receiving the proposed testing should be ensured appropriate follow-up to treat any abnormality
  - The utilisation estimates omit the large group of women with cervical lesions
  - Concerns about out-of-pocket costs for non-MBS funded services and long wait times to access public services
  - Notes that Hybrid Capture test has been superseded and no longer widely available. Modern PCR tests that separately identify HPV16 would be more appropriate.

- Colorectal Surgical Society of Australia and New Zealand supports and:
  - Seeks clarification regarding proposed populations, including patients with previous vaginal SCC or vaginal HSIL or cervical SCC or cervical HSIL as many of these patients often have field change in the perineum from exposure to HPV.
  - Noted that patients who develop recurrent anal SCC have generally done so from their previous cancers rather than developing “new” anal SCC, so value of surveying these patients is less clear.
  - Suggested that within these eligibility criteria, it is not clear if this will sufficiently allow women who otherwise form the bulk of the number of anal SCC cases to be diagnosed earlier. Although the risk of older MSM patients and TW patients are high, especially if they are living with HIV, these still present lower risk than women who otherwise have no other obvious risk factors. In considering funding such an intervention, would be ideal if some sort of modelling can be presented about the potential cost effectiveness of HRA.
  - Cost associated with treatment of anal HSIL seems high and may require justification. Treatment of cervical HSIL under MBS item 35645 attracts a lower fee and this
    may require some adjustment (upwards).
  - Examination of anus using HRA ‘fairly comparable’ to examination of lower genital tract using colposcope. Provided information about anal vs cervical ablation.

- Royal Australian College of General Practitioners seeks:
  - greater clarity on who is considered high-risk and eligible to be tested, for example women with high-risk types of HPV on cervical screening but have no lesions would be at risk of anal disease.
  - Increased fee for collection of samples consistent with Level B consultation.

Support for Public Funding

- Cancer Council: Strongly supports public funding across the cancer care continuum. It contributes to national screening guidelines and provides extensive support services. Its expert committees inform policy submissions.

- Rare Cancers Australia (RCA): Fully supports the proposed service, citing no barriers to access or care for affected patients.

Appropriateness of Target Population

- RCA: Agrees the proposed population is appropriate and well-targeted.

- Cancer Council (on behalf of Cancer Council Federation): Supports refined targeting based on risk, including PLHIV and women with prior vulval SCC/HSIL. Notes concerns about limited access to high-resolution anoscopy and underestimated demand.

Patient and Advocacy Group Insights

- Diagnosis Delays: RCA patients often face misdiagnoses and must self-advocate for proper care.
- Emotional Impact: Consumers report anxiety and difficulty accessing testing, even when willing to pay.
- Treatment Side Effects: Advocacy groups highlight severe impacts on quality of life.
- Equity Concerns: Some groups, like heterosexual HIV-negative women, may be excluded despite risk.

Perceived Advantages

- Early detection and treatment in high-risk groups.
- Potential reduction in anal cancer rates.
- Improved access for underserved populations via nurse-led care.
- Cost-effective and inclusive service delivery.
- Alignment with successful models like the National Cervical Screening Program.

Perceived Disadvantages

- RCA: No disadvantages noted.
- Others: Concerns about access for vulnerable populations and exclusion of nurse practitioners and sexual health nurses from service delivery and billing, which could limit access and increase GP workload.

Implementation Support

- Advocacy groups and nurse practitioners support the proposal but stress the need for inclusive implementation, especially regarding who can deliver and bill for services.

10. Characteristics of the evidence base

There was **direct evidence** to assess the proposed triaged investigative intervention (anal HPV testing, anal cytology testing and diagnostic HRA) followed by the therapeutic intervention (HRA-guided anal HSIL ablation), with the comparator (no testing), on health outcomes. Importantly, no evidence directly matched the PICO. Key differences were noted in included populations and interventions (testing methods and therapeutic intervention). For comprehensiveness, any evidence with relevance or cross-over to elements of the PICO was included, with limitations of applicability discussed.

Given applicability issues of the direct evidence, **linked evidence for the investigative intervention** is also presented, along with **evidence for the therapeutic intervention**. As MSAC 1752 is a codependent technology application, the combined use of different

services/technologies leads to the intended clinical effect, and the benefits of both technologies should therefore be assessed together.

Terminology and reporting protocol for cytology testing (Australian Modified Bethesda System)

The proposed testing algorithm uses the Australian Modified Bethesda System (AMBS)[24]. However, almost all identified studies reporting anal cytological outcomes use the Bethesda system (including those published in Australia). A summary of the comparative terminology is provided in Table 15 below. In the post-PASC proposed clinical management algorithm, potential HSIL (pHSIL), HSIL and SCC cytology results are referred for diagnostic HRA and biopsy, where potential low-grade squamous intraepithelial lesion (pLSIL) or low-grade squamous intraepithelial lesion (LSIL) are referred for repeat follow-up HPV testing in 12 months. ASC-H+ (atypical squamous cell, not excluding HSIL and high suspicious) is specified as meeting the HRA referral threshold which aligns with the PICO.

Table 15 Comparison of the AMBS (2004) and The Bethesda System (2001/2014) to report cytological results (reported directly from the National Cervical Screening Program Guidelines v2.20 and modified to reflect AIN rather than CIN)

AMBS 2004	The Bethesda system 2001/2014	Incorporates
Possible low-grade squamous intraepithelial lesion (pLSIL)	Atypical squamous cells, undetermined significance (ASC-US)	Nonspecific minor squamous cell changes; suggestive but not diagnostic of HPV/AIN1
Low-grade squamous intraepithelial lesion (LSIL)	Low-grade squamous intraepithelial lesion	HPV effect, AIN1
Possible high-grade squamous lesion (pHSIL)	Atypical squamous cells, possible high-grade lesion (ASC-H)	Suggestive but not diagnostic of AIN2, AIN3, or squamous cell carcinoma (SCC)
High-grade squamous intraepithelial lesion (HSIL)	High-grade squamous intraepithelial lesion	AIN2, AIN3
Squamous cell carcinoma	Squamous cell carcinoma	Squamous cell carcinoma

Source: Cancer Council Australia[24]
Abbreviations: AIN = anal intraepithelial neoplasia; AMBS = Australian Modified Bethesda system; ASC-H = Atypical squamous cells, possible high-grade lesion; ASC-US = Atypical squamous cells, undetermined significance; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = High-grade squamous intraepithelial lesion; pHSIL = Possible high-grade squamous lesion; pLSIL = Possible low-grade squamous intraepithelial lesion; SCC = squamous cell carcinoma

Cytological versus histological HSILs

Cytological HSIL refers to abnormalities of epithelial cells detected through anal cytology tests. Cytology testing is used as a preliminary test, as it has low sensitivity for detecting HSIL when using the PICO-specified threshold of ASC-H+/pHSIL+. In contrast, histological HSIL is diagnosed through biopsy of anal tissue via direct visualisation and collect sample of suspicious lesions, often guided by HRA. This is the gold standard for identification of HSIL (per PICO).

The PICO-specified algorithm uses histologically confirmed HSIL as the sole diagnostic endpoint, with anal HPV and cytology testing used to triage diagnostic HRA and biopsy. While some studies support the use of cytologically confirmed HSIL in combination with histologically confirmed HSIL

[24] Cancer Council Australia. (2025). National Cervical Screening Program Guidelines v2.20. Retrieved from https://www.cancer.org.au/clinical-guidelines/cervical-cancer/cervical-cancer-screening

as a diagnostic endpoint[25,26] , these accuracy benefits may not be seen when a stricter threshold is used than ASC-US+ (i.e., ASC-H+ as specified by the PICO).

Direct evidence

A total of 7 studies met the inclusion criteria for assessing the direct test to health outcomes evidence of testing for anal cancer (anal HPV testing, anal cytology testing and diagnostic HRA) followed by the therapeutic intervention (HRA-guided anal HSIL ablation). Five studies were comparative (to no testing), and two were non-comparative.

Importantly, there was no evidence which directly matched the PICO, in particular the direct evidence for HPV test is lacking. Key differences were noted in included populations and interventions. Most anal cancer screening programs were for PLWH, and results were not disaggregated into MSM, MSW and women who have different hrHPV prevalence rates. PLWH also represents only a small proportion of the total PICO population for testing (approximately 22%). Additionally, no comparative studies (and only one non-comparative study) included anal HPV testing as part of the testing strategy, and re-test intervals did not match those in the PICO. The direct evidence is, therefore, severely limited in applicability to the PICO and the intended MBS population.

The applicability of the direct comparative evidence to the PICO is summarised in Table 16 (non-comparative evidence not presented). A summary of the key features of the direct comparative evidence is provided in Table 17.

[25] Silva M, Peixoto A, Sarmento JA, Coelho R, Macedo G. Anal cytology, histopathology and anoscopy in an anal dysplasia screening program: is anal cytology enough? Rev Esp Enferm Dig. 2018 Feb;110(2):109-114. doi: 10.17235/reed.2017.4913/2017. PMID: 29168646.

[26] Gudur A, Shanmuganandamurthy D, Szep Z, Poggio JL. An Update on the Current Role of High Resolution Anoscopy in Patients With Anal Dysplasia. Anticancer Res. 2019 Jan;39(1):17-23. doi: 10.21873/anticanres.13075. PMID: 30591436.

Table 16 Summary of applicability of the direct comparative evidence to the PICO (k=5)

PICO criteria	Comparative evidence				
	Van der Zee 2023[27]	Barnell 2019[28]	Revollo 2020[29]	Squeo 2023[30]	Walker 2024[31]
Population					
MSM and TW living with HIV age ≥35 years	Y*	Y†	Y¶	-	Y‡
MSM and TW living without HIV age ≥45 years	-	-	-	-	Y‡
Women and MSW living with HIV age ≥45 years	Y*	Y†	Y¶	Y¶^	Y‡
People with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis	-	-	-	-	Y‡
SOTR, commencing 10 years post-transplant	-	-	-	-	Y‡
Patients being followed up after treatment for anal cancer	-	-	-	-	Y‡
Patients outside these above groups with incidental anal HSIL and patients presenting with symptoms suggestive of anal cancer	-	-	-	-	Y‡
People with history of cervical/vaginal cancer or precursor lesions (added by PASC)	-	-	-	-	Y‡
Testing					
Anal HPV test¶¶	-	-	-	-	-
Cytology test	-	Y§	Y	Y	Y
HRA-guided biopsy and diagnosis of HSIL	Y	Y	Y	Y	Y
Treatment					
HRA-guided anal HSIL ablation	Y##	Y	Y††	Y	Y‡‡

Source: Study reports
Notes: *No age restrictions, though 79.3% of the population met the specified PICO subpopulations based on age.
†No age restrictions, between 32.6% and 72.1% of the population met the specified PICO subpopulations based on age (breakdowns not available by subgroup, only 35 years or older, and 45 years or older for whole population).
‡People opportunistically referred for screening; 3.9% SOTR, 76.9% LWH, 19.2% prior cancer (possibly anal).
¶No age restrictions, age breakdown not provided.
^Women LWH only (not MSW LWH).
§While anal cytology was mentioned as part of screening, procedures were not described.
¶¶HPV was not specified as part of any testing strategy.
##Treatment procedures not specified. Unclear if methods outside of the PICO-specified ablative intervention were used (i.e., topical or surgical.
††Treatments included interventions (IRC) and non-included (surgery). A breakdown of the proportion of the total sample receiving treatment types was not provided.
‡‡Most patients (90%) received treatment outlined in the PICO (electrocautery ablation), with the remaining receiving topical therapies or surveillance
Abbreviations: HIV = human immunodeficiency virus; HPV= human papillomavirus; HRA = High Resolution Anoscopy.
HSIL= High-Grade Squamous Intraepithelial Lesion; IRC = infrared coagulation; LWH = living with HIV; MSM = men who have sex with men; MSW = men who have sex with women; SCC = squamous cell carcinoma; SOTR = solid organ transplant recipients; TW = transgender women

[27] van der Zee RP, Wit F, Richel O, van der Valk M, Reiss P, de Vries HJC, et al. Effect of the introduction of screening for cancer precursor lesions on anal cancer incidence over time in people living with HIV: a nationwide cohort study. Lancet HIV. 2023;10(2):e97-e106.

Table 17 Key features of the direct comparative evidence comparing anal HPV testing, cytology testing and diagnostic HRA in comparison to no testing (k=5)

Trial/Study	N	Study design Risk of bias#	Population	Intervention	Comparator	Key outcome(s)
Van der Zee 2023[271] Netherlands	28175	Observational cohort High risk of bias	PLWH MSM: 59.7% Men who do not have sex with men: 21.6% Women: 18.8% Median age increased from 38·0 (IQR 33·1–45·0) years in 1996 to 51·0 (41·4–58·8) years in 2020	Anal cancer screening involving HRA-guided biopsies and treatment of HSILs to prevent anal cancer. Gradually implemented in some HIV treatment centres in the Netherlands from Dec 2007, focusing mainly on MSM. Anal cytology was not conducted; there was no specification regarding HPV testing. If no lesions identified, screening was completed every 2 years. If low-grade lesions were detected, screening was completed annually. High-grade lesions were treated, and treatment was evaluated after 6 months. Treatment procedures not specified. Unclear if methods outside of the PICO-specified ablative intervention were used (i.e., topical or surgical).	No screening	Evaluated pre and post introduction of screening in 2007 • Anal cancer incidence • Anal cancer-related and all-cause mortality • Clinical staging (TNM)
Barnell 2019[282] USA	13552	Retrospective comparative cohort Moderate risk of bias	PLWH MSM: 70.9% Men who do not have sex with men: 19.5% Women: 9.6% Age at baseline (yrs): 18-34: 26.3% 35-44: 39.5%	Anal cancer screening involving patients with HSIL identified via HRA and biopsy. While anal cytology was mentioned as part of screening, procedures were not described; there was no specification regarding HPV testing. Patients with HSIL were scheduled for follow-up	No screening	Evaluated pre and post introduction of screening in 2008 • Anal cancer incidence

[28] Barnell, G. M., Merchant, M., Lam, J. O., & Silverberg, M. J. (2019). Early Outcomes of a High-Resolution Anoscopy-Based Anal Cancer Screening Program among People with HIV Enrolled in an Integrated Health Care System. Journal of Acquired Immune Deficiency Syndromes, 81(3), 292-299.

[29] Revollo, B., Videla, S., Llibre, J. M., Paredes, R., Piñol, M., García-Cuyàs, F., Ornelas, A., Puig, J., Parés, D., Corral, J., Clotet, B., & Sirera, G. (2020). Routine Screening of Anal Cytology in Persons With Human Immunodeficiency Virus and the Impact on Invasive Anal Cancer: A Prospective Cohort Study. Clinical Infectious Diseases, 71(2), 390-399.

[30] Squeo, G. C., Geba, M. C., Kane, W. J., Thomas, T. A., Newberry, Y., Wang, X. Q., Hedrick, T. L., Friel, C. M., & Hoang, S. C. (2023). Impact of a High-Resolution Anoscopy Clinic on Management of Anal Dysplasia in Women Living With HIV. Am Surg, 89(11), 4689-4695.

[31] Walker, R. J. B., Easson, A. M., Hosni, A., Kim, J., Weiss, E. S., Santiago, A. T., Chesney, T. R., & Salit, I. E. (2024). Anal Cancers in Previously Screened Versus Unscreened Patients: Tumor Stage and Treatment Outcomes. Dis Colon Rectum, 67(1), 32-41.

			45-54: 25.1% 55-64: 7.6% 65+: 1.6%	treatment with infrared coagulation or ECA. Patients were recommended to return for repeat HRA in 3, 6, or 12 months based on the extent of disease and pathological diagnosis.		
Revollo 2020[293] Spain	3111	Retrospective comparative cohort Serious risk of bias	PLWH; 1691 (54%) in the screening group Screening: Women 339 (20.1%) MSW 257 (15.2%) MSM 1095 (64,8%) Non-screening: Women 288 (20.3%) MSW 631 (44.4%) MSM 501 (35.3%)	Anal cancer screening involving digital rectal examination and cytology. Normal results were rescreened annually, abnormal results (ASC-US, LSILs, or HSILs) were referred for HRA within 3 months. If lesions were seen with HRA, a directed biopsy was performed. There was no specification regarding HPV testing. HSIL results following biopsy were treated with infrared coagulation or surgery.	No screening	• Anal cancer incidence
Squeo 2023[304] USA	201	Retrospective comparative cohort Serious risk of bias	Women LWH Age: Pre-screening cohort: 32.0 (25.0, 38.0); Post-screening cohort: 29.0 (23.0, 37.0)	Post-introduction of HRA screening: patients who screened positive on anal cytology underwent HRA and lesions biopsied and then treated with a non-grounded electrocautery device.	Pre-introduction of HRA screening: cytology positive for ASC-US, LSIL, or HSIL were referred for biopsies and treatment if abnormalities were found.	Evaluated pre and post introduction of HRA-based screening in 2017 • Anal cancer incidence
Walker 2024[315] Canada	612 Screening: 26 Non-screening 586	Retrospective comparative cohort Serious risk of bias	Adults with a pathologic diagnosis of invasive anal SCC; differences between screening-detected versus non-screening detected cancers were evaluated. PLWH 23% total; 76.9% of those screened; 19.2% prior cancer (possibly anal).	Anal cancer screening based on various pathways including cytology findings, incidental HSIL findings, or concerning symptoms of anal malignancy. All new and follow-up patients underwent anal cytology and HRA with targeted biopsies for suspected HSIL. Anal cytology testing and HRA-guided biopsy were part of the screening. HPV testing was not routinely performed. Most patients (90%) received treatment outlined in the PICO (ECA), with the remaining	No screening	Evaluated screening-detected versus non-screening-detected cancers • Anal cancer treatments received • Clinical staging (TNM) • Anal cancer treatment failure; overall survival

				receiving topical therapies or surveillance.		

Source: Study reports
Notes: *Screening was gradually implemented in some HIV treatment centres in the Netherlands from Dec 1, 2007, mainly for MSM.
Follow-up interval based on the extent of disease and pathological diagnosis.
† Assessed using ROBINS-I risk of bias tool for non-randomised studies of interventions[32]
‡ Referral pathways included abnormal cytology findings, incidental HSIL findings, or concerning symptoms of anal malignancy.
Abbreviations: ECA = electrocautery ablation, HIV = human immunodeficiency virus, HPV = human papillomavirus, HRA = High-Resolution Anoscopy, HSIL = high-grade squamous intraepithelial lesions, IRC = infrared coagulation, MSM = men who have sex with men, PLWH = people living with HIV, SCC = squamous cell carcinoma, STD = sexually transmitted disease, TNM = tumour, nodal, and metastatic stage

Linked evidence of test accuracy

The investigative intervention under consideration in the PICO is a triaged testing strategy, involving anal HPV testing, anal cytology testing and diagnostic HRA. To provide a comprehensive assessment of the test accuracy, both of the following were sought:

- Evidence for the test accuracy of the triaged testing strategy (i.e., anal cytology testing triaged by anal HPV testing results for referral to diagnostic HRA).
- Evidence for the test accuracy of the individual investigative tests (anal HPV testing, anal cytology testing and diagnostic HRA).

Other studies have examined strategies that include parallel testing (also known as co-testing) of anal HPV and cytology (either for referral to diagnostic HRA or otherwise), as well as HPV testing triaged by cytology results.[33] These have not been included in this evaluation as they do not align with the proposed triaged testing regimen. The Anal Cancer Screening Guidelines for PLWH published by the ASHM do not recommend co-testing based on the evidence showing no benefit of co-testing above primary HPV testing[23], unlike the IANS guidelines[34] which include co-testing as a screening option.

A summary of applicability of the linked evidence for test accuracy to the PICO is reported in Table 18. Most studies examined PLWH, and within this MSM LWH (representing approximately 7% of the total PICO population). Studies were primarily conducted in the USA (n=21/48); three were included in the Australian Study of the Prevention of Anal Cancer (SPANC) (for a population of MSM aged 35 or older), for HPV testing alone,[35] cytology testing alone,[36] and triaged cytology testing based on HPV test results[13]. The latter was the only study which examined the proposed testing strategy[13].

A variety of panels/assays were used for HPV testing (including PCR, CLART Genomica HPV2, Linear Array, HC2, Cobas 4800, Atila Biosystems, Abbott RealTime High-Risk HPV assay, INNO-LiPA HPV Genotyping Extra II assay, Cepheid Xpert®HPV and ELISA SPF10-LiPA25), with up to 39 hrHPV genotypes tested (though most tested 13 or 14). Some of these were site agnostic assays listed on the ARTG.

[32] Sterne, J. A., Hernán, M. A., et al. 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ, 355, i4919. doi: 10.1136/bmj.i4919.

[33] Clarke MA, Deshmukh AA, Suk R, Roberts J, Gilson R, Jay N, Stier EA, Wentzensen N. A systematic review and meta-analysis of cytology and HPV-related biomarkers for anal cancer screening among different risk groups. Int J Cancer. 2022 Dec 1;151(11):1889-1901. doi: 10.1002/ijc.34199. Epub 2022 Aug 6. Erratum in: Int J Cancer. 2023 Sep 1;153(5):E2.

[34] Stier EA, Clarke MA, Deshmukh AA, Wentzensen N, Liu Y, Poynten IM, Cavallari EN, Fink V, Barroso LF, Clifford GM, Cuming T, Goldstone SE, Hillman RJ, Rosa-Cunha I, La Rosa L, Palefsky JM, Plotzker R, Roberts JM, Jay N. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. Int J Cancer. 2024 May 15;154(10):1694-1702.

[35] Jin, F., Roberts, J. M., Grulich, A. E., Poynten, I. M., Machalek, D. A., Cornall, A., Phillips, S., Ekman, D., McDonald, R. L., Hillman, R. J., Templeton, D. J., Farnsworth, A., Garland, S. M., Fairley, C. K., & Tabrizi, S. N. (2017). The performance of human papillomavirus biomarkers in predicting anal high-grade squamous intraepithelial lesions in gay and bisexual men. AIDS, 31(9), 1303-1311.

[36] Jin, F., Grulich, A. E., Poynten, I. M., Hillman, R. J., Templeton, D. J., Law, C. L., Farnsworth, A., Garland, S. M., Fairley, C. K., & Roberts, J. M. (2016). The performance of anal cytology as a screening test for anal HSILs in homosexual men. Cancer Cytopathol, 124(6), 415-42

Table 18 Summary of applicability of the linked evidence for test accuracy to the PICO (k=48)

Outcome	MSM and TW living with HIV age ≥35 years	MSM and TW living without HIV age ≥45 years	Women and MSW living with HIV age ≥45 years	People with previous vulval SCC/HSIL (HPV associated)	SOTR, commencing 10 years post-transplant	Patients being followed up after treatment for anal cancer	Patients outside these above groups with incidental anal HSIL	*People with history of cervical/vaginal cancer or precursor lesions (added by PASC)*
Triaged testing strategy (n=1)								
Predictive test accuracy	1*	1*†	-	-	-	-	-	-
Anal HPV testing (n=29)								
Predictive test accuracy	1*	1*†	-	-	-	-	-	-
Cross-sectional test accuracy	24	9‡	9	-	2	-	-	-
Anal cytology testing (n=32)								
Predictive test accuracy	1*	1*†	-	-	-	-	-	-
Cross-sectional test accuracy	27	7‡	11	2	-	-	-	-
Diagnostic HRA (n=3)								
Cross-sectional test accuracy	2	-	2	-	1	-	-	-

Source: Study reports
Notes: *Transgender women not specified in included sample.
†Including people aged 35 years or older, therefore not in direct alignment to the PICO subpopulation of MSM and TW living without HIV age ≥45 years.
‡An ongoing Belgian study (NCT07029152[37]; estimated completion date December 2026) will provide additional evidence on the accuracy of anal HPV genotyping, anal cytology and methylation, together or as separate tests in the prediction of HSIL for MSM not LWH (using PrEP) aged ≥35 years. Given existing data from an Australian cohort (Jin 2025), and cross-sectional accuracy reported in this population for an additional 9 HPV and 7 cytology studies, this new evidence is unlikely to materially impact current findings related to the performance of these tests within the PICO. However, the specification of PrEP usage may be a moderator of results. PrEP coverage is not 100% in MSM, and there is evidence that people using PrEP may engage in higher-risk sexual behaviours, such as condomless anal sex, which can increase exposure to HPV, the primary cause of anal cancer.
Abbreviations: HIV = human immunodeficiency virus, HPV = human papillomavirus, HSIL = high-grade squamous intraepithelial lesions, IRC = infrared coagulation, MSM = men who have sex with men, MSW = men who have sex with women, PLWH = people living with HIV, PrEP = Pre-Exposure Prophylaxis, SCC = squamous cell carcinoma, SOTR = solid organ transplant recipients; STD = sexually transmitted disease, TNM = tumour, nodal, and metastatic stage

Most test accuracy studies had a low risk of bias across most QUADAS-2 domains[38] (the tool used to assess risk of bias of diagnostic accuracy studies).

[37] NCT07029152. (2025). Screening for Anal Cancer in Men Who Have Sex With Men Using Pre-Exposure Prophylaxis (SCOPE). https://clinicaltrials.gov/study/NCT07029152
[38] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

Inverse variance random effects meta-analyses were conducted for each PICO-specified subpopulation. Results were stratified by partial (HPV16, HPV18, HPV16/18) and expanded (any hrHPV) genotyping for HPV testing, and by ASC-H+ and HSIL+ HRA referral thresholds for cytology testing (aligning with the PICO-specified testing strategy). Only studies which had data extracted (or calculated by the DCAR assessment group based on information provided in study reports) to complete a 2x2 contingency table were included in meta-analyses. Sensitivity analyses including only studies assessed as "low risk of bias" (defined as no "high" risk of bias, 0-2 "unclear" risk of bias across all QUADAS-2 domains) was also completed.

Triaged testing

Jin et al. 2025[13] published analysis based on results of the SPANC study examining the use of anal cytology as a triage test (based on HPV testing results using expanded genotyping; 5 theoretical algorithms were presented). These results were compared with anal cytology testing and anal HPV testing alone in a three-year cohort of MSM in Sydney, Australia. The study was assessed as having a low risk of bias and was conducted in Australia recently with two of seven PICO subpopulations (approximately 74% of the total PICO population)[39], representing excellent applicability to the PICO context. It was not specified whether transgender women were included or excluded in the study; it is estimated that transgender women would account for a small portion of the two subpopulations (including MSM and TW).[40] Additionally, MSM living without HIV were aged 35 and older (rather than 45 and older as in the PICO subpopulation).

Table 19 Key features of the included test accuracy studies for the triaged testing strategy (k=1)

Study ID	N	Population	Intervention	Comparator	Outcome
Jin 2025 Australia	475	MSM ≥35 years*	Diagnostic HRA and cytology testing triaged by hrHPV testing	Anal HPV testing alone; anal cytology testing alone	Predictive test accuracy

Source: Jin 2025
Notes: *Results presented as both aggregate for MSM, and disaggregated by HIV status, aligning with PICO subpopulations of (1) MSM and TW living with HIV age ≥35 years (direct alignment), and (2) MSM and TW living without HIV age ≥45 years (including people aged 35-45 years where not specified in the PICO population).
Abbreviations: HPV = human papillomavirus, hrHPV = high risk HPV variants, MSM = men who have sex with men

Individual testing

A total of 30 studies were included for assessing the test accuracy of anal HPV testing (29 assessing cross-sectional test accuracy; 1 assessing test predictive accuracy), 33 studies were included for assessing the test accuracy of anal cytology testing (32 assessing cross-sectional test accuracy; 1 assessing test predictive accuracy), and 3 studies were included for assessing the cross-sectional test accuracy of diagnostic HRA. A summary of the key features of the studies for test accuracy is presented in Table 20.

[39] Table 3, Ratified PICO Confirmation – MSAC Application 1752
[40] Australian Bureau of Statistics. (2022). Estimates and characteristics of LGBTI+ populations in Australia. ABS. https://www.abs.gov.au/statistics/people/people-and-communities/estimates-and-characteristics-lgbti-populations-australia/latest-release.

Table 20 Key features of the included test accuracy primary studies for anal HPV testing, anal cytology testing and diagnostic HRA (k=48)

Study ID	N	Identified from*	Population	Intervention†				
				Cytology testing	Cytological reporting threshold	HPV assay	Genotypes	HRA
Predictive test accuracy								
Jin 2025 Australia	475	SR	MSM ≥35 years	LBC	ASC-US+; ASC-H+	Linear Array	Expanded – 13 genotypes Partial – HPV16	-
Cross-sectional test accuracy								
Albuquerque 2018 UK	323	SR	Women with a previous history of anogenital neoplasia	LBC	HSIL+	-	-	-
Bean 2010 USA	42	Dias Gonçalves Lima 2019	PLWH	LBC	HSIL+	-	-	-
Berry 2009 USA	125	2022	MSM LWH; MSM not LWH	LBC	ASC-H+; HSIL+	PCR	Expanded – 39, 13 genotypes Partial – HPV16	-
Burgos 2017 Spain	692	Clarke 2022	MSM LWH	LBC	-†	CLART Genomica HPV2	Expanded – 35 genotypes Partial – HPV16/18	-
Cheng 2015 Taiwan	196	Clarke 2022	MSM LWH	LBC	HSIL+	Linear Array	Expanded – 13, 7, 4 genotypes Partial – HPV16/18	-
Chiao 2020 USA	256	Clarke 2022	Women LWH	LBC4	ASC-H+	HC2	Expanded – 13 genotypes	-
Chowdhury 2023 USA	115	SR	PLWH	-	-	PCR	Expanded – 39 genotypes Partial – HPV16	-
Clifford 2018 France	513	Clarke 2022	MSM LWH	LBC	ASC-H+	Cobas 4800	Expanded – 14 genotypes, 13 genotypes (hrHPV NOT including HPV16) Partial – HPV16	-
Combes 2018 France	490	Dias Gonçalves Lima 2019	MSM LWH	LBC	ASC-H+	Cobas 4800	-‡	-
Cuen 2013 France	107	SR	PLWH	-	-	-	-	HRA

Dietrich 2015 Germany	123	Dias Gonçalves Lima 2019	MSM LWH	LBC	HSIL+	-	-	-
Díez-Martínez 2023 Spain	93	SR	MSM LWH	LBC	HSIL+	Cobas 4800	Expanded – 12 genotypes (hrHPV NOT including HPV16) Partial – HPV16, HPV18	-
Frank 2018 USA	147	Dias Gonçalves Lima 2019	MSM LWH	LBC	HSIL+	-	-	-
Gaisa 2021 USA	1837	Clarke 2022	MSM LWH; MSM, not LWH; Women LWH	LBC	ASC-H+; HSIL+	Cobas 4800	Expanded – 14 genotypes Partial – HPV16/18	-
Gimenez 2011 Brazil	128	SR	PLWH	-	-	-	-	HRA
Goldstone 2012 USA	298	Clarke 2022	PLWH (Men (97%), 45% LWH)	LBC	ASC-H+; HSIL+	HC2	Expanded –13 genotypes	-
Hernandez 2024 USA	238	SR	MSM – 54.2% LWH	-	-	Atila Biosystems	Expanded – 15 genotypes Partial – HPV16	-
Hidalgo-Tenorio 2017 Spain	319	Clarke 2022	MSM LWH	LBC	HSIL+	Linear Array	Expanded – 18 genotypes	-
Jin 2016 Australia	617	Clarke 2022	MSM – 35.7% LWH	LBC	HSIL+	-	-	-
Jin 2017 Australia	617	Clarke 2022	MSM – 35.7% LWH	-	-	Cobas 4800 and Linear Array	Expanded – 14, 13 genotypes Partial – HPV16/18	-
Kimura 2021 Brazil	366	Clarke 2022	72% Men, 82% LWH	LBC	HSIL+	Abbott RealTime High-Risk HPV assay	Expanded – 14 genotypes	-
Larsen 2021 Denmark	250	Clarke 2022	SOTR (renal)	-	-	INNO-LiPA HPV Genotyping Extra II assay	Expanded – 13 genotypes Partial – HPV16	-
Maia 2014 Brazil	33	Dias Gonçalves Lima 2019	PLWH	LBC	ASC-H+; HSIL+	-	-	-
Mallari 2012 USA	329	Clarke 2022	PLWH (87% MSM)	LBC	HSIL+	-	-	-
Matolka 2022 USA	625	SR	PLWH	-	-	Cobas 4800	Expanded – 14 genotypes	-

Mudrinich 2024 USA	199	SR	Men and TW LWH (91% MSM)	LBC	ASC-H+; HSIL+	-	-	-
Nahas 2009 Brazil	222	Dias Gonçalves Lima 2019	PLWH	Conventional	HSIL+	-	-	-
Palefsky 1997 USA	658	Clarke 2022	MSM LWH; MSM not LWH	Conventional	HSIL+	-	-	-
Palefsky 2005 USA	357	Clarke 2022	MSM LWH, no age restriction	-	-	PCR	Expanded – 39 genotypes	-
Pankam 2017 Thailand	95	Clarke 2022	MSM LWH; MSM, no HIV	-	-	ELISA SPF10-LiPA25	Expanded – 37, 13, genotypes Partial – HPV16, HPV18	-
Panther 2004 USA	153	Clarke 2022	MSM (65% LWH)	Conventional	HSIL+	-	-	-
Phanuphak 2013 Thailand	246	Clarke 2022	MSM LWH; MSM not LWH	LBC	HSIL+	Linear Array	Expanded – 13 genotypes Partial – HPV16/18	-
Ramos-Cartagena 2020 Puerto Rico	128	Clarke 2022	Women LWH; Women not LWH	LBC	ASC-H+	Cobas 4800	Expanded – 14 genotypes Partial – HPV16, HPV18	-
Ramos-Cartagena 2022 Puerto Rico	345	SR	PLWH	LBC	ASC-H+	Cobas 4800	Expanded – 14 genotypes Partial – HPV16, HPV18	-
Salit 2010 Canada	401	Clarke 2022	MSM LWH ≥18 years	LBC	HSIL+	HC2	NR	-
Sambursky 2018 USA	894	Clarke 2022	MSM (92%) – 44% LWH	LBC	ASC-H+; HSIL+	Cobas 4800	Expanded – 13 genotypes Partial – HPV16/18	-
Santoso 2010 USA	205	Clarke 2022	Women with intraepithelial neoplasia on the cervix, vagina, or vulva	LBC	HSIL+	-	-	-
Sendagorta 2015 Spain	101	Clarke 2022	MSM LWH	LBC	HSIL+	CLART Genomica HPV2	Expanded – 20 genotypes	-
Silva-Klug 2021 Spain	239	Clarke 2022	MSM LWH	LBC	HSIL+	-	-	-
Stier 2019 USA	256	Clarke 2022	Women LWH	LBC	ASC-H+	-	-	-
Stier 2023 USA	229	SR	Women LWH	-	-	HC2	Expanded – 13 genotypes	-

Sun 2023 USA	428	SR	MSM LWH; MSM not LWH	-	-†	Linear Array	Expanded – 13 genotypes	-
Torres 2023 Spain	274	SR	MSM LWH	LBC	ASC-H+; HSIL+	Linear Array and HC2	Expanded – 13 genotypes Partial – HPV16, HPV18, HPV16//18	-
Tramujas da Costa e Silva 2008 Brazil	42	SR	Renal graft recipients	-	-	-	-	HRA
Virgilio 2024 Italy	50	SR	MSM not LWH§	LBC	-†	Cepheid Xpert®HPV	Expanded – 14 genotypes	-
Wentzensen 2012 USA	363	Clarke 2022	MSM LWH	LBC	ASC-H+; HSIL+	Cobas 4800 and Linear Array	Exapnded – 14 genotypes Partial – HPV16/18	-
Wilkin 2013 USA	235	Clarke 2022	PLWH	LBC	-†	PCR¶	HPV16	-

Source: Study reports; Clarke 2022; Dias Gonçalves Lima 2019[41]
Notes: (a) Swanson 2021 was included in Clarke's 2022 review, however only presented aggregated results for the sample which included a cohort of 31% Men, 23% Receptive anal sex, 16% PLWH, 11% SOTR; this was not deemed to have enough crossover with PICO-specified subpopulations of interest.
*Any eligible studies identified in the supplemental search were extracted per systematic review processes (post September 2021 publish date of Clarke et al. 2022). Study information from studies from Clarke 2022 and Dias Gonçalves Lima 2019 was inputted directly from the original studies where possible.
†Only presented results for "abnormal" cytology, which included ASC-US. Raw data not provided.
‡Results not extractable
§Presented results for a sample of 80% MSM, 87% not LWH; therefore, included in subpopulation MSM and TW not living with HIV age ≥45 years
¶Not included in Clarke 2022; identified when rechecking results.
Abbreviations: ASC-H = atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; GBM = gay and bisexual men; HC2 = HC2 HPV DNA Test; HIV = human immunodeficiency virus; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LBC = liquid-based cytology, LGTD = lower genital tract dysplasia, LWH = living with HIV, MSM = men who have sex with men, PCR = polymerase chain reaction, PLWH = people living with HIV, SR = systematic review conducted as part of evaluation.

Relevant ongoing trials

There are two ongoing trials evaluating testing for anal cancer precursors (anal HPV and cytology testing) in women with a history of lower genital tract HSIL and cancer (NCT05217940[42]: estimated completion January 2027; NCT05566106[43]; estimated completion date December 2032). This would provide evidence for both (1) people with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis, and (2) people with history of cervical/vaginal cancer or precursor lesions (population added by PASC) – approximately 9% of the total PICO population. There is currently no evidence on the test accuracy of the triaged testing algorithm or HPV testing alone for these subpopulations.

[41] Dias Gonçalves Lima F, Viset JD, Leeflang MMG, Limpens J, Prins JM, de Vries HJC. The Accuracy of Anal Swab-Based Tests to Detect High-Grade Anal Intraepithelial Neoplasia in HIV-Infected Patients: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2019 Apr 16;6(5):ofz191

[42] NCT05217940. (2022). The Effectiveness of Screening Women With Lower Genital Tract Neoplasia or Cancers for Anal Cancer Precursors https://clinicaltrials.gov/study/NCT05217940

[43] NCT05566106. Anal Follow-up of Patients With a Gynecological History of High-grade Lesion and More Induced HPV (Cohorte_HPV). https://www.clinicaltrials.gov/study/NCT05566106

An additional ongoing study (NCT05074264[44]; estimated completion date December 2027) of MSM, MSW and women LWH (age ≥21 years) in Mexico and Puerto Rico may examine the triaged testing strategy. This is part of evaluation of the optimal combination of hrHPV testing, expanded hrHPV genotyping, cytology, and progression markers protein E6 and S5 methylation score, to identify anal HSIL or cancer.

A Multiphase Optimization Strategy Trial (MOST) is also underway in Thailand to evaluate optimal anal HSIL screening methods in HIV-positive MSM/TW aged ≥30 years and HIV-negative MSM/TW aged ≥40 years (NCT05531799[45]; estimated completion December 2029). However, this evidence is expected to be superseded by Jin 2025[13], which focuses on the comparable Australian population and employs the triaged testing algorithm which is not used in the Thai trial.

For all ongoing studies, it is unclear if the exact PICO-specified testing algorithm will be used (i.e., with the same thresholds for triage to cytology or diagnostic HRA).

Testing intervals

There was no evidence evaluating the proposed testing and follow-up intervals in the triaged testing strategy. The application suggested varying intervals for HPV testing based on (1) the population-specific risks of anal cancer and (2) comparable screening intervals for cervical cancer. Testing frequencies for all PICO-specified subpopulations are displayed above in Table 13.

Safety of the test

Evidence on safety related to testing procedures of anal HPV testing, anal cytology testing and diagnostic HRA are reported as physical and psychosocial adverse events, impact of false-positive and false-negative results, harms associated with the absence of testing, and the value of knowing/adverse events (AEs) from knowing test results (relating to assessment questions 5, 6, 8 and 9 from the ratified PICO). Only studies reporting experienced outcomes were included whereas studies reporting anticipated outcomes (such as barriers to testing) were not included.

For physical AE outcomes, additional studies were sought and included given there was limited evidence for the PICO-specified subpopulations. Physical AEs of the tests may differ based on scar tissue from previous treatments, tissue sensitivity and fragility or changes in anatomy, however this is not expected to be prevalent in most of the PICO population. Studies including non-PICO-specified populations are termed “supporting studies” henceforth.

A total of 10 studies (including 2 supporting studies) were included for evidence of health outcomes of HPV testing, anal cytology testing and diagnostic HRA compared to no testing. A summary of the applicability of the linked health outcome evidence to the PICO-specified subpopulations and investigative interventions is summarised in Table 21. Most studies were conducted with PLWH, no evidence for any outcomes was identified for:

- SOTR, commencing 10 years post-transplant
- Patients being followed up after treatment for anal cancer
- Patients outside these above groups with incidental anal HSIL and patients presenting with symptoms suggestive of anal cancer
- *People with a possible history of cervical/vaginal cancer or precursor lesions (added by PASC)*

[44] NCT05074264, Screening Algorithms for Cervical and Anal High-Grade Squamous Intraepithelial Lesions in People With HIV in Mexico and Puerto Rico (CAMPO-101). https://www.clinicaltrials.gov/study/NCT05074264

[45] NCT05531799. (2022). Optimizing an Anal High-grade Squamous Intraepithelial Lesion Screening Algorithm for Thai Men Who Have Sex With Men and Transgender Women https://clinicaltrials.gov/study/NCT05531799

Six studies reported both physical and psychosocial AEs of anal cancer screening. There was no evidence identified in any PICO-specified subpopulation for the following outcomes:

- Impacts of false positives and false negatives of the triaged testing strategy.
- Harms associated with the absence of testing
- Value of knowing (knowledge of pLSIL or LSIL diagnosis).
- AEs from knowing test results (knowledge of pLSIL or LSIL diagnosis).

However, potential impacts and implications are discussed in results.

Table 21 Summary of applicability of linked evidence of safety of the test to the PICO

PICO component	Psychosocial AEs (k=6)	Physical AEs (k=6)
Population		2 supporting studies*
MSM and TW living with HIV age ≥35 years	5	3
MSM and TW living without HIV age ≥45 years	2#	2#
Women and MSW living with HIV age ≥45 years	2	2
People with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis	1	1
SOTR, commencing 10 years post-transplant	-	-
Patients being followed up after treatment for anal cancer	-	-
Patients outside these above groups with incidental anal HSIL and patients presenting with symptoms suggestive of anal cancer	-	-
People with a possible history of cervical/vaginal cancer or precursor lesions	-	-
Testing		
Anal sampling (HPV testing and/or cytology testing)	6	5 (including 1 supporting study)*
HRA-guided biopsy and diagnosis of HSIL	5	5 (including 2 supporting studies)*

Source: Study reports
Notes: *For physical AE outcomes, supporting studies were sought for any population given the paucity of evidence for physical AEs in the PICO-specified populations.
#An ongoing Belgian study (NCT0702915237; estimated completion date December 2026) will provide additional evidence on the impact of anal HPV genotyping, anal cytology and HRA on quality of life in MSM not LWH (using PrEP) aged ≥35 years.
Abbreviations: AE = adverse event; HPV = human papillomavirus; HRA = High-Resolution Anoscopy; HIV = human immunodeficiency virus, HSIL= High-Grade Squamous Intraepithelial Lesion; LWH = living with HIV; MSM = men who have sex with men; MSW = men who have sex with women; SCC = squamous cell carcinoma; SOTR = solid organ transplant recipients; TW = transgender women.

A summary of the key features of the studies providing linked test safety evidence is provided in Table 22. All studies were at moderate or high risk of bias, primarily due to concerns about non-response bias (and lack of characterisation of non-responders), use of non-validated measures and small/unjustified sample sizes.

Table 22 Key features of the included test safety evidence comparing anal HPV testing, anal cytology testing and diagnostic HRA with no testing (k=10)

Trial/Study	Study design Risk of bias	N	Population	Investigative intervention	Comparator	Outcome domain	Outcome measures
Cvejic 2020 (SPANC study) Australia	Pre-post study (questionnaire) Moderate risk of bias	500	MSM ≥35 years	Anal swab for cytology and HPV DNA Testing Digital Anorectal Examination to check for any palpable lesions. HRA performed on all participants; biopsies of visual abnormalities suspicious of HPV-related lesions taken	None	Psychosocial AEs	• SF-36v2 • Screening-specific distress measures: modified Cervical Screening Questionnaire, perceived anal cancer risk, cancer-related worry, and intrusive thoughts about abnormal results (adapted from the Impact of Events Scale).
Kaufman 2020 Canada	Cross-sectional Moderate risk of bias	124	Women LWH	Study visits were completed every 6 months over a 2-year period. Each visit involved anal cytology and HPV testing. All participants underwent HRA with DARE and biopsies at baseline and 24 months. If HSIL detected, HRA repeated in 12 months. If HSIL was persistent, treatment offered.	None	Physical AEs	• Pain score (scale of 0 to 10)
Lam 2018 USA	Cross-sectional High risk of bias	1857 (48 completed patient experience survey)	PLWH	HRA (first time)	None	Physical AEs Psychosocial AEs	• Tolerance of HRA measured by if HRA with sedation, opioid prescription, or ED/urgent care visit within 1-week post-procedure was documented in patient file • Pain score (scale of 0 to 10) • Pain and bleeding (greater, equal to or less than expected) • Impact of AEs on lifestyle/normal activities
Landstra 2013 Australia	Prospective cohort study High risk of bias	291	Men LWH	Self-collected anal cytology swabs: those with negative or LSIL results formed the control group, while individuals with HSIL, ASC-H, or ASC-US cytology were offered	None	Psychosocial AEs	• Anal Screening Questionnaire • Distress Thermometer • SF-12 • Depression Anxiety Stress Scale

				further evaluation via HRA.			
Nitkowski 2024 USA	Cross-sectional (for outcome of interest) Moderate risk of bias	240	MSM and trans persons aged 25 years or older	Anal cancer screening involving either home (self-administered) or clinic-based (clinician administered) anal HPV swab, followed by HRA 1 year later (HPV results were not provided to participants)	None	Physical AEs†	• Pain immediately following HRA (single item, 4-point Likert scale)
Proctor 2019 USA	Cross-sectional High risk of bias	57	Women with a history of biopsy-proven vulvar HSIL Aged 30–80 years	Anal cytology, anal HPV, and DARE	None	Physical AEs Psychosocial AEs	• Multiple questions on 5-point Likert scale related to discomfort, pain and emotional responses
Russo 2018 (SPANC study) Australia	Qualitative study (interviews) Moderate risk of bias	21	MSM ≥35 years	Anal swab for cytology and HPV DNA Testing Digital Anorectal Examination to check for any palpable lesions. HRA performed on all participants; biopsies of visual abnormalities suspicious of HPV-related lesions taken	None	Psychosocial AEs	• Psychological AEs of anal sampling, HRA and biopsy
Tinmouth 2011 Canada	Prospective cohort study Moderate risk of bias	104	MSM LWH	Anal cytology, HPV testing, and HRA with biopsy of abnormal areas were conducted at baseline and at a planned 6-month follow-up	NA	Psychosocial AEs	• Impact of Events Scale • Illness Intrusiveness Ratings Scale • Psychological Consequences Questionnaire
Supporting studies							
Davis 2013 USA	Cross-sectional High risk of bias	296	97% male, 45% LWH	HPV brush, HPV swab, Cytology swab, HRA, Biopsy	None	Physical AEs	• Discomfort score (scale of 0 to 5)
De-Masi 2018 UK	Cross-sectional Moderate risk of bias	404	Females (29.4%) Males (64.6%)	HRA examinations and/or treatment	None	Physical AEs	• Pain score (scale of 0 to 10)

Source: Study reports
Notes: *required an HRA and either needed no biopsy or had reassuring histology results such as negative, warts or 'other inflammation'
#Reuqired HRA
†Only reported for HRA, not anal sampling.
Abbreviations: AE = adverse event, ASC-US = Atypical Squamous Cells of Undetermined Significance, ASC-H = Atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion, DARE = digital anorectal exam, HIV = human immunodeficiency virus, HPV = human papillomavirus, HRA = high-resolution anoscopy, LWH = living with HIV, HGAIN = High grade anal intraepithelial neoplasia, LSIL = low-grade squamous intraepithelial lesions, MSM = men who have sex with men, NA = not applicable, PLWH = people living with HIV, SF-12 = 12-Item Short-Form Health Survey, SF-36 = 36-Item Short-Form Health Survey

Linked evidence of change in management

Both clinician referral and patient uptake were considered in evaluating change in management outcomes, as early intervention relies on the active participation of both parties. In the context of patient-centred care and emphasis on shared decision-making, the patient's role in clinical decisions is increasingly recognised as essential.

Per the assessment framework, key patient management outcomes were:

1. Change in patient clinical management.
    a. Clinician referral to HRA-guided anal HSIL ablation (led from management decisions informed by anal HPV testing, cytology testing and diagnostic HRA).
    b. Change in anal HSIL or anal cancer treatment decisions.
2. Change in follow-up frequency.
3. Commencement of treatment. That is, patient uptake of HRA-guided anal HSIL ablation.

In addition, we have sought information on:

4. Patient uptake of the PICO-specified triaged testing strategy (anal HPV testing, cytology testing and diagnostic HRA)
5. Patient adherence to the PICO-specified triaged testing strategy prior to confirmed HSIL diagnosis or anal cancer (i.e., adherence to follow-up screening, either repeat HPV testing, cytology testing following HPV testing or diagnostic HRA).

No evidence for any additional change in management outcomes relevant to the proposed clinical management algorithm was identified.

A total of 16 studies were included for evidence of change in management of anal HPV testing, anal cytology testing and diagnostic HRA compared to no testing. A summary of applicability of the linked evidence for change in management to the PICO is reported in Table 23. Most studies were conducted with PLWH.

Table 23 Summary of applicability of linked evidence for change in management to the PICO (k=16)

PICO component	Key outcomes				Additional outcomes		
	Clinician referral to HRA-guided anal HSIL ablation (n=1)	Change in treatment decisions (n=1)	Change in follow up frequency (n=0)	Patient uptake of HRA-guided anal HSIL ablation (n=2)	Patient uptake of the PICO-specified triaged testing strategy (n=2)	Patient adherence to the PICO-specified triaged testing strategy prior to confirmed HSIL diagnosis or anal cancer	
						Adherence/ compliance (n=3)	HRA uptake (n=13)
Population				1 supporting study^			1 supporting study^
MSM and TW living with HIV age ≥35 years	1	1‡	-	1	2*	3	9
MSM and TW living without HIV age ≥45 years	-	1‡	-	1	2*	-	2
Women and MSW living with HIV age ≥45 years	1	1‡	-	1	-	2	5
People with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis	-	1‡	-	-	-	-	-
SOTR, commencing 10 years post-transplant	-	1‡	-	-	-	-	-
Patients being followed up after treatment for anal cancer	-	1‡	-	-	-	-	-
Patients outside these above groups with incidental anal HSIL and patients presenting with symptoms suggestive of anal cancer	-	1‡	-	-	-	-	-
People with a possible history of cervical/vaginal cancer or precursor lesions (added by PASC)	-	1‡	-	-	-	-	1

Source: Study reports
Notes: ^Including 1 supporting study. The included population was "patients eligible for HSIL screening". Given population not specified, included as supporting study.
*Anal cancer screening led by HPV testing (and followed by HRA), not the exact triaged testing strategy. Reported in two studies of 1 trial. For physical AE outcomes, supporting studies were sought for any population given the paucity of evidence for physical AEs in the PICO-specified populations.
‡People opportunistically referred for cytology and HRA-based anal cancer screening; 3.9% SOTR, 76.9% LWH, 19.2% prior cancer (possibly anal).
Abbreviations: AE = adverse event; HPV= human papillomavirus; HRA = High-Resolution Anoscopy; HSIL= High-Grade Squamous Intraepithelial Lesion; MSM = men who have sex with men; MSW = men who have sex with women; LWH = living with HIV; SCC = squamous cell carcinoma; SOTR = solid organ transplant recipients; TW = transgender women.

A summary of the key features of the studies providing change in management evidence is provided in Table 24.

Most studies were at serious or critical risk of bias (k=9 out of 15). In many cases, change in management outcomes were secondary and the study designs were not tailored to evaluate

them specifically. Consequently, potentially important confounding factors were not adequately considered in the reporting of these outcomes. Only one study was conducted in Australia.

Table 24 Key features of the included change in management evidence comparing HPV testing, cytology testing and diagnostic HRA with no testing (k=15)

Trial/Study	Study design Risk of bias	N	Population	Screening intervention	Treatment intervention	Comparator	Outcomes
Key evidence							
Achhra 2024 USA	Retrospective cohort study Serious risk of bias	432	MSM LWH aged 35 years or older	Anal cancer screening involving annual anal cytology testing and HRA with biopsy if ASC-US+ detected.	Typically, ablation or topical therapy	None	• Uptake of HRA following abnormal cytology results • Follow-up cytology/HRA testing as part of anal cancer screening
Alrefai 2013 USA	Retrospective cohort study Critical risk of bias	153	80.4% LWH#; 53% MSM	Anal cytology testing, followed by continued surveillance with HRA or ablation if indicated	Ablation	None	• "Compliance" (defined as continued surveillance or ablation within recommended time intervals)
Botes 2013 Australia	Prospective cohort study Critical risk of bias	41	MSM LWH	Anal cancer screening involving anal cytology testing followed by HRA with biopsy.	NR	None	• Uptake of HRA following abnormal cytology results
Cardenas 2022 USA	Retrospective cohort study Low risk of bias	821	PLWH; ≥30 years of age or experienced any symptom such as anal pain, itching, bleeding or lesions	Anal cancer screening involving anal cytology testing followed by HRA with biopsy. <u>Algorithm:</u> Normal cytology: Repeat annually. LSIL: HRA in 6–12 months. ASC-US: HRA in 3–6 months. HSIL: HRA within 3 months. Normal Biopsy After HRA: Repeat cytology in 12 months. AIN 1: Repeat HRA in 12 months; no treatment needed.	From HRA results: AIN 2–3: HRA with hyfrecation in 6 months. Invasive Cancer: Refer to colorectal surgery.	None	• Follow-up cytology/HRA testing as part of anal cancer screening • Uptake of HRA following abnormal cytology results

Digaetano 2019 Italy	Prospective cohort study Critical risk of bias	86	MSM LWH	Anal cancer screening involving anal HPV testing, anal cytology testing followed by HRA with biopsy.	NR	None	• Uptake of HRA following abnormal HPV or cytology results
Lam 2018 USA	Cross-sectional Low risk of bias	997	PLWH	HRA Follow-up HRA was advised in 3, 6, or 12 months, based on disease severity and pathology results.	NR	None	• Uptake of recommended follow-up HRA
Maguire 2013 USA	Cohort study Critical risk of bias	114	Women LWH	Anal cancer screening involving anal cytology testing followed by HRA with biopsy for abnormal results	NR	None	• Uptake of HRA following abnormal cytology results
McDonald 2015 USA	Retrospective cohort study Critical risk of bias	1970	PLWH	Anal cancer screening involving anal cytology testing followed by HRA with biopsy	Include use of intra-anal imiquimod, trichloroacetic acid, efudex and infrared coagulation. When indicated, patients referred to rectal surgery for excision and fulguration.	None	• Clinician referral for HSIL treatment •
Nyitray 2023 and Nitkowski 2024 The Prevent Anal Cancer Self-Swab Study USA	Randomised trial Low risk of bias	240	MSM and trans persons aged 25 years or older	Anal cancer screening involving either home (self-administered) or clinic-based (clinician administered) anal HPV swab, followed by HRA 1 year later (HPV results were not provided to participants)	NR	None	• Uptake of HPV testing as part of anal cancer screening (home versus clinic-based) • Uptake of HRA following home or clinic-based HPV testing
Saleh 2023 USA	Retrospective cohort study Critical risk of bias	83	Women with cervical cancer diagnoses (6% LWH)	Anal cancer screening involving anal cytology testing followed by HRA with biopsy.	NR	None	• Uptake of HRA following abnormal cytology results or direct referral for HRA
Silvera 2021 USA	Retrospective cohort study Low risk of bias	1179	Patients with an initial	Anal cancer screening involving anal cytology testing	Ablation or surgical	None	• Uptake of HSIL treatment

			HSIL diagnosis	followed by HRA with biopsy	subspecialty treatment		• Uptake of follow-up HRA following HSIL diagnosis •
Thirugnanasambandam 2023 USA	Retrospective cohort study Critical risk of bias	305	MSM LWH	Anal cancer screening involving anal cytology testing followed by HRA with biopsy.	NR	None	• Clinician referral rate for HRA • Uptake of HRA following abnormal cytology results
Walker 2024 Canada	Retrospective comparative cohort Serious risk of bias	612 Screening: 26 Non-screening 586	Adults with invasive anal SCC; differences between screening-detected versus non-screening detected cancers were evaluated. PLWH 23% total; 76.9% of those screened; 19.2% prior cancer (possibly anal).	Anal cancer screening based. anal cytology and HRA with targeted biopsies for suspected HSIL. HPV testing was not routinely performed.	Most patients (90%) received treatment outlined in the PICO (electrocautery ablation), with the remaining receiving topical therapies or surveillance.	Screening-detected versus non-screening detected cancers	• Anal cancer treatments received
Wells 2022 USA	Cross-sectional Moderate risk of bias	150	PLWH	Anal cancer screening involving anal cytology testing followed by HRA with biopsy.	NR	None	• Uptake of HRA following abnormal cytology results
Supporting evidence							
Krempasky 2020 USA	Retrospective cohort study Moderate risk of bias	3582	Patients eligible for HSIL screening*	Anal cancer screening involving anal cytology testing followed by HRA with biopsy for abnormal results	NR	None	• Uptake of HSIL treatment • Uptake of HRA following abnormal cytology results

Source: Study reports
Notes: #80.4% of population is PLWH, therefore determined to mostly meet PICO population criteria.
*The included population was “patients eligible for HSIL screening”. Given population not specified, included as supporting study.
Abbreviations: AIN = anal intraepithelial neoplasia, ASC-US = Atypical Squamous Cells of Undetermined Significance, HPV = human papillomavirus, HRA = high-resolution anoscopy, HSIL= high-grade squamous intraepithelial lesions, LSIL = low-grade squamous intraepithelial lesions, LWH = living with HIV, MSM = men who have sex with men, NR = not reported, PLWH = people living with HIV

Linked evidence of health outcomes

Linked evidence of health outcomes is directly related to change in management decisions arising from the proposed testing strategy. Given this is a co-dependent application, linked evidence of health outcomes can be derived from the evidence for the therapeutic intervention. As well as use of the proposed therapy itself, health outcomes led by change in management decisions also incorporate earlier intervention for HSIL and earlier identification and treatment of anal cancer. Linked evidence health outcomes also include the potential impacts of false positive and negative test results.

Evidence for the therapeutic intervention

Four studies assessed the effectiveness of anal HSIL ablation compared to no intervention (watchful waiting/active monitoring). This included results of the high-quality, large-scale ANCHOR trial[2]. Two additional comparative studies assessed the safety and effectiveness of anal HSIL ablation compared to other types of HSIL treatment. Other non-comparative evidence from 23 studies evaluating the efficacy of ablative treatment for anal HSILs was included to supplement the comparative trial information. A summary of the applicability of the direct evidence to the PICO is summarised in Table 25.

PLWH were the population examined in all comparative evidence studies; two studies only examined MSM LWH. Most studies included one or two of the identified subpopulations, but as with direct and linked evidence for the investigative intervention, were too inclusive or exclusive (e.g., MSM living with HIV aged 18 or older, where the PICO population is MSM living with HIV aged 35 or older).

There were key differences in treatment protocols; some studies did not directly specify whether treatment was HRA-guided. A key limitation identified by the authors of the ANCHOR trial was that trial results may not be replicable in clinicians with less training or support, given the expertise and experience required for HRA effectiveness. This is a critical consideration for applicability of the results.

The ANCHOR trial defined histological HSIL as AIN3 or p16-positive AIN2. p16-positivity is a proxy marker for hrHPV infection in AIN lesions. It does not directly identify HPV, but reflects the cellular changes caused by HPV. While HSIL is not defined specifically in the PICO clinical management algorithm, the PICO reports that HSIL is categorised as AIN2 or AIN3. Most AIN2 are p16 positive (76%, 95% CI: 61–88%)[46], though this means that some HSILs are eligible for ablation, in practice the PICO-specified testing strategy were not included in the ANCHOR trial. Additionally, treatments in the trial included those not specified in the PICO (topical fluorouracil or imiquimod, or excision under anaesthesia), with no presentation of outcomes by treatment type (though only a small proportion of patients were estimated to receive non-relevant therapies – 5.0% to 7.4% as first line treatment). In the first line, up to 2.3% (52/2227) of patients were treated with surgical excision under anaesthesia (though this figure included ablation under anaesthesia as well and a breakdown was not provided). While not included in the PICO, it is noted that in the post-PASC phase the Department flagged that surgical excision under anaesthesia may be a potential treatment option, either in addition to or as an alternative to ablation.

Of note, no single arm or comparative studies were from Australia. An ongoing non-comparative Australian pilot study (ACTRN12624000154505; the PANTHER study) is exclusively examining the use of electrocautery for anal HSIL treatment for PLWH (aged 18 years or older), to determine if larger studies are required to inform Australian guidelines (date of last data collection August

[46] Albuquerque A, Rios E, Dias CC, Nathan M. p16 immunostaining in histological grading of anal squamous intraepithelial lesions: a systematic review and meta-analysis. Mod Pathol. 2018 Jul;31(7):1026-1035. doi: 10.1038/s41379-018-0026-6. Epub 2018 Feb 13. PMID: 29434342.

2026).[47] Key outcomes will include partial/complete clearance of anal HSIL following treatment and frequency and severity of adverse events.

[47] ACTRN12624000154505. 2024. Pilot study of Anal Neoplasia Treatment in people with HIV Evaluation and monitoring (short title: PANTHER). https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=386651&isReview=true

Table 25 Summary of applicability of the comparative therapeutic evidence to the PICO (k=6)

PICO criteria	Comparative evidence					
	Palefsky 2022[2]	Atkinson 2025[48]	Goldstone 2019[49]	Richel 2013[50]	Siegenbeek van Heukelom 2016[51]	Weis 2012[52]
Population						
MSM and TW living with HIV age ≥35 years	Y^	Y^	Y^	Y*§	Y*§	Y*^¶
MSM and TW living without HIV age ≥45 years	-	-	-	-	-	-
Women and MSW living with HIV age ≥45 years	Y^†	Y^†	Y^‡	-	-	Y*^¶
People with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis	-	-	-	-	-	-
SOTR, commencing 10 years post-transplant	-	-	-	-	-	-
Patients being followed up after treatment for anal cancer	-	-	-	-	-	-
Patients outside these above groups with incidental anal HSIL and patients presenting with symptoms suggestive of anal cancer	-	-	Y**	-	-	-
People with a possible history of cervical/vaginal cancer or precursor lesions	-	-	-	-	-	-
Treatment						
HRA-guided anal HSIL ablation	Y#	Y#	Y	Y	Y	Y
Comparator						
No treatment/active monitoring	Y	Y	Y	-	-	Y
Other HSIL treatment	-	-	-	Y	Y	-
Safety outcomes	Y	Y	Y	Y	Y	-
Effectiveness outcomes	Y	-	Y	Y	-	Y

Source: Study reports
Notes: *Transgender women not specified in included sample.
^Results presented as an aggregate for PLWH.
†Including people aged 35 years or older, therefore not in direct alignment to the PICO subpopulation of MSM and TW living without HIV age ≥45 years.
‡Including people aged 27 years or older, therefore not in direct alignment to the PICO subpopulation of MSM and TW living without HIV age ≥45 years.
§Including people aged 18 years or older, therefore not in direct alignment to the PICO subpopulation of MSM and TW living with HIV age ≥35 years.
¶Age criteria not reported but included younger than 35 years.
**Method of identification of lesions not specified; possibly incidental.
#Treatment options included office-based ablative procedures, ablation or excision under anaesthesia, or the administration of topical fluorouracil or imiquimod. Selected by clinicians in alignment with clinician and participant preference from a list of options defined in the trial protocol using method-specific algorithms; HRA guidance for ablative procedures not specified.

A summary of the key features of the key evidence (6 studies) is provided in Table 26.

[48] Atkinson, T. M., Mazumdar, M., Van Hyfte, G., Lee, J. Y., Li, Y., Lynch, K. A., Webb, A., Holland, S. M., Lubetkin, E. I., Goldstone, S., Einstein, M. H., Stier, E. A., Wiley, D. J., Mitsuyasu, R., Rosa-Cunha, I., Aboulafia, D. M., Dhanireddy, S., Schouten, J. T., Levine, R., . . . Palefsky, J. M. (2025). Health-Related Quality of Life for Persons Treated or Monitored for Anal High-Grade Squamous Intraepithelial Lesions (AMC-A01). JCO Oncology Practice, 0(0), OP-24-00830. https://doi.org/10.1200/OP-24-00830

[49] Goldstone, S. E., Lensing, S. Y., Stier, E. A., Darragh, T., Lee, J. Y., Van Zante, A., Jay, N., Berry-Lawhorn, J. M., Cranston, R. D., Mitsuyasu, R., Aboulafia, D., Palefsky, J. M., & Wilkin, T. (2019). A Randomized Clinical Trial of Infrared Coagulation Ablation Versus Active Monitoring of Intra-anal High-grade Dysplasia in Adults With Human Immunodeficiency Virus Infection: An AIDS Malignancy Consortium Trial. Clinical Infectious Diseases, 68(7), 1204-1212.

Table 26 Key features of the included evidence comparing HRA-guided anal HSIL ablation to no intervention (k=6)

Trial/Study	N	Study design Risk of bias	Population	Intervention	Comparator	Key outcome(s)	Result used in economic model
Key trials/studies							
Palefsky 2022 ANCHOR trial (NCT02135419) USA	4459 (4446 included in analysis)	RCT Low risk of bias	PLWH aged 35 years or older Median age: 51 (range: 44–57) years in both treatment and active monitoring groups	HSIL treatment (HRA guidance not specified)* Returned for HRA at least every 6 months, suspicious lesions biopsied, recurrences treated	Active monitoring without treatment HRA every 6 months, visible lesions biopsied annually to confirm ongoing HSIL and absence of cancer	• Progression to anal cancer in a time-to-event analysis • Adverse events	Yes
Atkinson 2025 ANCHOR trial (NCT02135419) USA	124‡	RCT High risk of bias	PLWH aged 35 and older 51.5% MSM	HSIL treatment (HRA guidance not specified)* N=70 (87.1% received HRA-guided ablative therapy)	Active monitoring without treatment N=54	• Adverse events (HRQoL) measured at T1: Pre-randomisation; T2: 2–7 days (up to 13 days) post-randomisation; T3: 28 days (up to 67 days) post-randomisation	No
Goldstone 2019 (NCT01164722) USA	121 (120 included in analysis)	RCT Moderate risk of bias	PLWH Mean age: Treatment: 49.0 (range 25–78) years Active monitoring: 50.5 (range 27–67) years	HRA-guided HSIL ablation with IRC	Active monitoring without treatment	• Progression to anal cancer • HSIL recurrence/ treatment response • HSIL-free survival • Adverse events	No
Richel 2013 (NTR1236) Netherlands	156 (148 included in analysis)	RCT Moderate risk of bias	MSM LWH Median age: Imiquimod: 45 (41–51) years	HRA-guided monthly electrocautery for 4 months N=46	16 weeks of imiquimod (three times a week) N=54	• HSIL recurrence/ treatment response • Adverse events	No

[50] Richel, O., de Vries, H. J. C., van Noesel, C. J. M., Dijkgraaf, M. G. W., & Prins, J. M. (2013b). Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. The Lancet Oncology, 14(4), 346-353.

[51] Siegenbeek Van Heukelom ML, Richel O, Nieuwkerk PT, De Vries HJC, Prins JM. Health-Related Quality of Life and Sexual Functioning of HIV-Positive Men Who Have Sex with Men Who Are Treated for Anal Intraepithelial Neoplasia. Diseases of the Colon and Rectum. 2016;59(1):42-7

[52] Weis, S. E., Vecino, I., Pogoda, J. M., & Susa, J. S. (2012). Treatment of high-grade anal intraepithelial neoplasia with infrared coagulation in a primary care population of HIV-infected men and women. Diseases of the Colon and Rectum, 55(12), 1236-1243.

Siegenbeek van Heukelom 2016 Netherlands	148	Prospective cohort embedded within RCT High risk of bias	Fluorouracil: 47 (40–54) years Electrocautery : 47 (42–55) years		OR 16 weeks of topical fluorouracil (twice a week) N=48	• Adverse events (pain/discomfort , usual activity, anxiety/depression, overall satisfaction with sex life)	No
Weis 2012 USA	124	Prospective cohort study High risk of bias	PLWH Mean age (SD): 39.6 (9.0) Receptive anal sex: 82.3%	HRA-guided HSIL ablation with IRC	Voluntarily delayed or did not receive treatment and were reevaluated at a subsequent time point	• Progression to anal cancer • HSIL recurrence/ treatment response	No

Source: Study reports
Notes: *Including: office-based ablative procedures, ablation or excision under anaesthesia, or the administration of topical fluorouracil or imiquimod. Selected by clinicians in alignment with clinician and participant preference from a list of options defined in the trial protocol using method-specific algorithms.
‡Enrolment in the ANCHOR HRQoL study was still in progress when the ANCHOR Data and Safety Monitoring Board terminated randomisation to the study for efficacy.
Abbreviations: cRFA = circumferential radiofrequency ablation, ECA = electrocautery ablation, HIV = human immunodeficiency virus, HPV = human papillomavirus, HRA = high-resolution anoscopy, HRQoL = health-related quality of life, HSIL= high-grade squamous intraepithelial lesions, IRC = infrared coagulation, LWH = living with HIV, MSM = men who have sex with men, MSW = men who have sex with women, PLWH = people living with HIV, RCT = randomised controlled trial, RCT = randomised controlled trial; RFA = radiofrequency ablation

11. Comparative safety

Safety of the investigative technology

Physical AEs

No studies were conducted in Australia, however, procedures are standardised globally, and so it is not expected that physical AEs would significantly differ by country.

Anal sampling

Anal sampling is a well-established, minimally invasive procedure. Per the St Vincent's Hospital Sydney website[53], patients are communicated that side effects may include (1) slight discomfort; (2) minor bleeding immediately afterwards, particularly with pre-existing lesions of the anal canal; and (3) small amounts of blood in first bowel movement following the procedure (though this should not persist).

Three studies reported the physical AEs associated with anal sampling (including one supporting study with non-PICO-specified populations); pain/discomfort was reported in four studies, bleeding was reported in 1 study. No other AE outcomes were reported. Due to heterogeneity of measures used, meta-analysis was not possible, instead results are presented narratively in Table 27 below.

[53] St Vincent's Hospital Sydney. (2025). Anal Swab Tests. https://www.svhs.org.au/our-services/list-of-services/hiv-immunology-infectious-disease/dysplasia-and-anal-cancer-services/anal-pap-tests

Table 27 Key findings from included studies reporting physical AEs of anal sampling (grouped by PICO subpopulation) (k=3)

Study	Population*	Procedure	Findings (Pain/Discomfort/Bleeding)
Kaufman 2020	Women LWH	Anal cytology & HPV testing	• Median pain associated with anal cytology and HPV testing was reported as 1 out of 10. Notably, this was compared to pain experienced in cervical HPV and cytology testing which was also 1 out of 10.
Proctor 2019	Women with biopsy-proven vulvar HSIL	Anal swab	• Around half of women reported that swab insertion was "not at all" uncomfortable; Almost 90% reported that swab insertion hurt "not at all". None of the five women who experienced pain used any form of pain relief, and all reported that the discomfort lasted only a few minutes.
Davis 2013	Mixed population	Anal brush vs. swab (HPV test)	• Anal brush caused significantly more discomfort than the HPV swab (mean difference = 0.30, p = .03) during one visit, but not at the second visit (mean difference = 0.03, p = .79). Among patients who underwent HPV sampling using a brush, 27 individuals (18%) experienced lingering discomfort lasting an average of 1.2 days, while 25 (17%) reported minor bleeding that persisted for about 1.3 days. In comparison, for those sampled with a swab, 26 patients (18%) noted discomfort averaging 1.7 days, and 20 (14%) experienced bleeding for approximately 1.2 days. The differences in outcomes between the brush and swab methods were not statistically significant.

Source: Study reports
Notes: *An ongoing French trial (NCT06507917[54], estimated completion November 2026) will report adverse events (discomfort, pain, bleeding, itching) related to anal sampling in MSM, women, and MSW living with HIV aged ≥30 years. This will address evidence gaps for MSM LWH and MSW LWH. While adverse events may be more common in individuals with inflammation or lesions (more prevalent among MSM) anal sampling is generally safe and well tolerated, so findings are unlikely to significantly alter the current safety profile relevant to the PICO.
Abbreviations: AE = adverse event; HPV = human papillomavirus; LWH = living with HIV

Overall, anal sampling was found to be minimally painful with most patients reporting mild to moderate. Notably, one study compared this to pain during cervical HPV and cytology testing, finding the same reported pain levels[55]. Evidence was not available for most PICO subpopulations; however, the results are expected to be broadly applicable across populations. For those with existing anal lesions, bleeding and pain may be greater, though these impacts are still considered minimal. Therefore, for all PICO subpopulations, the physical risks of anal sampling are considered minimal compared to the risk of developing anal cancer and consequent morbidity (including physical AEs) associated with diagnosis.

HRA

Five studies reported the physical AEs associated with HRA (including two supporting studies with non-PICO-specified populations). Due to heterogeneity of measures and measurement timepoints used, meta-analysis was precluded. Three studies reported pain levels on a 10-point Likert scale (results presented in Table 28).

[54] NCT06507917. (2024). Concordance and Acceptability of Self-screening Versus Screening by a Healthcare Professional for HPV, a Risk Factor for Anal Cancer, by Swab in People Living With HIV (a-HPVVIH). https://clinicaltrials.gov/study/NCT06507917
[55] Kaufman E, de Castro C, Williamson T, Lessard B, Munoz M, Mayrand MH, Burchell AN, Klein MB, Charest L, Auger M, Marcus V, Coutlée F, de Pokomandy A; EVVA Study Group. Acceptability of anal cancer screening tests for women living with HIV in the EVVA study.

Table 28 Reported pain levels from HRA for studies reporting pain on a 10-point Likert scale, presented by measurement timepoint (k=5)

Study	Population	Measurement timepoint	Average pain score (10-point Likert scale; 10 being worse pain imaginable)
Lam 2018	PLWH	During HRA	Mean = 2.65
Kaufman 2020	Women LWH	During HRA	Median = 5
De Masi 2018	Mixed population	Immediately after HRA	Median = 2 (IQR 3)
Lam 2018	PLWH	2–3 days after HRA	Mean = 4.28
Lam 2018	PLWH	1 week after HRA	Mean = 2.54

Source: Study reports
Abbreviations: HRA = High-Resolution Anoscopy; LWH = living with HIV; PLWH = people living with HIV

Generally, pain was reported to be mild to moderate and tolerable, though higher among women and possibly those undergoing biopsy. In two studies, 14.3–30% of patients reported "no pain at all" during the HRA[56,57], while difficulty tolerating the procedure or "problematic pain" was reported as 5–9% in two studies[56,58]. One study reported that bleeding was a common side effect of HRA, experienced by 68.8% of participants, though most found it milder than expected and acceptable. [582] The same study found minimal impact on daily life, with most participants maintaining social and physical activities without needing time off to recover.

As with anal sampling, evidence was not available for most PICO subpopulations, and given HRA is more invasive, there is greater potential for differences across subgroups to exist (particularly for those with existing anal lesions, bleeding and pain). However, considering existing evidence, for all PICO-subpopulations the physical risks of HRA are considered minimal compared to the risk of developing anal cancer and consequent morbidity (including physical AEs) associated with diagnosis.

Psychosocial AEs

Six studies reported psychosocial outcomes of anal cancer screening. No studies directly matched the PICO-specified triaged testing strategy, but four did report results of anal sampling (usually for cytology, not HPV) followed by HRA (which are the two tests involved in the PICO). Due to heterogeneity in study design and measures used, meta-analysis was not possible. Instead, results are presented narratively in Table 29.

Overall, findings indicated that anal cancer screening (through a combination of anal HPV testing, anal cytology testing and HRA) can cause psychological burden, though individual experiences varied. Reported risk factors for worse psychosocial outcomes included more severe anal or HIV symptoms, younger age, higher initial distress levels and not LWH,[59,60] indicating psychosocial effects may differ among PICO subpopulations. Positive psychosocial impacts, such as relief and reassurance, were also reported in two studies.[59,60]

[56] De-Masi, A., Davis, E., Cuming, T., Chindawi, N., Pesola, F., Cappello, C., Chambers, S., Bowring, J., Rosenthal, A. N., Sasieni, P., & Nathan, M. (2018). The acceptability of high resolution anoscopy examination in patients attending a tertiary referral centre

[57] Nitkowski, J., Ridolfi, T. J., Lundeen, S. J., Giuliano, A. R., Chiao, E. Y., Fernandez, M. E., Schick, V., Smith, J. S., Brzezinski, B., & Nyitray, A. G. (2024). The influence of home versus clinic anal human papillomavirus sampling on high-resolution anoscopy uptake in the Prevent Anal Cancer Self-Swab Study. Sexual Health, 21(3)

[58] Lam, J., Barnell, G., Merchant, M., Ellis, C., & Silverberg, M. (2018). Acceptability of high-resolution anoscopy for anal cancer screening in HIV-infected patients. HIV Medicine, 19(10), 716-723.

[59] Russo, S., McCaffery, K., Ellard, J., Poynten, M., Prestage, G., Templeton, D. J., Hillman, R., Law, C., & Grulich, A. E. (2018). Experience and psychological impact of anal cancer screening in gay, bisexual and other men who have sex with men: a qualitative study. Psychooncology, 27(1)

[60] Tinmouth, J., Raboud, J., Ali, M., Malloch, L., Su, D., Sano, M., Lytwyn, A., Rourke, S. B., Rabeneck, L., & Salit, I. (2011). The psychological impact of being screened for anal cancer in HIV-infected men who have sex with men. Dis Colon Rectum, 54(3), 352-359.

Several Australian studies (two from the SPANC trial)[59,61,62] reported psychological distress linked to abnormal HRA results (e.g., HSIL). While other studies contradicted this, the SPANC study was Australian with similar testing protocols to the PICO. However, the SPANC study was observational, with HSIL lesions monitored over time. Treatment, such as infrared coagulation or topical therapies, were offered based on severity and clinical judgment. Immediate referral for HSIL treatment (rather than monitoring), as per PICO, may therefore reduce psychosocial burden from abnormal findings.

The three Australian studies included men LWH or MSM,[59,61,62] covering three of the largest PICO subpopulations in the relevant Australian context. However, psychosocial impacts of testing for anal cancer likely differ across subgroups, especially considering the role of HPV and associated stigma, and experienced sexual discrimination for some groups. There was no evidence regarding psychosocial AEs identified for the following PICO subpopulations:

- People with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis.
- SOTR, commencing 10 years post-transplant.
- Patients being followed up after treatment for anal cancer.
- Patients outside other PICO groups with incidental anal HSIL and patients presenting with symptoms suggestive of anal cancer.
- People with a possible history of cervical/vaginal cancer or precursor lesions.

Anal cancer diagnosis and treatment is associated with psychosocial AEs such as distress and cancer-specific worry.[63] Although testing may increase AEs by identifying cancer, it enables earlier diagnosis in asymptomatic individuals, making these effects likely less severe than those from later-stage, symptomatic detection. Testing also enables early intervention via HSIL treatment, preventing progression to cancer and reducing future psychosocial burden. Therefore, across all PICO-defined groups, the psychosocial impact of anal HPV testing, anal cytology testing and diagnostic HRA is considered relatively minor compared to the potential burden of anal cancer.

[61] Cvejic, E., Poynten, I. M., Kelly, P. J., Jin, F., Howard, K., Grulich, A. E., Templeton, D. J., Hillman, R. J., Law, C., Roberts, J. M., & McCaffery, K. (2020). Psychological and utility-based quality of life impact of screening test results for anal precancerous lesions in gay and bisexual men: Baseline findings from the Study of the Prevention of Anal Cancer. Sexually Transmitted Infections, 96(3), 177-183.

[62] Landstra, J. M., Ciarrochi, J., Deane, F. P., Botes, L. P., & Hillman, R. J. (2013). The psychological impact of anal cancer screening on HIV-infected men. Psychooncology, 22(3), 614-620. https://doi.org/10.1002/pon.3040

[63] van Dongen, J., de Heus, E., Eickholt, L., Schrieks, M., Zantingh, I., Brouwer, O. R., Oonk, M. H. M., Grotenhuis, B. A., Ezendam, N. P. M., & Duijts, S. F. A. (2022). Challenges and controversies patients and (health care) professionals experience in managing vaginal, vulvar, penile or anal cancer: The SILENCE study. European journal of cancer care, 31(6), e13676. https://doi.org/https://doi.org/10.1111/ecc.13676

Table 29 Key findings from included studies reporting psychosocial AEs of HPV testing, cytology testing and diagnostic HRA with no testing (grouped by PICO subpopulation) (k=6)

Study	Population	Key findings
Russo 2018 (SPANC study)	MSM ≥35 years	• Participants reported experiencing psychological distress, guilt and regret associated with abnormal results. Men LWH were perceived as less anxious or distressed than those not LWH. • Normal test results created feelings of reassurance and gratitude. • Testing often associated with feelings of greater control over anal health.
Cvejic 2020 (SPANC study)	MSM ≥35 years	• Modest but significant differences in HR-QoL and utility-based QoL, cancer worry, perceived cancer risk and unwanted intrusive thoughts about cancer were associated with perceived (abnormal) test results 2 weeks after screening. • For HR-QoL and utility-based outcomes, these did not persist 3-months post-screening. However, other outcomes of feeling worse than usual about anal health, concern that something was seriously wrong and fear about anal cancer remained at this timepoint.
Tinmouth 2011	MSM LWH	• 15–32% of participants reported elevated psychological distress at various time points, with the highest distress occurred immediately after screening. • Positive psychological effects increased over time. • Younger age, higher HIV symptom burden, and greater baseline distress were associated with higher psychological burden. • Diagnosis of anal HSIL did not significantly increase distress after results were received.
Landstra 2013	Men LWH	• Cancer-specific worry increased after cytology and remained high in those with high-grade results. • Anal health perception worsened among those undergoing HRA. • Optimism about future health dropped after abnormal results but rebounded in the those who did not have HSIL on HRA and biopsy. • Distress was higher in the HSIL group post-HRA. • No changes were found in general anxiety, depression, or overall quality of life.
Lam 2018	PLWH	• Most participants (83.3%) reported that, before their first HRA, they felt little to no worry. • 72.9% of PLWH after receiving a first-time HRA reported that they would be less worried about their second HRA.
Proctor 2019	Women with a history of biopsy-proven vulvar HSIL	• Most women reported feeling no nervousness (68.4%) or embarrassment (86.0%) during examinations, and 91.2% indicated that the screening process was not emotionally distressing at all.

Source: Study reports
Abbreviations: AE = adverse event; HIV = human immunodeficiency virus, HSIL= High-Grade Squamous Intraepithelial Lesion; HRA = High-Resolution Anoscopy; HR-QoL = health related quality of life, LWH = living with HIV, HR-QoL = health-related quality of life, PLWH = people living with HIV.

Impacts of false positive and false negative results

There was no identified evidence for the impact of false positive and false negative results in the PICO-specified triaged testing strategy on health outcomes. In the absence of longitudinal evidence for anal cancer screening using the PICO-specified triaged testing algorithm, the cumulative false positive rate is not estimable. This rate is particularly relevant for tests with high sensitivity and low specificity (which the proposed triaged testing strategy is estimated to have [per Jin 2025]), as low specificity will mean higher rates of false positives.

False positive results at each stage of the triaged testing strategy would have different consequences. For HPV testing, false positive results would mean that an individual without hrHPV would then receive triaged cytology testing and/or diagnostic HRA (if positive for HPV16). Physically, if sent for cytology testing alone, this would likely have minimal physical AE impacts given samples are often taken at the same time for both HPV and cytology testing, and if not, anal sampling is a minimally invasive procedure. However, there is the potential for HPV-associated stigma and related psychological burden.

If patients falsely test positive for HPV16 and are unnecessarily referred for diagnostic HRA, they would be subjected to an invasive and uncomfortable procedure that carries potential risks of adverse events such as pain or bleeding. However, findings indicate pain is generally manageable, and in some cases not experienced at all. Unnecessary HRAs may have flow on impacts at a system level. Given existing concerns around demand for HRAs not meeting available supply, unnecessary HRAs not only lead to inefficient use of resources, inconvenience for the patient and unnecessary spending but may also hinder timely access for a true positive case.

False positive results of HSIL on a diagnostic HRA would mean that patients are referred for HSIL ablation when not needed. Harms associated with ablative treatment (specifically related to pain, bleeding and infection [detailed in Section 2B.3]) would therefore be incurred unnecessarily.

False negative results at each stage of the triaged testing strategy would have impacts of possible delayed diagnosis and treatment. This would equate to worse clinical outcomes, as later-stage anal cancer is more difficult to treat and has a lower survival rate.

Overdiagnosis and overtreatment

A key safety risk of any form of cancer screening is overdiagnosis of anal HSIL or anal cancers that would not have resulted in clinically meaningful outcomes over a person's lifetime.[64] Types of overdiagnosed cancers include those that would regress spontaneously if not treated; those where progression is too slow to be any clinical risk over a lifetime; and those that would progress enough to present clinically meaningful risk, however, co-existing morbidities would mean that is not the cause of death.[65,66] Detection of these subclinical lesions means that all investigations and subsequent treatments are unnecessary, resulting in physical, psychological and financial harms to individual and costs to the health system.

There is no published evidence for the potential rate of overdiagnosis in anal cancer screening.[66] Across randomised trials of other types of cancer screening, rates of overdiagnosis have been estimated at between 17% to 38%.[66] Trials and cancer screening programs are generally not set up to measure overdiagnosis as an outcome, making this an underreported and underrecognised issue.[66] Notably, overdiagnosis can be difficult to estimate as it can be impossible to tell if cancers, once detected, would regress, or were too slow growing to cause harm.

Harm associated with the absence of testing

The primary harm associated with the absence of testing is the delayed diagnosis of HSIL which significantly increases the risk of progression to anal cancer. Without timely detection through screening, individuals may experience greater morbidity due to advanced lesion development and reduced opportunities for early, potentially curative intervention. This delay not only compromises clinical outcomes but also contributes to increased mortality associated with anal HSIL and subsequent cancer. Evidence supporting these harms is drawn from direct comparisons between screened and non-screened populations, where the "non-screening" groups consistently demonstrate poorer prognoses and more advanced disease at diagnosis. This is presented as part of the Direct to health outcomes evidence.

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[64] Carter, S. M., & Barratt, A. (2017). What is overdiagnosis and why should we take it seriously in cancer screening? Public Health Res Pract, 27(3). https://doi.org/10.17061/phrp2731722

[65] Srivastava, S., Koay, E. J., Borowsky, A. D., De Marzo, A. M., Ghosh, S., Wagner, P. D., & Kramer, B. S. (2019). Cancer overdiagnosis: a biological challenge and clinical dilemma. Nat Rev Cancer, 19(6), 349-358. https://doi.org/10.1038/s41568-019-0142-8

[66] Voss, T., Krag, M., Martiny, F., Heleno, B., Jørgensen, K. J., & Brandt Brodersen, J. (2023). Quantification of overdiagnosis in randomised trials of cancer screening: an overview and re-analysis of systematic reviews. Cancer Epidemiology, 84, 102352. https://doi.org/https://doi.org/10.1016/j.canep.2023.102352

Value of knowing/AEs of knowing test results

There was no identified evidence for the value of knowing or potential AEs of anal HPV testing. However, a potential clinical utility outcome of HPV diagnosis is reduced transmission of infection. HPV is highly contagious and often asymptomatic, making it easy to unknowingly pass to sexual partners. By identifying an HPV infection early, individuals can take informed steps to reduce transmission, such as using barrier protection, limiting the number of sexual partners, and encouraging partners to get vaccinated or screened.

A potential adverse effect of knowing HPV test results is the risk of stigmatisation or discrimination. While no studies were identified that specifically evaluate this issue in the context of anal cancer screening, the experience of stigma following an HPV diagnosis is well-documented in cervical screening contexts.[67,68,69] Studies have also reported stigma as a barrier to anal cancer screening (though these were not included in the present review as they were not experienced outcomes).[70] Additionally, knowing one's HPV status (and subsequent disclosure to partners) can negatively impact intimate relationships.[68] It may lead to tension or mistrust, particularly if partners misunderstand the nature of HPV infection. Concerns about transmission and future sexual activity can also affect confidence and intimacy, further contributing to emotional distress.[68]

There was no identified evidence for the value of knowing or potential AEs of a pLSIL or LSIL cytology test result. Unlike HSIL or pHSIL results, which have direct clinical utility by prompting referral for HRA, pLSIL and LSIL results lead to a recommendation for repeat HPV testing in 12 months under the PICO-specified testing strategy. This delay in definitive action may contribute to a decreased sense of control or uncertainty for patients, as they are left in a monitoring phase without immediate intervention. This approach is clinically conservative and aims to avoid overtreatment, however, it may cause psychological distress.

Summary of comparative safety of the investigative intervention

For psychosocial and physical AEs, anal HPV testing, cytology testing and diagnostic HRA all have an inferior safety profile (i.e., physical and psychosocial adverse events associated with testing) compared to no testing. Physical AEs of anal sampling are minimal; physical AEs of HRA are generally tolerable, but problematic for up to 10% of people. Psychosocial AEs associated with testing are present for some individuals, and certain subpopulations may be more at risk considering the role of HPV and associated stigma, and experienced sexual discrimination for some groups. However, there is a paucity of evidence on the psychosocial impacts of the proposed investigative intervention for each PICO population. Psychosocial AEs and the potential for stigma and related burden in each subpopulation will also have implications for uptake of the proposed intervention.

Considering the downstream implications of anal cancer and related morbidity (both physical and psychosocial), for all PICO-subpopulations, the use of anal HPV testing, cytology testing and diagnostic HRA is considered comparatively safe.

There is not enough evidence for the rate of false positive and false negative results of the triaged testing strategy, or of overdiagnosis in anal cancer screening, to evaluate the risks comparative to the downstream impacts of anal cancer.

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[67] Bennett, K. F., Waller, J., Ryan, M., Bailey, J. V., & Marlow, L. A. V. (2019). The psychosexual impact of testing positive for high-risk cervical human papillomavirus (HPV): A systematic review. Psycho-Oncology, 28(10), 1959-1970. https://doi.org/https://doi.org/10.1002/pon.5198

[68] McCaffery, K., Waller, J., Nazroo, J., & Wardle, J. (2006). Social and psychological impact of HPV testing in cervical screening: a qualitative study. Sexually Transmitted Infections, 82(2), 169. https://doi.org/10.1136/sti.2005.016436

[69] Waller, J., Marlow, L. A. V., & Wardle, J. (2007). The association between knowledge of HPV and feelings of stigma, shame and anxiety. Sexually Transmitted Infections, 83(2), 155. https://doi.org/10.1136/sti.2006.023333

[70] Sam, I., Dang, W., Iu, N., Luo, Z., Xiang, Y. T., & Smith, R. D. (2025). Barriers and facilitators to anal cancer screening among men who have sex with men: a systematic review with narrative synthesis. BMC Cancer, 25(1), 586. https://doi.org/10.1186/s12885-025-13980-w

Safety of the therapeutic intervention

Safety of the therapeutic intervention was reported in four studies, including in three comparative trials (key evidence).

Physical AEs

Treatment-related AEs from key comparative evidence are reported in Table 30 and Table 31.. Two studies reported AEs as related to the PICO-specified comparator (no treatment/active monitoring); two studies were compared to other therapies for HSILs (fluorouracil and imiquimod).

Table 30 Treatment-related physical adverse events reported in key comparative evidence (k=3)

Treatment-related adverse events	Treatment arm		Comparator arm – active monitoring		Comparator arm – Imiquimod		Comparator arm – Fluorouracil	
	AEs†	SAEs‡	AEs	SAEs	AEs	SAEs	AEs	SAEs
Palefsky 2022	**1.9% (43/2227)**	**0.3% (7/2227)***	**0.2% (4/2219)**	**0.1% (1/2219)**	**-**	**-**	**-**	**-**
Anal abscess due to electrocautery		1		0	-	-	-	-
Pain due to electrocautery		1		0	-	-	-	-
Pain due to treatment under anaesthesia		1		0	-	-	-	-
Pain due to infrared coagulation		1		0	-	-	-	-
Infection or abscess due to anal biopsy		2		1	-	-	-	-
Goldstone 2019	**87% (52/60)**	**0**	**7% (4/60)**	**0**	**-**	**-**	**-**	**-**
Anal pain	80% (48/60)	0	5% (3/60)	0	-	-	-	-
Postoperative haemorrhage/ anal haemorrhage	78% (47/60)	0	0	0	-	-	-	-
Richel 2013	**76% (34/45)**	**18% (8/45)**	**-**	**-**	**47% (25/53)**	**43% (23/53)**	**65% (31/48)**	**27% (13/48)**
Pain	42% (19/45)	18% (8/45)	-	-	38% (20/53)	32% (17/53)	52% (25/48)	15% (7/48)
Itching	2% (1/45)	0% (0/45)	-	-	15% (8/53)	4% (2/53)	10% (5/48)	2% (1/48)
Bleeding	69% (31/45)	0% (0/45)	-	-	30% (16/53)	0% (0/53)	40% (19/48)	0% (0/48)
Slimy stool	7% (3/45)	0% (0/45)	-	-	4% (2/53)	2% (1/53)	2% (1/48)	2% (1/48)
Urge	11% (5/45)	2% (1/45)	-	-	4% (2/53)	2% (1/53)	46% (22/48)	8% (4/48)
Incontinence	0% (0/45)	0% (0/45)	-	-	4% (2/53)	0% (0/53)	6% (3/48)	2% (1/48)
Diarrhoea	7% (3/45)	0% (0/45)	-	-	4% (2/53)	2% (1/53)	6% (3/48)	4% (2/48)
Flatulence	0% (0/45)	0% (0/45)	-	-	2% (1/53)	0% (0/53)	10% (5/48)	4% (2/48)
Influenza-like symptoms	2% (1/45)	0% (0/45)	-	-	11% (6/53)	2% (1/53)	2% (1/48)	0% (0/48)
Fatigue	2% (1/45)	0% (0/45)	-	-	11% (6/53)	2% (1/53)	4% (2/48)	0% (0/48)

Source: Study reports

Notes: *In the treatment arm, 7 SAEs were related to treatment (though one was clearly attributed to fluorouracil and therefore not relevant to the PICO intervention); †All adverse events with a possible, probable, or definite relationship to trial interventions; ‡ All serious

adverse events with a possible, probable, or definite relationship to trial interventions. There was no significant between-group difference (p=0.07). Abbreviations: AE = adverse events; SAEs = serious adverse events

Across all comparative and single arm studies, overall, adverse events related to ablative treatment were primarily mild to moderate pain, bleeding or (rarely) infection, and were normally resolved within 1-3 weeks and managed successfully with mild analgesics as required. In comparative evidence, significantly more AEs and SAEs were reported in the treatment group versus active monitoring.[2] Severe or life-threatening side effects were less common for those receiving electrocautery (18%) versus imiquimod (43%) or fluorouracil (27%) treatment in one study, though AEs were higher in the electrocautery group. Additionally, duration of AEs was much shorter for electrocautery (lasting for days; versus weeks in non-ablative treatment groups).

One study examined physical components of HRQoL. Results are summarised in Table 31. Individuals receiving electrocautery were more likely to report pain or discomfort, and problems with usual activities at week 20 than patients in the fluorouracil group (though noting serious risk of bias concerns associated with different follow-up methods).

Of note, there is an ongoing single arm Australian pilot study (ACTRN12624000154505[71] the PANTHER study) examining the use of electrocautery for anal HSIL treatment for PLWH (aged 18 years or older) (date of last data collection August 2026). This study will report adverse events associated with treatment.

Table 31 Key findings of physical AEs related to HSIL treatments reported in Siegenbeek van Heukelom 2016

Outcome	Findings
Pain/Discomfort	Significant differences were found among the 3 treatment groups. Imiquimod arm reported more pain/discomfort at week 8 compared to the electrocautery arm (OR, 3.6; 95% CI, 1.2–11.3; p = 0.03). Electrocautery arm reported more pain/discomfort at week 20 compared to fluorouracil arm (OR, 3.6; 95% CI, 1.1–12.1; p = 0.04).
Usual Activity	Marginally significant differences were found among the 3 treatment groups. Electrocautery group reported more problems with usual activities at week 20 compared to the fluorouracil group (OR, 5.5; 95% CI, 1.4–21.8; p = 0.02).

Source: Siegenbeek van Heukelom 2016
Abbreviations: AE = adverse event; CI = confidence interval, OR = odds ratio

Psychosocial AEs

Two comparative studies reported psychosocial HRQoL outcomes. One used the PICO-specified comparator (active monitoring) in PLWH; the other compared to different HSIL treatments (imiquimod, fluorouracil, and electrocautery ablation) for MSM LWH aged 18 or older.

Comparison to active monitoring

The HRQoL study in the ANCHOR trial found worsened impact on psychological functioning 2-7 days after treatment for those receiving HSIL therapy, though not for active monitoring.[2] Though, all missing data from the purpose built measure (ANCHOR Health-Related Symptom Index; A-HRSI) were from the Impact on Psychological Functioning domain (12, 10 and 9 results missing from each timepoint, respectively). The authors attributed this likely to sensitive questions, specifically about desire and enjoyment of sexual activity. This trend in missing information may impact results, especially considering the small overall sample size. Risk of bias concerns around complete case analysis, lack of responsiveness cut-offs and confounding variables further undermine confidence in results. As with testing, psychosocial impacts of ablative treatment for

[71] ACTRN12624000154505. 2024. Pilot study of Anal Neoplasia Treatment in people with HIV Evaluation and monitoring (short title: PANTHER). https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=386651&isReview=true

HSIL may differ across the PICO-specified subgroups (associated with HPV and stigma, and experienced sexual discrimination for some groups). Only PLWH were examined in this study (representing approximately 22% of the total PICO population), and further evidence in other subpopulations is needed.

Comparison to different treatments

Key psychosocial results from Siegenbeek van Heukelom 2016 are presented narratively in Table 32 Key findings of psychological AEs related to HSIL treatments reported in Siegenbeek van Heukelom 2016according to outcomes measured. All treatments negatively affected HRQoL, though anxiety and satisfaction with sex life outcomes were significantly worse for electrocautery treatment compared to treatment with imiquimod or fluorouracil, though there were serious risk of bias concerns. However, the electrocautery arm completed questionnaires at different follow up points than imiquimod and fluorouracil arms. Confounders were also not considered (particularly in differences by AIN grade) and drop-out rates at each timepoint were high, meaning results may not be reliable.

Table 32 Key findings of psychological AEs related to HSIL treatments reported in Siegenbeek van Heukelom 2016

Outcome	Findings
Anxiety/Depression	Significant differences were found among the 3 treatment groups. The electrocautery group were more likely to report anxiety/depression at week 16 compared to imiquimod group (OR, 3.7; 95% CI, 1.2–11.4; p = 0.03) or fluorouracil group (OR, 3.8; 95% CI, 1.2–11.8; p = 0.02).
Overall Satisfaction with Sex Life	Significant treatment group-by-time interaction effect was found (p = 0.04). Electrocautery group had significantly lower satisfaction with overall sex life at week 16 compared to imiquimod (p = 0.01) and tended to have lower scores than fluorouracil (p = 0.08). More than half of the patients in all groups reported no sexual intercourse during the evaluation period.

Source: Siegenbeek van Heukelom 2016
Abbreviations: AE = adverse event; CI = confidence interval, HSIL= High-Grade Squamous Intraepithelial Lesion; OR = odds ratio

Summary of comparative safety of the therapeutic intervention

The evidence suggests that HRA-guided anal HSIL ablation has an inferior safety profile compared with no treatment/active monitoring for PLWH. However, considering the progression rate of HSIL to anal cancer without treatment, for all PICO-subpopulations the use of HRA-guided anal HSIL ablation is considered comparatively safe relative to the risk of developing anal cancer and consequent morbidity associated with diagnosis. There is limited evidence for PICO-specified subpopulations other than PLWH. Given PLWH have some of the highest anal cancer incidence rates,[7] the balance of safety risks and benefits associated with treatment may differ in lower-risk populations, potentially making the safety profile less favourable in these subpopulations.

Notably, there are multiple treatment options for HSIL (including surgical excision) that are used in practice that have a different AE profile to ablation (evidence suggests less pain and bleeding, though possibly worse HRQoL). Additionally, metachronous HSILs (independent lesions occurring at different site from the original treated lesions) following ablative treatment were common in the evidence, possibly caused by a host or viral response, which would require further ongoing treatment and incur additional related AEs.

12. Comparative effectiveness

Direct evidence

Key direct evidence was derived from large-scale ecological cohort studies providing real-world, longitudinal evidence of the impact of anal cancer screening followed by treatment. However,

given the studies' observational, retrospective nature these were subject to several potential biases, primarily related to suboptimal screening practices, possible missing data, and retrospective classification of the intervention and outcomes. The latter may underestimate the true effects of screening by misclassification of screening-detected cancers (as an individual was defined as participating in screening from 180 days after the first HRA). Additionally, the population, screening intervention and therapeutic intervention did not directly match the PICO in any studies; HPV testing was not included in any comparative direct evidence and so applicability to the PICO is limited.

A summary of findings of key health outcomes with comparative direct evidence, and assessment of the evidence using GRADE is presented in Table 33. Results are not summarised numerically in tables given the differences in study designs, populations, interventions and outcome measures.

Overall, direct evidence suggested that (specifically for PLWH), anal cancer screening (including anal cytology testing and diagnostic HRA) to identify HSIL, followed by treatment, may contribute to improved clinical outcomes. However, no direct comparative evidence included HPV testing. As expected with a screening program, the evidence also suggested that the introduction of anal cancer screening initially increases anal cancer incidence, though this reduced over time.

In the key real-world, large scale evidence study,[271] anal cancer-related and all-cause mortality rates were significantly lower among screened participants compared to those not screened, suggesting a significant survival benefit of screening. Although lead time bias may contribute to these results, improved clinical staging in two studies supports the conclusion that earlier detection likely drove the observed mortality reductions. There was no evidence presenting the estimates of contributors to reduced mortality (i.e., early detection of cancer versus removal of pre-cancerous lesions).

There is limited applicability of the direct evidence to the PICO. Most direct evidence was only available for PICO subpopulations of (1) MSM and TW living with HIV age ≥35 years and (2) women and MSW living with HIV age ≥45 years, which only comprises approximately 22% of the total PICO population. There was one study[31] which possibly included populations outside of these subgroups, however a breakdown of participant-level data required was not provided and so applicability could not be determined.

Only one non-comparative study included HPV testing in screening procedures, and treatment protocols were either not specified or explicitly included therapies outside of PICO.

Table 33 Summary of findings table – key direct from test to health outcomes evidence (k=11)

Outcomes	Participants and studies	Results, interpretation and key uncertainties	Certainty of the evidence (GRADE) Evidence statement
Anal cancer incidence	6 studies (n=45943)	It is expected that the introduction of screening would initially increase the incidence of anal cancer. Aligning with this, two key real-world, large scale evidence study[27,28] found an increased incidence of anal cancer post-introduction of anal cancer screening in the Netherlands (HRA only) and the USA (anal cytology testing and HRA only) for PLWH. In van der Zee 2023, overall, screening participation (using HRA only) was independently associated with an increased risk of being diagnosed with anal cancer (RR 2.41, 95% CI 1.60–3.63, p<0.0001). Similar outcomes were reported in Barnell 2019 – when compared to the time before HRA availability (1998–2007), anal cancer incidence rates increased in initial years (2008-2010) (adjusted RRs (aRR) of 1.32, 95% CI 0.77–2.27; p=.31) and subsequently decreased following this (2011–2012) to the lowest of the entire study period (aRR of 0.35, 95% CI 0.12–0.99; p=.048). Both studies had moderate to serious risk of bias primarily stemming	⊕⊕⊙⊙ **Low**[a] Anal HPV testing, cytology testing and diagnostic HRA compared to no testing may result in an increase in anal cancer incidence.

		from the ecological design using timeframes pre- and post-introduction of screening using HRA as a proxy for the intervention. Key issues related to suboptimal screening practices, possible missing data, and classification of the intervention and outcome may impact results; the latter likely underestimates the true effects of screening. Some risk of bias issues in the two comparative studies were unavoidable due to the large population-level retrospective dataset, and key issues are reflective of issues seen in a "real-world" program (e.g., screening adherence). A study comparing anal cancer incidence of anal cancer in PLWH who opted in versus out of screening (using cytology, HRA and DARE) found anal cancer incidence was significantly lower in the screening group (HR 0.17; 95% CI 0.03–0.86), though issues with selection bias may limit conclusions.29 There were a limited number of anal cancer events in this cohort, however (n=3111), which may underestimate true incidence.	
Clinical staging (TNM)	2 studies (n=28787)	Key comparative evidence[27] found that those who were screened with HRA had more favourable staging at diagnosis (i.e., earlier stage; p=0.033). In addition, 5.1% of unscreened individuals had distant metastases at diagnosis, whereas none of the screened individuals did (p = 0.60). Though, there was no reported difference in TNM nodal stages between the two groups (p = 0.86). A key risk of bias issue for this outcome is missing data; 25.1%, 13.7% and 16.7% of participants had missing information on tumour, nodal and metastases stage, respectively. For both tumour and nodal staging, there was also more missing data in those not participating in screening. The implications of this were not discussed in the paper. Additionally, classification of screening participation was based on participation 180 days after the first HRA which may categorise more people "not" in screening. Staging results favouring the intervention were supported by the other key comparative study[31]; screened patients (using cytology and HRA) had significantly greater odds of presenting at Stage I (rather than a later stage) in all analyses (OR 9.95, 95% CI 3.95–25.08). Due to the small number of screened patients, analysis was underpowered, and CIs were extremely wide. Though, the lower bounds on all analyses still indicated an appreciable benefit for screening populations. Staging benefits are likely from screening alone (and not the treatment) as ablation should reduce the chance of cancer but will not impact the stage at which it is detected.	⊕⊕⊙⊙ **Low**[b] Anal HPV testing, cytology testing and diagnostic HRA compared to no testing may result in improved clinical staging of anal cancer at diagnosis.
Anal cancer-related and all-cause mortality	1 study (n=28175)	In the key real-world, large scale evidence study[27] despite increasing incidence rates, the risk of anal cancer mortality within five years of diagnosis decreased over time. Five-year anal cancer-related mortality was significantly lower in screened participants (using HRA) (3.7%, 95% CI 0.5–23.5) than in those who did not participate in screening (24.0%, 95% CI 18.1–31.3; p = 0.023). The same trends were seen for all-cause mortality (10.6%, 95% CI 3.6–29.5) in screened participants compared with (34.9%, 95% CI 28.3–42.6) in non-screened participants (p=0.020). While lead time bias is a concern and may be present to some extent, the improved tumour staging and metastasis for screened participants supports the likelihood that improvements in mortality are a result of earlier detection due to screening. Importantly, estimates only included men, further limiting applicability to the PICO.	⊕⊕⊙⊙ **Low**[c] Anal HPV testing, cytology testing and diagnostic HRA compared to no testing may result in reduced anal cancer-related and all-cause mortality.
Anal cancer treatment failure; overall survival	1 study (n=612)	In one comparative study[31], screening (using cytology and HRA) did not significantly affect treatment failure or overall survival rates. The 5-year cumulative incidence of treatment failure was similar between screened and unscreened patients, with no significant difference (Competing Risk Analysis (Treatment Failure), Adjusted HR 0.89	⊕⊙⊙⊙ **Very Low**[d] The evidence is very uncertain about the effect of anal HPV

		(95% CI, 0.45–1.74)). Although screened patients had a higher 5-year overall survival rate, the difference was not statistically significant (Multivariable Cox Model (Death); adjusted HR 0.44 (95% CI, 0.14–1.40)). Due to the small number of screened patients, analysis was underpowered, and CIs were extremely wide. There were also issues with selection bias.	testing, cytology testing and diagnostic HRA compared to no testing on Anal cancer treatment failure and overall survival.
Treatment response	1 study (n=204)	A non-comparative case series study[72] examined outcomes following screening (including HPV testing, cytology testing, high-resolution video-proctoscopy and anoscopy). Results showed four AIN II patients (100%), and four AIN III patients (44%) had a complete response to the treatment, with 56% (5/9) undergoing repeated treatment cycles. This study was at very high risk of bias, was non-comparative and did not consider confounders. Included PICO subpopulations only comprise approximately 22% of the total PICO population, and exact participant information to assess relevance was not available. Treatments also included vaccination, surgical and topical therapies, though a breakdown was not provided.	⊕⊙⊙⊙ **Very Low**[e] The evidence is very uncertain about the effect of anal HPV testing, cytology testing and diagnostic HRA compared to no testing on treatment response.

Notes:

a. Moderate to serious risk of bias in key comparative evidence studies (downgrade one rating for risk of bias). Key comparative evidence studies do not align with PICO-specified screening algorithm (i.e., screening procedures did not specify anal HPV testing and/or cytology testing), though this should not materially impact incidence calculations as anal HPV testing or cytology testing have high sensitivity limiting false negatives. Population is PLWH only (downgrade one rating for indirectness). Confidence intervals of primary effect estimate are wide in all comparative studies, though both upper and lower bound indicate an appreciable benefit (no change in rating for imprecision). Only one study contributing information (no change in rating for inconsistency). No evidence of publication bias (no change in rating for publication bias).

b. Serious risk of bias in both comparative evidence studies, key risk of missing data in van der Zee 2023 (downgrade one rating for risk of bias). Studies do not align with PICO-specified screening algorithm (i.e., screening procedures did not specify anal HPV testing), though this should not materially impact staging outcomes as anal HPV testing or cytology testing have high sensitivity limiting false negatives. Most of the total population was PLWH only (downgrade one rating for indirectness). Confidence intervals of primary effect estimates are wide, though both upper and lower bound indicate an appreciable benefit (no change in rating for imprecision). Both studies indicating same direction of effect (no change in rating for inconsistency). No evidence of publication bias (no change in rating for publication bias).

c. Serious risk of bias in key comparative evidence study and risk of lead time bias (downgrade one rating for risk of bias). Key comparative evidence study does not align with PICO-specified screening algorithm (i.e., screening procedures did not specify anal HPV testing), though this should not materially impact mortality estimates as anal HPV testing or cytology testing have high sensitivity limiting false negatives. Population is PLWH only, and results only calculated for men (downgrade one rating for indirectness). Confidence intervals of estimates are extremely wide, though both upper and lower bound indicate an appreciable benefit (no change in rating for imprecision). Only one study contributing information (no change in rating for inconsistency). No evidence of publication bias (no change in rating for publication bias).

d. Serious risk of bias in comparative evidence study, analysis underpowered (downgrade one rating for risk of bias). Key comparative evidence study does not align with PICO-specified screening algorithm (i.e., screening procedures did not specify anal HPV testing), though this should not materially impact anal cancer treatment outcomes as anal HPV testing or cytology testing have high sensitivity limiting false negatives. Included population is all adults with anal cancer (downgrade one rating for indirectness). Confidence intervals of primary effect estimate are wide, with the upper bound CI indicating an effect (downgrade one rating for imprecision). Only one study contributing information (no change in rating for inconsistency). No evidence of publication bias (no change in rating for publication bias).

e. Very high risk of bias in non-comparative evidence study, no confounders considered (downgrade two ratings for risk of bias). Study aligns closely with PICO-specified screening algorithm, though not enough information was provided to assess applicability of population and treatment (downgrade one rating for indirectness). No primary effect estimates provided, descriptive only (downgrade one rating for imprecision). Only one study contributing information (no change in rating for inconsistency). No evidence of publication bias (no change in rating for publication bias).

Abbreviations: AE = adverse events, AIN = anal intraepithelial neoplasia, aRR = adjusted rate ratio, ASC-US = Atypical Squamous Cells of Undetermined Significance, ASC-H = Atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion, CI = confidence interval, GBM = gay and bisexual men, HIV = human immunodeficiency virus, HPV = human papillomavirus, HR = hazard ratio, HRA = high-resolution anoscopy, HSIL= high-grade squamous intraepithelial lesions, OR = odds ratio, SOTR = solid organ transplant recipients, TNM = tumour, nodal, and metastatic stage, WLE = wide local excision

[72] Santorelli, C., Leo, C. A., Hodgkinson, J. D., Baldelli, F., Cantarella, F., & Cavazzoni, E. (2018). Screening for Squamous Cell Anal Cancer in HIV Positive Patients: A Five-Year Experience. Journal of Investigative Surgery, 31(5), 378-384. https://doi.org/10.1080/08941939.2017.1334845

Linked evidence of test accuracy

Predictive test accuracy of cytology testing triaged by anal HPV testing, compared with anal HPV testing and anal cytology testing alone for predicting persistent anal HSIL at 12 months

Results of Jin 2025's examination of a triaging algorithm compared to HPV (using expanded genotyping) or cytology testing alone are presented in Table 34. Findings demonstrated that a triaging protocol (aligning with the PICO-specified testing strategy) improved the specificity of HPV testing in predicting persistent 12-month anal HSIL, while maintaining high sensitivity for MSM aged 35 and older. Triaging also improved sensitivity of cytology testing alone, while decreasing specificity.

This study was assessed as having a low risk of bias and was conducted in Australia recently with two of seven PICO-specified subpopulations (approximately 85% of the total PICO population) representing excellent applicability. Though, it was not specified whether transgender women were included or excluded in the study (estimated to account for ~10% of the two subpopulations including MSM and TW). Additionally, MSM living without HIV were aged 35 and older (rather than 45 and older as in the PICO subpopulation).

Table 34 Test performance of triaging algorithm, versus cytology testing only (ASC-H+ threshold) and HPV testing only (any hrHPV at baseline, or HPV16 positive at baseline or persistent non-16 hrHPV) in predicting persistent 12-month anal HSIL (histologically confirmed), stratified by HIV status of MSM from Jin 2025

Algorithm	Screen positive		Sensitivity#		Specificity#	
	n (%)	95% CI	%	95% CI	%	95% CI
Algorithm 1*	281 (59.2)	54.6-63.6	0.96	0.89-0.99	0.49	0.44-0.54
MSM LWH age ≥35 years†	65.9	58.3-72.9	0.93	0.82-0.99	0.44	0.35-0.53
MSM not LWH age ≥35 years^†	55.3	49.5-61.0	0.98	0.88-1.00	0.52	0.46-0.58
Cytology testing only – ASC-H as cut-off	159 (33.5)	29.2-37.9	0.71	0.60-0.80	0.75	0.70-0.79
MSM LWH age ≥35 years†	31.8	24.9-39.3	0.64	0.49-0.78	0.80	0.72-0.86
MSM not LWH age ≥35 years^†	34.4	29.1-40.1	0.77	0.61-0.88	0.73	0.67-0.78
HPV testing only – Any hrHPV at baseline	369 (77.7)	73.7-81.4	1.00	0.99-1.00	0.27	0.23-0.32
MSM LWH age ≥35 years†	84.3	78.1-89.4	1.00	0.92-1.00	0.21	0.14-0.29
MSM not LWH age ≥35 years^†	73.8	68.5-78.7	1.00	0.92-1.00	0.31	0.25-37
HPV testing only – HPV16 positive at baseline or persistent non-16 hrHPV*	327 (68.8)	64.5-73.0	0.98	0.92-1.00	0.38	0.33-0.43
MSM LWH age ≥35 years†	76.3	69.3-82.4	0.96	0.85-1.00	0.31	0.23-0.39
MSM not LWH age ≥35 years^†	64.6	58.9-70.0	1.00	0.92-1.00	0.41	0.35-0.48

Source: Jin 2025, Table 3 and Table 4
Notes: hrHPV = HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 considered high risk variants.
#Compared to the gold standard of histological evaluation of HRA-guided biopsies.
*Screening positive: Participants who: (a) tested HPV16 positive at baseline regardless of cytology status or (b) tested non-16hrHPV positive at baseline and ASC-H or worse cytology at baseline or (c) tested negative to HPV16 at baseline but had evidence of persistent type-specific non-16 hrHPV at 12 months AND ASC-US or worse cytology at baseline.
†Not including transgender women, though otherwise directly aligning to the PICO subpopulation group.
^Including people aged 35-45 years, therefore not in direct alignment to the PICO subpopulation of MSM and TW living without HIV age ≥45 years.
Abbreviations: ASC-H = atypical squamous cells cannot exclude high grade squamous intraepithelial lesion, CI = confidence interval, HIV = human immunodeficiency virus, HPV = human papillomavirus, hrHPV = high-risk human papillomavirus, HSIL= high-grade squamous intraepithelial lesions, LWH = living with HIV, MSM = men who have sex with men

Cross-sectional test accuracy of anal HPV testing

A summary of the test accuracy results of anal HPV testing for identifying HSIL are presented in Table 35, summarised according to PICO-specified subpopulations and expanded (any hrHPV; 13 to 14 genotypes were most commonly tested) versus partial (HPV16, HPV18 or HPV16/18 only) genotyping. Estimates with low heterogeneity (I^2<25%) per random effects meta-analysis are highlighted in yellow. Only two studies (of 29) directly matched a PICO-specified subpopulation; others were too inclusive, primarily including younger cohorts.

Overall, sensitivity was higher, and specificity was lower when expanded genotyping was conducted:

- For PLWH (approximately 22% of the total PICO population), sensitivity for HPV16/18 genotyping was 0.51 (95% CI 0.24 – 0.78) versus 0.94 (95% CI 0.90 – 0.97) for expanded genotyping. Specificity was 0.74 (95% CI 0.60 – 0.86) versus 0.27 (95% CI 0.22 – 0.33), respectively.
- For MSM (approximately 74% of the total PICO population), sensitivity for HPV16/18 genotyping was 0.49 (95% CI 0.32 – 0.66) versus 0.93 (95% CI 0.89 – 0.97) for expanded genotyping. Specificity was 0.75 (95% CI 0.68 – 0.82) versus 0.31 (95% CI 0.25 – 0.38), respectively.

Estimates suggesting high sensitivity and moderate specificity for any hrHPV genotyping align with previous meta-analyses,[41,33] as does low-moderate sensitivity and specificity for partial genotyping. Similar test accuracy estimates for expanded genotyping were found across the four PICO-specified subpopulations for which there was evidence identified. For the PICO-specified subpopulations, results for partial genotyping differed. These generally included a small number of data sets and total sample size and had significant heterogeneity.

There was no evidence available for the following subpopulations:

- People with previous vulval SCC/HSIL (HPV associated)
- Patients being followed up after treatment for anal cancer
- Patients outside these above groups with incidental anal HSIL and patients presenting with symptoms suggestive of anal cancer
- *People with a possible history of cervical/vaginal cancer or precursor lesions (added by PASC).*

Table 35 Summary of test accuracy results for anal HPV testing, stratified by subpopulation and expanded/partial genotyping^

Population	Genotyping (partial, expanded)	Data sets*	N	Sensitivity (95% CI)	I^2	Specificity (95% CI)	I^2	Immediate HSIL Risk			
								Test Positives (95% CI) PPV	I^2	Test Negatives (95% CI) False Omission Rate	I^2
PICO-specified subpopulation											
MSM and TW living with HIV age ≥35 years	HPV16	4†	726	0.58 (0.45 – 0.72)	28%	0.72 (0.65 – 0.79)	42%	0.30 (0.20 – 0.40)	38%	0.16 (0.03 – 0.36)	91%
	HPV18	2‡	223	0.22 (0.06 – 0.48)	-	0.84 (0.74 – 0.91)	-	0.24 (0.10 – 0.40)	0%	0.18 (0.10 – 0.29)	-
	HPV16/18	4	1249	0.51 (0.24 – 0.78)	95%	0.74 (0.60 – 0.86)	95%	0.36 (0.05 – 0.76)	99%	0.13 (0.09 – 0.19)	71%
	Any hrHPV	15	5025	0.95 (0.91 – 0.98)	83%	0.24 (0.19 – 0.30)	93%	0.28 (0.20 – 0.38)	97%	0.04 (0.01 – 0.08)	75%
MSM and TW living	HPV16	2§	149	0.35 (0.15 – 0.59)	-	0.92 (0.82 – 0.97)	-	0.85 (0.30 – 1.00)	86%	0.19 (0.10 – 0.30)	-

without HIV age ≥45 years	HPV18	1¶	68	-	-	-	-	1.00 (0.54 – 1.00)	-	-	-
	HPV16/18	1	123	0.09 (0.00 – 0.41)	-	0.87 (0.79 – 0.92)	-	0.06 (0.00 – 0.30)	-	0.09 (0.05 – 0.17)	-
	Any hrHPV	4	393	0.74 (0.38 – 0.99)	87%	0.46 (0.26 – 0.66)	92%	0.24 (0.10 – 0.42)	85%	0.10 (0.05 – 0.15)	0%
Women and MSW living with HIV age ≥45 years	HPV16	1	74	0.25 (0.11 – 0.43)	-	0.71 (0.55 – 0.84)	-	0.40 (0.19 – 0.64)	-	0.44 (0.31 – 0.59)	-
	HPV18	1	74	0.29 (0.16 – 0.46)	-	0.79 (0.61 – 0.91)	-	0.63 (0.38 – 0.84)	-	0.53 (0.39 – 0.66)	-
	HPV16/18	-	-	-	-	-	-	-	-	-	-
	Any hrHPV	4	579	0.84 (0.60 – 0.99)	89%	0.45 (0.29 – 0.62)	91%	0.33 (0.20 – 0.49)	88%	0.10 (0.05 – 0.15)	25%
SOTR, commencing 10 years post-transplant	HPV16	1#	13	-	-	-	-	0.54 (0.25 – 0.81)	-	-	-
	HPV18	-		-	-	-	-	-	-	-	-
	HPV16/18	-		-	-	-	-	-	-	-	-
	Any hrHPV	2	275	0.91 (0.41 – 1.00)	88%	0.53 (0.09 – 0.95)	95%	0.33 (0.24 – 0.43)	0%	0.08 (0.00 – 0.68)	92%
Other/aggregated population											
PLWH (any)	HPV16	8**	1245	0.48 (0.36 – 0.61)	77%	0.75 (0.70 – 0.80)	44%	0.47 (0.29 – 0.66)	92%	0.28 (0.13 – 0.46)	96%
	HPV18	4††	463	0.21 (0.15 – 0.27)	0%	0.83 (0.78 – 0.88)	0%	0.42 (0.23 – 0.61)	70%	0.39 (0.20 – 0.61)	93%
	HPV16/18	4	1249	0.51 (0.24 – 0.78)	95%	0.74 (0.60 – 0.86)	95%	0.36 (0.05 – 0.76)	99%	0.13 (0.09 – 0.19)	71%
	Any hrHPV	19	5758	0.94 (0.90 – 0.97)	85%	0.27 (0.22 – 0.33)	94%	0.34 (0.25 – 0.42)	97%	0.06 (0.03 – 0.09)	75%
MSM (any)	HPV16	7‡‡	985	0.50 (0.39 – 0.62)	52%	0.82 (0.68 – 0.92)	92%	0.56 (0.30 – 0.80)	93%	0.18 (0.07 – 0.33)	93%
	HPV18	3§§	117	0.22 (0.06 – 0.48)	-	0.84 (0.74 – 0.91)	-	0.49 (0.07 – 0.92)	88%	0.18 (0.10 – 0.29)	-
	HPV16/18	7	2308	0.49 (0.32 – 0.66)	94%	0.75 (0.68 – 0.82)	91%	0.35 (0.15 – 0.57)	98%	0.15 (0.11 – 0.18)	73%
	Any hrHPV	21	6966	0.93 (0.89 – 0.97)	84%	0.31 (0.25 – 0.38)	95%	0.93 (0.89 – 0.97)	97%	0.05 (0.02 – 0.08)	78%

Source: Analysis conducted by DCAR
Notes: (a) Estimates with low heterogeneity are highlighted yellow. This is based on consideration of I^2 value (less than 25% is considered low), and other heterogeneity indicators.
^Compared to the gold standard of histological evaluation of HRA-guided biopsies.
*Some studies included multiple data sets (i.e., if testing using different assays).
†3 datasets (N=604) for false omission rate, sensitivity, specificity
‡1 dataset (N=93) for false omission rate, sensitivity, specificity
§1 datasets (N=81) for false omission rate, sensitivity, specificity
¶0 dataset for false omission rate, sensitivity, specificity
#0 datasets for false omission rate, sensitivity, specificity
**7 datasets (N=1227) for false omission rate, sensitivity, specificity
††3 datasets (N=445) for false omission rate, sensitivity, specificity
‡‡5 datasets (N=919) for false omission rate, sensitivity, specificity,
§§1 datasets (N=93) for false omission rate, sensitivity, specificity
Abbreviations: AIN = anal intraepithelial neoplasia, CI = confidence interval, HIV = human immunodeficiency virus, HRA = high-resolution anoscopy, HPV = human papillomavirus, hrHPV = human papillomavirus, HSIL= High-Grade Squamous Intraepithelial Lesion; LWH = living with HIV, MSM = men who have sex with men, NPV = negative predictive value, PLWH = people living with HIV, PPV = positive predictive value, SOTR = solid organ transplant recipients

Cross-sectional test accuracy of anal cytology testing

A summary of the test accuracy results of anal cytology testing for identifying HSIL are presented in Table 36, summarised according to PICO-specified subpopulations and threshold for HSIL identification (ASC-H+ or HSIL+). Significant heterogeneity was seen across almost all random

effects meta-analyses of test accuracy results for all populations and genotyping subgroups. Estimates with low heterogeneity are highlighted in yellow in Table 36.

In PICO-specified populations, anal cytology testing has overall low-moderate sensitivity, and high specificity, noting that no evidence was available for the following subpopulations:

- SOTR, commencing 10 years post-transplant
- Patients being followed up after treatment for anal cancer
- Patients outside these above groups with incidental anal HSIL and patients presenting with symptoms suggestive of anal cancer
- *People with a possible history of cervical/vaginal cancer or precursor lesions (added by PASC)*

In the context of the triaging algorithm based on HPV test results, the low sensitivity of cytology testing may be balanced out by the high sensitivity of the HPV test. This was observed in Jin 2025's predictive test accuracy results, however there were no studies evaluating the cross-sectional test accuracy of the triaged testing algorithm.

Sensitivity was higher, and specificity was slightly lower when ASC-H+ was used as the threshold, rather than HSIL+. ASC-US+ has been used as the threshold for HSIL identification (i.e., "abnormal") in most studies, which has routinely demonstrated a higher sensitivity and lower specificity than ASC-H+. In the Australian Modified Bethesda System, this is equivalent to pLSIL, which is not referred for HRA. Since HPV testing already offers high sensitivity, the primary aim of triaging with cytology is to enhance specificity. Using a lower cytology threshold such as ASC-US+ would undermine this goal by increasing false positives and reducing specificity, making it a less effective strategy for guiding HRA referrals. Estimates from this systematic review and meta-analysis align with use of cervical cytology (which generally use a threshold for immediate referral of ASC-H+).[73]

[73] Abulafia, O., Pezzullo, J. C., & Sherer, D. M. (2003). Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: a quantitative survey. Gynecol Oncol, 90(1), 137-144

Table 36 Summary of test accuracy results for anal cytology testing, stratified by subpopulation and threshold^

Population	Threshold	Data sets*	N	Sensitivity (95% CI)	I^2	Specificity (95% CI)	I^2	Immediate HSIL Risk			
								Test Positives (95% CI) PPV	I^2	Test Negatives (95% CI) False Omission Rate	I^2
PICO-specified subpopulation											
MSM and TW living with HIV age ≥35 years	ASC-H+	5	1231	0.40 (0.29 – 0.52)	64%	0.91 (0.84 – 0.96)	89%	0.50 (0.43 – 0.58)	6%	0.17 (0.08 – 0.28)	94%
	HSIL+	15*	3579	0.24 (0.16 – 0.32)	79%	0.96 (0.94 – 0.98)	83%	0.60 (0.50 – 0.70)	54%	0.18 (0.11 – 0.26)	96%
MSM and TW living without HIV age ≥45 years	ASC-H+	1	83	0.25 (0.09 – 0.49)	-	0.95 (0.87 – 0.99)	-	0.62 (0.24 – 0.91)	-	0.20 (0.12 – 0.31)	-
	HSIL+	3†	465	0.00 (0.00 – 0.10)	0%	0.99 (0.96 – 1.00)	73%	0.25 (0.00 – 0.98)	67%	0.08 (0.00 – 0.25)	96%
Women and MSW living with HIV age ≥45 years	ASC-H+	2	339	0.31 (0.19 – 0.43)	38%	0.96 (0.90 – 0.99)	55%	0.78 (0.63 – 0.90)	0%	0.26 (0.17 – 0.36)	65%
	HSIL+	0	-	-	-	-	-	-	-	-	-
People with previous vulval SCC/HSIL (HPV associated)	ASC-H+	0	-	-	-	-	-	-	-	-	-
	HSIL+	2‡	516	0.11 (0.00 – 0.54)	94%	0.99 (0.96 – 1.00)	82%	0.86 (0.71 – 0.95)	-	0.18 (0.07 – 0.33)	93%
Other/aggregated population											
PLWH (any)	ASC-H+	10	2080	0.32 (0.22 – 0.42)	82%	0.94 (0.90 – 0.97)	84%	0.66 (0.54 – 0.77)	66%	0.23 (0.14 – 0.34)	96%
	HSIL+	20§	4078	0.21 (0.15 – 0.28)	78%	0.97 (0.95 – 0.98)	79%	0.63 (0.53 – 0.73)	53%	0.20 (0.13 – 0.27)	96%
MSM (any)	ASC-H+	8	2796	0.36 (0.19 – 0.55)	95%	0.92 (0.84 – 0.98)	97%	0.55 (0.49 – 0.62)	26%	0.17 (0.11 – 0.22)	91%
	HSIL+	21¶	5396	0.21 (0.14 – 0.29)	85%	0.97 (0.95 – 0.99)	90%	0.63 (0.54 – 0.71)	60%	0.17 (0.12 – 0.23)	96%

Source: Analysis conducted by DCAR
Notes: (a) Estimates with low heterogeneity are highlighted yellow. This is based on consideration of I^2 value (less than 25% is considered low), and other heterogeneity indicators.
^Compared to the gold standard of histological evaluation of HRA-guided biopsies.
*14 datasets (N=3298) for PPV
†2 datasets (N=214) for PPV, sensitivity
‡1 dataset (N=323) for PPV
§19 datasets (N=3962) for PPV
¶19 datasets (N=5029) for PPV
Abbreviations: AIN = anal intraepithelial neoplasia, ASC-H = Atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion, CI = confidence interval, HIV = human immunodeficiency virus, HPV = human papillomavirus, HRA = high-resolution anoscopy, HSIL= high-grade squamous intraepithelial lesions, LWH = living with HIV, MSM = men who have sex with men, NPV = negative predictive value, PLWH = people living with HIV, PPV = positive predictive value; PICO = Population, Intervention, Comparator, Outcome, TW = transgender women

Cross-sectional test accuracy of diagnostic HRA

Histological evaluation of HRA-guided biopsies is considered the gold standard for diagnosis of HSIL and is used as the reference standard used for both anal HPV testing and anal cytology testing. However, HRA is an imperfect procedure, with a considerable learning curve and inter-operator inconsistency. Accuracy also varies based on biopsy protocols, diagnostic thresholds, clinician expertise, patient tolerability of the procedure, and additional anatomical challenges or variability in lesion presentation.

A summary of the test accuracy results of diagnostic accuracy of diagnostic HRA with biopsy for identifying HSIL are presented in Table 37. The reference standard used was standard biopsy

without HRA guide (i.e., not based on HRA-guided assessment of potential lesions); only studies in which biopsies were completed for all participants were included.

Three studies met the inclusion criteria, however, meta-analysis was precluded due to variability in study populations and biopsy thresholds during diagnostic HRA (i.e., while some studies relied solely on the presence of acetowhite lesions, one study incorporated additional parameters). There were significant limitations in the body of evidence, and results should be interpreted with caution.

For two studies using acetowhite lesions as the biopsy threshold (one in PLWH and one in renal transplant recipients), sensitivity was calculated as between 0.90–100 and specificity was 0.19–0.51. These results may suggest a trend towards high sensitivity and low to moderate specificity of diagnostic HRA using acetowhite lesions, however these were two different populations and the sample sizes were very small. For the study using macroscopic lesions (rather than acetowhite lesions) such as presence of mucosal punctuations, warty raises, and mosaic pattern as the biopsy threshold, the sensitivity and specificity were reported as 0.41 and 0.63, respectively.

There was no evidence for the following populations:

- MSM and TW living without HIV age ≥45 years
- people with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis
- patients being followed up after treatment for anal cancer (i.e. chemoradiotherapy/surgery)
- 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
- *People with a possible history of cervical/vaginal cancer or precursor lesions (added by PASC)*

Table 37 Test accuracy results of diagnostic HRA in all populations (k=3)

Study ID	N	Population	Positive	HSIL (true positives)	No HSIL (false positive)	PPV	False discovery rate	Negative	No HSIL (true negatives)	HSIL (false negatives)	NPV	False omission rate	Sensitivity	Specificity
Cuen 2013‡	107	PLWH	-#	-	-	-	-	-	-	-	-	-	0.41	0.63
Gimenez 2011	128	PLWH	108*	45	63	0.42	0.58	20	15	5	0.75	0.25	0.90	0.19
Tramujas da Costa e Silva 2008	42	Renal graft recipients	21†	1	20	0.05&	0.95	21	21	0	1.00	0.00	1.00	0.51

Source: Study reports
Notes:
#Positivity was determined as presence of macroscopic lesions, mucosal punctuations, warty raises, and mosaic pattern. Biopsies were systematically made on both abnormal and normal areas. Findings were unexpected, given that theoretically, a lower threshold should increase the number of biopsies performed, thereby enhancing the detection of true HSIL cases and improving sensitivity. Conversely, their reported higher specificity is also counterintuitive, as a lower threshold typically results in more false positives, which would reduce specificity.
*Positivity was determined as presence of acetowhite lesions (AWL). When no AWL was observed, biopsies were performed in a standardized location (just above the pectinate line at the 7 o'clock position, considering 12 o'clock the anterior commissure).
†Positivity was determined as presence of acetowhite lesions. In cases where no lesions were present, a biopsy was taken from a standardized location within the transformation zone epithelium—specifically at the 7 o'clock position, approximately 0.5 cm above the dentate line.
‡Abstract only, no full-text available. Not enough information to determine data points other than sensitivity and specificity.
&The authors reported moderate PPV (0.476), but this included identification of condyloma acuminatum and LSIL. In identifying HSIL alone, PPV was far lower (0.05).

Abbreviations: AWL = acetowhite lesion; HRA = High-Resolution Anoscopy; HSIL= High-Grade Squamous Intraepithelial Lesion; NPV = negative predictive value; PLWH = people living with HIV; PPV = positive predictive value.

Linked evidence for change in management

There was no evidence evaluating whether information arising from the PICO-specified testing strategy resulted in change in management (earlier intervention) for treatment of HSIL.

Change in patient clinical management (Clinician referral to HRA-guided anal HSIL ablation based on management decisions informed by anal HPV testing, cytology testing and diagnostic HRA)

One study with PLWH[74] (conference abstract only available, assessed as having a critical risk of bias) reported on an anal dysplasia screening program incorporating cytology, HRA with biopsy, and treatment of abnormal findings. Treatment included topical agents and infrared coagulation, with surgical referral when needed. The reported referral rate for treatment following abnormal results was 38% (495/1309), though it was unclear whether this referred specifically to biopsy-confirmed HSIL or included cytologic abnormalities. Given the critical risk of bias of this study outside of an Australian context, the reported referral rate should be interpreted with caution.

While ablation is the specified therapeutic intervention in the PICO, other treatment modalities such as surgical excision (raised by PASC) may also be relevant. Treatment selection for anal HSIL depends on lesion characteristics, anatomical location, and patient factors. There was no identified evidence that earlier identification of HSIL led to change in treatment decisions related to ablative therapy compared to excision or topical treatment. However, earlier detection inherently changes the clinical presentation which influences both the feasibility and appropriateness of treatment options. A summary of treatment options for biopsy-confirmed anal HSIL, their indications and advantages/limitations are presented in Table 38 below.

Table 38 Comparative summary of treatment options for biopsy-confirmed anal HSIL[83]

Treatment Type	Indications	Advantages	Limitations / Considerations
Ablative Treatments	• Suitable for both intra-anal and peri-anal HSIL	• Robust evidence of reduced progression to anal cancer (ANCHOR trial)[2] • Office-based, targeted treatment	• High recurrence rates/metachronous lesions • Requires HRA guidance • Chronic disease model with repeated treatments given likelihood of recurrence
Surgical excision*	• Historically used due to lack of other available treatments	-	• High risk AEs (anal stenosis, faecal incontinence and damaged sexual function)
Topical Treatments	• Recommended for peri-anal HSIL (due to issues around self-application and common AEs) • Patients unable to undergo ablation	-	-
• HRA-guided trichloroacetic acid	• ≤2 small perianal lesions under HRA guidance.	• Minimal AEs	• Requires HRA guidance • Less effective for bulky lesions • Multiple applications often needed

[74] McDonald, J. E., & Lea, M. Z. (2015). Observational data base of anal dysplasia in persons living with HIV/AIDS [PLWH] in an HMO. Sexual Health, 12(1), 85. https://doi.org/10.1071/SHv12n1abs

• 5-fluorouracil, cidofovir, and imiquimod	• Generally used to "downstage" rather than eradicate extensive disease.	• No HRA-guidance required • Self-application	• Compliance issues associated with self-application (due to AEs)

Notes: *Not recommended in Anal Cancer Screening Guidelines for PLHIV by PLWH
Abbreviations: AE = adverse events, HRA = high-resolution anoscopy, HSIL= high-grade squamous intraepithelial lesions

Although surgical excision under anaesthesia was used in up to 2.3% of cases in the ANCHOR trial and is listed as a treatment option in the PICO by PASC, its role in managing anal HSIL has significantly diminished. Historically, wide local excision (WLE) was more commonly employed due to limited alternatives and the belief that full-thickness excision could prevent recurrence.[83] However, recent evidence and expert consensus have led to a shift away from this approach.[2, 83] A systematic review has highlighted that surgical excision has largely been superseded by less invasive modalities due to its association with high complication rates, including anal stenosis and impaired sexual function. Reflecting this, the ASHM guidelines no longer recommend surgical excision for HSIL (though evidence suggests the WLE is still a preferred treatment option for anal cancer, as opposed to other therapeutic alternatives). Despite this, surgical excision may still be used in practice.

Change in patient clinical management (Change in treatment decisions)

Walker 2024[31] was the only study identified which evaluated differences in anal cancer treatment decisions as a result of testing (cytology and HRA-based screening). Screening was found to significantly increase the likelihood of undergoing WLE compared to not screening (in univariable analysis) (12.5% vs 3.2%; OR 4.38; 95% CI, 1.20–16.04; p = 0.03). WLE is far less invasive and with lower morbidity than chemoradiotherapy or resection treatments.

This study was a retrospective chart review with significant limitations and risk of bias, chiefly being underpowered (only 26 patients were diagnosed with anal cancer via screening). Participation in screening was defined retrospectively (as >1 screening visit), which introduces the risk of selection bias or misclassification.

Change in follow-up frequency

There was no evidence evaluating whether information available because of the PICO-specified testing strategy resulted in change in follow-up frequency.

Commencement of treatment (Patient uptake of HRA-guided anal HSIL ablation led from management decisions informed by anal HPV testing, cytology testing and diagnostic HRA)

Patient uptake of HRA-guided anal HSIL ablation as reported in two studies: one with PLWH[75] and MSM, and one with "patients eligible for HSIL screening"[76]. Both studies reported that 58% (81/140; 684/1179) of patients with biopsy-confirmed HSIL returned for ablative, topical or surgical treatment. While both studies were conducted in real-world testing and treatment programs for anal dysplasia and were assessed as having a low risk of bias, they were conducted in the USA with patient groups that do not represent all PICO-specified subpopulations.

Patient uptake/adherence of the PICO-specified triaged testing strategy (anal HPV testing, cytology testing and diagnostic HRA)

[75] Silvera, R., Martinson, T., Gaisa, M. M., Liu, Y., Deshmukh, A. A., & Sigel, K. (2021). The other side of screening: predictors of treatment and follow-up for anal precancers in a large health system. AIDS, 35(13), 2157-2162. https://doi.org/10.1097/qad.0000000000002948

[76] Krempasky, C., DeWitt, W., Braun, J., & Guadron, R. (2020). The "hRA cascade": Assessing engagement at steps of preventive care for anal cancer at an urban community health center. Journal of Lower Genital Tract Disease, 24, S1. https://doi.org/10.1097/LGT.0000000000000537

Uptake of HPV testing for anal cancer screening purposes was reported in 2 studies in the USA with low risk of bias (1 trial; the Prevent Anal Cancer Self-Swab Study).[77,78] 81.7% of MSM and transgender individuals returned HPV swabs, with higher uptake when offered mailed self-collection kits compared to clinic-based testing (89.2% vs. 74.2%, p=.003); this difference was even further pronounced for PLWH (89.5% vs. 51.9%, p<.001). However, results may be influenced by reduced clinic attendance during the COVID-19 pandemic, particularly among immunocompromised individuals. Additionally, this was in a trial context: uptake in real-world practice is likely to be lower considering trial participants are highly motivated.

Two studies reported "retention" to cytology- and/or HRA-based screening, defined as receipt of at least 2 cytology tests (surveillance) or HRAs.[79,80] Rates of retention were reported as 52% for MSM LWH (aged 35 years and older; assessed as having serious risk of bias)[79] and 85% for PLWH (assessed as having low risk of bias).[80] An additional study reported "compliance" with a screening program as 63%, though the definition was not specified.[81] All three studies were conducted in the USA primarily with PLWH. Both individual and health system specific barriers may limit applicability of results to the Australian context and PICO.

Twelve studies reported uptake of HRA, with referral criteria varying widely, which precluded meta-analysis. Completion rates ranged from 0%–100%, with naïve comparison suggesting no consistent trend across subpopulations. An Australian study using the PICO-relevant referral threshold (ASC-H+) reported high uptake (95.1%) among MSM LWH.[82] When using ASC-US+, uptake dropped to 68.2%. This may suggest that higher-risk cytological results, as defined by the PICO criteria, may be associated with increased HRA uptake. However, due to the critical risk of bias in this study, results should be interpreted with caution.

Overall, results suggest that referral, uptake and adherence to any testing or treatment protocol in the anal cancer context is not 100%, though exact uptake rates for the PICO-specified populations in Australia are unknown.

Linked evidence of health outcomes

As this is a co-dependent application, evidence for the effectiveness of the therapeutic intervention arising from change in management decisions linked to the testing strategy is detailed in the therapeutic intervention section. Overall, the evidence suggests that HRA-guided ablation of anal HSIL lesions leads to improved health outcomes (specifically, reduced progression to anal cancer) in PLWH compared with no treatment. Key therapeutic evidence (ANCHOR trial) is highly applicable to the PICO, as patients were identified via anal cancer screening using physical examination and HRA, suggesting comparable disease stage and clinical context to the proposed use in practice. However, this evidence is currently limited to two of the eight PICO-specified subpopulations.

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[77] Nitkowski, J., Ridolfi, T. J., Lundeen, S. J., Giuliano, A. R., Chiao, E. Y., Fernandez, M. E., Schick, V., Smith, J. S., Brzezinski, B., & Nyitray, A. G. (2024). The influence of home versus clinic anal human papillomavirus sampling on high-resolution anoscopy uptake in the Prevent Anal Cancer Self-Swab Study. Sexual Health, 21(3). https://doi.org/10.1071/SH23210

[78] Nyitray, A. G., Nitkowski, J., McAuliffe, T. L., Brzezinski, B., Swartz, M. D., Fernandez, M. E., Deshmukh, A. A., Ridolfi, T. J., Lundeen, S. J., Cockerham, L., Wenten, D., Petroll, A., Hilgeman, B., Smith, J. S., Chiao, E. Y., Giuliano, A. R., Schick, V., & The Prevent Anal Cancer Self-Swab Study, T. (2023). Home-based self-sampling vs clinician sampling for anal precancer screening: The Prevent Anal Cancer Self-Swab Study. International Journal of Cancer, 153(4), 843-853. https://doi.org/https://doi.org/10.1002/ijc.34553

[79] Achhra, A. C., Chan, E., Applebaum, S., Guerrero, M., Hao, R., Pantel, H., Virata, M., Fikrig, M., & Barakat, L. (2024). Five-year evaluation of Anal Cancer Screening Program in Men Who Have Sex With Men with HIV at Two Academic Center Clinics [Article in Press]. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. https://doi.org/10.1093/cid/ciae541

[80] Cardenas, B., Geba, M., Williams, B., Hoang, S., Quass-Ferdinand, L., Newberry, Y., Woodberry, L., Dillingham, R., & Thomas, T. (2022). EVALUATING THE CASCADE OF CARE FOR ANAL CANCER SCREENING WITHIN A RYAN WHITE HIV/AIDS PROGRAM CLINIC [Conference Abstract]. Sexual Health, 19(2), xvi. https://doi.org/10.1071/SHv19n2abs

[81] Alrefai, S., & Levine, R. A. (2013). 1. Patient compliance with screening and treatment protocols for anal dysplasia in a high-risk population. Sexual Health, 10(6), 570-570. https://doi.org/10.1071/SHv10n6ab1

[82] Botes, L. P., Pett, S., Carr, A., Marriott, D., Cooper, D. A., Matthews, G., Carbone, S., Kumaradevan, N., McHugh, L., & Hillman, R. J. (2013). Anal cytological abnormalities are poor predictors of high-grade intraepithelial neoplasia amongst HIV-positive men who have sex with men. Sexual Health, 10(1), 9-17. https://doi.org/10.1071/SH11135

There was no linked evidence for whether the PICO-specified testing strategy leads to a change in clinical or patient management decisions resulting in earlier intervention or different treatment decisions for HSIL. Earlier intervention for HSIL, enabled by timely identification through the testing strategy, is biologically plausible to be more effective than later identification, as lesions are less progressed and treatment is more likely to be effective. Smaller lesions are also candidates for other types of therapy (see Table 38).

Ablation is the preferred treatment strategy for most HSIL. This is evidenced by most (88.4%) of the ANCHOR trial receiving ablative treatment, by the ASHM guidelines for PLWH supporting ablative or topical therapy and by the PICO.[2] In terms of efficacy of topical treatments compared to electrocautery, the ASHM guidelines[23] report that topical agents typically have comparable efficacy to ablative therapies for intra-anal and peri-anal disease clearance primarily based on a 2021 systematic review.[83] However, results from Richel 2013 (the only comparative RCT for treatment modalities) reported better outcomes for the electrocautery group, versus fluorouracil or imiquimod. Excision was not examined in this study.

Similarly, earlier identification of anal cancer via the testing strategy allows for earlier treatment intervention, which is associated with better outcomes. For example, change in management evidence showed that earlier identification of anal cancer via cytology-based or HRA-based anal cancer screening led to a higher likelihood of use of WLE treatment alone, rather than more invasive treatments with higher morbidity (i.e., chemoradiotherapy or abdominoperineal resection). When tumours originate in the perianal skin, early detection reduces the likelihood of anal canal involvement, increasing the chance that the tumour remains confined to the perianal region at diagnosis, and perianal tumours are candidates for WLE.

False positive and false negative results

While HRA is considered the gold standard for identifying histological HSIL, there is currently limited evidence supporting its diagnostic accuracy. Consequently, false positive and false negative results remain a possibility, particularly due to variability in biopsy protocols. False positive results may lead to unnecessary ablative treatment, exposing patients to avoidable risks such as pain, bleeding, and other procedural complications.

Conversely, false negative results may result in HSIL lesions remaining untreated, with the potential to progress to anal cancer. In such cases, detection may only occur once symptoms develop, at which point existing clinical pathways would typically intervene. While this is no worse than current standard practice, there is a plausible risk that a false negative result could provide false reassurance, potentially delaying future help-seeking. Although there is no direct evidence of this effect in the context of anal cancer screening, the concern is consistent with broader behavioural responses observed in other cancer contexts.[84]

Evidence for the therapeutic intervention

The key evidence study was from the ANCHOR trial, a high-quality phase 3 RCT which assessed HSIL treatment versus active monitoring in PLWH aged 35 years or older (approximately 22% of the total PICO population). Importantly, treatments in the trial included those not specified in the PICO (topical fluorouracil or imiquimod, or excision under anaesthesia), with no presentation of outcomes by treatment type in the report. Though, the number of patients not receiving ablative treatment is likely to be small (estimated at 5.0% to 7.4% for first line treatment).

At 48 months, the cumulative cancer incidence was 0.9% in the treatment group and 1.8% in the active monitoring group. There was a 57% lower risk of cancer progression in the treatment group (95% CI, 6–80; p = 0.03). In the treatment group, the cancer progression rate was 173

[83] Brogden DRL, Walsh U, Pellino G, Kontovounisios C, Tekkis P, Mills SC. Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review. Int J Colorectal Dis. 2021 Feb;36(2):213-226.

[84] Renzi C, Whitaker KL, Wardle J. Over-reassurance and undersupport after a 'false alarm': a systematic review of the impact on subsequent cancer symptom attribution and help seeking. BMJ Open. 2015 Feb 4;5(2):e007002.

cases per 100,000 person-years (95% CI, 90–332), compared to 402 cases per 100,000 person-years (95% CI, 262–616) in the active monitoring group.

All studies included different populations, used different ablative protocols, had different follow-up procedures and timings and presented different outcome measures; therefore, meta-analysis was not possible, and results are primarily presented narratively in a Summary of Findings table in Table 40.

There was no identified evidence for treatment effectiveness for four PICO-specified population groups:

- People with previous vulval SCC/HSIL (HPV associated), testing commencing within 1 year of diagnosis.
- SOTR, commencing 10 years post-transplant.
- Patients being followed up after treatment for anal cancer.
- Patients outside these above groups with incidental anal HSIL.

Progression to anal cancer from key studies is summarised in Table 39. The evidence suggests that certain risk factors may predict effectiveness of ablative treatment (HPV strains, lesion size, the lowest recorded CD4 count) which may logically extend to risk factors associated with different populations; therefore, evidence for the therapeutic intervention in these specific populations is needed.

Additionally, all comparative evidence studies had a median follow-up of 12 to 28 months, which may not be adequate to assess progression of HSIL to anal cancer.

Table 39 Progression to anal cancer results from key comparative evidence for the therapeutic intervention (k=3)

Study	Population	Ablative technique	Progression to anal cancer		Follow-up (median)
			Treatment group	Comparator group	
Key trials					
Palefsky 2022	PLWH - 77.3% MSM	HSIL treatment*	9/2227	21/2219	25.8 months
Goldstone 2019	PLWH	HSIL ablation with IRC	0% (0/60)	0% (0/60)	12 months
Weis 2012	PLWH	HSIL ablation with ECA	0% (0/98)	5% (2/42)	28 months

Source: Study reports
Notes: *Including: office-based ablative procedures, ablation or excision under anaesthesia, or the administration of topical fluorouracil or imiquimod. Selected by clinicians in alignment with clinician and participant preference from a list of options defined in the trial protocol using method-specific algorithms.
^All anal cancer cases in PLWH.
Abbreviations: ECA = electrocautery ablation; HSIL= high-grade squamous intraepithelial lesions, IRC = infrared coagulation, LWH = living with HIV, MSM = men who have sex with men, PLWH = people living with HIV

Table 40 Summary of findings table – key therapeutic intervention evidence (k=32)

Outcomes	Participants and studies	Results, interpretation and key uncertainties	Certainty of the evidence (GRADE) Evidence statement
Progression to anal cancer	3 comparative studies (key trials; N=4690) 9 single arm studies (8 data sets; N=1640)	The key evidence RCT (ANCHOR trial) found that patients receiving treatment had a 57% (95% CI 6–80; p=0.03) lower rate of cancer progression compared to those receiving active monitoring (9/2227 versus 21/2219, respectively). This trial had a low risk of bias, however some non-PICO specified treatment methods were used (though most patients, between 88.4% and 92.8% in the first line) were estimated to have received relevant ablative therapies. Included participants were PLWH aged 35 and older, matching the two of the eight PICO subpopulations (approximately 22% of total PICO population). The study	⊕⊕⊙⊙ **Low**[a] HRA-guided ablative treatment of HSILs compared to no treatment may reduce progression to anal cancer.

		authors identified that results were likely not replicable for clinicians with less training or support. In a smaller RCT (Goldstone et al., 2019)[49], no patients in either treatment or active monitoring arms had progression to cancer, however observation was only completed for 12 months in a small sample, so this was likely not sufficient to identify progression. Additionally, only participants with small lesions were enrolled which may be inherently less likely to progress to cancer. In a non-randomised comparative study (Weis et al., 2012)[52] two patients in the delayed or non-treated group (n=42) developed anal cancer (5%; 95% CI 1–16%), compared to none in the treatment group (p < 0.0001). Though, follow up for the treatment group was significantly shorter, so it is possible that treated patients' disease status could more closely match untreated patients if followed for a similar duration. Similar to comparative studies, single arm and cohort studies (n=9) reported nil or very low rates (0–0.7%) of progression to anal cancer following ablative treatment of HSILs.	
HSIL recurrence/ treatment response and HSIL-free survival	3 comparative studies (key trials; N=392) 17 single arm studies (N=2190)*	In comparative evidence (n=3)[49,50,52], all treatment response/recurrence outcomes favoured the ablative intervention over no treatment (n=2) or imiquimod/fluorouracil (n=1). Goldstone 2019 reported complete clearance of index lesions was significantly more likely for treatment versus active monitoring (62% vs 30%; RD 32%, 95% CI 13–48%; p<.001). However, sample size was small, and only small lesions were enrolled (which may be inherently more likely to resolve with treatment or regress without treatment). Additionally, at baseline the comparator group had more HSILs than the intervention group which may have led to overestimations of the absolute difference in HSILs (however, results were still significant in a multivariable model). In Richel 2013, 4 weeks after treatment completion, treatment response favoured electrocautery and was significantly better than fluorouracil and non-significantly better than imiquimod. However, there was no significant difference at final timepoint (72 weeks). In Weis 2012, patients treated with ablation using IRC were significantly less likely to have high-grade AIN at follow-up compared to untreated patients. Untreated patients had a longer follow-up period than those receiving treatment, though adjusting for time between initial evaluation and follow-up evaluation showed minimal impact on results. Total cure rates reported in single arm studies (n=17) supported key trial results, though with wide variations (9–100%). Variation is likely due to varied study procedures (including follow-up intervals and biopsy protocols – i.e., all previous lesions areas versus only those still visible). There was generally moderate risk of bias in cohort studies, primarily arising from potentially unaddressed confounders. Goldstone 2019 found significantly more incident metachronous lesions in the treatment arm after 12 months (25/53, 47%) versus the active monitoring arm (12/57, 21%; p=.004). This could be a result of treatment arm biopsies being performed at any point lesions were identified, versus only at 12 months in the active monitoring arm (therefore metachronous lesions may have regressed before biopsy). However, high rates of metachronous lesions after initial ablative treatment were also reported in single arm/cohort studies (n=9; 7.3–82%). This may be caused by a host or viral response resulting in the development of additional metachronous lesions.	⊕⊙⊙⊙ **Very Low**[b] The evidence is very uncertain about the effect of HRA-guided ablative treatment of HSILs compared to no treatment on HSIL recurrence and HSIL-free survival.

Notes:

a. Low risk of bias in key trial (Palefsky 2022), though possible risks of bias for this outcome in other key evidence (no change in rating for risk of bias). Key evidence only included PLWH. Further evidence required for other PICO-specified subpopulations given risk factors may impact efficacy of treatment in different groups. Palefsky 2022 also included non-ablative interventions (downgrade one rating for indirectness). CI in key trial wide, lower bound approaching no appreciable difference (downgrade one rating for imprecision). All studies indicating same direction of effect (no change in rating for inconsistency). No evidence of publication bias (no change in rating for publication bias).

b. Moderate to high risk of bias in key comparative evidence studies (downgrade one rating for risk of bias). Key evidence only included PLWH. Further evidence required for other PICO-specified subpopulations given risk factors may impact efficacy of treatment in

different groups (downgrade one rating for indirectness). CIs of primary effect estimate in Goldstone 2019 are wide, and lower bound would not indicate an appreciable benefit. Most studies single arm studies support cure, though effect estimates are highly varied (downgrade one rating for imprecision). Most studies indicate same direction of effect (no change in rating for inconsistency). No evidence of publication bias (no change in rating for publication bias).

*An ongoing single arm Australian pilot study (ACTRN12624000154505; the PANTHER study) is examining the use of electrocautery for anal HSIL treatment for PLWH (aged 18 years or older) (date of last data collection August 2026). A primary outcome is partial/complete clearance of anal HSIL following treatment.

Abbreviations: AE = adverse events, CI = confidence interval, HPV = human papillomavirus, HSIL= high-grade squamous intraepithelial lesions, IRC = infrared coagulation, RCT = randomised controlled trial, RD = risk difference, SAE = serious adverse events, SCC = squamous cell carcinoma, SOTR = solid organ transplant recipient

Clinical claim

Direct evidence

The direct evidence for the specific co-dependent technologies of the PICO is limited; in particular, there was no direct comparative evidence for anal HPV testing. However, findings suggested that, for PLWH, anal cancer screening using other testing methods (including anal cytology testing and diagnostic HRA) to identify HSIL contributes to improved clinical outcomes (reduced anal cancer-related and all-cause mortality). However, the proportion of improved mortality outcomes which are due to (1) the earlier detection of anal cancer versus and (2) the treatment of HSIL before they progress to cancer remains uncertain. In addition, anal cancer screening improves clinical staging of anal cancer at diagnosis, offering morbidity benefits of earlier diagnosis and intervention. The evidence also suggested that the introduction of anal cancer screening leads to a reduction in anal cancer incidence over time. However, as is typical with the implementation of cancer screening, an initial rise in incidence was observed due to the detection of previously undiagnosed cases during the early rounds of screening.

Importantly, there is limited evidence for PICO subpopulations other than PLWH. Given that PLWH have some of the highest anal cancer incidence rates, comparative effectiveness of the intervention may be less favourable in lower risk groups.

Linked evidence

The evidence suggested that use of anal HPV testing, cytology testing and diagnostic HRA compared to no testing likely results in superior effectiveness compared with no testing. However, further evidence for the specific clinical triaging algorithm in all PICO-specified populations is needed, including longitudinal evidence for (1) the efficacy of proposed screening intervals, and (2) health outcomes associated with long-term participation in the testing strategy.

The evidence suggested that anal HPV testing, cytology testing and diagnostic HRA has an inferior safety profile (i.e., physical and psychosocial adverse events associated with testing) compared with no testing. However, for all PICO-subpopulations, the use of anal HPV testing, cytology testing and diagnostic HRA is considered comparatively safe relative to the risk of developing anal cancer and consequent morbidity associated with diagnosis. There is, however, a paucity of evidence on the psychosocial impacts of the proposed investigative intervention for each PICO population; given the potential for stigma and related burden in each subpopulation, this will also have implications for uptake of the proposed tests. Effectiveness also hinges on the accuracy of diagnostic HRA in identifying HSILs for ablation. While considered the gold standard, HRA is an imperfect procedure, with a considerable learning curve and inter-operator inconsistency. Diagnostic accuracy likely differs based on protocol for biopsy; however, there was not enough evidence to evaluate the impacts of this.

The evidence suggests that both clinician referral to ablation and patient uptake through the proposed testing and treatment strategy will not be 100%. Ablation may also not be suitable for all HSIL cases (e.g., topical treatments may be preferred for smaller, perianal lesions). Imperfect referral and uptake rates will likely be a result of multiple factors, including individual patient factors and clinical judgement, patient preference, and individual and system-level barriers (e.g., stigmatisation). However, there was not enough evidence to draw conclusions about these outcomes relevant to the PICO.

There was not enough evidence for the rate of false positive and false negative results of the triaged testing strategy, value of knowing or AEs associated with knowledge of test results, or overdiagnosis, to evaluate the risks comparative to downstream impacts of potential anal cancer diagnoses.

Therapeutic evidence

The evidence suggests that use of HRA-guided anal HSIL ablation for removal of HSIL lesions results in superior effectiveness for PLWH compared with no treatment.

The evidence suggests that HRA-guided anal HSIL ablation has an inferior safety profile compared with no treatment/active monitoring for PLWH (including increased pain, bleeding, and potential for metachronous HSILs requiring additional treatment). However, considering the progression of HSIL to anal cancer without treatment, for all PICO-subpopulations the use of HRA-guided anal HSIL ablation is considered comparatively safe relative to the risk of developing anal cancer and consequent morbidity associated with diagnosis.

There is limited evidence for PICO-specified subpopulations other than PLWH. Given PLWH have some of the highest anal cancer incidence rates,[7] the balance of risks and benefits associated with treatment may differ in lower-risk populations, potentially making the safety and effectiveness profile less favourable in these subpopulations.

13. Economic evaluation

Based on the clinical claim of superior effectiveness a cost utility analysis (CUA - cost per quality-adjusted life years [QALY]) gained was conducted. Table 41 provides a brief overview of the model parameters.

Table 41 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	The population was based on the PICO population, as follows: 1. men who have sex with men (MSM) and/or people who identify as transgender women (TW) who are positive for human immunodeficiency virus (HIV). 2. MSM and/or who identify as TW who are HIV negative. 3. women who have sex with women who are HIV positive. 4. men who have sex with women (MSW) who are HIV positive. 5. women with previous vulval HPV-associated squamous cell carcinoma (SCC) and/or HSIL. 6. solid organ transplant recipients (SOTR). 7. people being followed up after treatment for anal cancer. 8. people with incidental HSIL. 9. people with history of cervical/vaginal cancer or precursor lesions.
Prior testing	NA
Comparator	No testing (partial genotyping with HPV 16/18 only as supplementary analysis)
Type(s) of analysis	Nine models were created to cover all population groups individually. CUA
Outcomes	QALYs gained
Time horizon	Long-term: lifetime

Component	Description
Computational method	Monte Carlo Simulation (100,000 iterations) Markov Model
Generation of the base case	Modelled
Health states	No or undetected cancer Cancer (local) Cancer (regional) Cancer (distal) Cancer remission (cancer-free post-treatment) (local) Cancer remission (cancer-free post-treatment) (regional) Cancer remission (cancer-free post-treatment) (distal) Death The treatment arm had two additional health states to deal with the testing procedures: Test positive (intervention arm only) Post ablation
Cycle length	6 months
Transition probabilities	All transition probabilities were from the clinical evidence (Section 2), budget impact analysis, published literature and assumptions: • proportion HPV + that are MSM and TW living with HIV • proportion HPV + that are MSM and TW living without HIV • proportion HPV + that are Women living with HIV • proportion HPV + that are MSW living with HIV • proportion HPV + that are People with previous vulval SCC/HSIL (HPV associated) • proportion HPV + that are SOTR • proportion HPV + that are people being followed up after treatment for anal cancer (i.e. chemoradiotherapy/surgery) • proportion HPV + that are people with incidental HSIL (e.g. lesions found at haemorrhoidectomy, colonoscopy or during diagnosis of other anal conditions) • proportion HPV + that are people with a possible history of cervical/vaginal cancer or precursor lesions • Proportion of patients referred for HRA • Proportion of patients referred to HRA-guided anal HSIL ablation • Proportion of patients developing anal cancer (false negatives) • Proportion of untested developing anal cancer • Proportion metastatic
Discount rate	5% for both costs and QALYs
Software	Excel and TreeAge Pro

Abbreviations: PICO = Population, Intervention, Comparator, Outcome; MSM = men who have sex with men; TW = transgender women; HIV = human immunodeficiency virus; HPV = human papilloma virus; SSC = squamous cell carcinoma; HSIL = high grade intraepithelial squamous cell carcinoma, SOTR = solid organ transplant recipients; QALY = quality-adjusted life year

There was considerable uncertainty in the transition probabilities used in the model as they were gathered from multiple studies, often with a high risk of bias. However, the published literature and data supporting all populations is limited.

Table 42 Transition probabilities used in the nine models

Parameter	Value	Source
proportion MSM and TW living with HIV - HPV +	0.843	(Jin et al., 2025)
proportion MSM and TW living without HIV - HPV +	0.738	(Jin et al., 2025)
proportion Women living with HIV - HPV +	0.695	(Tadese 2025)
proportion MSW living with HIV - HPV +	0.548	(Tadese 2025)
proportion that are People with previous vulval SCC/HSIL (HPV associated) - HPV +	0.263	(Proctor 2019)
proportion organ transplant recipients - HPV +	0.094	(Rosales et al., 2018)
proportion People being followed-up after treatment for anal cancer (i.e. chemoradiotherapy/surgery) - HPV +	0.74	(De Vuyst et al., 2009)
proportion of People with incidental HSIL (e.g. lesions found at haemorrhoidectomy, colonoscopy or during diagnosis of other anal conditions) - HPV +	0.91	(De Vuyst et al., 2009)
Proportion of people with a possible history of cervical/vaginal cancer or precursor lesions	0.173	(Hillman et al., 2015)
Proportion of patients referred for HRA guided biopsy	MSM and TW living with HIV age ≥35 years positive for cytology	0.553 (Jin et al., 2025)
	MSM and TW living without HIV age ≥45 years positive for cytology	0.659 (Jin et al., 2025)
	Others positive for cytology	0.775 (Jin et al., 2025) - proxy
Proportion of patients referred to HRA-guided anal HSIL ablation	0.462	(Gimenez et al., 2011)
Probability of being HPV positive post Ablation	0.29	(Goldstone et al., 2017)
Proportion of patients developing Anal cancer without treatment	MSM and TW living with HIV age ≥35 years	0.00085 (Clifford et al., 2021)
	MSM and TW living without HIV age ≥45 years	0.00019 (Clifford et al., 2021)
	Women living with HIV age ≥45 years	0.00022 (Clifford et al., 2021)
	MSW living with HIV age ≥45 years	0.00032 (Clifford et al., 2021)
	People with previous vulval SCC/HSIL (HPV associated)	0.0009 (Clifford et al., 2021)
	SOTR	0.0005 (Clifford et al., 2021)
	People being followed up after treatment for anal cancer (i.e. chemoradiotherapy/surgery)	0.00004 (Faber et al., 2020)

	People with incidental HSIL (e.g. lesions found at haemorrhoidectomy, colonoscopy or during diagnosis of other anal conditions)	0.00401 (Joel M Palefsky et al., 2022)
	People with history of cervical/vaginal cancer or precursor lesions	0.00019 (Clifford et al., 2021)
Proportion of patients developing Anal cancer with ablation treatment	MSM and TW living with HIV age ≥35 years	0.00037 (Clifford et al., 2021)
	MSM and TW living without HIV age ≥45 years	0.00008 (Clifford et al., 2021)
	Women living with HIV age ≥45 years	0.00009 (Clifford et al., 2021)
	MSW living with HIV age ≥45 years	0.00014 (Clifford et al., 2021)
	People with previous vulval SCC/HSIL (HPV associated)	0.00039 (Clifford et al., 2021)
	SOTR	0.00021 (Clifford et al., 2021)
	People being followed up after treatment for anal cancer (i.e. chemoradiotherapy/surgery)	0.00002 (Faber et al., 2020)
	People with incidental HSIL (e.g. lesions found at haemorrhoidectomy, colonoscopy or during diagnosis of other anal conditions)	0.001734 (Joel M Palefsky et al., 2022)
	People with history of cervical/vaginal cancer or precursor lesions	0.000083 (Clifford et al., 2021)
Proportion of cancer that are distal	0.1669	(SEER, 2022)
Proportion of cancer that are regional	0.4195	(SEER, 2022)
Proportion of cancer that are local	0.4137	(SEER, 2022)
Progression from remission for distal cancer patients	0.0200	Proxy - (Cheng et al., 2023)
Probabiltiy of local cancer progressing to distal	0.0200	(Cheng et al., 2023)
Progression for local remission patients	0.02	Proxy - (Cheng et al., 2023)
Probabiltiy of regional cancer progressing to distal	0.041	(Cheng et al., 2023)
Progression for regional cancer patients in remission	0.041	Proxy - (Cheng et al., 2023)

Table 43 Results of the economic evaluationpresents the overall results of the base case.

Table 43 Results of the economic evaluation

Intervention/control arms	Costs	Incremental cost	QALYs	Incremental effectiveness	ICER
MSM and TW living with HIV					
HPV genotyping and codependent technologies	$15,422	$12,702	23.4146	0.1949	$65,142
No testing	$2,720		23.2196		
MSM and TW living without HIV					
HPV genotyping and codependent technologies	$13,457	$10,481	20.7666	0.0877	$119,516

No testing	$2,976		20.6789		
MSW living with HIV					
HPV genotyping and codependent technologies	$16,679	$14,296	23.4172	0.0983	$145,465
No testing	$2,382		23.3189		
Women living with HIV					
HPV genotyping and codependent technologies	$16,541	$14,240	23.4516	0.0732	$194,452
No testing	$2,301		23.3784		
Patients with incidental anal HSIL					
HPV genotyping and codependent technologies	$17,050	$14,742	23.4166	0.0849	$173,640
No testing	$2,308		23.3317		
SOTR					
HPV genotyping and codependent technologies	$16,525	$14,019	23.4342	0.1504	$93,195
No testing	$2,507		23.2837		
Patients being followed up after treatment for anal cancer					
HPV genotyping and codependent technologies	$17,199	$15,006	23.4263	0.0740	$202,825
No testing	$2,193		23.3523		
People with previous vulval SCC/HSIL					
HPV genotyping and codependent technologies	$16,629	$13,854	23.3950	0.2150	$64,442
No testing	$2,775		23.1800		
People with a possible history of cervical/vaginal cancer or precursor lesions					
HPV genotyping and codependent technologies	$16,519	$14,238	23.4314	0.0686	$207,610
No testing	$2,282		23.3628		
Weighted results					
HPV genotyping and codependent technologies	$14,491	$11,684	21.7553	0.0955	$130,105
No testing	$2,807		21.6598		

Abbreviations: MSM = men who have sex with men; TW = transgender women; HIV = human immunodeficiency virus; HPV = human papilloma virus; SSC = squamous cell carcinoma; HSIL = high grade intraepithelial squamous cell carcinoma, ICER=Incremental cost-effectiveness ratio; SOTR = solid organ transplant recipients; QALY = quality-adjusted life year.

Summary of base-case results

When considering the costs of treatments and associated costs relating to anal cancer, compared to no testing, genotyping and the codependent technologies were more costly and more effective than no testing, the ICER was $130,105/QALY.

Effect of Vaccination

Australia began offering the HPV vaccine to male students aged 12–13 years in schools starting in 2013 as part of the National HPV Vaccination Program. Smith et al., (2017) predicted a 44% reduction after 10 years. We modelled a 44% reduction to estimate the effects of vaccination on the cost effectiveness of the co-dependant technologies resulting in an ICER of $168,579.

One-way sensitivity analysis was conducted and observed that parameters sensitivity varies across subpopulation-specific models. The model for the highest risk PICO set (MSM and TW LWH) was most sensitive, but not limited to the following parameters:

- Normal/undetected cancer health state utility
- Cost for HRA guided ablation
- Cancer incidence in untreated population.

Table 44 Key drivers of the model for men that have sex with men and transgender women living with HIV subpopulation

Description	Method/Value	Impact Base case for MSM LWH ($65,142/QALY)
Normal/undetected cancer health state utility	The utility associated with the healthiest health state is uncertain. At a lower utility (0.68) the co-dependant technologies have an ICER of ~ $82,703/QALY, however, at 0.946 the ICER is ~ $45,928/QALY.	High, favours codependent technologies when this value increased.
The cost for HRA guided ablation	The cost of HRA guided ablation is uncertain in this population as it is unclear what the severity and stage cancer are first detected in Australian populations.	High, favours standard care when this value increased.
Cancer incidence in untreated population	The probability of developing cancer is uncertain as it is based on multiple sources. This can lead to the intervention being considered not cost effective (especially in patients that have had previous anal cancer.	High, favours codependent technologies when this value increased.

Abbreviations: HRA = high-resolution anoscopy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; MSM = Men that have sex with men and transgender women; LWH= Living with HIV.

Based on the economic evaluation, the cost-effectiveness results of the codependent technologies vary depending on the outcomes and indications. In relation to QALYs gained, the codependent technologies were overall more costly and more effective, though this was not the case for all populations.

These results are largely dependent on clinical evidence from various studies, which introduces considerable uncertainty into the economic model especially considering the limited evidence for some PICO subpopulations. There was a large amount of input data for transition probabilities that were based on proxy data and may vary considerably for the real world. The model assumes everyone re-enters the testing process after one year which may overestimate the costs of the intervention but also overestimate its effectiveness.

The model adopts a number of simplifying assumptions due to scarcity of evidence. There was no clinical evidence available that covered the full spectrum of patients using the co-dependent technologies (i.e. no evidence on the probability of the following patients progressing to cancer: HPV positive patients that were negative to cytology, HPV positive and reflex cytology positive patients that were negative to HRA guided biopsy). Therefore, the model assumed that the probability of developing cancer for these groups of patients was the same as that associated with post ablation therapy. This may overestimate disease progression for these groups. On the

other hand, in the model HPV positive/reflex cytology/ HRA guided biopsy positive patients always received an ablation rather than developing cancer directly from that stage.

As the model assumed that all cancer developed in both the intervention and standard of care arms was treated (i.e. there was zero probability of undetected cancer in the standard of care arm), this may underestimate the early detection benefits of patients in the intervention arm presenting themselves for testing at regular intervals.
It is unclear what the overall impacts of these model assumptions and features is. Therefore, the interpretation of the cost-effectiveness evidence should be approached with caution.

14. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of anal HPV genotyping and the co-dependant technologies. The financial implications to the MBS resulting from the proposed listing of the codependent technologies are summarised in Table 45.

Table 45 Net financial implications of the codependent technologies to the MBS – DCAR estimates

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology						
Number of people eligible HPV genotyping	133,370	135,492	137,750	140,030	142,346	144,672
Number of people/ services who receive HPV genotyping	75,950	77,115	78,364	79,632	80,925	82,226
Number of services of reflex cytology	50,885	51,892	52,938	53,980	55,027	56,069
Number of services of diagnostic HRA	68,437	69,778	71,174	72,566	73,964	75,358
Number of guided biopsies	136,874	139,556	142,347	145,131	147,929	150,716
Number of services of HRA-guided anal HSIL ablations	63,236	64,475	65,764	67,051	68,343	69,631
Cost to the MBS of new items	$51,091,520	$53,164,051	$55,283,315	$57,408,321	$59,547,423	$61,692,871
Change in the cost of current items used to implement the new items						
MBS 17610 anaesthesia consultation	$2,738,576	$2,792,246	$2,848,089	$2,903,798	$2,959,768	$3,015,536
MBS 23025 Anaesthesia	$2,254,575	$2,298,760	$2,344,733	$2,390,597	$2,436,675	$2,482,587
MBS 20902 Anaesthesia Initiation	$4,509,151	$4,597,520	$4,689,466	$4,781,194	$4,873,350	$4,965,173
MBS 23 Professional attendance by a general practitioner	$4,727,221	$6,526,801	$8,340,165	$10,166,490	$12,008,073	$13,865,567
MBS 73043 Cytology	$1,190,697	$1,214,264	$1,238,742	$1,263,140	$1,287,632	$1,312,007

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
MBS 104 Colorectal surgeon consultation - initial	$2,675,040	$2,727,465	$2,782,012	$2,836,429	$2,891,100	$2,945,574
MBS 105 Colorectal surgeon consultation	$1,967,036	$2,005,586	$2,045,696	$2,085,710	$2,125,912	$2,165,968
MBS 72816 Examination of complexity level 3 biopsy material	$2,334,388	$2,380,137	$2,427,738	$2,475,225	$2,522,934	$2,570,471
Total cost to MBS of implementing the co-dependant technologies	**$73,488,205**	**$77,706,831**	**$81,999,955**	**$86,310,905**	**$90,652,868**	**$95,015,754**
Change in health budgets due to a reduction in anal cancer						
Reduction in anal cancer (multiple MBS items)	0	23	23	23	24	24
Net change in costs to the MBS (with appropriate copayments excluded)	$0	-$87,539	-$89,126	-$90,722	-$92,333	-$93,938
Net financial impact to other government health budgets	$0	-$315,803	-$321,528	-$327,286	-$333,099	-$338,890
Net financial impact to all government health budgets	$73,488,205	$77,303,488	$81,589,301	$85,892,896	$90,227,436	$94,582,926

Source: Excel workbook "Utilisation and Cost Model".
Abbreviations: HPV = human papilloma virus; MBS = Medicare Benefits Scheme; HRA = high resolution anoscopy; HSIL = high grade intraepithelial squamous cell carcinoma

It was estimated that in the first year of listing the new MBS item would have a net financial implication to whole of government through MBS, PBS and state governments of almost $73.5 million, rising to $94.6 million in year 6. This equates to a net six-year financial implication of approximately $503 million. The sensitivity analysis was conducted and is presented in Table 46 below. Sensitivity analysis demonstrated that the budget impact is most sensitive to uptake rates of HPV testing, the difference in price and the prevalence of HPV genotypes, which can change the estimates from costing between $41 million and $167 million in year 6.

Table 46 Results of sensitivity analysis for net budget impact of marking the codependent technologies available on the MBS

	2026	2027	2028	2029	2030	2031
Base case (net cost to government)	$73,488,205	$77,303,488	$81,589,301	$85,892,896	$90,227,436	$94,582,926
***HPV* genotyping uptake (base case = 56.7%)**						
100% uptake	$129,608,827	$136,645,742	$144,210,078	$151,805,809	$159,456,169	$167,143,457
25% uptake	$32,402,207	$33,858,929	$35,744,529	$37,637,946	$39,544,968	$41,461,243
Proportion of patients with anal cancer post testing						
Cancer rate +20%	$73,488,205	$77,364,430	$81,651,348	$85,956,054	$90,291,715	$94,648,322
Cancer rate - 20%	$73,488,205	$77,242,547	$81,527,255	$85,829,739	$90,163,156	$94,517,529
Proportion of patients with HPV (base case DCAR epidemiology)						
PICO set estimates	$51,789,385	$57,030,552	$62,767,145	$68,566,997	$74,439,017	$80,376,228
20% reduction from base case	$60,382,441	$65,059,745	$70,219,273	$75,420,225	$80,673,798	$85,972,320
MBS Item fee for HPV genotyping (base case = $50)						
$70	$74,674,245	$78,817,556	$83,556,096	$88,315,657	$93,109,969	$97,929,232

Source: Excel workbook "Utilisation and Cost Model"
Abbreviations: MBS = Medicare Benefits Scheme; HPV = human papilloma virus: DCAR = Department-contracted assessment report; PICO = Population, Intervention, Comparator, Outcome

There is considerable uncertainty in the financial impact analysis. These results are largely dependent on epidemiological data with uncertainty, that may not be relative to Australia. Clinical evidence comes from numerous studies, which introduces further uncertainty into the budget model.

Using this data, only 38 patients from the proposed testing population were estimated to develop cancer in 2026. This would only account for 6% of the expected total number of patients with anal cancer (using AIHW data for the total population in 2025 (AIHW, 2024)). It is unclear whether this is a reasonable estimate as there are no Australia specific data on the incidence in each population. However, the population tested in the financial estimates only accounts for approximately 0.5% of the total Australian population aged 35 years and over (74,887/15,322,274). If the data on the incidence of anal cancer in the included populations is correct, the introduction of co-dependent technologies would only lead to a reduction of 25 anal cancers annually. The number of patients needed to test and treat (if needed) to prevent one anal cancer is approximately 3,400 per annum.

There was a large amount of input data for clinical proportions that were based on proxy data and may vary considerably for the real world. The model assumes everyone re-enters the testing process after one year, however, this was tested in a sensitivity analysis. Given the uncertainty around the inputs to the financial model, care should be taken when interpreting the results.

15. Other relevant information

Definitions

Definitions of PICO-specified subpopulations associated with sexual behaviour may impact estimations. Sexual orientation is fluid, and sexual identities and behaviours can change.[85] Stigma and privacy concerns can result in underreporting or misreporting sexual behaviours.[86]

MSM are a diverse group of people; and not all MSM identify as gay or homosexual. People who identify as a different gender to their assigned sex at birth do not always identify as transgender.[86]

Testing intervals and requirements

There was no evidence identified to support the proposed intervals for HPV testing where results are negative. 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. For PLWH, these align with the ASHM Anal Cancer Screening Guidelines (recommending 3 yearly re-screening for PLWH who test negative for HPV).

In the ratified PICO, 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 and is particularly unlikely in underserved populations. In addition, PASC expressed concern around which entity would be responsible for monitoring testing intervals. 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. However, the extent of this is not estimable.

Organisational issues – capacity and workforce

Anal sampling (HPV testing and cytology testing)

PASC noted that if the proposed anal HPV/HSIL surveillance program is to be pursued, it would likely need to utilise the infrastructure of the existing cervical screening program. However, PASC acknowledged that there are potential differences between liquid based cytology 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.

HRA

HRA is a technically complex procedure currently performed at a limited number of centres throughout Australia. It is generally conducted by a specialist (consultant) in a dedicated room during an hour-long appointment. There is a learning curve associated with HRA, which means that outcomes will improve as a user becomes more skilled.[87] Specific training in HRA is instrumental to achieving effectiveness outcomes, and significant upskilling of the current workforce would be required to meet the HRA demand.

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Access to HRA has been flagged as a barrier to anal cancer screening in the literature, even in high-resource settings.[88] *PASC noted in the ratified PICO that there is currently a shortage of trained staff to perform diagnostic HRA and HRA/ablation. 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 ASHM Anal Cancer Screening Guidelines for PLWH website[23] cite that *"for at-risk individuals who do not have access to diagnostic HRA: anal swabs for HPV and cytology should NOT be collected. Anal cancer screening should consist of an annual symptom assessment and DARE."* This suggests that the current capacity for HRAs is insufficient to meet the demand associated with current use of HRA for PLWH alone. As this group represents only 22% of the total PICO population, there are significant concerns regarding access and capacity if the testing strategy were to be listed on the MBS. Rates of uptake of HPV testing and colposcopy in cervical cancer screening are significantly lower in multiple underserved priority groups, including Aboriginal and Torres Strait Islander people, those in remote or very remote areas, and those with lower socioeconomic status.[89] System-level issues with HRA access are likely to widen potential equity gaps seen in other types of cancer screening.

Legal issues around consultant training and accreditation for HRA were also raised in the ratified PICO, due to the complexity of the procedure and the fact that currently there is no limitation or accreditation regarding practice of HRA in Australia. Accreditation may be needed to minimise patient harm and improve the quality of care provided.

Uptake and stigmatisation

Unlike other cancer screening programs which are population-based, anal cancer triaged testing strategy and HSIL treatment therapy would be risk-targeted to specific priority groups. These groups (particularly MSM, TW and PLWH) have a considerable history of stigmatisation, discrimination and negative experiences with the healthcare system. Rates of cancer screening uptake in non-cis-gender and sexual minorities are significantly lower than other groups.[90] Stigma is also associated with reduced rates of use of HIV-specific health care for those LWH.[91,92]

Patients will need to overcome psychosocial barriers to participate in anal cancer targeted testing, including feeling safe to disclose their sexual orientation and gender identity to their healthcare provider, and being willing to endure the social and physical discomfort associated with testing for sexual transmitted infections such as HPV. Unique access and uptake considerations are therefore critical, including the patient communication and support infrastructure required to encourage engagement.

Patient education and communication

For low grade anal lesions (LSIL or pLSIL) no active treatment is generally recommended in Australia unless symptoms exist. PASC noted that patient education regarding the procedure and what an LSIL or pLSIL result means (given there is no active treatment) requires consideration.

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[88] Barnell, G. M., & Schechter, M. S. (2024). Anal Cancer Screening and Prevention-A New Era, Limited by Access to High-Resolution Anoscopy. JAMA Netw Open, 7(3), e240019.

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[90] Jackson, S. S., Patel, S., & Parker, K. (2023). Cancer disparities among sexual and gender minority populations. J Natl Med Assoc, 115(2s), S32-s37.

[91] Katz, I. T., Ryu, A. E., Onuegbu, A. G., Psaros, C., Weiser, S. D., Bangsberg, D. R., & Tsai, A. C. (2013). Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. Journal of the International AIDS Society, 16(3S2), 18640.

[92] Saxby, K., Chan, C., & Bavinton, B. R. (2022). Structural Stigma and Sexual Health Disparities Among Gay, Bisexual, and Other Men Who Have Sex With Men in Australia. JAIDS Journal of Acquired Immune Deficiency Syndromes, 89(3).

Cvejic 2020's findings of patients receiving results in the SPANC study highlighted a gap between the actual and perceived outcomes of the cytology and histology tests.[61] A quarter of patients misunderstood their test results (composite cytology-histology results) to be normal (when they were "abnormal") despite having access to a dedicated website and printed materials explaining all possible test results and what they meant in relation to anal cancer. Notably, HPV results were not provided to participants. Other behavioural or psychosocial impacts from perception of results were not explored. In cervical cancer screening in Australia, psychosocial barriers, including knowledge gaps, have been associated with being overdue for follow-up screening, although it was unclear whether knowledge levels are directly related to test results. Additionally, in both cervical and lung cancer screening, there is concern that negative results may be misinterpreted as an "all clear," potentially leading to attrition from ongoing screening programs.[93] However, the impact of low-risk or indeterminate results is not clear.

For the tests themselves, knowledge, awareness and risk perception will be key drivers of uptake. Research with TW, PLWH and sexual minority men indicate large gaps in understanding about HPV and risk, including unawareness of HPV disease as a male health issue.[94,95,96] Given most of the proposed population in the PICO is men (MSM LWH, MSM not LWH and MSW with LWH alone comprise approximately 86% of the total PICO population), the latter is a particular issue and wider health promotion on HPV, HSILs and risk groups will be needed.

Impact of HPV vaccination

Australia was the first country in the world to initiate a national publicly funded HPV vaccination program and to document its effects on intermediate outcomes. The Australian National HPV Vaccination Program (NHVP) was commenced in 2007 for girls and used a quadrivalent vaccine (Gardasil [Merck]) in a three-dose schedule. It was subsequently introduced for boys in 2013. the The HPV vaccine is given in adolescence in Australia to allow for it to administered before any exposure to the virus. The quadrivalent vaccine protects against HPV types, 6, 11, 16, and 18. In 2014, it was estimated in an Australian sample that 90% of anal cancers were associated with HPV covered by the quadrivalent HPV vaccine.[97]

In 2018, the quadrivalent vaccine was replaced by a two-dose course of the nonvalent vaccine. In Australia, this vaccine is predicted to reduce the lifetime risk of diagnosis with cervical cancer in vaccinated cohorts by 10% compared with those offered the quadrivalent vaccine, and by 52% compared with unvaccinated cohorts, in the context of primary HPV screening.[98] Based on the underlying HPV type distribution among cervical cancers in Australia, the nonvalent vaccine will protect against HPV types that are implicated in about 96% of anal cancers.[97]

A recent systematic review with evidence from 14 studies,[99] including both clinical trials and observational research, demonstrated that HPV vaccination offers strong protection against anal HPV infection and precancerous anal lesions in HIV-negative individuals aged 26 or younger, particularly when administered before any exposure to the virus. This protective effect is most pronounced in controlled trial settings where participants were HPV-naïve, and less so in broader or real-world populations where prior exposure is more common. In contrast, studies involving people over 26 years old (primarily PLWH) showed no significant benefit in preventing anal HPV

[93] Azar D, Murphy M, Fishman A, Sewell L, Barnes M, Proposch A. Barriers and facilitators to participation in breast, bowel and cervical cancer screening in rural Victoria: A qualitative study. Health Promot J Austr. 2022

[94] Cruz, G., Ramos-Cartagena, J. M., Torres-Russe, J. L., Colón-López, V., Ortiz-Ortiz, K. J., Pericchi, L., Deshmukh, A. A., & Ortiz, A. P. (2023). Barriers and facilitators to anal cancer screening among people living with HIV in Puerto Rico. BMC public health, 23(1), 1940.

[95] Fein, L. A., Cunha, I. R., Wong, A., Schlumbrecht, M. P., Duthely, L. M., & Potter, J. E. (2021). Low Perceived Anal Cancer Risk and Screening Utilization Among High-Risk Transgender Men and Women Living in an HIV / STI Epicenter. *AIDS Behav*, *25*(7), 2210-2218.

[96] Finneran, C., Johnson Peretz, J., Blemur, D., Palefsky, J., & Flowers, L. (2021). "That's Only for Women": The Importance of Educating HIV-Positive Sexual Minority Men on HPV and High Resolution Anoscopy (HRA). J Int Assoc Provid AIDS Care, 20, 23259582211016134

[97] Hillman RJ, Garland SM, Gunathilake MP, Stevens M, Kumaradevan N, Lemech C, Ward RL, Meagher A, McHugh L, Jin F, Carroll S, Goldstein D, Grulich AE, Tabrizi SN. Human papillomavirus (HPV) genotypes in an Australian sample of anal cancers. Int J Cancer. 2014 Aug 15;135(4):996-1001.

[98] Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, Canfell K. Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. Lancet Public Health. 2016

[99] Wei F, Alberts CJ, Albuquerque A, Clifford GM. Impact of Human Papillomavirus Vaccine Against Anal Human Papillomavirus Infection, Anal Intraepithelial Neoplasia, and Recurrence of Anal Intraepithelial Neoplasia: A Systematic Review and Meta-analysis. J Infect Dis. 2023

infection or AIN, nor in reducing recurrence of advanced AIN or anal warts. These variations in vaccine performance were largely attributed to differences in prior HPV exposure.

Overall, HPV vaccination is expected to play a key role in reducing future cases of anal cancer, although this impact will take decades to become measurable due to the slow progression of disease and its rarity compared to cervical cancer. In the interim, Australia has already observed a decline in anal HPV16 infections at the population level, including among unvaccinated individuals, suggesting that herd immunity is taking effect through its national vaccination program.[99]

Self-collection of anal swab samples

In the ratified PICO, it was noted that the application stated 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).

A recent systematic review examined the concordance of self- and clinician-collected anal swab samples for the purpose of anal cancer screening.[101] The adequacy of samples for HPV testing was found to be nearly identical between self-collected and clinician-collected swabs, with a meta-adequacy ratio of 1.01 (95% CI 0.97-1.05). However, for cytology, the adequacy of self-collected samples was slightly lower compared to those collected by clinicians, with a meta-adequacy ratio of 0.91 (95% CI 0.88-0.95).

Biomarkers

PASC noted in the ratified PICO that dual immunohistochemistry for p16/Ki67 on the LBC sample is being investigated as a mechanism for assessing cases with persistent non-16/18 hrHPV to determine the likelihood of significant disease and may assume greater relevance in this area. The ACES study is ongoing, and will assess the performance of HPV genotyping, dual stain, and HPV and host methylation biomarkers for detecting anal precancer.

Environmental impacts

The environmental impact of medical waste from disposable anoscopes must be considered. Single-use anoscopes are discarded after one procedure, while reusable devices require reprocessing after each use—including cleaning, disinfection, inspection, and sterilization—which consumes staff time and generates waste (e.g., PPE, detergents, and consumables). While single-use devices eliminate reprocessing waste and may reduce operational burden, they contribute to overall waste volume.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The applicant proposed 7 high-risk subgroups, and PASC added an additional subgroup (people with a history of cervical or vaginal cancer or precursor lesions) to capture what PASC considered would be the largest population at risk for anal cancer. However, ESC considered that the evidence for including this subgroup requires further consideration and justification.
- Expanded genotype testing for up to 14 HPV (human papillomavirus) genotypes should be covered in the proposed anal HPV testing. The risk of false positive results following HPV testing is mitigated by the inclusion of triage reflex liquid-based cytology (LBC).
- Surgical excision of high-grade squamous intraepithelial lesions (HSIL) is generally not performed and unlikely to be widely used, but it should remain available as a treatment option for specific clinical circumstances and would be covered by existing MBS rebates.
- Using the proposed triage strategy of HPV testing, cytology, and high-resolution anoscopy (HRA), likely leads to earlier detection, more favourable disease staging at presentation and potential reductions in mortality. However, ESC considered that the overall certainty of this direct evidence was low and findings were limited by bias in certain groups. Direct evidence was primarily collected from people living with HIV (PLWH), with high representation of men who have sex with men (MSM), some women living with HIV, and smaller subgroups including men who have sex with women (MSW) and transgender persons. There was little or no direct evidence for other subgroups.
- HRA-guided ablative treatment of HSIL may reduce progression of anal cancer compared to no treatment based on evidence derived from people living with HIV, particularly the MSM population. However, ESC considered that the evidence for effects of ablative treatment on HSIL recurrence and HSIL-free survival was very uncertain, and these findings were limited to the PLWH and MSM population.
- The majority of the available evidence is for PLWH (k=64 studies, n = 67,034 participants), with a reasonable volume of evidence for MSM (k= 48 studies, n= 14,663 participants). There was limited evidence for other subgroups. ESC considered whether the proposed testing and follow-up interventions could be limited to subgroups with more evidence or whether exemplar populations (e.g. MSM with or without HIV, females with history of vulval cancer and immunosuppression) could be proposed as the basis for assessment.
- There is broad support from public consultation, but there are concerns about the access, equity, patient education, and workforce capacity to support follow-up and treatment. If these issues are not addressed, this could cause unnecessary anxiety and distress for patients.

Economic and Financial issues:

- The limitations in the clinical estimates have created uncertainty in the economic model and financial estimates. ESC noted serious issues with both the economic model and financial estimates, including the model structure, inputs, variables and transition probabilities. The economic model did not account for the benefits of earlier cancer detection and downstaging in the intervention arm nor did it incorporate test outcomes

such as false positives and false negatives. These omissions limit its ability to assess the impacts of test performance. ESC considered that both the economic model and financial analyses require substantial revision to be useful for MSAC decision-making.

- ESC noted that supplementary cost-effectiveness analyses estimating cost per HPV-positive case or persistent HSIL identified would have allowed comparison with other applications to MSAC where incremental cost-effectiveness based on diagnostic yield has been informative for decision-making.
- Cancer incidence and testing uptake are key drivers for the economic and financial analyses, but both are uncertain. An underestimated financial impact would likely result from these uncertainties. ESC advised that additional sensitivity analyses around these variables would have been informative.
- To evaluate the relative value of the proposed testing, it would be helpful for MSAC decision-making to compare the proposed testing and follow-up interventions with established screening programs, considering factors such as total cost, accrued benefit and cost-effectiveness.
- ESC provided advice on revised MBS fees for testing and HRA procedures and noted that these would need to be incorporated in future revisions to the economic evaluation and financial estimates.

Other relevant information:

ESC noted that the Department had advised that this proposal does not qualify as a screening program under the Population Based Screening Framework. However, ESC noted that the proposal appears to fulfill World Health Organisation criteria for a screening program so it is unclear why it would not meet the Framework requirements for a screening program. Further advice is required from the Department to better understand the rationale for not classifying the proposed testing and follow-up interventions as a screening program.

ESC discussion

ESC noted that this application from the Royal College of Pathologists of Australasia and St Vincent's Hospital, Sydney is requesting Medicare Benefits Schedule (MBS) listing of:

- anal human papillomavirus (HPV) testing and cytology testing in populations at high risk for anal precursor lesions and anal cancer, and
- high-resolution anoscopy (HRA) and ablative treatment to prevent anal cancer.

ESC noted that this proposal has many similarities to the HPV-based National Cervical Screening Program (NCSP) which aims to screen for cervical cancer via HPV testing as the first-line screening investigation. The key difference between the NCSP and the proposed testing and follow-up interventions is that the latter is targeted towards populations at high-risk of the medical condition of interest (anal cancer) only. The application is proposing 7 MBS item numbers to implement targeted investigation and assessment (from investigation through to preventive treatment) for anal cancer:

- Item BBBB – HPV genotyping in asymptomatic patients
- Item CCCC – HPV genotyping in higher-risk or symptomatic patients
- Item DDDD – Repeat of BBBB or CCCC
- Item EEEE – Cytology testing of HPV-positive anal specimens
- Item FFFF – Diagnostic HRA
- Item HHHH – Biopsy during HRA
- Item GGGG – HRA-guided ablation.

ESC noted that almost all anal cancers are squamous carcinomas, with some being adenocarcinomas. More than 90% of anal cancers are driven by HPV infections. Rising incidence rates of anal cancer are related to changing sexual behaviours and increased duration of HPV infection in human immunodeficiency virus (HIV) positive patients. The incidence of anal cancer has sharply increased by 2.7% per year from 2001 to 2015. Latency between HPV infection and cancer is long, with most patients diagnosed in the sixth decade of their life or later. Immunodeficiency contributes to anal cancer presenting at a younger age. In most nations, women experience higher incidence rates of anal squamous cell carcinoma (ASCC), but unlike in men, this is not related to HIV infection and is less strongly related to other identifiable risk factors.

ESC noted that there are more than 200 known genotypes of HPV. Low-risk HPV genotypes (including types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89) cause low-risk lesions (such as wart and condyloma) that are transient and are very unlikely to progress to cancer. High-risk HPV genotypes (including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) cause high-risk lesions that may progress to cancer. ESC noted that anal HPV infections are often transient, similar to HPV infections involving the cervix. The original human papillomavirus vaccine (Gardasil) that was first given to Australian girls in 2007 and Australian boys in 2013 protects against 2 low-risk HPV genotypes (6, 11) and 2 high-risk HPV genotypes (16, 18). Since 2019, the updated vaccine, human papillomavirus 9-valent vaccine, recombinant (Gardasil 9), protects against additional 5 high-risk HPV genotypes: 31, 33, 45, 52 and 58. In 2023, the routine 2-dose HPV vaccine schedule provided to young people aged 12–13 years became a single-dose schedule, but people with immunosuppression (a key target population of the proposed testing) should receive a full 3-dose schedule. The latter population has a higher risk of developing persistent HPV infection and progressing to ASCC, and there is also evidence that the vaccine is less effective in people with immunosuppression.

ESC noted that the efficacy of the vaccine in preventing anogenital precursor malignant lesions has been adequately proven in clinical trials, but there is a paucity of data looking directly at the efficacy of the vaccine against anal HPV infection and anal cancer. Vaccination of children and adolescents with Gardasil 9 is expected to prevent a large majority of anal cancer cases, but HPV vaccination of adults after sexual debut may not significantly affect anal cancer rates. However, the effects of vaccination will not be known for decades, as there is a long lag time between HPV infection and the development of anal cancer (≥35 years of age for men who have sex with men [MSM] and are HIV positive, and ≥45 years of age for most other populations).

In Australia, the 14 high-risk HPV genotypes commonly tested in the NCSP are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Genotypes 16 and 18 account for 70–80% of cervical cancer cases, with HPV 16 causing 50–60% of cases and HPV 18 causing 10–15%. In anal cancer, HPV 16 accounts for 78.5% of cases, HPV 33 accounts for 10.7% of cases, and HPV 18 accounts for 8.9% of cases. However, this distribution varies in different risk groups – HPV 16 accounts for 88% of ASCC in immunocompetent patients, but accounts for less than 70% of cases in immunosuppressed patients. ESC considered it appropriate that the anal cancer HPV testing reports on the 14 genotypes. There are different oncogenic risks in the anus and cervix, with higher risks for non-HPV 16 to cause ASCC in immunosuppressed patients, and HPV 33 causes more ASCC than HPV 16. ESC considered that further justification would be needed if HPV genotyping for this intervention should incur different fees to HPV genotyping for the NCSP.

ESC noted that, in some people, persistent infection with HPV leads to cellular changes in the anal region which may result in squamous intraepithelial lesions, that are either low-grade (LSIL) or high-grade squamous intraepithelial lesions (HSIL). HSIL is considered to be a precancerous lesion and has a high risk of recurrence. A proportion of people with HSIL will progress to invasive ASCC. Populations at high risk of progression to ASCC include men with HIV who have sex with men, and people who are immunosuppressed.

ESC considered that targeted investigation for HSIL followed by HSIL treatment, could decrease progression to ASCC. ESC noted that the Anal Cancer/HSIL Outcomes Research (ANCHOR) study

by Palefsky et al. (2022)[100], a randomised controlled trial (RCT) of 4,459 HIV-positive patients aged older than 35 years with biopsy-proven HSIL, demonstrated a statistically significant difference in progression to ASCC in patients who had received treatment for HSIL compared to the active monitoring group. The cumulative progression to ASCC at 48 months was 0.9% in the treatment group compared to 1.8% in the active monitoring group. ESC also noted that the ANCHOR trial showed that patients treated for anal HSIL (primarily by office-based electrocautery) have approximately 60% lower rates of progression to ASCC than those who only undergo active monitoring without treatment. ESC noted that treatment options for anal HSIL include ablation with electrocautery or infrared coagulation, various topical therapies, or monitoring. Patients require close post-treatment surveillance, due to the high recurrence rate of HSIL following all treatment options (varying from 10% to 75%).

ESC noted that the selected population in the PICO are those with a 10-fold or greater risk of HSIL, which, when treated, can reduce the risk of ASCC by 60%. The applicant proposed 7 high-risk subgroups:

1. MSM and/or people who identify as transgender women (TW) who are positive for HIV and aged ≥35 years
2. MSM aged ≥45 years and/or who identify as TW who are HIV negative
3. Women and men who have sex with women (MSW) aged ≥45 years who are HIV positive
4. Women with previous vulval HPV-associated SCC and/or HSIL commencing within one year of diagnosis
5. Solid organ transplant recipients (SOTR) commencing 10 years post-transplant
6. People being followed up after treatment for anal cancer
7. People with incidental HSIL (lesions founds during diagnosis of anal conditions).

An additional subgroup – people with a history of cervical or vaginal cancer or precursor lesions – was added by PASC as the first 7 subgroups do not capture this largest subgroup. This additional group has a 5–10-fold greater risk of ASCC than the general population. PASC considered that including this subgroup increases the size of the testing population. The increase was estimated by the DCAR to be by 8.8%, but ESC considered that this increase would likely be much greater than this and that the subgroup's share of the proposed population would be larger than estimated by the Department Commissioned Assessment Report (DCAR). ESC also considered that the addition of this subgroup, especially the group with cervical lesions only, would require further justification for inclusion as a subgroup including greater scrutiny of the available evidence.

ESC noted different incidence rates of ASCC in the literature, ranging from 4.2 per 100,000 person-years (for patients who have been treated for previously diagnosed anal cancer) to 85 per 100,000 person-years (for MSM and TW who are HIV positive). ESC noted that incidence rates for other risk groups – people with systemic lupus erythematosus, ulcerative colitis and Crohn's disease – have similar ASCC incidence rates to subgroup 8 (people with a history of cervical or vaginal cancer or precursor lesions).

ESC noted public consultation feedback was received from patient groups, representatives of patient groups, and professional bodies. ESC noted that feedback concerns included the need for a follow-up pathway after testing and a supervising clinician or organisation to oversee follow-up to ensure that appointments for testing and delivery of test results occur. Although the proposal included a pathway for ablative treatment for patients testing positive to HSIL it was unclear which clinician would be responsible for this follow-up. ESC noted concern about the availability of an adequate workforce and resources. If these issues are not addressed before implementation, it may introduce unnecessary anxiety and distress for patients. ESC noted that

[100] Palefsky, J. M., Lee, J. Y., Jay, N., Goldstone, S. E., Darragh, T. M., Dunlevy, H. A., Rosa-Cunha, I., Arons, A., Pugliese, J. C., & Vena, D. (2022). Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. New England journal of medicine, 386(24), 2273-2282.

there were also concerns about HRA access but considered it unlikely that this would be a substantial issue for implementation.

ESC noted that PASC had also raised concerns regarding follow-up and the proposed time intervals between HPV genotyping tests, as it was unclear whether the proposed intervals were sufficiently evidence-based. ESC noted that the submission assumes patients have a stable relationship with a clinical practitioner, which may not be the case for all patients from vulnerable groups.

ESC noted that consultation feedback also highlighted the importance of patient education and communication, especially regarding follow-up appointments to receive test results if patients choose the self-collection option. While self-collection can improve accessibility, it also requires appropriate education and support, noting that some populations reported that self-collection could be distressing. Although self-collection is not specifically proposed in this application, it was raised as a possible option in the feedback and the PICO confirmation. ESC also acknowledged that while regular testing can provide some sense of assurance and control for patients, it can also contribute to ongoing anxiety due to the need for ongoing monitoring.

ESC noted other issues raised in the feedback, including concerns around false positive and false negative results, the risk of harm from HRA, stigma, equity issues due to a lack of specialist access in rural and remote areas, and environmental impacts from anoscopy, use of disposable anoscopes and high-water requirements for sterilisation. ESC acknowledged the potential psychological impact of false positive HSIL results. However, ESC considered that the psychological impact of a false positive HSIL is relatively minor compared to the distress typically associated with a cancer diagnosis as the latter involves the confirmed presence of cancer while the former refers to factors such as HPV infections inducing temporary cellular changes leading to incorrectly identifying a HSIL (which may may lead to cancer if left untreated) when one is not present.

ESC had the following comments on the proposed MBS item descriptors:

- Item BBBB – ESC noted that this item descriptor does not identify the target population and queried whether this information should be included.
- Item CCCC – ESC considered whether ‘high-risk’ should be defined in the item descriptor or whether the item can refer to guidelines that contain this information. ESC also questioned whether the descriptor should specify ‘for the investigation of a patient with symptoms suggestive of anal cancer’, given that the overall purpose of the testing is to target mainly asymptomatic patients. However, ESC also considered that HPV genotyping may be helpful in managing symptomatic patients.
- Item GGGG – ESC noted that this descriptor did not explicitly state that it cannot be billed with item FFFF (anoscopy). For the purpose of the evaluation, it was assumed that these items would not be billed together (that is, item GGGG covered both the HRA-guided procedure and the ablation procedure). However, ESC considered that this should be stated in the item descriptor.

ESC noted that the descriptors do not specify frequency of testing, based on subpopulations, even though frequency of testing is included in the relevant cervical screening MBS items. However, ESC considered that it would be difficult to include frequency of testing in the proposed item descriptors as each subpopulation has a different proposed testing frequency. ESC noted there are legislative restrictions associated with identifying HIV+ people in MBS items.

ESC considered the proposed fees for each MBS item are high and require further justification from the applicant. ESC considered the following fees, generally based on similar NCSP items, may be more appropriate:

- Items BBBB, CCCC and DDDD – $35.85 for each (based on similar NCSP items; also noting that item DDDD will be redundant if no frequency restrictions are placed on items BBBB or CCCC)
- Item EEEE – $47.10 (as advised by PASC)

- Items FFFF and HHHH – no specific fee advised by ESC, but ESC advised that in order to discourage unnecessary biopsies these items should align with other MBS items that do not have a fee per biopsy and which incorporate biopsies as part of a complete medical service
- Item GGGG – similar items (of similar complexity) for colposcopy following cervical screening have a fee lower than the $700 proposed by the applicant. Additional justification for the proposed higher fee is required from the applicant. ESC noted that MBS item 35645 for cervical ablation, which also includes ablation in the anal region, has an MBS fee of $371.80.

ESC noted the proposed clinical management algorithm. If high-risk anal HPV is not detected, patients undergo follow-up testing at a later date, with the proposed interval between testing determined by subpopulation risk of ASCC. If HPV 16 is detected, patients are immediately referred for HRA assessment. If non-16 high-risk HPV is detected, patients undergo triage liquid-based cytology (LBC). ESC agreed that expanded HPV genotype testing for up to 14 genotypes (similar to cervical screening) should be covered in the proposed anal HPV testing. ESC considered that the risk of false positive results following HPV testing would be mitigated by the proposed inclusion of triage reflex LBC and that this approach aligns with the approach in the NCSP.

ESC noted that P16 immunohistochemistry (IHC) on biopsies (not cytology) is routinely used as a biomarker of integration of high-risk HPV, specifically in the differential diagnosis between LSIL and HSIL. However, ESC considered that this was not relevant for this application as P16 IHC is only used on biopsies (taken at anoscopy). P16 immunohistochemistry, if required for pathological assessment of anal biopsies, would be funded as a ladder item for surgical pathology.

ESC considered that, although surgical excision of HSIL is generally not performed and will not be used widely, it should not be excluded as a treatment option for specific clinical circumstances. ESC considered that surgical excision would be covered by existing MBS items.

ESC noted that the clinical claim is that HPV and LBC testing in mainly asymptomatic patients at high risk of anal cancer to determine access to HRA and ablative treatment is superior to routine clinical care. The routine clinical care in this scenario is no HPV or LBC testing and no treatment of asymptomatic patients. Regarding this comparator, ESC noted that, in practice, there are several other avenues through which individuals at high risk of anal cancer may be identified, although these may or may not be pursued. For example, a patient presenting to a doctor for a check-up, sexual health examination or for other illness, may opportunistically be offered asymptomatic testing if the patient is considered at high risk of anal cancer. ESC considered the clinical claim to be supported, but noted nuances regarding which patient subgroups are at sufficiently high risk to justify the associated cost and risk to benefit consideration.

ESC noted that the most evidence (on efficacy, incidence, and natural history) was presented for the highest-risk subgroups (people who are HIV positive, k=64 studies of various designs, n = 67,034 participants) which comprised 22% of the proposed population though noting the caveat that the eighth subgroup's share of the proposed population may be underestimated), while some evidence was presented for the largest subgroup (MSM who comprised 74% of the proposed population, k= 48 studies of various designs, n= 14,663 participants, again noting the caveat about the flawed estimate of population shares). Nonetheless, most anal cancers detected in Australia are in women. There was little evidence presented for other subgroups. ESC noted that the body of evidence was limited for the people being followed up after anal cancer treatment (subgroup 6) and incidental anal HSIL (subgroup 7) and noted that these subgroups would already be receiving follow-up due to their medical history. ESC considered that it would be beneficial for MSAC decision-making if the applicant could comment on the strength and applicability of the evidence base presented for each of the subgroups, as well as how in practice each of these asymptomatic subgroups would be identified for testing.

ESC considered whether given the limited evidence available for some subgroups it may be appropriate to either limit the intervention to a subset of the listed subgroups and/or propose one or two of the defined subgroups for which the strongest evidence is available as exemplar populations as the basis of assessment, in order to facilitate listing for the others. ESC noted that the highest certainty evidence not just for efficacy but also on factors which are important to modelling such as incidence and natural history are for the highest risk subgroups. ESC further noted that possible candidates for exemplar populations would be the MSM subgroups (both those living with and without HIV) and females with history of vulval cancer and immunosuppression.

ESC noted that using the proposed triage strategy of HPV testing, cytology, and high-resolution anoscopy (HRA), likely leads to earlier detection, more favourable disease staging at presentation and potential reductions in mortality. However, ESC considered that the overall certainty of this direct evidence was low and findings were limited by bias. Direct evidence was primarily collected from PLWH, with high representation of MSM, some women living with HIV, and smaller subgroups including men who have sex with women (MSW) and transgender persons. There was little or no direct evidence for other subgroups.

ESC noted that the evidence indicated that HRA-guided ablative treatment of HSIL may reduce progression of anal cancer compared to no treatment based on evidence derived from PLWH, particularly the MSM population. However, ESC considered that the evidence for effects of ablative treatment on HSIL recurrence and HSIL-free survival was very uncertain, and these findings were limited to the PLWH and MSM population.

In particular, ESC noted that the ANCHOR trial, which underpinned the treatment effect for the whole submission, was restricted to patients with HIV and high-grade lesions identified through an anal swab for liquid-based cytology, a complete physical examination and HRA biopsy. This means that there is only evidence of accrued benefit from identifying patients with HSIL for ablative treatment in that particular group of patients. The applicability of this evidence for the effectiveness of the ablative treatment to other subgroups is uncertain.

ESC noted that there is evidence (as reported in the meta-analysis by Dyer et al. 2025)[101] that self-collection of anal swab samples gives similar detection rates of HPV 16 and any HPV genotype than clinician-collected samples. However, self-collection was 10% less likely to meet the minimum cell count required for cytology assessment compared to the clinician-collected samples. Nonetheless, ESC considered that it would be reasonable to allow self-collection of HPV anal swab samples. Patients with positive HPV results for subtypes other than HPV16 (i.e. non-16 high-risk HPV) will require reflex LBC. If the self-collected sample has insufficient cells for cytology assessment, these patients may need to be recalled for a repeat clinician-collected sample for LBC.

ESC noted that the economic evaluation was the same model used to generate 9 separate cost-utility analyses (CUAs) for the 8 populations (one of the populations was separated into two subpopulations: MSW who are HIV positive; and women who are HIV positive) though with a truncated model structure variation for two of those populations (incidental HSIL, previous anal cancer) to account for their already having undergone other testing. The testing component of the intervention was modelled as sequential testing, meaning that patients must receive a positive result before undergoing the next test. The outcome was quality-adjusted life years (QALYs) gained, with no intermediate outcomes, such as diagnostic yield. ESC considered that it would have been helpful to know how many HPV-positive cases and how many persistent HSIL cases would be identified for each subpopulation. The model used a cycle length of 6 months which ESC considered introduced complexity into the model structure. ESC considered that an annual cycle would have better facilitated comparisons of outcomes against incidence or factors associated with natural progression of cancer.

[101] Dyer, C. E. F., Jin, F., Hillman, R. J., Nyitray, A. G., Roberts, J. M., Law, C., Grulich, A. E., & Poynten, I. M. (2025). Self-collected versus clinician-collected anal swabs for anal cancer screening: A systematic review and meta-analysis. Int J Cancer, 156(1), 79-90

ESC also noted there was significant uncertainty in other aspects of the economic model, including absent or insufficient clinical evidence for clinical effectiveness and the accuracy of HPV testing with cytology for a number of the subpopulations modelled and uncertain uptake (the model assumes HPV testing uptake will mirror HIV testing uptake).

ESC noted that the costs and benefits of partial versus expanded genotyping were not explored in the CUAs, with only expanded genotyping considered. ESC considered this appropriate as expanded genotyping is standard practice. The model was also based on an assumption of annual testing, which does not align with guidelines relied on in the proposal, for example, 3 yearly testing is recommended for the highest risk group (MSM with HIV). ESC noted from the pre-ESC response that the incidental HSIL and post-anal cancer follow up groups would not need to face the full extent of testing in clinical practice.

ESC considered there were issues with the economic model structure. ESC noted that the current model structure does not capture the benefits from finding otherwise undetected cancers earlier in the intervention arm compared to the comparator arm since in both arms all incident local cancers receive treatment. If the model was able to take account of the benefits of earlier detection (and hence earlier treatment) of cancers in the intervention arm relative to the comparator arm (resulting in incrementally more downstaging of cancers in the intervention arm), the incremental cost-effectiveness ratio (ICERs) could be lower than estimated. However, as the model is unable to account for downstaging of detected cancers in either arm, it does not count the number of cancer lesions at different stages (only fewer cancers in the intervention arm are captured). Additionally, the model is not structured to include false positive and false negative results, so the sensitivity and specificity of the tests cannot be investigated in sensitivity analyses.

ESC also considered there to be issues with the validity of model inputs, variables and transition probabilities, including errors in values and calculations, the adjustments for 6-month cycles, and the failure to account for the impacts of HIV in background mortality in the models for populations who are HIV positive. ESC noted that the pre-ESC response suggested adding a cost-effectiveness analysis (CEA) that estimates the cost per HPV-positive case detected. ESC noted that in the current model for MSM living with HIV the cost associated with following up each HPV positive case identified was $626. ESC also considered that sensitivity analyses should consider age, as risk of anal cancer increases with age, and should exclude the vaccinated population. However, regarding age, ESC advised that competing risks should also be considered; for example, the lung cancer screening program has maximum age thresholds because the older the patient is, the less benefit there is from screening as the risk of dying from other causes increases.

ESC noted the base-case results of the economic evaluation showed an ICER of $132,897/QALY weighted by subgroup size, which ESC considered high. On the other hand, the highest-risk subgroup (MSM who are HIV positive) had an ICER of $65,142/QALY. However, ESC noted that in a recent Australian economic model published by Cheng et al. (2023)[102] this subgroup had a much higher ICER of $135,800/QALY. ESC noted that the key drivers of the DCAR model were the health utility weights (normal population or undetected cancers), the cost of HRA-guided ablation, and cancer incidence in the treated population. ESC noted that a study by Smith et al. (2017)[103] predicted that, as a result of the NCSP, there would be a 44% reduction in HPV-related diseases after 10 years. ESC noted that the DCAR reported that based on an assumed 44% reduction due to the effects of vaccination the ICER increased to $168,579/QALY.

[102] Cheng, Q., Poynten, I. M., Jin, F., Grulich, A., Ong, J. J., Hillman, R. J., Hruby, G., Howard, K., Newall, A., & Boettiger, D. C. (2023). Cost-effectiveness of screening and treating anal pre-cancerous lesions among gay, bisexual and other men who have sex with men living with HIV. The Lancet Regional Health – Western Pacific, 32. https://doi.org/10.1016/j.lanwpc.2022.100676

[103] Smith MA, Canfell K. Projected impact of HPV vaccination and primary HPV screening on cervical adenocarcinoma: Example from Australia. Papillomavirus Res. 2017 Jun;3:134-141. doi: 10.1016/j.pvr.2017.04.003. Epub 2017 Apr 19. PMID: 28720447; PMCID: PMC5883242.

ESC suggested the following amendments would be needed for the economic modelling to be useful for MSAC decision-making:

- focus on the main subpopulation with the best evidence (MSM who are HIV positive)
- amend the structure to incorporate test outcomes so that the number and impacts of false positive and false negative results are accounted for
- check input values
- model the testing interval for this specific population as recommended in guidelines i.e. once every 3 years
- include a supplementary CEA that estimates incremental costs associated with intermediate test outcomes such as the incremental cost per persistent HSIL identified for treatment (this will then allow comparison to other diagnostic yield applications previously considered by MSAC)
- account for earlier detection (and treatment) of cancer in the intervention arm relative to the comparator arm
- update costs to take account of the recommendations made by ESC above on MBS item fees
- perform additional sensitivity analyses on uptake rates, cancer incidence and other highly uncertain values.

ESC considered that although a CEA (as discussed above) was useful for a supplementary analysis, evaluation of this application still required a CUA given the high cost of the proposed HPV testing and follow-up investigations. Overall ESC considered that a model structure adapted from or based on the Australian model developed by Cheng et al. (2023) would have been more appropriate for MSAC decision-making.

ESC noted that an epidemiological approach was used to estimate the financial impact. ESC considered this appropriate, although data were lacking. The main source of uncertainty in the financials related to the incidence of anal cancer in the PICO populations, which was sourced from a meta-analysis of studies from different countries in the absence of Australian-specific data for each subgroup.

As discussed above, ESC proposed that a lower MBS item fee should apply to the HPV genotyping test. ESC noted the argument that the high proposed costs for anal HRA procedures were because the procedures are more difficult to perform than cervical HRA. However, ESC noted that its proposed amendments to other fees (as discussed above) should also apply to the financial model. ESC noted that the financial analysis estimated that implementation would result in approximately 25 cancers being prevented each year, which is likely an underestimate.

ESC noted that, assuming an HPV genotyping uptake of 56.7%, the estimated cost to the MBS when considering all subpopulations together is $51.1 million in year 1 to $61.7 million in year 6. When considering the cost of current items that will be used to implement the new items (anaesthesia, doctor's attendances, pathology, cytology), the total cost to the MBS increases to $73.5 million in year 1 to $95.0 million in year 6. ESC considered it would be helpful for MSAC decision making to have each of the costs separated by subpopulation.

ESC noted sensitivity analyses of the financial impacts. ESC considered that the financial impacts are likely underestimated due to the uncertainty associated with the data on cancer incidence and the likely underestimate of the size of the population for subgroup 8 (as discussed above).

ESC noted that the estimated total costs of the proposed anal cancer investigative items are about one-third of the cost of the NCSP. ESC further noted that the cervical screening program reaches around 940,000 women (68% participation), while the proposed anal cancer early detection strategy is estimated to comprise around 130,000 people with 56% participation. ESC considered that it would be helpful for MSAC decision-making to put the proposed HPV testing items for anal cancer in the context of screening programs, considering factors such as total cost, accrued benefit (numbers of cancer avoided), and modelled ICERs.

ESC noted that the Department had advised that this proposal does not qualify as a screening program under the Population Based Screening Framework. However, ESC noted that the proposal appears to fulfil World Health Organisation criteria for a screening program so it is unclear why it would not meet the Framework requirements for a screening program. Further advice is required from the Department to better understand the rationale for not classifying the proposed testing and follow-up items as a screening program.

17. Applicant comments on MSAC's Public Summary Document

The Royal College of Pathologists of Australasia (RCPA) thanks MSAC for its ongoing consideration of Application 1752, and for the detailed feedback provided in the Public Summary Document, including the Committee's identification of key areas of uncertainty requiring further assessment. The RCPA remains committed to supporting MSAC, ESC and the Department as this work progresses, and is willing to contribute further evidence, technical input, and clarification (including identifying priority populations, wording of the item descriptors, fee justification, and utilisation assumptions) as needed to help resolve remaining uncertainties and facilitate timely reconsideration of the application.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website