Population

Describe the population in which the proposed health technology is intended to be used:
Anal cancer, although relatively rare in Australia, has been rapidly rising in terms of incidence and mortality, with both rates increasing over time (Figure 1 to Figure 4). Although more often a cancer associated with gay and bisexual men, especially those who are human immunodeficiency virus (HIV)-positive, the incidence in Australian women is increasing (Lum et al 2020; Palefsky et al 2022). Women diagnosed with HPV-related gynaecological pre-cancerous lesions or cancer, as well as solid organ transplant recipients and patients with autoimmune diseases such as systemic lupus erythematosus, ulcerative colitis or Crohn's disease, are at higher-than-average risk of anal cancer (Clifford et al 2021).

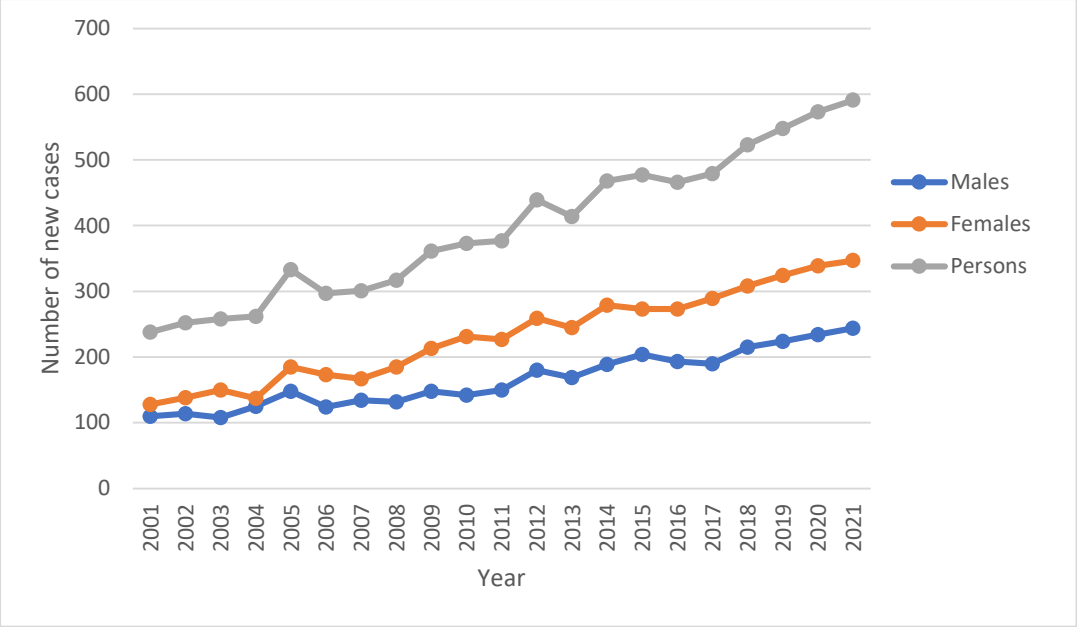

Figure 1 The number of new anal cancer cases in Australia (2001-2021)(AIHW 2021a)

The natural history of anal cancer is not as well characterised as that of cervical cancer; however, there are similarities. Persisting high-risk HPV infection can lead to the development of HSIL (categorised as AIN 2 and 3). Persisting infection with low-risk HPV genotypes can lead to the development of low grade squamous intraepithelial lesions (LSIL or AIN 1), which are not usually associated with progression to invasive malignancy (Lum et al 2020). HSIL are the precursor of squamous cell carcinoma of the anus (SCCA), which represent approximately 70-80% of all anal cancers (Berry et al 2014; Lum et al 2020). Like cervical cancer, human papillomavirus (HPV) infection, primarily HPV type 16 or 18, has a causal relationship in approximately 90 per cent of SCCA cases (Berenson et al 2022; Palefsky et al 2011). HIV co-infection markedly increases the risk of HPV-associated anal SCC, particularly in those individuals with low CD4 counts (Lum et al 2020).

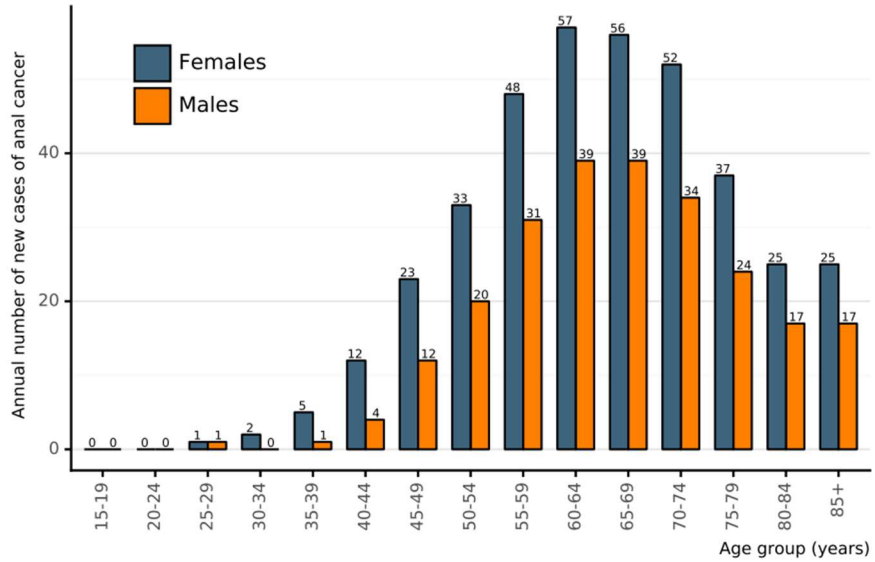

Figure 2 Estimated number of new cases of anal cancer in Australia for 2020) by sex and age (Bruni et al 2021)

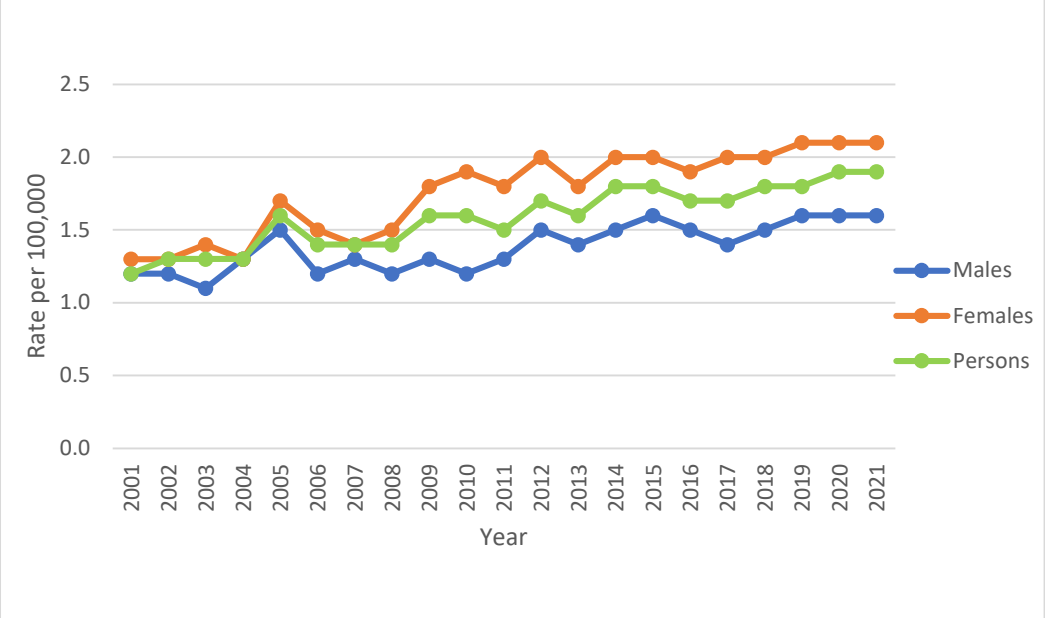

Figure 3 Rate of new anal cancer cases (per 100,000) in Australia (2001-2021) (AIHW 2021a)

Anal cancer is among the limited number of cancer types, including cervical and colon cancer, that are potentially preventable through treatment of known cancer precursors. Programs that identify HSIL early enable the early detection, prevention, and treatment of anal cancer. Due to the histological and biological similarities between SCC of the anus and cervix, and the causal association with infection with HPV, like cervical cancer, the treatment (most often by ablation) of HSIL significantly reduces the progression to anal cancer (Palefsky et al 2022). Patients treated for anal HSIL (primarily office-based electrocautery) have rates of progression to anal cancer approximately 60% lower than those who only undergo active monitoring without treatment (Palefsky et al 2022).

Like cervical cancer, gender-neutral HPV vaccination is expected to be the long-term primary prevention strategy to SCCA; however, the full impact of vaccination programmes will not be felt for decades (Clifford et al 2021).

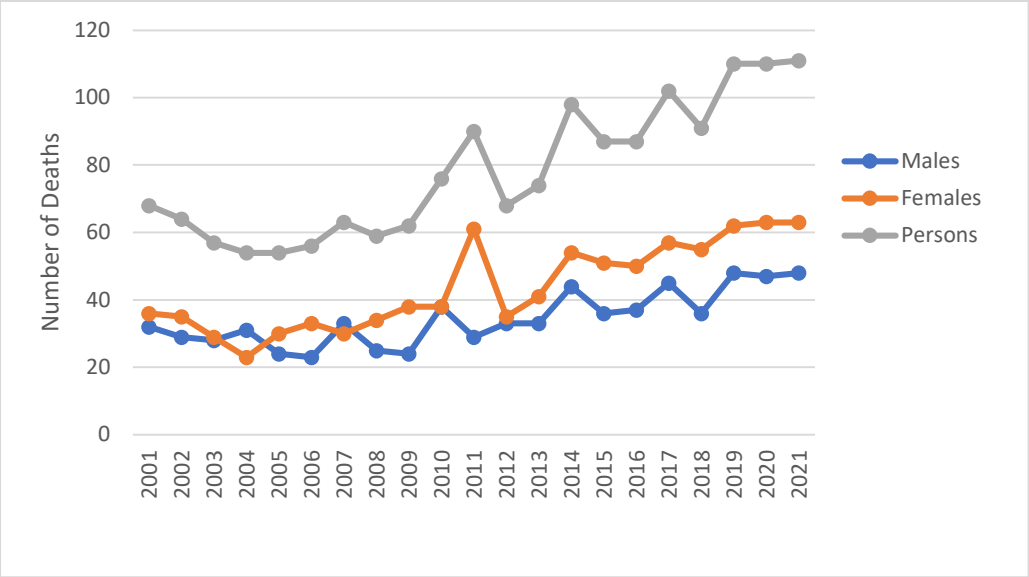

Figure 4 Number of deaths per year from anal cancer in Australia, by sex (2011-2021)(AIHW 2021b)

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

The target populations for testing include:

i) people living with HIV;

ii) MSM;

iii) women with other gynaecological HPV-associated lesions, including cancers;

iv) solid organ transplant recipients.

As such, these populations are likely to be cared for in the health system by specialists and/or general practitioners. This high-risk population would normally undergo standard clinical care until they are symptomatic of an anal cancer. For example, a person living with HIV would have their CD4+ count, a transplant patient would have organ function tested

Those with defined abnormalities (such as HPV16/persisting non-16 high-risk HPV, cytology ≥ pHSIL1) will be referred on to specialised services, where the extent and nature of histologically-established HSIL can be characterised. People with HSIL deemed to be at high risk of progression to SCCA will be offered treatment. Both high-risk HPV testing and cytology can be used to assess response to treatment.

[1] pHSIL = possible low-grade intraepithelial lesion (pLSIL)

Provide a rationale for the specifics of the eligible population:
Although relatively rare, rates of anal cancer have been rapidly increasing over time in Australia. The natural history of anal cancer is similar to that of cervical cancer, in that persistent infection with HPV has a causal relationship with squamous cell carcinoma of the anus (SCCA). As with cervical cancer, detection and treatment of the precursor to cancer will significantly reduce the progression to full cancer, and in so doing, reduce the associated rate of morbidity and mortality. By the early detection of anal high-grade squamous intraepithelial lesions (HSIL), the precursor to SCCA, patients can be treated effectively, usually by electrocautery, improving patient outcomes by reducing the rate of progression to anal cancer by 60% compared to those patients who are actively monitored without treatment.

Currently, there are no publicly funded testing and treatment options available to patients considered to be at high-risk of developing SCCA, including people living with HIV, HIV-negative men who have sex with men, women with other gynaecological HPV-associated lesions and solid organ transplant recipients. In comparison to the Australia-wide cervical cancer screening program, this lack of testing and treatment options represents a situation of significant inequity for this relatively small and vulnerable population. Listing of this testing on the MBS would address this issue of inequity whist improving patient outcomes.

Are there any prerequisite tests?
No

Are the prerequisite tests MBS funded?
No

Please provide details to fund the prerequisite tests:
-

Intervention

Name of the proposed health technology:
Anal human papillomavirus (HPV) and anal cytology testing for the detection of anal pre-cancer and cancer in high-risk populations.

Describe the key components and clinical steps involved in delivering the proposed health technology:
Anal sampling is routinely obtained blindly, with no bowel preparation required. After placing the patient in a lateral decubitus position, a moistened Dacron swab or cytology brush is inserted about 4 cm into the nonlubricated anal canal, ideally up to the distal rectal canal. The swab is slowly withdrawn over 20-30 seconds using a circular movement, applying gentle lateral pressure. The swab is then vigorously eluted in a specific transport medium. Hybrid capture is the most widely used test for HPV, capable of distinguishing between defined high- and low-risk HPV genotypes. If clinically indicated (hr-HPV testing is positive), an aliquot of the transport medium can be analysed for cytological changes, or if required, patients may undergo another smear for cytology, where the exudate is spread onto a glass microscope for processing (Albuquerque 2020; Repiso Jiménez et al 2017).

For HIV negative individuals, partial genotyping is probably adequate, because the great majority of cases are caused by HPV16. For individuals with immune deficiency, a higher proportion of cases are caused by non-16 types, and the range is wide (not just 18). Thus, in people with immune deficiency, there is a justification to identify all hr-HPV types. For HIV positive individuals, a full high-risk HPV panel should be conducted.

Identify how the proposed technology achieves the intended patient outcomes:
Anal cancer is among the limited number of cancers, including cervical and colon cancer that are potentially preventable through treatment of known cancer precursors. Identifying HSIL early enables the early detection, prevention and treatment of anal cancer. Patients treated for anal HSIL (primarily office-based electrocautery) have rates of progression to anal cancer approximately 60% lower than those only undergo active monitoring without treatment (Palefsky et al 2022).

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
No

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

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

Provide details and explain:
Patients considered to be at high-risk, including those with a history of biopsy-proven HSIL/cancer anywhere in the anogenital region, should be tested for HPV annually. For HIV negative and HIV positive individuals testing should be conducted every 5-years and 3-years, respectively.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
This service requires collection of patient samples primarily by a sexual health practitioner; however, specialists already involved in a patient's care may also conduct sampling e.g colorectal surgeons. HPV testing and cytology will be delivered by trained scientists in an accredited laboratory. Testing would be requested by the treating clinician and provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

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

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
HPV testing and cytology will be delivered by trained scientists in an accredited laboratory. Testing would be requested by the treating clinician and provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

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

Yes

Provide details and explain:
The sensitivity of the HPV testing technology, together with the use of internal controls suggests that only instructions (rather than specific training) will be required for sample collection.

Testing would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners in line with other tests in the MBS Pathology Table.

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

☒ Consulting rooms	Sample collection
☐ Day surgery centre	
☐ Emergency Department	
☐ Inpatient private hospital	
☐ Inpatient public hospital	
☒ Laboratory	Testing
☒ Outpatient clinic	Sample collection
☐ Patient's home	
☐ Point of care testing	
☐ Residential aged care facility	

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

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:
There is no direct comparator for this service. The different at-risk patient groups would experience different routine health care until symptomatic of an anal cancer.

People living with HIV: patients would be monitored under the care of their general practitioner, or a sexual health practitioner. When on anti-retroviral therapy, HIV positive patients may undergo viral load testing or HIV genotyping. In addition, patients may have their CD4+ counts taken to monitor therapy effectiveness or disease progression.

MBS item number 69378 (P3 – Microbiology)
Quantitation of HIV viral RNA load in plasma or serum in the monitoring of a HIV sero-positive patient not on antiretroviral therapy - 1 or more tests

Fee: $180.25 Benefit: 75% = $135.20 85% = $153.25

MBS item number 69381 (P3 – Microbiology)
Quantitation of HIV viral RNA load in plasma or serum in the monitoring of antiretroviral therapy in a HIV sero-positive patient - 1 or more tests on 1 or more specimens

Fee: $180.25 Benefit: 75% = $135.20 85% = $153.25

MBS item number 69380 (P3 – Microbiology)
Genotypic testing for HIV antiretroviral resistance in a patient with confirmed HIV infection if the patient's viral load is greater than 1,000 copies per ml at any of the following times:

(a) at presentation; or
(b) before antiretroviral therapy: or
(c) when treatment with combination antiretroviral agents fails;

maximum of 2 tests in a 12-month period
Fee: $770.30 Benefit: 75% = $577.75 85% = $677.10

MBS item number 73802 (P9 - Simple Basic Pathology Tests)
Leucocyte count, erythrocyte sedimentation rate, examination of blood film (including differential leucocyte count), haemoglobin, haematocrit or erythrocyte count - 1 test

Fee: $4.55 Benefit: 75% = $3.45 85% = $3.90

Men who have sex with men: patients would be monitored under the care of their general practitioner, or a sexual health practitioner. Individuals may undergo testing for HIV antibodies or p24 antigen in addition to any routine health checks (recommended for up to 4 times a year). Many individuals may opt to use point of care rapid HIV test self-testing; however, approved self-tests that are purchased by the end user are not eligible for an MBS rebate. At-risk individuals may have their CD4+ counts taken in order to identify those who would benefit from an early HIV diagnosis.

MBS item number 69384 (P3 – Microbiology)
Quantitation of 1 antibody to microbial antigens not elsewhere described in the Schedule - 1 test (This fee applies where a laboratory performs the only antibody test specified on the request form or performs 1 test and refers the rest to the laboratory of a separate APA)

Fee: $15.65 Benefit: 75% = $11.75 85% = $13.35

MBS item number 73802 (P9 - Simple Basic Pathology Tests)
Leucocyte count, erythrocyte sedimentation rate, examination of blood film (including differential leucocyte count), haemoglobin, haematocrit or erythrocyte count - 1 test

Fee: $4.55 Benefit: 75% = $3.45 85% = $3.90

Women with previous anogenital HPV cancer or cervical HSIL: Women with previous HPV-related lower genital tract cancer or cervical HSIL receive regular follow-up by their gynaecologist,

surgeon or general practitioner. This includes cervical cytology, pelvic examination and HPV testing. There is no current anal HPV/ cytology test routinely offered by medical practitioners to these patients. It is only when a woman develops symptoms /signs of anorectal cancer (PR bleeding, mass) that they are referred for assessment.

People with previous anal cancer: receive regular follow up by their surgeon, oncologist or radiation oncologist. This includes imaging and clinical examination.

Organ transplant recipients: require regular quarterly check-ups with their specialist, where routine blood tests are conducted including a full blood examination and biochemistry, lipid studies, viral screens (polyomaviruses, cytomegalovirus) and testing levels of immunosuppressive agents. In addition, regular bone density scans (3 years) and skin cancer checks (2 years) should be conducted, with kidney transplant recipients undergoing regular renal function testing.

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

Please provide a rationale for why this is a comparator:
N/A

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

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

Please outline and explain the extent to which the current comparator is expected to be substituted:
There are currently no MBS item numbers for anal HPV testing or cytology. At-risk patients are either managed in private settings or in state-based sexual health clinics until symptomatic of an anal cancer.

Outcomes

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

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

Safety

- Harms associated with testing/not testing

Clinical effectiveness

- Impact on clinical management
- Morbidity associated with anal carcinoma
- Mortality due to anal carcinoma
- Health-related quality of life
- Other patient-relevant outcomes

Clinical validity

- Clinical sensitivity and specificity
- Positive and negative predictive values
- Prognostic value

Healthcare resource use

- Number of events, and cost associated with anal carcinoma (e.g. hospitalisation; specialist visits; requirements for subsequent therapy; cost of testing)
- Cost-effectiveness of HPV testing and cytology
- Total Australian Government healthcare costs

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

Anal cancer is among the limited number of cancers, including cervical and colon cancer that are potentially preventable through treatment of known cancer precursors. Identifying HSIL early enables the early detection, prevention and treatment of anal cancer. Patients treated for anal HSIL (primarily office-based electrocautery) have rates of progression to anal cancer approximately 60% lower than those only undergo active monitoring without treatment (Palefsky et al 2022).

Proposed MBS items

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

-

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention:

-

Proposed item details

MBS item number	AAAAA
Category description	PROFESSIONAL ATTENDANCES
Proposed item descriptor	Based on item number 2497 Category 1 – Professional attendances AAAA Professional attendance at consulting rooms by a treating physician: (a) involving taking a short patient history and, if required, limited examination and management; and (b) at which a specimen for an anal screening service is collected from the patient: i. if the patient has no history of biopsy-proven anal high-grade squamous intraepithelial lesions (HSIL) or cancer ii. is human immunodeficiency virus (HIV) negative iii. is at least 35 years of age; and iv. has not been provided with an anal screening service or an anal smear service in the last 5 years. OR (c) at which a specimen for an anal screening service is collected from the patient: i. if the patient has no history of biopsy-proven anal high-grade squamous intraepithelial lesions (HSIL) or cancer ii. is human immunodeficiency virus (HIV) positive iii. is at least 35 years of age; and iv. has not been provided with an anal screening service or an anal smear service in the last 3 years. OR (d) at which a specimen for an anal screening service is collected from the patient; i. if the patient has a history of biopsy-proven anal high-grade squamous intraepithelial lesions (HSIL) or cancer and ii. has not been provided with an anal screening service or an anal smear service in the last year
Proposed MBS fee	$17.90
Indicate the overall cost per patient of providing the proposed health technology	$17.90

Anticipated out of pocket expenses	$0.00
Provide details and explain	An amendment to cervical screening sample collection MBS items to include anal sample collection. MBS item numbers: 2497, 2501, 2504, 2507, 2598, 2600, 2603, 2606 in addition to item numbers 2503, 2506, 2509, 2610, 2613, 2616, when a cervical screen is done outside of a general practice.

MBS item number	BBBBB
Category description	PATHOLOGY SERVICES
Proposed item descriptor	Based on item number 73070 Category P6 – Cytology BBBB A test, including partial genotyping, for oncogenic human papillomavirus that may be associated with anal pre cancer or cancer: (a) performed on a liquid based anal specimen; and (b) for an asymptomatic patient who is at least 35 years and has satisfied the conditions of sample collection using MBS item AAAA
Proposed MBS fee	$35.00
Indicate the overall cost per patient of providing the proposed health technology	$35.00
Anticipated out of pocket expenses	$0.00
Provide details and explain	An amendment to cervical screening sample collection MBS items MBS item numbers: 73070, 73071, 73072, 73073, 73074, 73075 A test, including partial genotyping, for oncogenic human papillomavirus that may be associated with cervical pre-cancer or cancer

MBS item number	CCCCC
Category description	PATHOLOGY SERVICES
Proposed item descriptor	Based on item number 73072 Category P6 – Cytology CCCC A test, including partial genotyping, for oncogenic human papillomavirus, 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.
Proposed MBS fee	$35.00
Indicate the overall cost per patient of providing the proposed health technology	$35.00
Anticipated out of pocket expenses	$0.00
Provide details and explain	An amendment to cervical screening sample collection MBS items MBS item numbers: 73070, 73071, 73072, 73073, 73074, 73075 A test, including partial genotyping, for oncogenic human papillomavirus that may be associated with cervical pre-cancer or cancer

MBS item number	DDDDD
Category description	PATHOLOGY SERVICES
Proposed item descriptor	Based on item number 73075 Category P6 – Cytology DDDD A test, including partial genotyping, for oncogenic human papillomavirus, 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
Proposed MBS fee	$35.00
Indicate the overall cost per patient of providing the proposed health technology	$35.00
Anticipated out of pocket expenses	$0.00
Provide details and explain	An amendment to cervical screening sample collection MBS items MBS item numbers: 73070, 73071, 73072, 73073, 73074, 73075 A test, including partial genotyping, for oncogenic human papillomavirus that may be associated with cervical pre-cancer or cancer

MBS item number	EEEEE
Category description	PATHOLOGY SERVICES

Proposed item descriptor	Based on item number 73076 Category P6 – Cytology EEEE Cytology of a liquid based anal specimen, 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 for a patient mentioned in paragraph (c) of that item; 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
Proposed MBS fee	$35.00
Indicate the overall cost per patient of providing the proposed health technology	$35.00
Anticipated out of pocket expenses	$0.00
Provide details and explain	An amendment to cervical screening sample collection MBS items MBS item number: 73076 Cytology of a liquid based cervical or vaginal vault specimen, where the stained cells are examined microscopically or by automated image analysis by or on behalf of a pathologist

Algorithms

Preparation for using the health technology

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

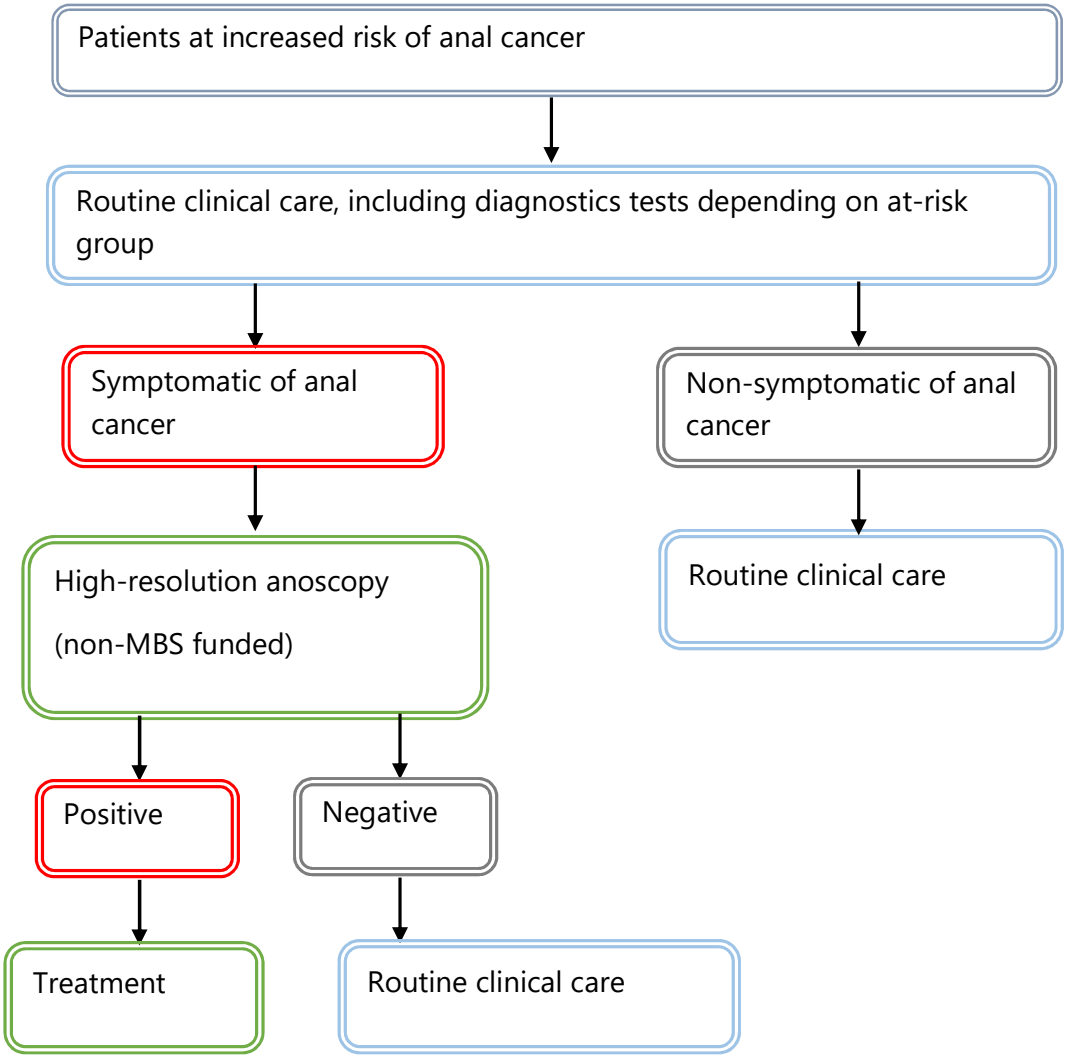

Figure 5 Clinical management algorithm without intervention

Patients would receive routine clinical care, which would vary according to their risk profile. Men who have sex with men would be monitored under the care of their general practitioner, or a sexual health practitioner. Individuals may undergo testing for HIV antibodies or p24 antigen in addition to any routine health checks. Many individuals may opt to use point of care rapid HIV test self-testing; however, approved self-tests that are purchased by the end user are not eligible for an MBS rebate. At-risk individuals may have their CD4+ counts taken in order to identify those who would benefit from an early HIV diagnosis. People living with HIV would be monitored under the care of their general practitioner, or a sexual health practitioner. When on anti-retroviral therapy, HIV positive patients may undergo viral load testing or HIV genotyping. In addition, patients may have their CD4+ counts taken to monitor therapy effectiveness or disease progression. Organ transplant recipients may have regular quarterly clinical examinations with their transplant specialist, where routine blood tests are conducted including a full blood examination and biochemistry, lipid studies, viral screens (polyomaviruses, cytomegalovirus) and testing levels of immunosuppressive agents. In addition, imaging, and clinical examination should be conducted including regular bone density scans (3 years), skin cancer checks (2 years), with kidney transplant patients undergoing regular renal function tests. Women with previous HPV-related lower genital tract cancer or cervical HSIL receive regular follow-up by their gynaecologist,

surgeon or general practitioner. This includes cervical cytology, pelvic examination and HPV testing. People with previous anal cancer receive regular follow up by their surgeon, oncologist or radiation oncologist. This includes imaging and clinical examination.

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

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
There is no direct comparator for this service. The different at-risk patient groups would experience different routine health care until symptomatic of an anal cancer.

Figure 5 describes the clinical algorithm with HPV testing of high-risk individuals, whereas Figure 6 (below) describes the proposed clinical management algorithm with reflex cytology testing after a positive HPV test.

If a positive HPV test is followed by positive cytology, indicating the presence of HSIL, it is recommended that (non-MBS funded) high-resolution anoscopy (similar to colposcopy in cervical cancer) is performed. This may then be followed by treatment such as (non-MBS funded) office-based electrocautery.

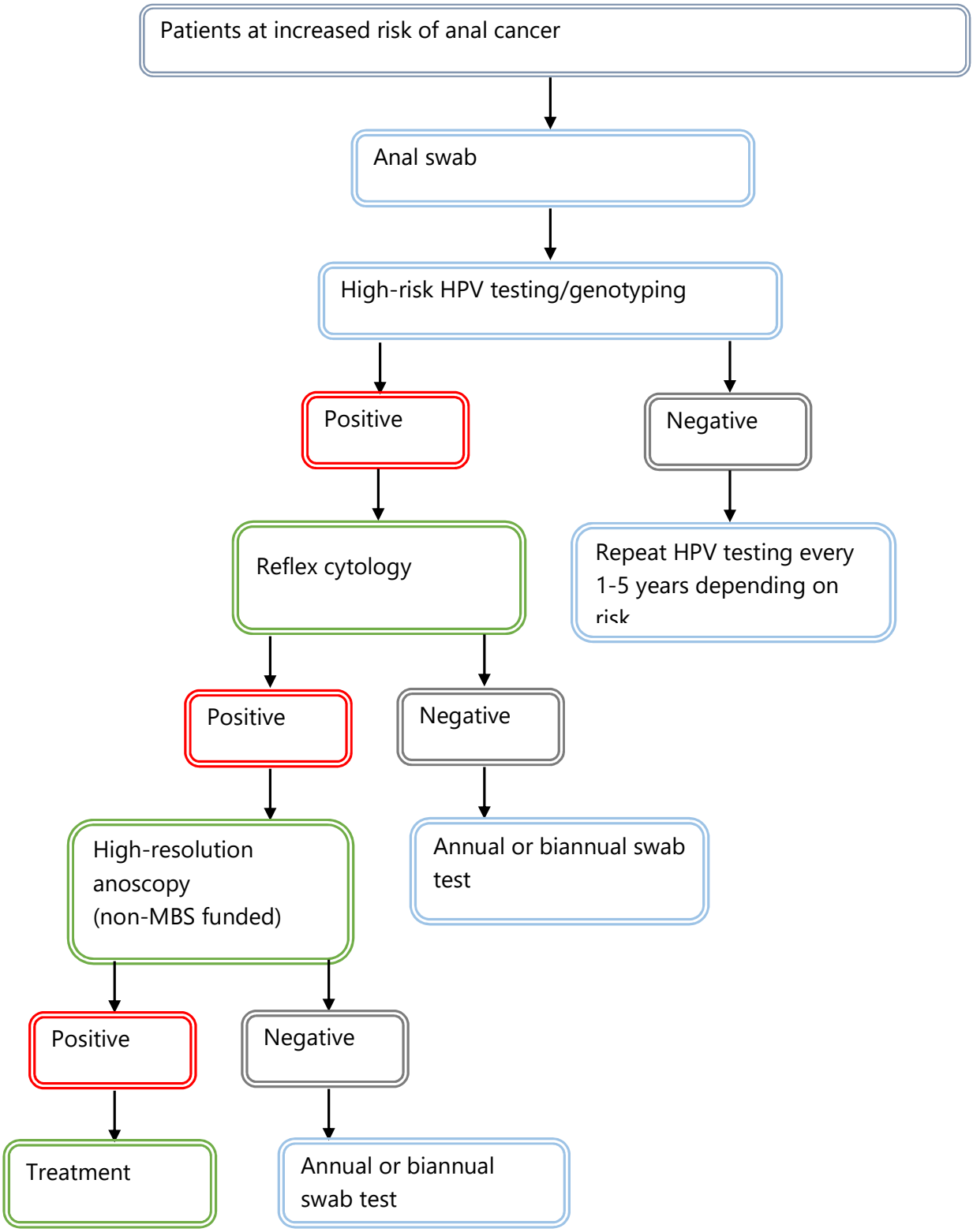

Figure 6: Clinical management algorithm without intervention

Use of the health technology

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

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

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

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
Those with defined abnormalities (such as HPV16/persisting non-16 high-risk HPV, cytology ≥ pHSIL[2]) will be referred on to specialised services, where the extent and nature of histologically-established HSIL can be characterised. People with HSIL deemed to be at high risk of progression to SCCA will be offered treatment. Both high-risk HPV testing and cytology can be used to assess response to treatment.

If a positive HPV test is followed by positive cytology, indicating the presence of HSIL, it is recommended that (non-MBS funded) high-resolution anoscopy (similar to colposcopy in cervical cancer) is performed. This may then be followed by treatment such as (non-MBS funded) office-based electrocautery.

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

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:
There is no appropriate comparator, therefore this will be the introduction of a new test, that will provide early identification of at-risk individuals. . By the early detection of anal high-grade squamous intraepithelial lesions (HSIL), the precursor to SCCA, patients can be treated effectively, usually by electrocautery, improving patient outcomes by reducing the rate of progression to anal cancer by 60% compared to those patients who are actively monitored without treatment.

[2] pHSIL = possible low-grade intraepithelial lesion (pLSIL)

Algorithms

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

Note: Please ensure that the diagrams provided do not contain information under copyright.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)? (please select your response)

- ☒ Superior
- ☐ Non-inferior
- ☐ Inferior

Please state what the overall claim is, and provide a rationale:
Anal cancer is among the limited number of cancers, including cervical and colon cancer that are potentially preventable through treatment of known cancer precursors. Identifying HSIL early enables the early detection, prevention and treatment of anal cancer. Patients treated for anal HSIL (primarily office-based electrocautery) have rates of progression to anal cancer approximately 60% lower than those only undergo active monitoring without treatment (Palefsky et al 2022).

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
Currently, there are no publicly funded testing and treatment options available to patients considered to be at high-risk of developing SCCA, including people living with HIV, HIV-negative men who have sex with men, women with other gynaecological HPV-associated lesions and solid organ transplant recipients. In comparison to the Australia-wide cervical cancer screening program, this lack of testing and treatment options represents a situation of significant inequity for this relatively small and vulnerable population. Listing of this testing on the MBS would address this issue of inequity whilst improving patient outcomes.

Identify how the proposed technology achieves the intended patient outcomes:
By the early detection of anal high-grade squamous intraepithelial lesions (HSIL), the precursor to SCCA, patients can be treated effectively, usually by electrocautery, improving patient outcomes by reducing the rate of progression to anal cancer by 60% compared to those patients who are actively monitored without treatment.

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

A change in clinical management?	Yes
A change in health outcome?	Yes
Other benefits?	-

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

-

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

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

As there is no appropriate comparator, these item numbers will be for new item numbers, which will obviously cost more than doing nothing.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary (repeat columns as required).

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary (repeat columns as required).

Type of study design	Title of journal article	Short description of research	Website link to journal article or research
Systematic review and meta-analysis USA (2022) (Clarke et al 2022)	A systematic review and meta-analysis of cytology and HPV-related biomarkers for anal cancer screening among different risk groups	A total of 39 articles were included. The prevalence of HSIL (AIN2+) was 20% (95% CI, 17-29%), and ranged from 22% in MSM living with HIV to 13% in women and 12% in MSM without HIV. The sensitivity and specificity of cytology and HPV testing were 81% and 62% and 92% and 42%, respectively, and 93% and 33%, respectively for cytology and HPV co-testing.	https://pubmed.ncbi.nlm.nih.gov/35793241/
Systematic review and meta-analysis Netherlands (2019) (Dias Gonçalves Lima et al 2019)	The Accuracy of Anal Swab-Based Tests to Detect High-Grade Anal Intraepithelial Neoplasia in HIV-Infected Patients: A Systematic Review and Meta-analysis	From a total of 22 studies, using cytology with a cut-off of any SIL to detect HSIL sensitivity was 82% and specificity was 45%; with the cut-off of HSIL, sensitivity was 44% and specificity was 79%. For HPV testing, sensitivity was 91% and specificity was 27%. For MSM, the PPV of cytology with a cut-off of any SIL was 36% and NPV was 87%, whereas cytology with a cut-off of HSIL had a PPV of 62% and an NPV of 78%. The PPV of HR-HPV detection was 37% and NPV was 87%.	https://pubmed.ncbi.nlm.nih.gov/31123696/
RCT USA (2022) (Palefsky et al 2022)	Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer	4,459 persons living with HIV (>35 years of age) with biopsy-proven anal HSIL were randomly assigned, in a 1:1 ratio, to receive either HSIL treatment or active monitoring without treatment. Treatment included office-based ablative procedures, ablation or excision under anaesthesia, or the administration of topical fluorouracil or imiquimod. With a median follow-up of 25.8 months, 9 cases were diagnosed in the treatment group (173 per 100,000 person-years) and 21 cases in the active monitoring group (402 per 100,000 person-years). The rate of progression to anal cancer was lower in the treatment group than in the active monitoring group by 57% (95% CI, 6 to 80; p = 0.03).	https://pubmed.ncbi.nlm.nih.gov/35704479/
Comparative Australia (2016) (Jin et al 2016)	The performance of anal cytology as a screening test for anal HSILs in homosexual men	At baseline, all participants underwent a liquid-based anal cytology test and the diagnostic test, high-resolution anoscopy (HRA) at the same time. Biopsies were obtained for histological assessment if lesions suspicious for HPV infection were visible during HRA. Overall, the sensitivity of cytology was 83.2%, specificity 52.6%, the PPV 45.8%, and the NPV 86.7%. Specificity improved with increasing age.	https://pubmed.ncbi.nlm.nih.gov/26915346/
Observational cohort	Effect of the introduction of screening for cancer precursor lesions on anal cancer incidence over time	Among 28,175 individuals in HIV care (59·7% MSM), 227 primary anal cancer cases were diagnosed. Despite the increasing average age of the cohort, crude incidence rates of anal cancer in MSM declined slowly over time, from 107·0 per 100 000 person-years in 1996–2005 to 93·7 per 100 000 person-years in 2013–20 (p=0·49). Crude incidence rates	https://pubmed.ncbi.nlm.nih.gov/36640800/

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Netherlands (2023) van der Zee et al	in people living with HIV: a nationwide cohort study	in men who do not have sex with men (non-MSM) and women were generally lower than in MSM, but increased slightly over time, from 51·08 to 67·82 (p=0·52) per 100 000 person-years in non-MSM and from 8·09 to 24·95 (p=0·29) per 100 000 person-years in women. Anal cancer-related mortality was 3·7% in all men who had been screened and 24·0% in men who had not been screened (p=0·023).	
Comparative cohort Australia (2022) (Poynten et al 2022)	Comparison of four assays for human papillomavirus detection in the anal canal	A total of 475 participants had baseline results available for all 4 assays (166, 35.0% HIV positive), and 169 participants had a diagnosis of cytological and/or histological HSIL.HPV16 and any HRHPV detection were highest with Anyplex II HPV28 (+) (156, 32.8% 95% CI 28.6-37.2 and 359, 75.6%, 95% CI 71.5-79.4 respectively). For detection of concurrent HSIL and HPV16, the assay sensitivity was similar ranging from 49.1%, 95% CI 41.4-56.9 (Anyplex II HPV28 ++) to 55.0%, 95% CI 47.2-62.7 (Anyplex II HPV28 +). For concurrent HSIL and any HRHPV detection, EuroArray was more specific than Anyplex II HPV28 (+) (45.9% 95% CI 40.2-51.7 vs 36.7%, 95% CI 31.3-42.4, p=0.021) and had comparable specificity with Anyplex II HPV28 (++) (45.9% vs 47.2%, 95% CI 41.5-53.0, p=0.75). All assays had high sensitivities for predicting HPV16 detected on LCM (92.5-97.5%). Anyplex II HPV28 and EuroArray were significantly more sensitive than LA for lesions caused by non-HPV16 HRHPV types on LCM	https://www.sciencedirect.com/science/article/abs/pii/S1198743X22003421
Comparative cohort Australia (2018) (Poynten et al 2018)	Human Papillomavirus Seroprevalence and Association with Anal HPV Infection and Squamous Intraepithelial Lesions in Australian Gay and Bisexual Men	Cohort study of gay and bisexual men (GBM) aged >35 years. At six visits over three years, anal samples are collected for cytology, HPV DNA testing, and histology. Baseline serum was tested for HPV L1, E6, and E7 antibodies for 10 HPV types. Seroprevalence and associated predictors were analysed. A total of 436 (74.2%) were seropositive for at least one of the 10 HPV types. Almost half had L1 antibodies to HPV6 (48.5%), over a third to HPV11 (36.4%) and HPV16 (34.5%). HIV-positive men were more likely to be HPV L1 seropositive. HSIL detection was highest among participants who were HPV serology and DNA positive. There was a borderline significant association between presence of HPV16 E6 antibodies and prevalent HSIL (OR = 2.97; P = 0.068 HPV seropositivity with concurrent DNA detection predicted anal HSIL detection	https://pubmed.ncbi.nlm.nih.gov/29700009/
Comparative Australia (2016) (Machalek et al 2016)	Prevalence and risk factors associated with high-grade anal squamous intraepithelial lesions	At the baseline visit all men underwent anal swabbing for cytology and HPV genotyping, followed by high resolution anoscopy. Composite-HSIL prevalence was 47% and 32% among 220 HIV-positive and 396 HIV-negative men, respectively. HSIL-AIN3 (37.7% versus 24.7%; p<0.001), but not HSIL-AIN2 (9.5% versus 7.6%; p=0.395) was more common in HIV-positive men. Recent receptive anal partners (p-trend=0.045), and	https://pubmed.ncbi.nlm.nih.gov/29074193/

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	(HSIL)-AIN2 and HSIL-AIN3 in homosexual men	increasing number of high-risk (HR)-HPV types (p-trend<0.001) were associated with HSIL-AIN2. Lifetime receptive partners (p-trend<0.001), HIV status (OR 1.74) and HPV16 (OR 3.00) were associated with HSIL-AIN3. HPV16 was the most common HR-HPV type detected in men with HSIL-AIN3, both HIV-negative (61.1%) and HIV-positive (54.9%). HPV16 was less commonly detected in men with HSIL-AIN2. Given the strong link between HPV16 and anal cancer, men with HSIL-AIN3 and HPV16 are likely to be at greatest risk of cancer.	
RCT USA (2019) (Goldstone et al 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	120 HIV-infected adults aged ≥27 years with 1-3 biopsy-proven anal HSILs were randomised 1:1 to HSIL ablation with IRC (treatment) or no treatment (active monitoring). Complete index HSIL clearance occurred more frequently in the treatment group than in the AM (62% vs 30%, p < .001). Complete or partial clearance (clearance of ≥1 index HSIL) occurred more commonly in the treatment group (82% vs 47%; p < .001). Having a single index lesion, compared with having 2-3 lesions, was significantly associated with complete clearance (relative risk, 1.96).	https://pubmed.ncbi.nlm.nih.gov/30060087/
Cost-effectiveness USA (2017) (Deshmukh et al 2017)	Management of precancerous anal intraepithelial lesions in human immunodeficiency virus-positive men who have sex with men: Clinical effectiveness and cost-effectiveness	A decision analytic model of the natural history of anal carcinoma and HSIL management strategies was constructed for HIV-positive MSM who were 27 years old or older. Outcomes included the lifetime cost, life expectancy, quality-adjusted life expectancy, cumulative risk of cancer and cancer-related deaths, and cost-effectiveness from a societal perspective. Active monitoring was the most effective approach in patients 29 years or younger; thereafter, HSIL treatment plus adjuvant qHPV vaccination became most effective. When cost-effectiveness was considered, do nothing was cost-effective until the age of 38 years, and HSIL treatment plus adjuvant qHPV vaccination was cost-effective beyond the age of 38 years. The ICER decreased as the age at HSIL management increased. Outcomes were sensitive to the rate of HSIL regression or progression and the cost of high-resolution anoscopy and biopsy.	https://pubmed.ncbi.nlm.nih.gov/28950043/
Cohort	5-Year Prospective Evaluation of Cytology, Human Papillomavirus Testing, and Biomarkers for	363 HIV+ MSM had anal cytology and a high-resolution anoscopy at baseline. For each biomarker (HPV16/18, HPV E6/E7 mRNA, and p16/Ki-67), baseline sensitivity and specificity for a combined endpoint of HSIL and anal intraepithelial neoplasia grade 2 or more severe diagnoses (HSIL/AIN2+), were calculated. 2- and 5-year cumulative risks of	https://pubmed.ncbi.nlm.nih.gov/30418518/

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USA (2019) (Clarke et al 2019)	Detection of Anal Precancer in Human Immunodeficiency Virus-Positive Men Who Have Sex With Men	HSIL/AIN2+ were calculated. 129 men were diagnosed with HSIL/AIN2+ during the study. HR-HPV testing had the highest positivity and sensitivity of all assays, but the lowest specificity. HPV16/18 and HPV E6/E7 mRNA had high specificity, but lower sensitivity. The 2- and 5-year risks of HSIL/AIN2+ were highest for those testing HPV16/18- or HPV E6/E7 mRNA-positive, followed by those testing dual stain-positive. Those testing HR-HPV- or dual stain-negative had the lowest 2- and 5-year risks of HSIL/AIN2+. HPV-related biomarkers provide long-term risk stratification for anal precancers.	
Cohort USA (2016) (D'Souza et al 2016)	Anal Cancer Screening in Men Who Have Sex With Men in the Multicenter AIDS Cohort Study	723 HIV-infected and 788 HIV-uninfected MSM with ACyt, with a second ACyt collected 2 years later. A referral for high-resolution anoscopy was suggested for abnormal ACyt. Prevalence of any abnormal ACyt was 25% in HIV-uninfected MSM and increased to 38% -47% among HIV-infected MSM. Anal HPV16 DNA was also more common in HIV-infected than HIV-uninfected MSM (25% versus 16%, $P < 0.001$). Abnormal baseline ACyt together with prevalent HPV16 DNA detection was present in only 7% of HIV-uninfected MSM compared to 18% of HIV-infected MSM with current CD4 < 350, $P < 0.001$. 19% of untreated HIV-infected men with ASC-H/HSIL cytology maintained that same grade of cytology in their second test approximately 2 years later, and 15% with ASC-US/LSIL "progressed" to ASC-H/HSIL. Abnormal ACyt had high sensitivity (96%) but low specificity (17%) for biopsy-proven HSIL.	https://pubmed.ncbi.nlm.nih.gov/26656784/
Comparative USA (2021) (Gaisa et al 2021)	Comparing Anal Cancer Screening Algorithms Using Cytology and Human Papillomavirus DNA Testing in 3 High-Risk Population	Comparison of anal cytology to high-risk human papillomavirus (hrHPV) DNA testing and 2 novel cytology/hrHPV co-testing algorithms among 3 high-risk populations: 1837 participants (1504 HIV-infected men who have sex with men (MSM), 155 HIV-uninfected MSM, and 178 HIV-infected women). Performance to detect HSIL/cancer was compared between 4 strategies. Histological HSIL/cancer was detected in 756 (41%) participants. Cytology had the lowest sensitivity (0.76-0.89) but highest specificity (0.33-0.36) overall and for each subgroup. Algorithm B was the most sensitive strategy overall (0.97) and for MSM (HIV-infected 0.97; HIV-uninfected 1.00). For women, hrHPV testing and both algorithms yielded higher sensitivity than cytology (0.96, 0.98, and 0.96). Specificity was low for all strategies/subgroups (range, 0.16-0.36). Cytology and hrHPV testing significantly increased sensitivity but decreased specificity to detect anal precancer/cancer among high-risk populations.	https://pubmed.ncbi.nlm.nih.gov/33388757/

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Retrospective comparative **USA (2009) (Goldstone et al 2009)**	Detection of oncogenic human papillomavirus and other predictors of anal high-grade dysplasia in men who have sex with men with abnormal cytology	Retrospective chart review of men who have sex with men undergoing anal screening with atypical squamous cells of undetermined significance cytology, Hybrid-Capture(R) II testing, and biopsy. A total of 597 men who have sex with men enrolled and had 1,015 atypical squamous cells of undetermined significance cytology results: 185 (18.2 percent) had HSIL and 156 (84 percent) HPV+. The rates for sensitivity, specificity, positive predictive value, and negative predictive value were 84, 53, 29, and 94 percent, respectively. Of 390 low-grade squamous intraepithelial lesion cytology results, HSIL was found in 141 and 127 (90%) were HPV+. Those with previous HSIL or human immunodeficiency virus had increased risk of HSIL (hazard ratio = 2.2 and 1.95, respectively). Referring only those with oncogenic human papillomavirus for biopsy reduces the number requiring this by almost half but some HSIL are missed.	https://pubmed.ncbi.nlm.nih.gov/19273953/
Case series Italy (2021) (Rollo et al 2021)	Evaluation of HPV-Related Biomarkers in Anal Cytological Samples from HIV-Uninfected and HIV-Infected MSM	The association between high-risk (hr)HPV DNA, HPV16/18 DNA, hrHPV E6/E7 mRNA, and p16/Ki-67 with cytological abnormalities (any grade) and high-grade intraepithelial lesions (HSIL) was assessed in HIV-uninfected and HIV-infected MSM. 150 cytological samples in PreservCyt (Hologic), negative to HSIL report, were analysed. In HIV-infected MSM, positivity for all the biomarkers significantly increased with the cytological grade. In both populations, the association of hrHPV E6/E7 mRNA and p16/Ki-67 positivity with HPV16 did not differ significantly compared to hrHPVs other than HPV16. In HIV-uninfected MSM, the odds of having an HSIL increased approximately six times for the p16/Ki-67 positive cases. In HIV-infected individuals, all the biomarkers showed a significant association with HSIL, except for hrHPV DNA, with the strongest association observed for p16/Ki-67. The odds of HSIL increased almost 21 times in those positive for this biomarker.	https://pubmed.ncbi.nlm.nih.gov/34358038/
Case series Italy (2018) (Donà et al 2018)	Anal Cytological Lesions and HPV Infection in Individuals at Increased Risk for Anal Cancer	1021 MSM, 38.0% were HIV-infected Anal cytological lesions were observed in 32.5% and 53.2% of the HIV-uninfected and HIV-infected individuals, respectively (P<.0001). The highest ASCUS1 prevalence was observed among >45-year-old HIV-uninfected MSM (37.3%) and 25-to 29-year-old HIV-infected MSM (66.7%). High-grade squamous intraepithelial lesions (HSILs) peaked in >45-year-old HIV-uninfected subjects and 35- to 39-year-old HIV-infected subjects. Individuals with anal infections with high-risk (HR) HPV types were 3 to 4 times more likely to have an ASCUS1 report. An HPV-16 and/or HPV-18 infection increased the odds of HSIL or more severe cytology (HSIL1) for HIV-	https://pubmed.ncbi.nlm.nih.gov/29694716/

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		infected MSM almost 4 times. MSM concurrently infected with HR and low risk HPVs were significantly more likely to have low-grade squamous intraepithelial lesions or more severe cytology (LSIL1) than those infected with only HR types.	
Retrospective case series Italy (2018) (Santorelli et al 2018)	Screening for Squamous Cell Anal Cancer in HIV Positive Patients: A Five-Year Experience	A retrospective study on 204 HIV patients who underwent a screening program for SCC with digital anorectal examination, anal Pap test, including HPV test and cytology, and high-resolution video-proctoscopy (HR-VPS) with and without acetic acid 3%. Depending on macroscopic appearance and biopsies, patients underwent observation or treatment. Median follow-up was 36 months. Cytologic abnormalities (Cyt+) for high-risk HPV genotypes were recorded in 34% of patients. HR-VPS was positive in 59 patients (29%), of whom 13 patients (22%) were positive for warts; the rest have typical features of anal intraepithelial neoplasia (AIN). Sixteen (8%) patients had AIN (AIN I-III) and underwent wide local excision, ablation, or imiquimod. Absence of progression was recorded. Fourteen patients (7%) had SCC: eight (57%) with no evidence of recurrence, two (14%) had recurrence, and four (29%) died from metastatic disease.	https://pubmed.ncbi.nlm.nih.gov/28644711/