

Updates in Anal cytology

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Disclosure

PathAI: Consultant

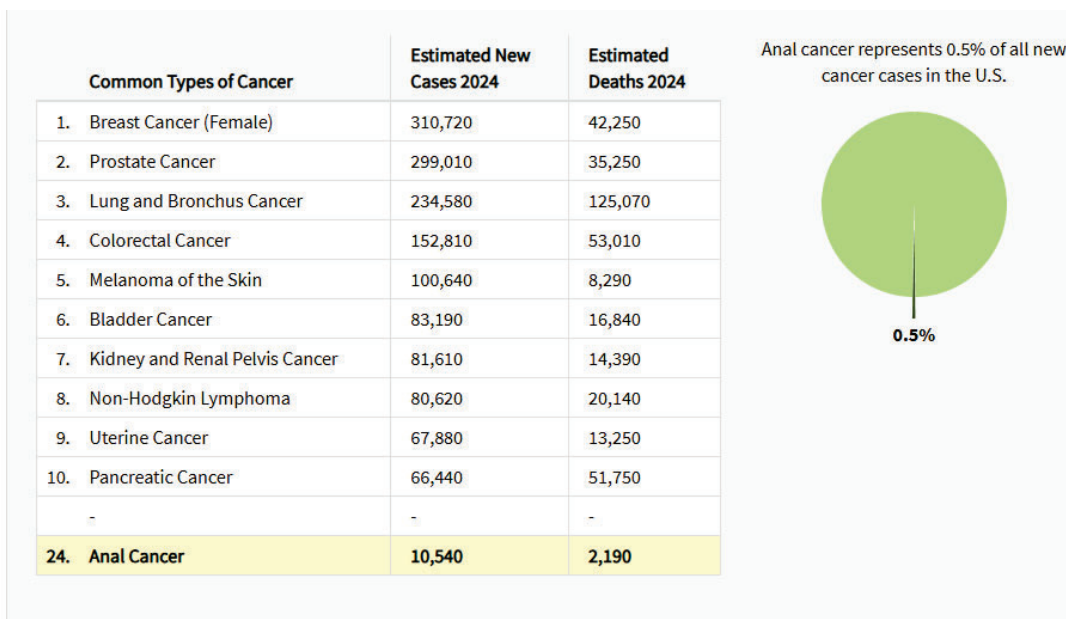
I have no conflict of interest in relation to this presentation.

Outlines

- ❖ Updated anal cancer statistics
- ❖ High-risk populations for anal cancer screening
- ❖ Techniques for anal cancer screening
- ❖ The primary goal of anal cancer screening
- ❖ The role and performance of anal cytology
- ❖ Updated screening guidelines for anal cancer screening

Anal cancer statistics

Compared to other cancers, **anal cancer is rare**

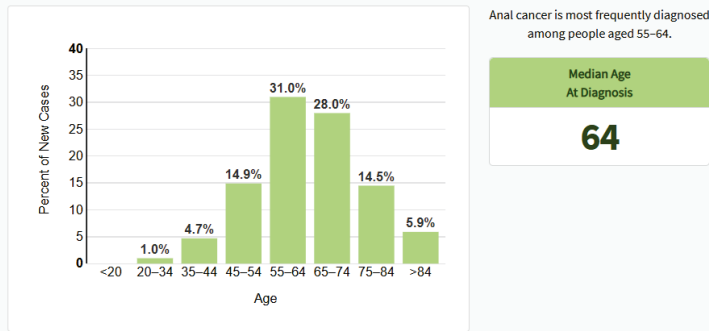


In 2024, it is estimated that there will be 10,540 new cases of anal cancer and an estimated 2,190 people will die of this disease.

<https://seer.cancer.gov/statfacts/html/anus.html>

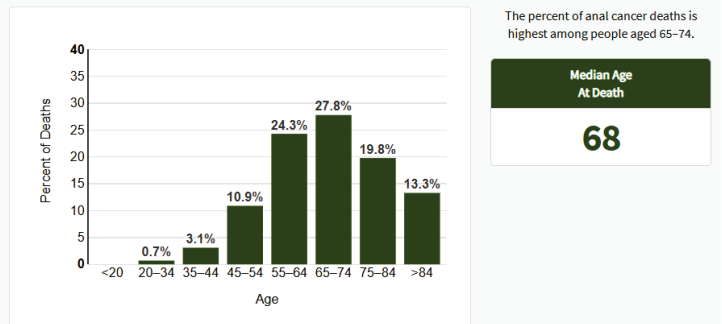
Anal cancer statistics

Percent of New Cases by Age Group: Anal Cancer



SEER 22 2017-2021, All Races, Both Sexes

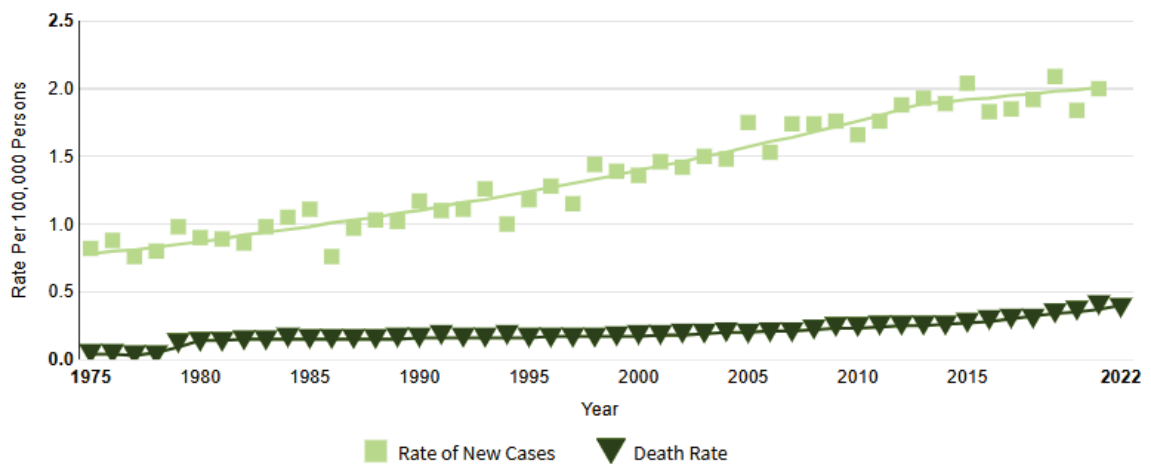
Percent of Deaths by Age Group: Anal Cancer



<https://seer.cancer.gov/statfacts/html/anus.html>

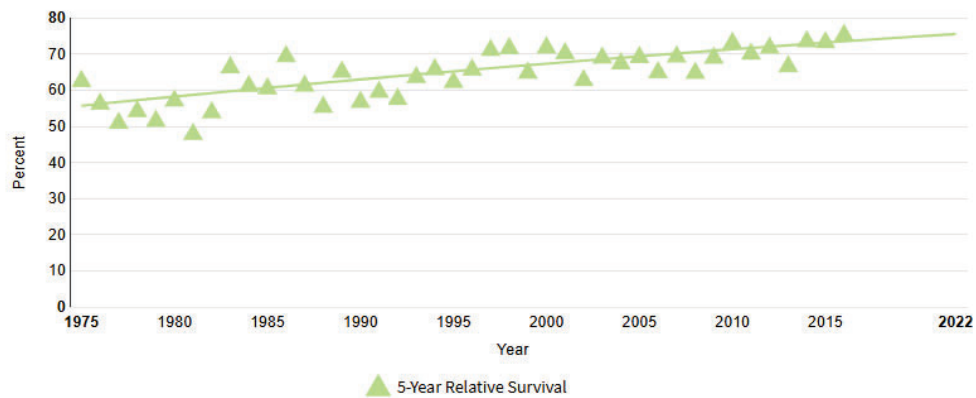
Anal cancer statistics

New Cases, Deaths and 5-Year Relative Survival



<https://seer.cancer.gov/statfacts/html/anus.html>

Anal cancer statistics



SEER 8 5-Year Relative Survival Percent from 1975–2016, All Races, Both Sexes.

Modeled trend lines were calculated from the underlying rates using the [Joinpoint Survival Model Software](https://seer.cancer.gov/statfacts/html/anuss.html).

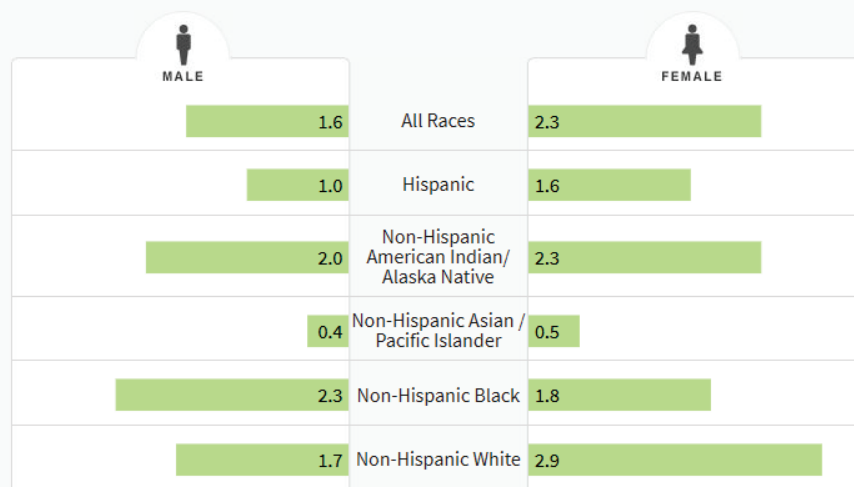


<https://seer.cancer.gov/statfacts/html/anuss.html>

Anal cancer statistics

Anal cancer is slightly more common in women than men. Infection with human papillomavirus (HPV) has been associated with this cancer. The rate of new cases of anal cancer was **1.9 per 100,000 men and women per year** based on 2017–2021 cases, age-adjusted.

Rate of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Anal Cancer

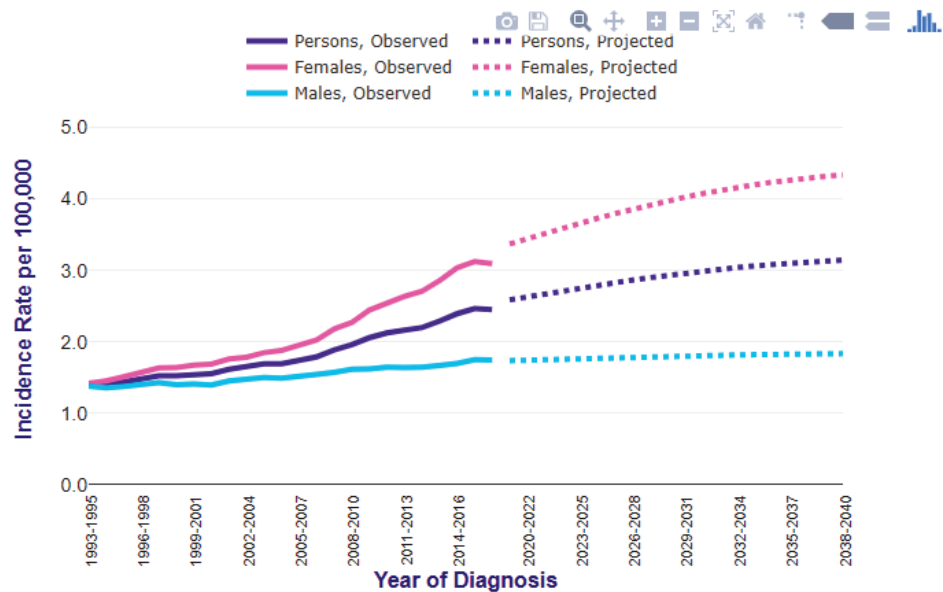


SEER 22 2017–2021, Age-Adjusted

<https://seer.cancer.gov/statfacts/html/anuss.html>

Anal cancer statistics

Anal cancer (C21), Observed and Projected Age-Standardised Incidence Rates, by Sex, UK, 1993-2040



<https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/anal-cancer/incidence#heading-One>

Cervical cancer screening: universal

Anal cancer screening: only high-risk populations

Who is at risk?

TABLE 1 Populations for screening.

Population—Risk category	When	Anal cancer incidence ^{2,5} per 100,000 person-years
Risk Category A (incidence ≥ 10-fold compared to the general population)		
MSM and TW with HIV	Age 35	>70/100,000 age 30–44 >100/100,000 age 45+
Women with HIV	Age 45	>25/100,000 age 45+
MSW with HIV	Age 45	>40/100,000 age 45+
MSM and TW not with HIV	Age 45	>18/100,000 age 45–59 >34/100,000 age 60+
History of vulvar HSIL or cancer	Within 1 year of diagnosis	>40/100,000
Solid organ transplant recipient	10 years post-transplant	>25/100,000
Risk Category B (incidence up to 10-fold higher compared to the general population)		
Cervical/vaginal cancer	Shared decision age 45 ^a	9/100,000
Cervical/vaginal HSIL	Shared decision age 45 ^a	8/100,000
Perianal warts (male or female)	Shared decision age 45 ^a	Unknown
Persistent cervical HPV 16 (>1 year)	Shared decision age 45 ^a	Unknown
Other immunosuppression (e.g., Rheumatoid arthritis, Lupus, Crohn's, Ulcerative colitis, on systemic steroid therapy)	Shared decision age 45 ^a	6/100,000
Incidence among the general population: 1.7 per 100,000 ⁸		

Abbreviations: HSIL, high grade squamous intraepithelial lesion; MSM, Men who have sex with men; MSW, Men who have sex with women; TW, Transgender women.

^aShared decision-making is defined as the process in which a health care provider and patient work together to make a health care decision. The optimal decision considers evidence-based information regarding available options, the provider's knowledge and experience, and the patient's values and preferences.

Stier EA, et al. *Int J Cancer*. 2024 May 15;154(10):1694-1702. PMID: 38297406.

Primary goal of anal cancer screening

To identify anal HSIL

How?

Why ?

Techniques for anal cancer screening

- ❖ DARE (digital anorectal examination): systematically palpating the anal canal and perianal region for potential lesions.
- ❖ Anal cytology: non –palpable precancer lesions, directed at high-risk populations
- ❖ HPV testing
- ❖ Referrer for HRA (high-resolution anoscopy)

Similarities of anal and cervical cytology

- ❖ Both aim to identify HPV associated cancer precursors
- ❖ Both mainly aim the squamous lesions
- ❖ Both include transformation zone, including squamous epithelial cells and glandular cells on cytology
- ❖ Both use Bethesda system as the cytology reporting system

Differences of anal and cervical cytology

	Anal cancer	Cervical cancer
Incidence	Rising	Declining
Screening	Only high-risk groups	Routine
Sampling	Blinded	Not blinded
Unsatisfactory rate	Higher	Lower
Typical koilocytes	Less frequently seen	More frequently seen
Interobserver variability	Higher	Lower
Cytohistologic correlation	Poor	Good
Treatment cancer	Radiation + chemotherapy	surgical ± radiation + chemo

Table 2 Similarities and differences between cervical and anal cytology, based on multiple studies.¹⁰⁻¹³

Clinico-pathological characteristics	Anal cancer	Cervical cancer
Affected population	Men and women	Women
Incidence	Rising	Declining
The risk of being diagnosed with anal cancer during one's lifetime	1 in 500	0.7%
Prevalence (American Cancer Society's estimates for cervical cancer in the United States for 2023)	~9760 new cases (3180 in men and 6580 in women) ~1870 deaths (860 in women and 1010 in men)	~13,960 new cases ~4310 deaths
Average age at diagnosis	60 years	50 years
Incidence of anal cancer in general population.	1.7 per 100,000 person-years	7.5 per 100,000 person-years
HPV infection	HPV associated	HPV associated
Screening guidelines	None to limited	Yes
Anal cancer screening	Advocated for only high risk groups	Routine
Rate of progression from AIN to ASCC in the general population estimate	5%-11%	N/A
HR-HPV testing	Not FDA approved	FDA approved
Precancerous lesions	AIN 2-3	CIN 2-3
Site of origin	Transformation zone	Transformation zone
Transformation zone	Rectal columnar/metaplastic cells	Endocervical/metaplastic cells
Risk of HSIL progression to cancer	Not well established, estimated to be 1 in 377	Well established 1 in 80
Prevalence of disease/abnormalities	High in high-risk population	296,981 women living with cervical cancer (2020)
Type of cancer (most common)	Squamous cell carcinoma	Squamous cell carcinoma and glandular carcinoma
Sampling	Blinded	Not blinded
Cytohistologic correlation	Poor	Good
Reporting	Bethesda System	Bethesda System
Interobserver variability	Higher than cervical cytology	Lower than anal cytology
Palpation used for detection of cancer	Yes, DARE	No
Keratizing lesions	Frequently seen	+/-
Unsatisfactory rate	Higher	+/-
Degenerative changes	Frequently seen	+/-
Typical koilocytes	Less frequently seen	More frequently seen
Mixture of LSIL + HSIL	Frequently seen	+/-
Atypical parakeratosis	Frequently seen	+/-
Management	Anoscopy	Colposcopy
Treatment HSIL	Ablation: infrared coagulation, fulguration	Ablation: cryotherapy, laser
	Surgical excision	LEEP
Treatment cancer	Radiation + Chemotherapy	Surgical ± radiation + chemotherapy

Anal cytology often with underdiagnosis

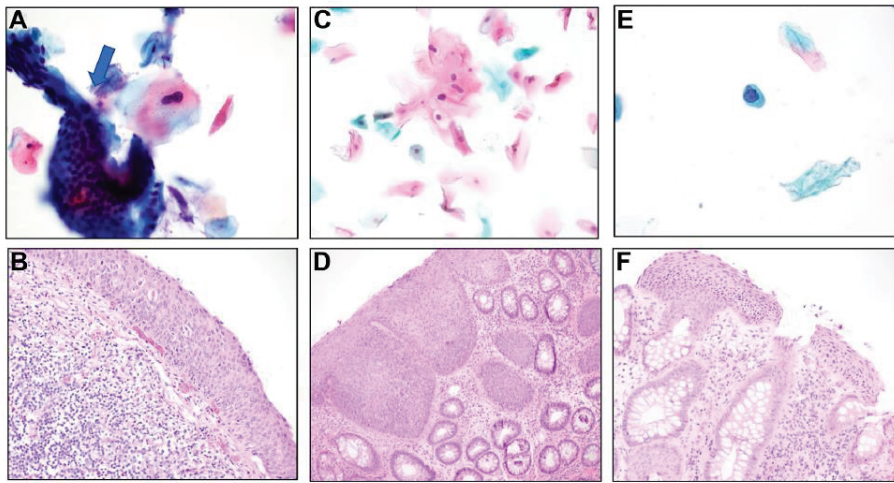
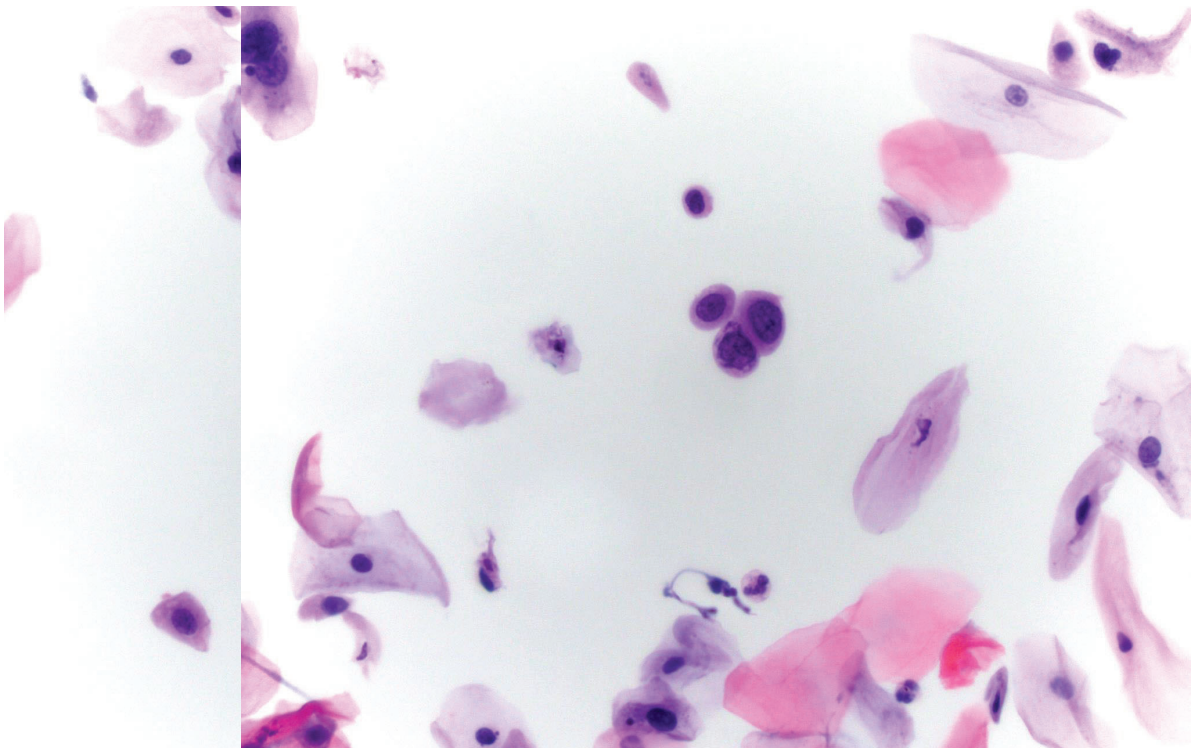


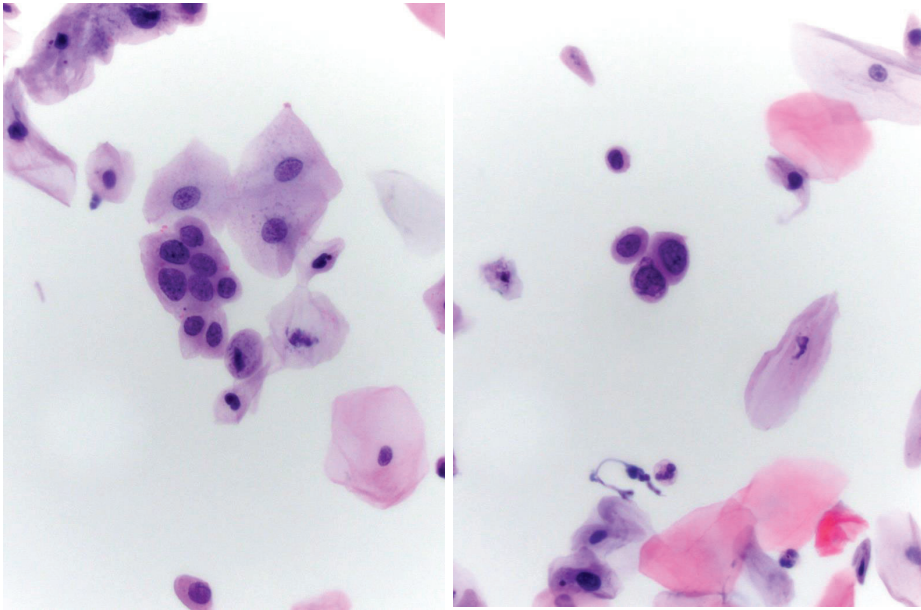
Figure 4 Anal dysplasia. A, Intermediate squamous cells with binucleation and hyperchromasia best classified as atypical squamous cells of undetermined significance (ASC-US) (ThinPrep, 400X). B, Follow-up biopsy showed high grade squamous intraepithelial lesion (HSIL) (hematoxylin and eosin [H&E], 200X). C, Koilocytic change and nuclear atypia characteristic of low-grade squamous intraepithelial lesion (LSIL) (SurePath, 400X). D, Follow-up anal biopsy demonstrated HSIL (H&E, 200X). E, A cell with high N:C ratio, hyperchromatic nuclei and irregular nuclear membranes best classified as atypical squamous cells cannot exclude high grade squamous intraepithelial lesion (ASC-H) (SurePath, 40X). F, Follow-up anal biopsy demonstrated HSIL (H&E, 200). These examples represent cases in which cytology underestimates severity of anal dysplasia seen in follow-up HRA directed anal biopsy.

Vohra P, Khorsandi N, Baskota SU. *J Am Soc Cytopathol.* 2024 Mar-Apr;13(2):122-140PMID: 38097479.

45 yo M with HIV

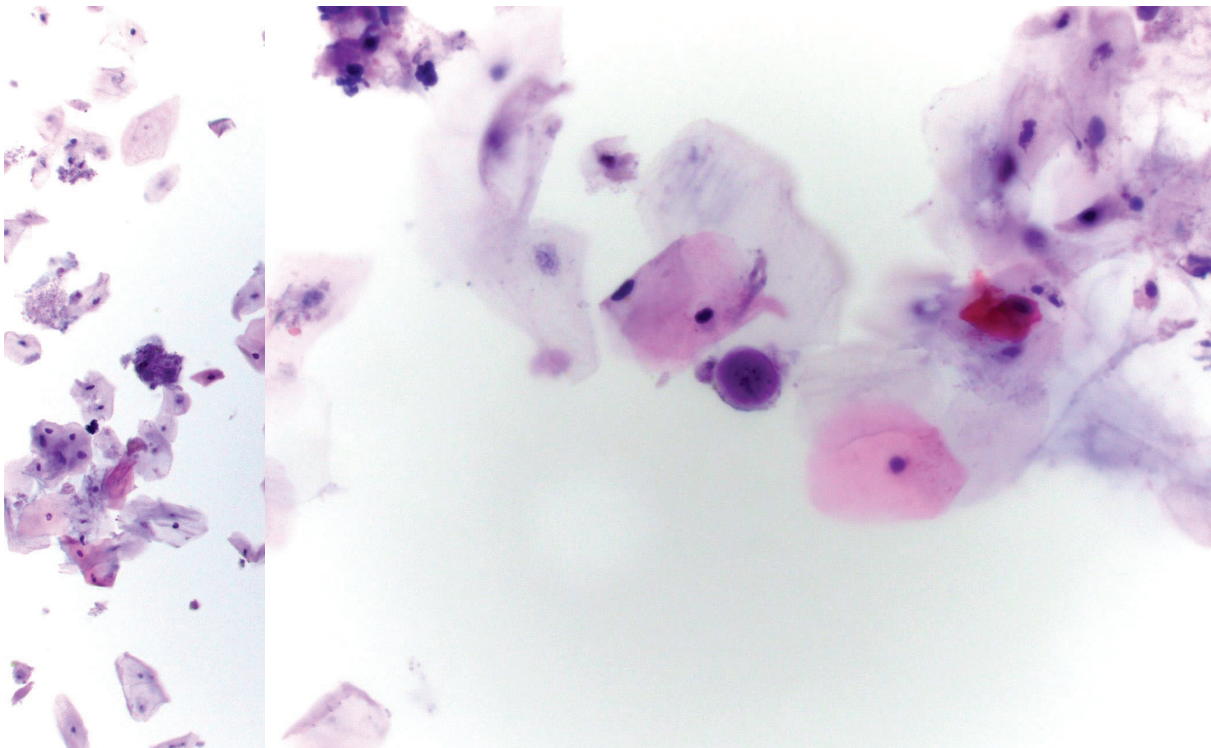


45 yo M with HIV

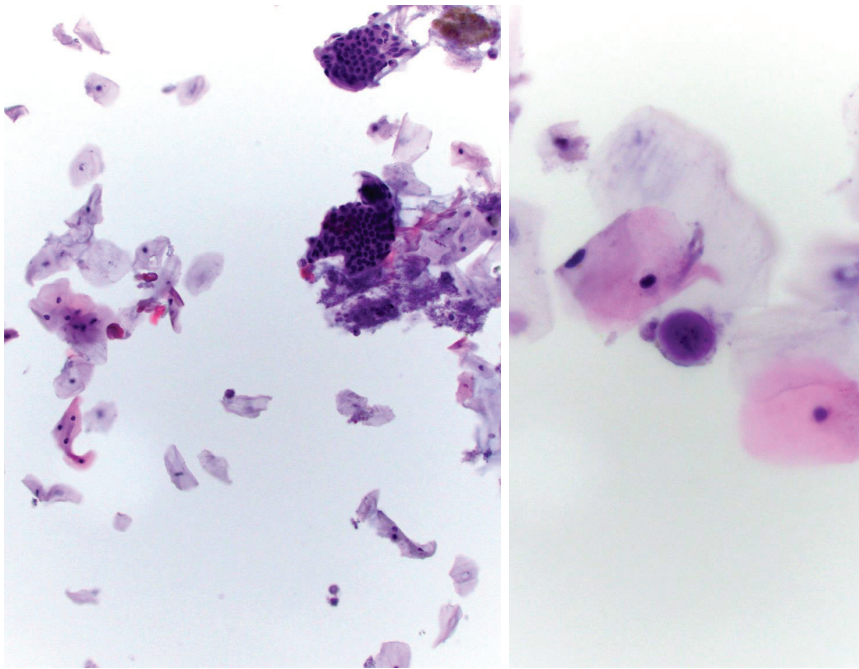


- ❖ Final dx: HSIL
- ❖ High PPV
- ❖ A useful quality control measure for the anoscopist

35 yo M with well controlled HIV and h/o anal dysplasia



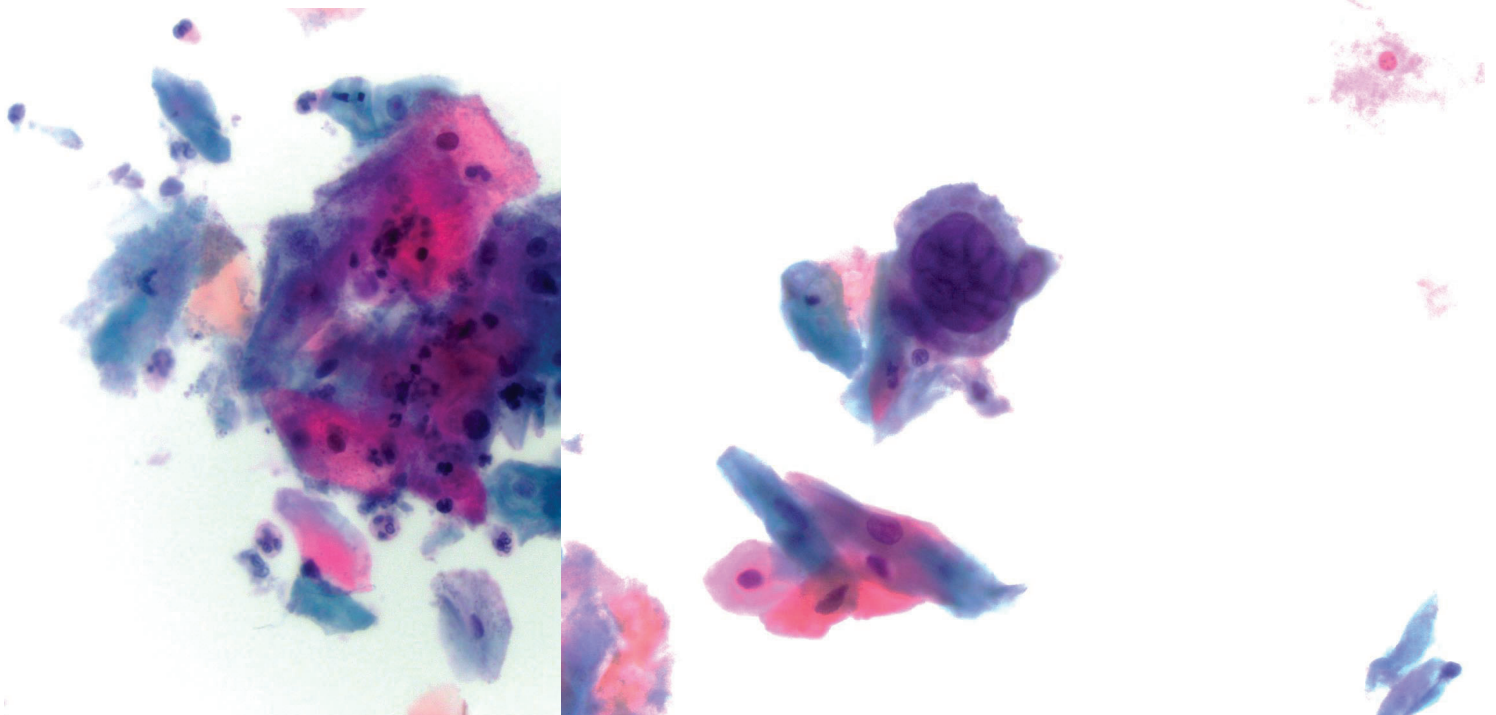
35 yo M with well controlled HIV and h/o anal dysplasia



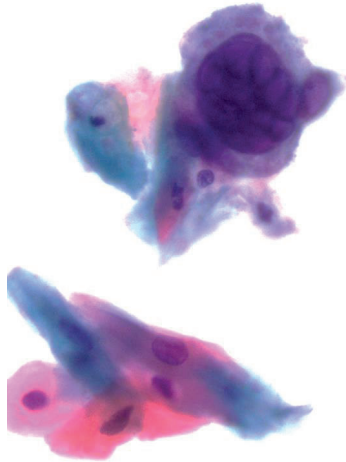
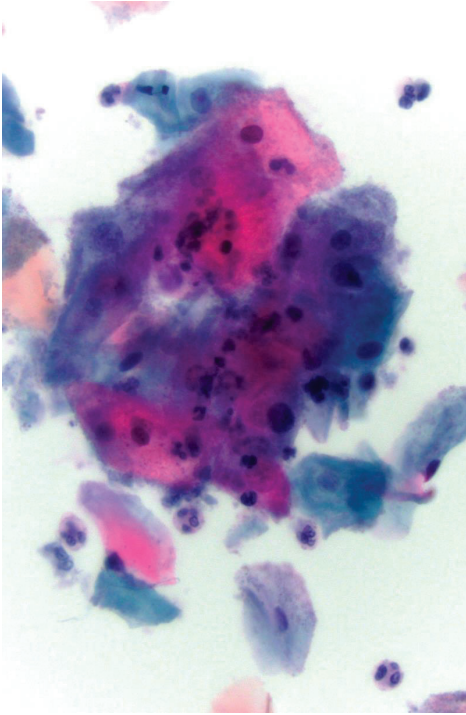
- ❖ Final diagnosis:
NILM
Forms consistent with
Entamoeba coli
- ❖ A NILM diagnosis: up to
16% of AIN (7% of HSIL,
9% of LSIL) on follow-up
anal biopsy

Silva M, et al. Rev Esp Enferm Dig. 2018 Feb;110(2):109-114. PMID: 29168646.

35 yo M with HIV



35 yo M with HIV

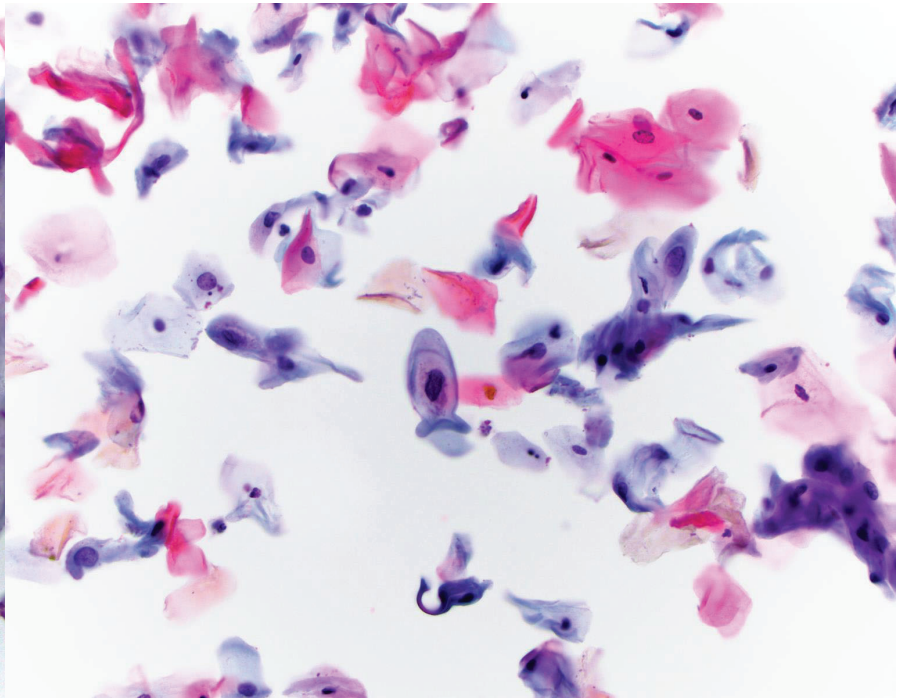
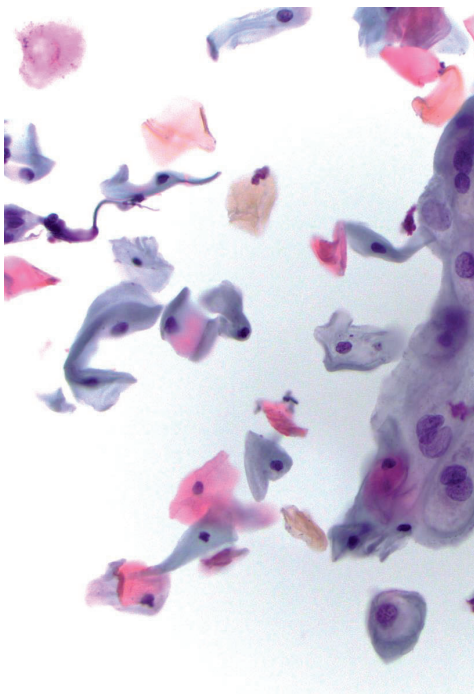


❖ Final diagnosis:
ASC-US
Cellular changes
characteristic of Herpes
simplex virus

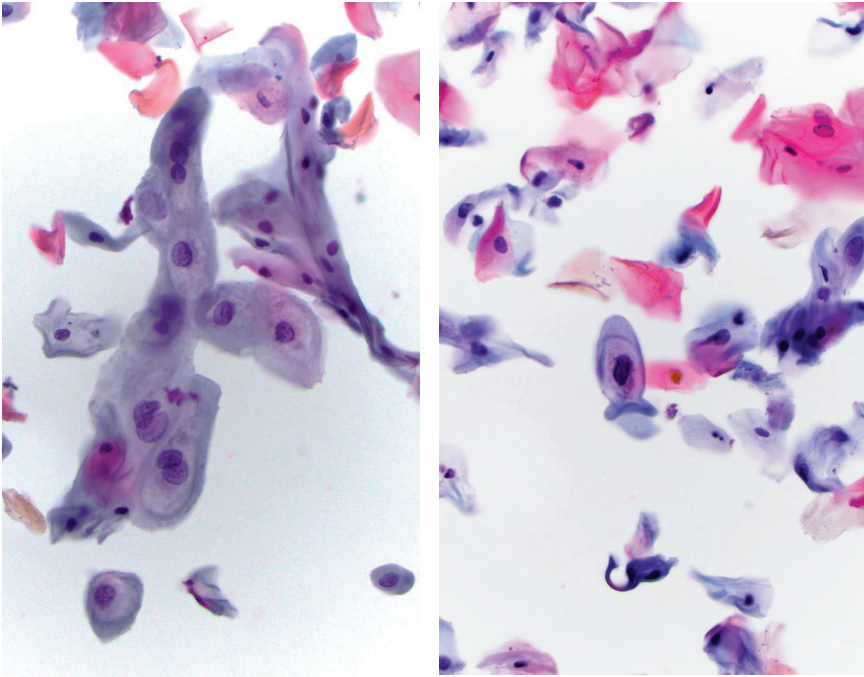
❖ An ASC-US diagnosis: up to
15% of HSIL on the
subsequent biopsy

Silva M, et al. Rev Esp Enferm Dig. 2018 Feb;110(2):109-114. PMID: 29168646.

49 yo F with HIV and asymptomatic gonococcal pharyngitis



49 yo F with HIV and asymptomatic gonococcal pharyngitis



❖ Final diagnosis: LSIL

❖ A LSIL diagnosis: Up to 48% of HSIL on follow up biopsy in MSM.

Johnson GE, et al.. J Am Soc Cytopathol. 2016 May-Jun;5(3):145-153. PMID: 31042517.

Primary goal of anal cancer screening

To identify anal HSIL

How?

Why?

The whole purpose of anal cancer screen is to identify HSIL

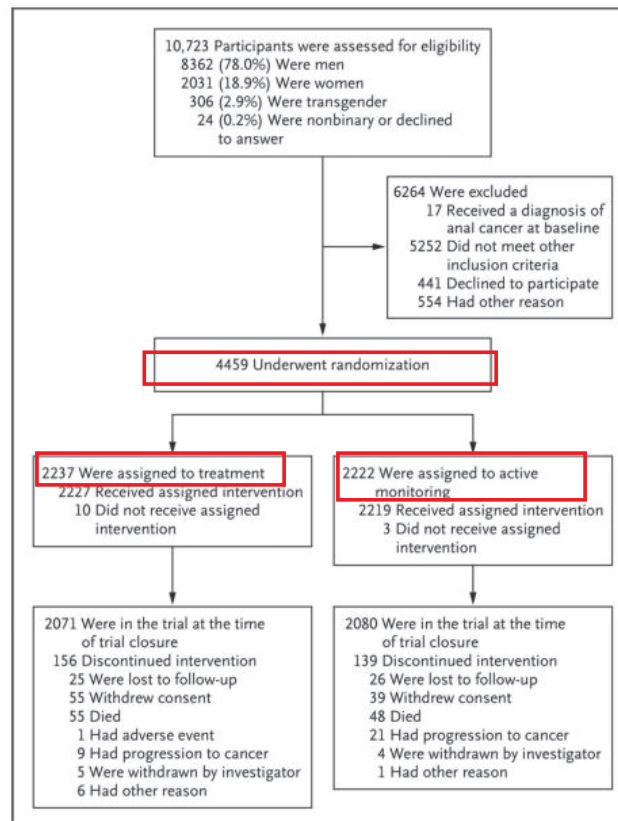
Can the treatment of anal HSIL reduce anal cancer?



Published in final edited form as:
N Engl J Med. 2022 June 16; 386(24): 2273–2282. doi:10.1056/NEJMoa2201048.

**Treatment of Anal High-Grade Squamous Intraepithelial Lesions
to Prevent Anal Cancer**

- ❖ The objective is to determine whether treating anal HSIL reduces the risk of progression to anal cancer in persons living with HIV.



L, Barroso LF, et al. *N Engl J Med.* 2022 Jun 16;386(24):2273-2282. PMID: 35704479; PMCID: PMC9717677.

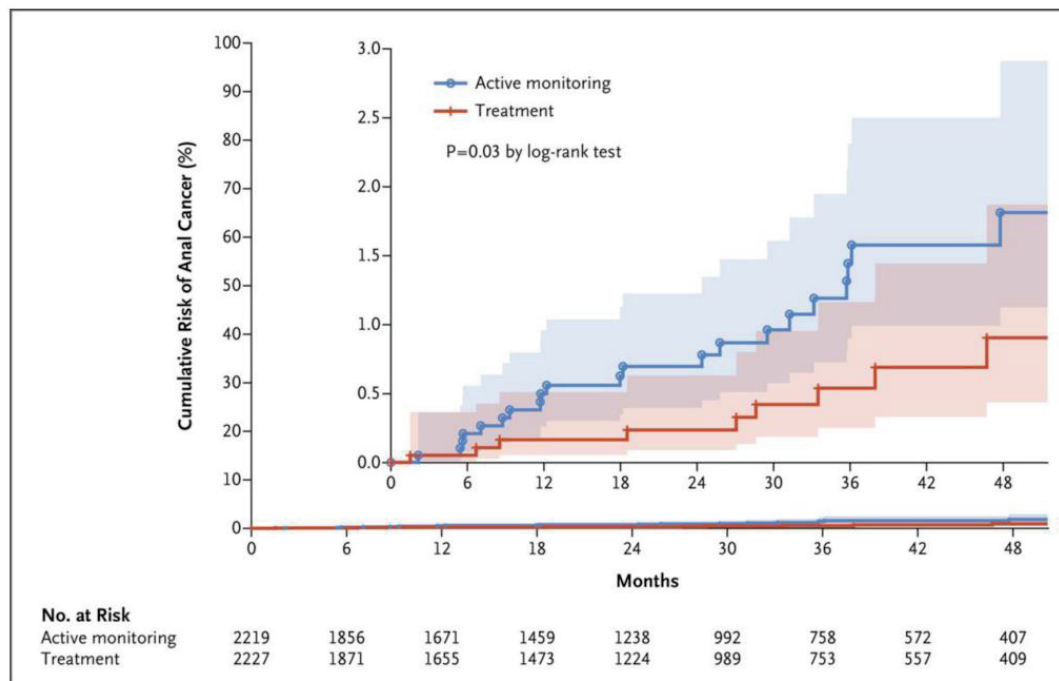


Figure 2. Kaplan-Meier Curve of the Time to Progression to Anal Cancer.

The inset shows the data on an expanded y axis. The shaded areas represent 95% confidence intervals.

L, Barroso LF, et al. *N Engl J Med.* 2022 Jun 16;386(24):2273-2282. PMID: 35704479; PMCID: PMC9717677.

Conclusion:

- ❖ The data show that treatment of anal HSIL, primarily with **office-based electrocautery**, significantly reduced the risk of progression to anal cancer among persons living with HIV who were 35 years of age or older.
- ❖ The data provide support for the use of screening and treatment for anal HSIL as the standard of care for persons living with HIV who are 35 years of age or older.
- ❖ The data may also be relevant for other groups at increased risk for anal cancer.
- ❖ The data supports integrating anal cancer prevention into clinical guidelines.

L, Barroso LF, et al. *N Engl J Med*. 2022 Jun 16;386(24):2273-2282. PMID: 35704479; PMCID: PMC9717677.

Updates for anal cancer screen guidelines

International Anal Neoplasia Society's consensus guidelines for anal cancer screening

Elizabeth A. Stier¹ | Megan A. Clarke² | Ashish A. Deshmukh^{3,4} |
Nicolas Wentzensen² | Yuxin Liu⁵ | I. Mary Poynten⁶ |
Eugenio Nelson Cavallari⁷ | Valeria Fink⁸ | Luis F. Barroso⁹ |
Gary M. Clifford¹⁰ | Tamzin Cuming¹¹ | Stephen E. Goldstone¹² |
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¹⁹Douglass Hanly Moir Pathology, Sydney, New South Wales, Australia

Recommendations, but no consensus

- ❖ The Infectious Diseases Society of America (IDSA)
- ❖ The New York State Department of Health AIDS Institute (NYSDOH-AI)
- ❖ American Society for Colposcopy and Cervical Pathology (ASCCP)
- ❖ The International Anal Neoplasia Society (IANS)

Management of screening test results

TABLE 2 Screening tests for anal high-grade squamous intraepithelial lesion (HSIL) and cancer.

Primary screening test	Triage test	Level of evidence	Special considerations
Cytology	None	BII	Anal cytology is the most widely used and evaluated test for anal cancer screening. Providers may consider using different thresholds for referral to HRA depending on capacity (see Table 3).
	hrHPV (with or without genotyping)	CII	hrHPV testing to triage ASC-US cytology (or other results, see Table 3) could be used to reduce HRA referral rates. This strategy has not been widely evaluated in the literature.
hrHPV (with or without genotyping)	None	BII	The efficiency of primary testing with a pooled hrHPV test is limited in populations with high HPV prevalence (e.g., MSM with HIV). This strategy could be considered in settings with no cytology infrastructure, or to reduce HRA (for patients testing hrHPV negative) in practices providing HRA on all patients. In most settings, additional triage will be needed for individuals who test hrHPV positive. Use of hrHPV genotyping, specifically for HPV16, may help identify patients with high risk of HSIL or cancer. Performance does not seem to improve with the addition of HPV18. ⁴ hrHPV testing may not be available in many settings.
	Cytology	CII	Triage of hrHPV-positive results with cytology (e.g., at an ASC-US or worse threshold) can improve specificity of hrHPV-testing and reduce HRA referral. However, observational data on this approach are lacking in the literature.
Cytology/hrHPV co-test (with or without genotyping)	None	BII	Current available data suggest that anal co-testing does not provide any benefit over primary hrHPV testing for anal HSIL. However, anal co-testing may be especially beneficial for its negative predictive value. Co-testing may be less efficient in populations with high hrHPV prevalence.
Digital anal rectal exam (DARE)	None	BII	All populations at-risk for anal cancer receive DARE at time of screening tests (or in lieu of screening tests in absence of HRA availability).

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; hr, high risk; HRA, high resolution anoscopy; HSIL, high grade squamous intraepithelial lesion; MSM, men who have sex with men.

Stier EA, et al. *Int J Cancer*. 2024 May 15;154(10):1694-1702. PMID: 38297406.

Management of screening test results

TABLE 3 Management of screening test results.

Primary screening test	Triage test	Test results	Management	Modification for low HRA capacity ^a
Cytology	None	NILM	Repeat screening 12 months	Repeat 12–24 months
		ASC-US or worse	HRA referral	ASC-US/LSIL—repeat 12 months HSIL and ASC-H—HRA referral
	hrHPV testing of ASC-US or worse	ASC-US/hrHPV negative	Repeat screening 12 months	Repeat 24 months
		LSIL/hrHPV-negative	Provider discretion—either HRA referral or repeat screening in 12 months	Repeat 12 months
		ASC-US or LSIL/ hrHPV positive	HRA referral	ASC-US/LSIL/hrHPV positive (non 16)—repeat 12 months hrHPV16 positive (regardless of cytology)—HRA referral
		ASC-H/HSIL (regardless of HPV)	HRA referral	HRA referral

Stier EA, et al. *Int J Cancer*. 2024 May 15;154(10):1694-1702. PMID: 38297406.

Management of screening test results

Primary screening test	Triage test	Test results	Management	Modification for low HRA capacity ^a
hrHPV testing [HPV16 genotyping]	None	hrHPV negative	Repeat screening 12–24 months	Repeat 24 months
		hrHPV positive	HRA referral	hrHPV positive (non16)– repeat 12 months HPV16 positive—HRA referral
	Cytology of hrHPV positive	NILM/hrHPV positive [hrHPV positive (non16)]	Provider discretion—either HRA referral or repeat screening in 12 months	Repeat 12 months
		ASC-US or worse/ hrHPV positive [HPV16 positive/ regardless of cytology]	HRA referral	ASC-US/LSIL/hrHPV positive (non16)— repeat 12 months HSIL, ASC-H (regardless of hrHPV)—HRA referral hrHPV16 positive (regardless of cytology)— HRA referral

Stier EA, et al. *Int J Cancer*. 2024 May 15;154(10):1694-1702. PMID: 38297406.

Management of screening test results

Primary screening test	Triage test	Test results	Management	Modification for low HRA capacity ^a
Cytology/hrHPV co-testing [HPV16 genotyping]	None	NILM/hrHPV negative	Repeat screening 12–24 months	Repeat 24 months
		ASC-US/hrHPV negative	Repeat screening 12 months	ASCUS/hrHPV negative—repeat 24 months
		NILM/hrHPV positive [NILM/hrHPV positive (non16)]	Provider discretion—either HRA referral or repeat screening in 12 months	Repeat 12 months
		LSIL/hrHPV negative	Provider discretion—either HRA referral or repeat screening in 12 months	Repeat 12–24 months
		ASC-US or LSIL/ hrHPV positive HSIL, ASC-H (regardless of HPV) [HPV16 positive, regardless of cytology]	HRA referral	ASC-US/LSIL/hrHPV positive (non16)—repeat 12 months HSIL, ASC-H (regardless of hrHPV)—HRA referral hrHPV16 positive (regardless of cytology)— HRA referral

Abbreviations: ASC-H, atypical squamous cells cannot exclude high grade; ASC-US, atypical squamous cells of undetermined significance; hr, high risk; HRA, high resolution anoscopy; HSIL, high grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.

^aLow HRA capacity is defined as greater than 6 month wait for HRA referral for an abnormal screening test.

Stier EA, et al. *Int J Cancer*. 2024 May 15;154(10):1694-1702. PMID: 38297406.

Take home messages

- ❖ Anal cancer is rare, and currently anal cancer screening is only directed to the high-risk populations
- ❖ Screening methods: anal cytology, hrHPV, cytology/hrHPV cotest, DARE
- ❖ Anal cytology and cervical cytology share similarities and differences
- ❖ Anal cytology has a tendency underdiagnose the anal dysplasia
- ❖ The randomized ANCHOR study showed that treating HSIL can significantly lower (60% lower) the risk of anal cancer in individuals living with HIV, emphasizing the importance of anal cancer screening
- ❖ International Anal Neoplasia Society (IANS) developed consensus guidelines for anal cancer screening among various high-risk groups, delineated the referral for HRA, and informed management of abnormal screening results

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