ASCP2019 ANNUAL MEETING

SEPTEMBER 11-13 | PHOENIX, AZ

EDUCATION ▸ ADVANCEMENT ▸ DISCOVERY

Anal Neoplasia: An update

Steven D Hart, MD
David Geffen School of Medicine at UCLA

Disclosure

I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation.

Learning Objectives

- To understand the background and recommendations of the Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions (LAST Project)
- To learn about some of the practical aspects of the use of biomarkers (p16 immunohistochemistry) in anal biopsies
- To understand the similarities and differences of evaluating and reporting anal vs. cervical cytology specimens
- To understand the approach and limitations of screening strategies in high risk populations

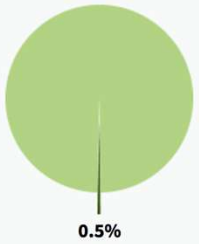
Anal Cancer

How Common Is This Cancer?

Compared to other cancers, anal cancer is rare.

	Common Types of Cancer	Estimated New Cases 2019	Estimated Deaths 2019
1.	Breast Cancer (Female)	268,600	41,760
2.	Lung and Bronchus Cancer	228,150	142,670
3.	Prostate Cancer	174,650	31,620
4.	Colorectal Cancer	145,600	51,020
5.	Melanoma of the Skin	96,480	7,230
6.	Bladder Cancer	80,470	17,670
7.	Non-Hodgkin Lymphoma	74,200	19,970
8.	Kidney and Renal Pelvis Cancer	73,820	14,770
9.	Uterine Cancer	61,880	12,160
10.	Leukemia	61,780	22,840
	-	-	-
25.	Anal Cancer	8,300	1,280

Anal cancer represents 0.5% of all new cancer cases in the U.S.



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

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

SEER 21 2012-2016, Age-Adjusted

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

TYPES OF ANAL CANAL CANCERS

- Squamous cell carcinoma, majority of cases
  - 90% in USA
- Adenocarcinoma, percentage varies
  - ~10% in USA
  - <15% in Northern Europe
  - More frequent in some African and Asiatic countries
  - Majority of anal cancers in Japan
- Other
  - Melanoma, neuroendocrine tumors

At a Glance

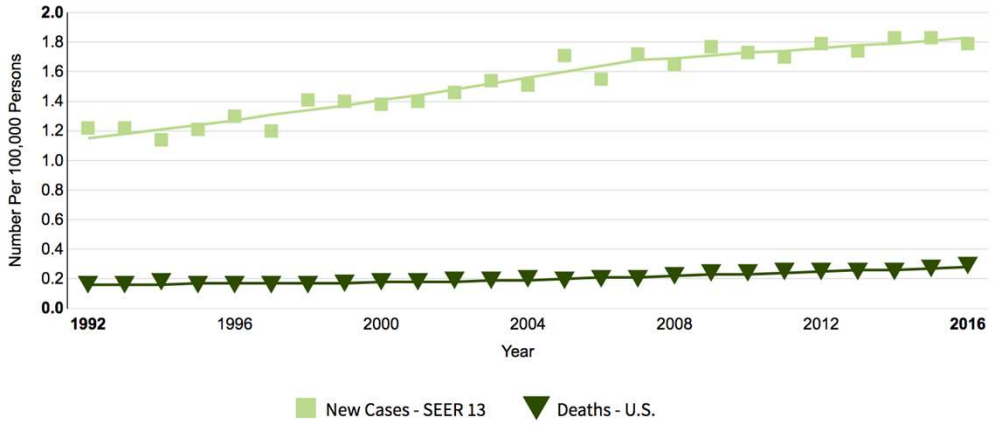
Estimated New Cases in 2019	8,300
% of All New Cancer Cases	0.5%

Estimated Deaths in 2019	1,280
% of All Cancer Deaths	0.2%

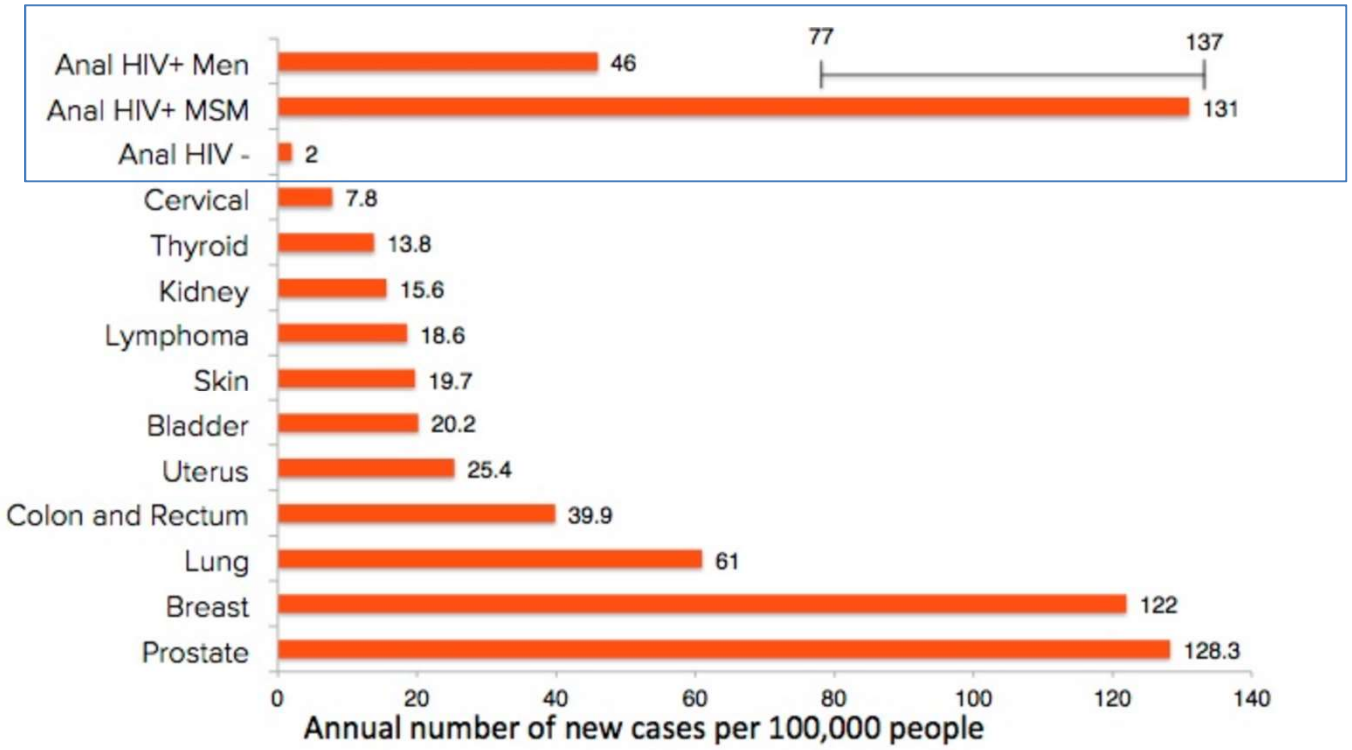
Percent Surviving 5 Years

68.3%

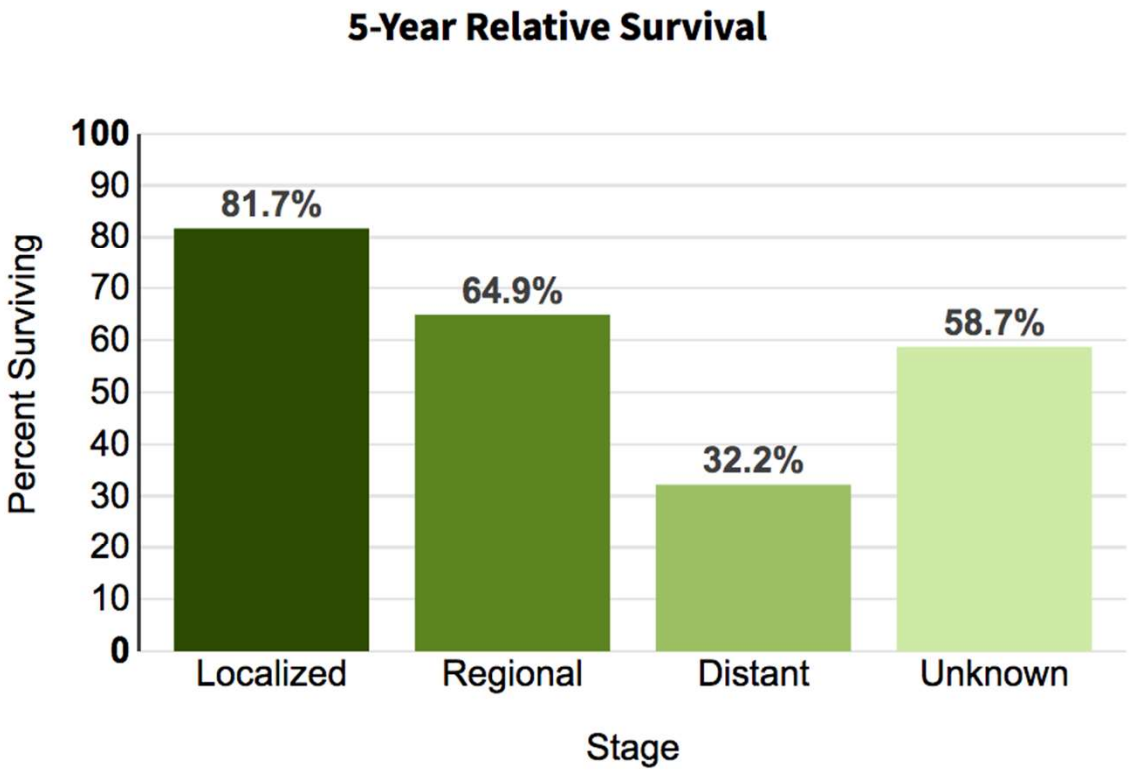
2009-2015



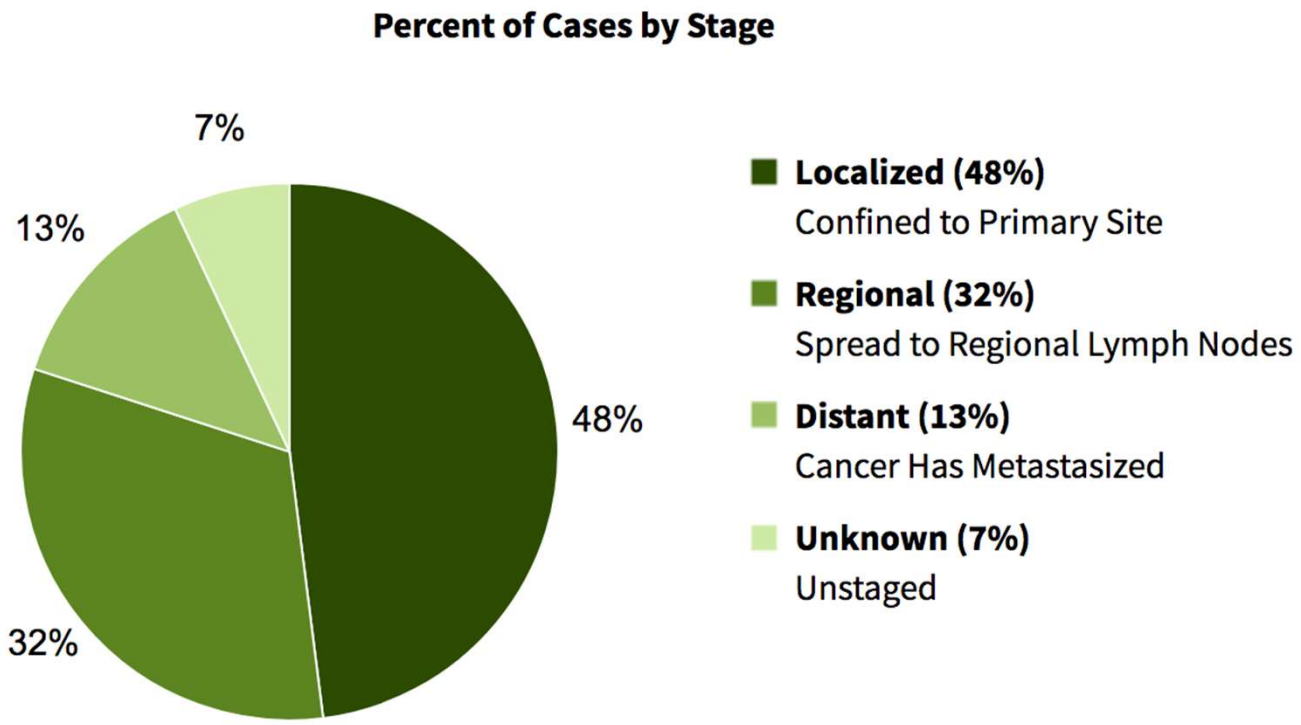
https://seer.cancer.gov/statfacts/html/anus.html



https://anchorstudy.org/anal-cancer-risk-among-hiv-positive-men-and-women



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



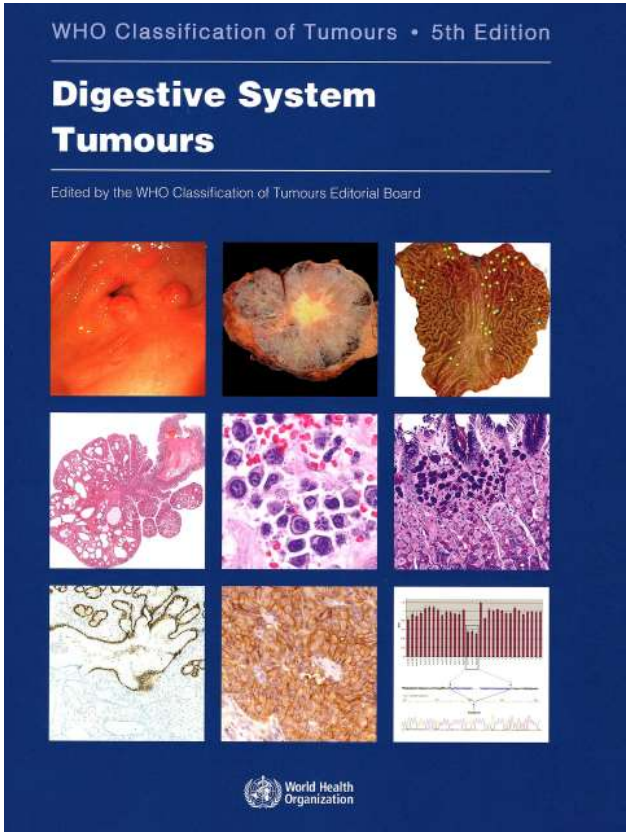
https://seer.cancer.gov/statfacts/html/anus.html

Treatment

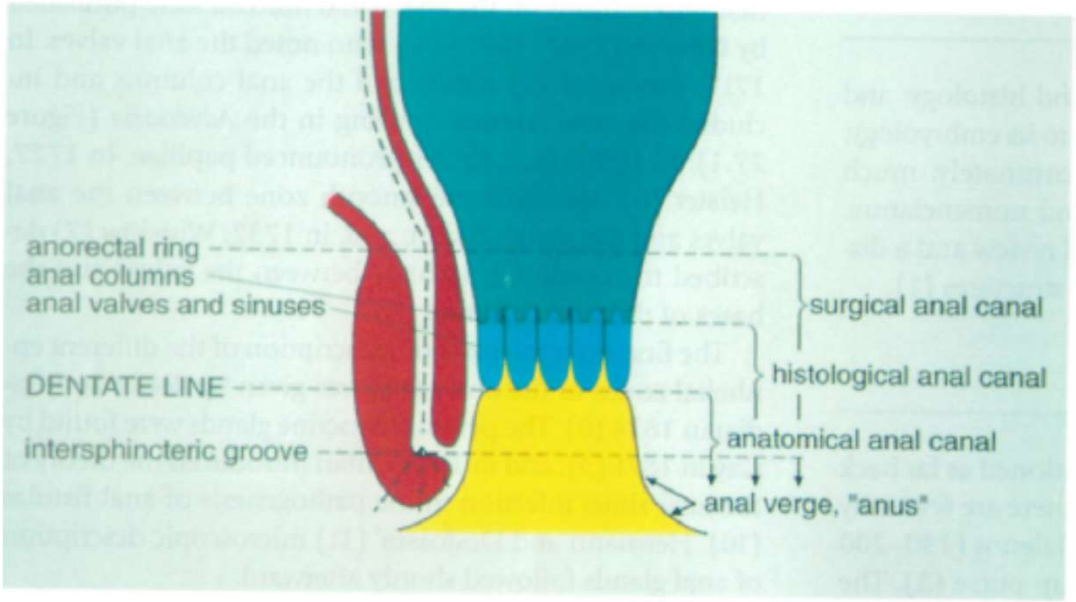
- Chemoradiation
- Surgery in selected cases

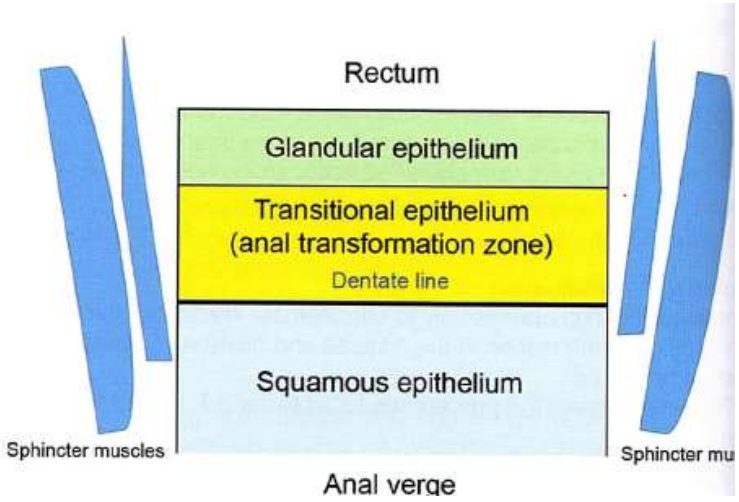
TAKE HOME MESSAGE

- Anal cancer is rare, but the incidence is rising especially in groups known to be at increased risk
  - (HIV infected men and women, MSM, otherwise immunocompromised men and women (e.g. solid organ transplant), women with a history of HSIL or HPV related genital cancer)
- Targeted screening in high risk groups might be useful


WHO Classification of Tumours • 5th Edition
Digestive System Tumours
Edited by the WHO Classification of Tumours Editorial Board
World Health Organization

ANAL CANAL





Fenger C. Anal Canal. In: Mills S, ed. *Histology for Pathologists*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:663-683.

Alfred Lam and John Goldblum (2019). Tumors of the Anal Canal. Digestive System Tumours. W. C. o. T. E. Board. Lyon, France, IARC**: 193-212.**

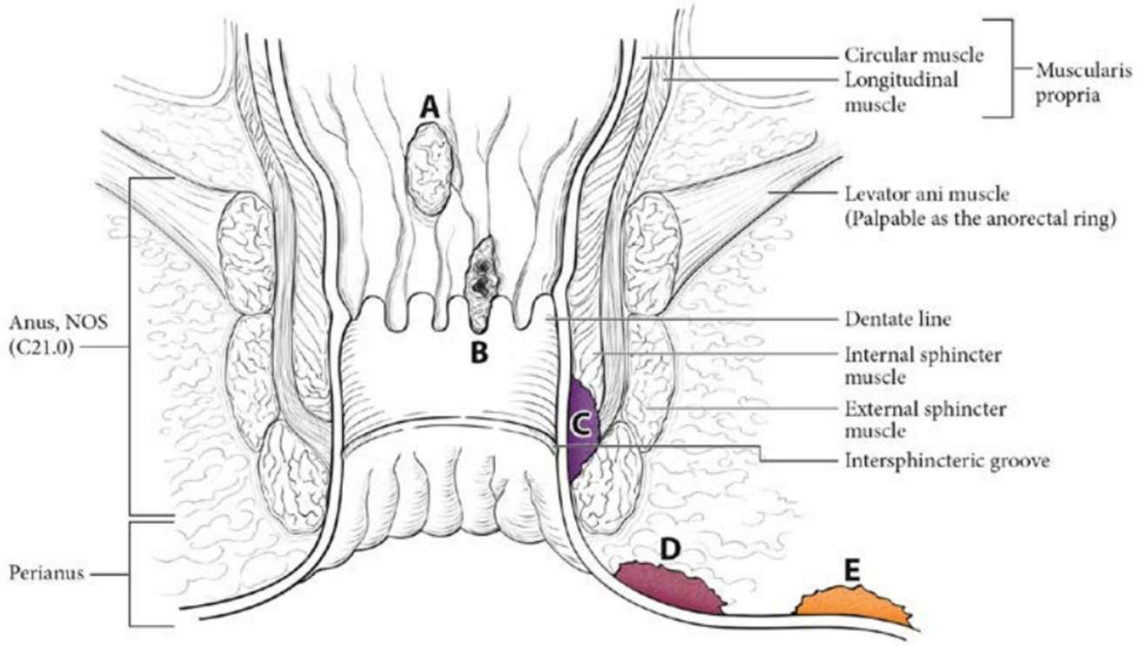


Figure 2. Anal cancer (A–C), perianal cancer (D), and skin cancer (E) as visualized with gentle traction placed on the buttocks. From Amin et al.[2] Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual* (2016) published by Springer Science and Business Media LLC, www.springerlink.com.

Percent of Anal SCC due to HPV by site:

Cervix	100%
Vagina	40-60%
Anus	**90-93%**
Vulva	40-50%
Penis	40%
Scrotum	Rare
Perianus	**80% female/29% male**

Anal squamous dysplasia (intraepithelial neoplasia)

Table 7.01 The terminology applied to various anal and perianal dysplastic lesions

Description of lesion	Lower Anogenital Squamous Terminology (LAST) project	Anal squamous intraepithelial neoplasia (ASIN)	Anal intraepithelial neoplasia (AIN)
Condyloma acuminatum	LSIL (condyloma acuminatum)	Condyloma acuminatum	Condyloma acuminatum
Mild dysplasia	LSIL	ASIN-L	AIN I
Moderate dysplasia	HSIL	ASIN-H	AIN II
Severe dysplasia	HSIL	ASIN-H	AIN III
Carcinoma in situ	HSIL	ASIN-H	AIN III
Bowenoid papulosis	HSIL (bowenoid papulosis)	PSIN-H	n/a
Bowen disease	HSIL	PSIN-H	n/a

ASIN-H, high-grade anal squamous intraepithelial neoplasia; ASIN-L, low-grade anal squamous intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; n/a, not applicable; PSIN-H, high-grade perianal squamous intraepithelial neoplasia.

Lam, A. K. and J. R. Goldblum (2019). Tumors of the Anal Canal. WHO Classification of tumors 5th ed: Digestive System Tumours. WHO Classification of Tumours Editorial Board. Lyon, France, IARC**: 193-212.**

TAKE HOME MESSAGE

- Use LAST terminology for the histological diagnosis of squamous dysplasia in the anal canal

THE CAP-ASCCP LAST PROJECT

The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions:

Background and Consensus Recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

Teresa M. Darragh, MD;[1] Terence J. Colgan, MD;[2] J. Thomas Cox, MD;[3] Debra S. Heller, MD;[3] Michael R. Henry, MD;[4] Ronald D. Luff, MD;[5,6] Timothy McCalmont, MD;[1] Ritu Nayar, MD;[7] Joel M. Palefsky, MD;[1] Mark H. Stoler, MD;[8] Edward J. Wilkinson, MD;[9] Richard J. Zaino, MD;[10] David C. Wilbur, MD,[11] for members of the LAST Project Work Groups

1268 Arch Pathol Lab Med—Vol 136, October 2012 *The CAP-ASCCP LAST Project*—Darragh et al

Proposed Terminology for Anal Squamous Lesions

Its Application and Interobserver Agreement Among Pathologists in Academic and Community Hospitals

Andres A. Roma, MD,[1] Xiuli Liu, MD, PhD,[2] Deepa T. Patil, MD,[2] Hao Xie, MD, PhD,[3] and Daniela Allende, MD[2]

Goal of the LAST project

"…to create a histopathologic nomenclature system that reflects current knowledge of HPV biology, optimally uses available biomarkers, and facilitates clear communication across different medical specialties"

The LAST Workgroups:

- WG1: Historical review of LAT HPV-associated squamous lesion terminology
- WG2: Squamous intraepithelial lesions, with subgroups:
  - Cervix and vagina
  - Vulva, penis, and scrotum
  - Anal canal and perianus
- WG3: Superficially invasive squamous cell carcinoma (SISCCA) with subgroups:
  - Cervix and vagina
  - Vulva, penis, and scrotum
  - Anal canal and perianus
- WG4: Biomarkers in HPV-associated lower anogenital squamous lesions
- WG5: Implications and implementation of standardized terminology

Pre-LAST Terminology

- Complex, from differing points of view
  - Mucosal (cervix, vaginal, anal) tended to be developed by general pathologists, gynecologic pathologists, and gynecologists
  - Cutaneous (vulvar, penile, perianal) tended to be developed by dermatopathologists and dermatologists

Biology of HPV: Two lesions

1. LOW GRADE LESION:

   Squamous epithelium supports virion production, but lesions are transient, produce a LG lesion at some point, but may be undetected clinically [most common HPV 6 or 11)

2. HIGH GRADE LESION:

   Precancerous lesions – coordinated control between viral gene expression and epithelial differentiation is broken. Viral oncogene overexpression drives cell proliferation leading to a clonal expansion of relatively undifferentiated cells, clinical persistent viral detection, persistent colposcopic abnormalities, and increased risk of cancer. [most common HPV16 or 18]

Squamous Intraepithelial lesions (WG2)

- Recommendation 1
  - Unified histopathologic nomenclature with a single set of diagnostic terms for all HPV-associated preinvasive squamous lesions of the LAT
- Recommendation 2
  - Two-tiered nomenclature for non-invasive HPV-associated lesions of the LAT (may be further qualified by appropriate –IN terminology)
- Recommendation 3
  - The recommended terminology for HPV-associated squamous lesions is **LSIL** and **HSIL**, which may be further classified by the applicable –IN terminology (CIN for cervix; VaIN for vagina; VIN for vulva; AIN for anus; PAIN for perianus; PeIN for penis)

WG1

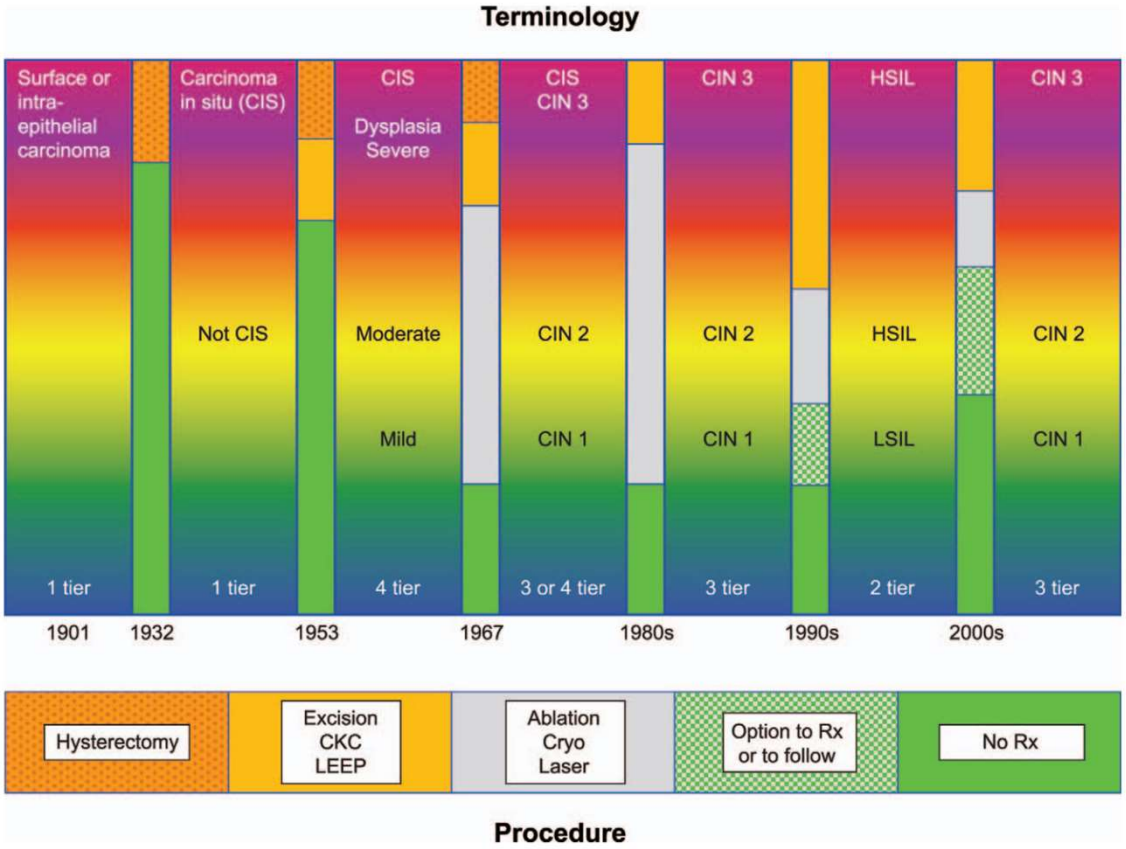


Figure 2. Changes to the terminology and number of tiers used to describe cervical precancer over time with corresponding management options (procedure). See text for additional details. CKC, cold knife conization; Cryo, cryotherapy; RX, treatment. Modified with permission. Courtesy of J. Thomas Cox.

Superficially Invasive Squamous Cell Carcinoma (WG3)

- The term superficially invasive squamous cell carcinoma (SISCCA) is recommended for minimally invasive SCC of the LAT that has been completely excised and is potentially amenable to conservative surgical therapy
- For cases of invasive squamous cell carcinoma with positive biopsy/resection margins the pathology report should state whether
  1. The examined invasive tumor exceeds the dimensions for SISCCA (as defined by organ)

  OR

  2. The examined tumor component is less than or equal to the dimensions for SISCCA and therefore is “at least SISCCA”
- In cases of SISCCA, the following parameters should be reported
  - The presence or absence of LVI
  - The presences, number, and size of independent multifocal carcinomas (after excluding the possibility of a single carcinoma

SISCCA of the Anal canal and Perianus

Suggested definition

Has an invasive depth of depth of ≤ 3 mm from the basement membrane of the point of origin

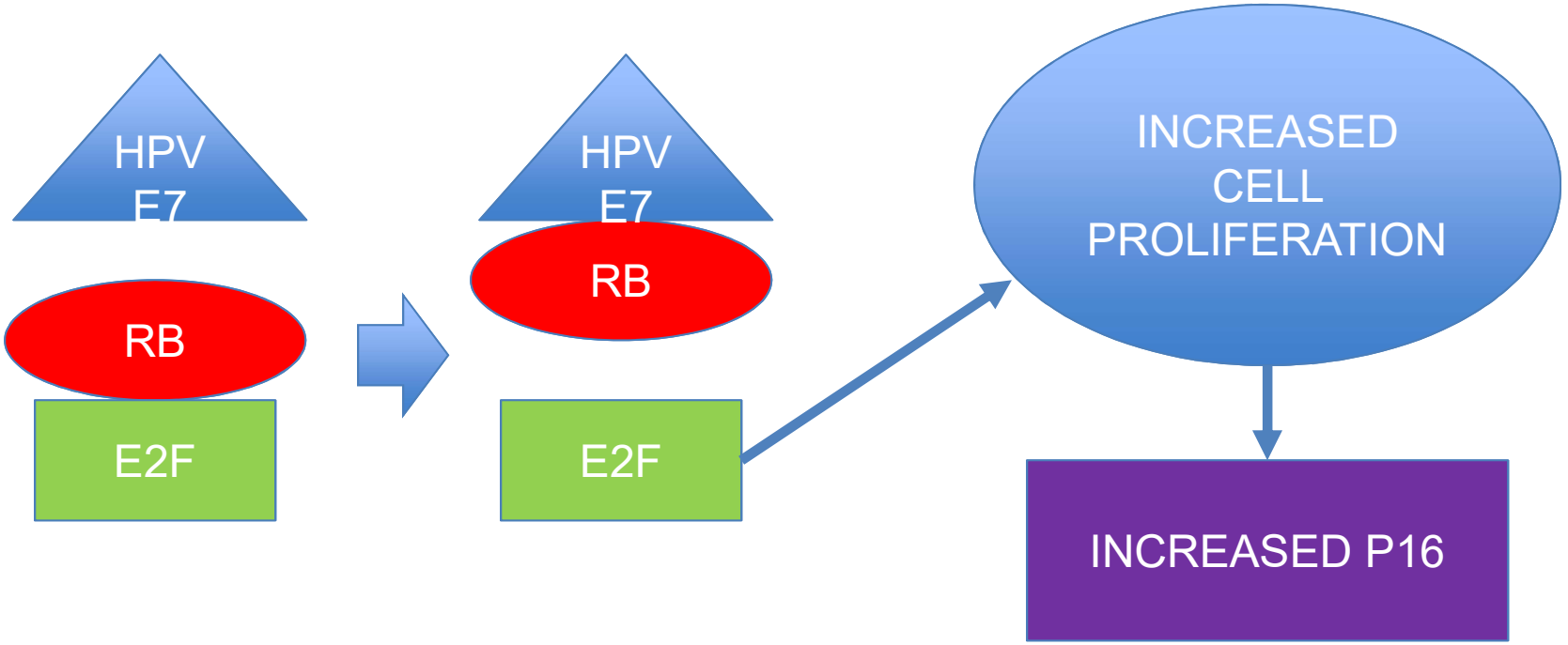
And has horizontal spread of ≤ 7 mm

AND

Has been completely excised

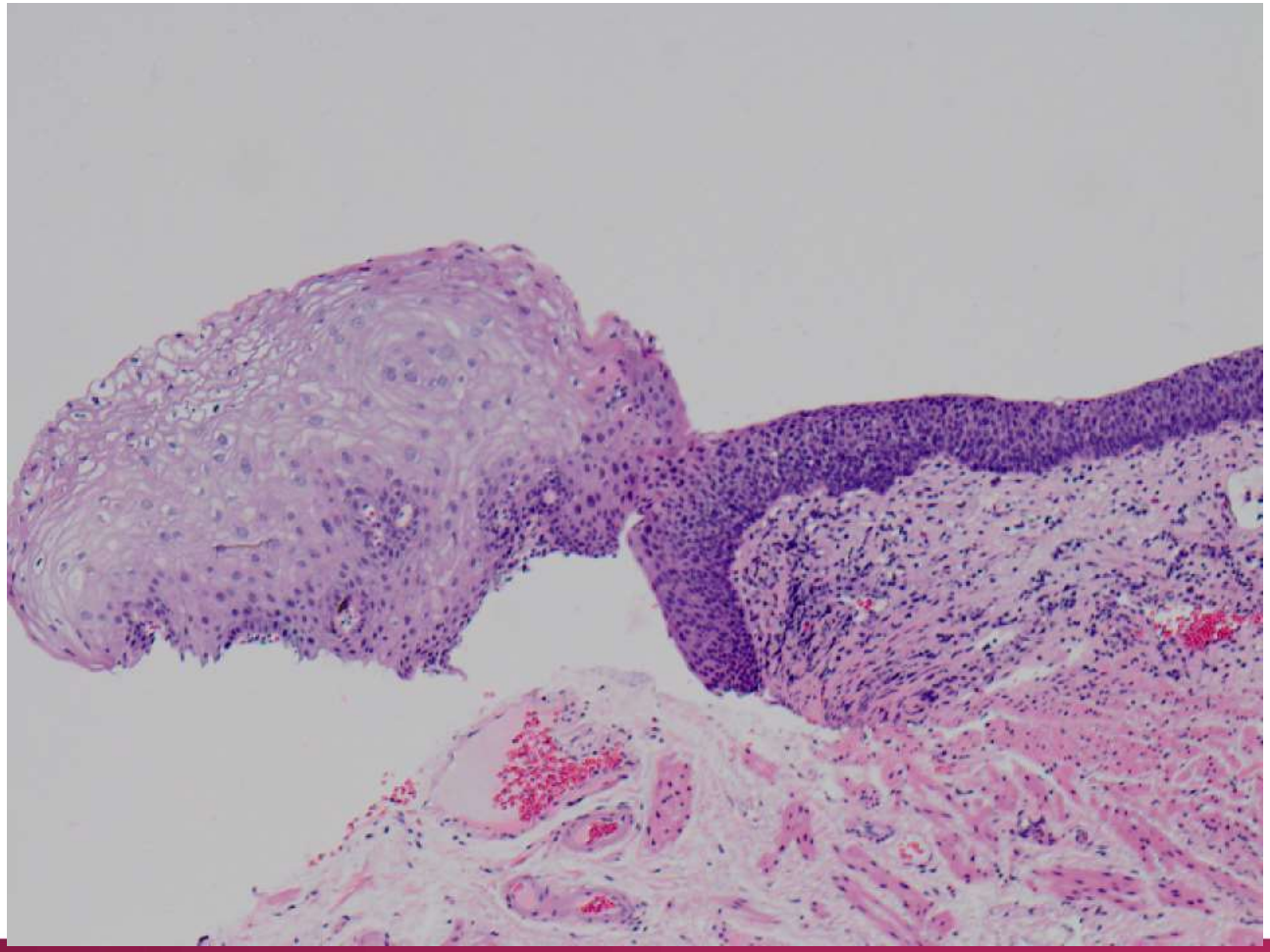
Biomarkers in HPV-Associated LAT Squamous lesion (WG 4)

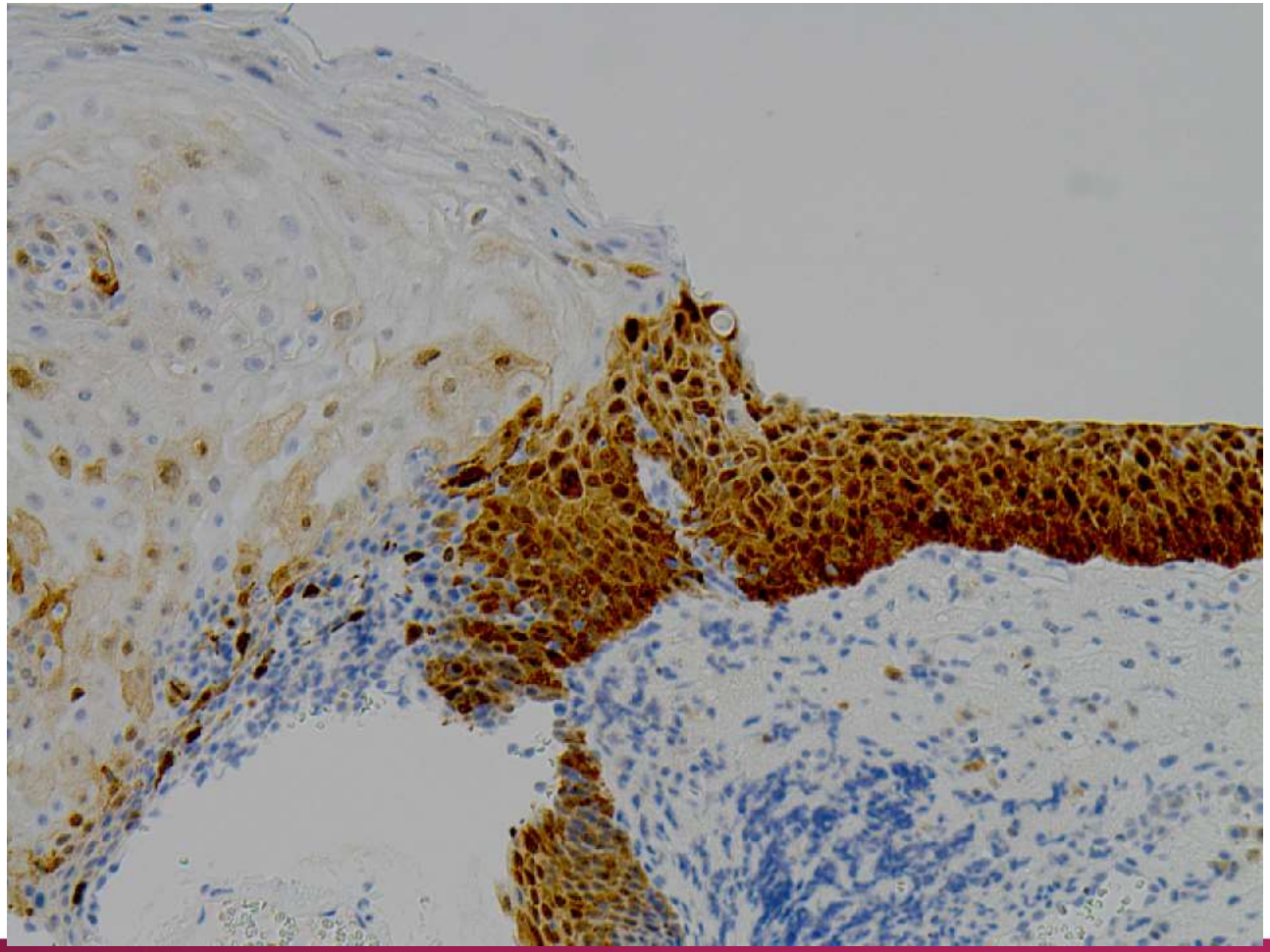
- **When is P16 IHC recommended?**
  1. When the histologic differential diagnosis is between precancer (-IN2 or –IN3) and a mimic of precancer - **Strong and diffuse block-positive p16 results support a categorization as a precancerous lesion**.
  2. When –IN2 would be considered in the old terminology
  3. When there is professional disagreement in a case where a precancerous lesion (-IN2 or IN3) is in the differential diagnosis
  4. WG4 recommends **AGAINST** the routine use of P16 if the morphologic interpretation is NEGATIVE, -IN1, OR –IN3
     - SPECIAL CIRCUMSTANCE: p16 is recommended in patients that are at high risk for missed high grade disease (cytology HSIL, ASC-H, ASCUS/HPV+, OR AGC(NOS))

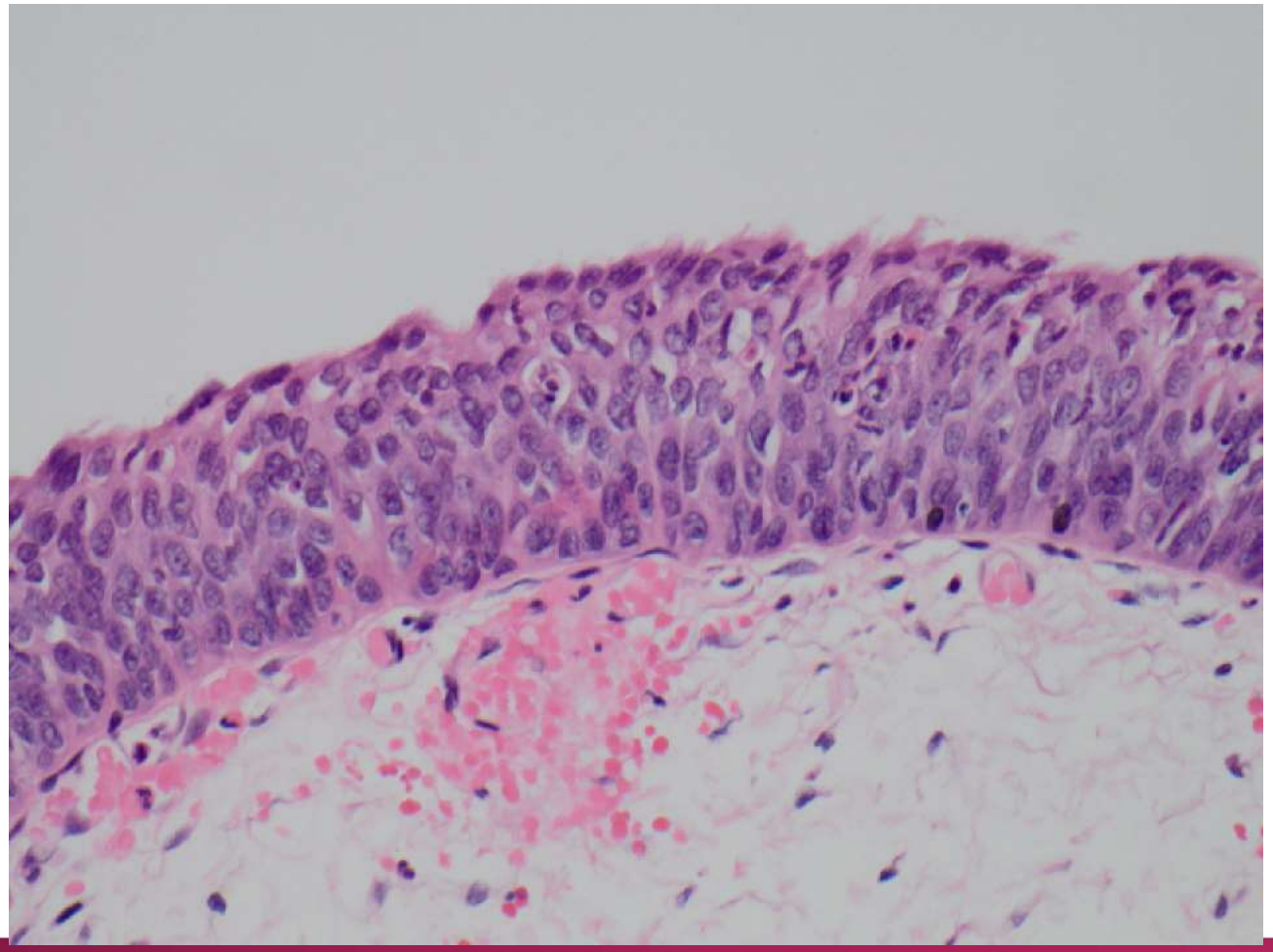

HPV
E7
RB
E2F
HPV
E7
RB
E2F
INCREASED
CELL
PROLIFERATION
INCREASED P16

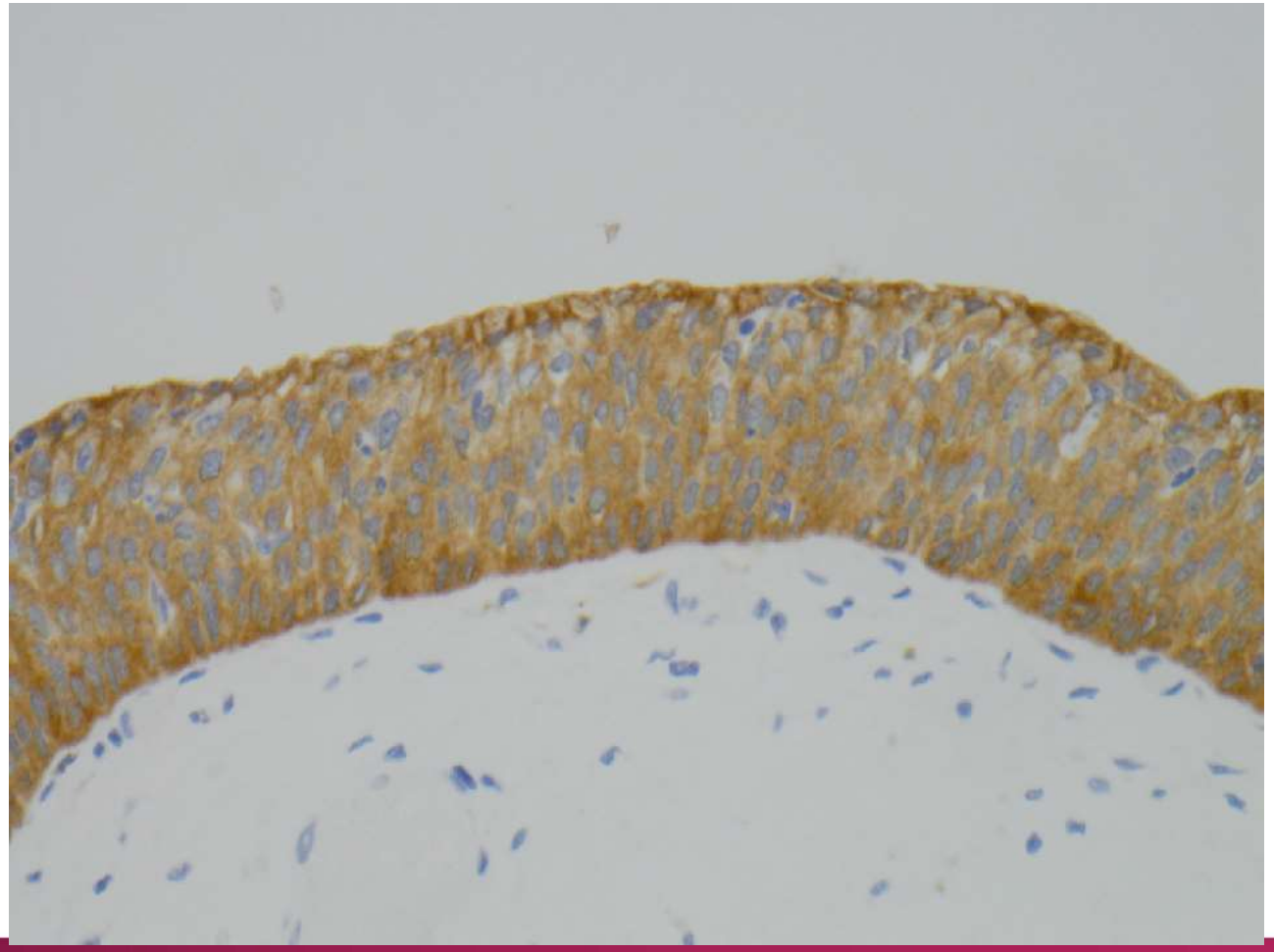
“Strong and diffuse block staining”

“Strong and diffuse block staining for p16 = p16- positive.—In squamous epithelia, this is defined as continuous strong **nuclear or nuclear plus cytoplasmic staining** of the basal cell layer with extension upward involving at least one third of the epithelial thickness. The latter height restriction is somewhat arbitrary but adds specificity. Note that full-thickness staining or extension into the upper third or upper half is specifically not required to call a specimen positive (see Figures 14 and 15). Focal or patchy nuclear staining is nonspecific and can be seen with reactive squamous metaplasia, as well as low-grade disease (LSIL, –IN 1). **All other staining patterns, described as cytoplasmic only, wispy, blob-like, puddled, scattered, single cells, and others, are defined as negative…”**

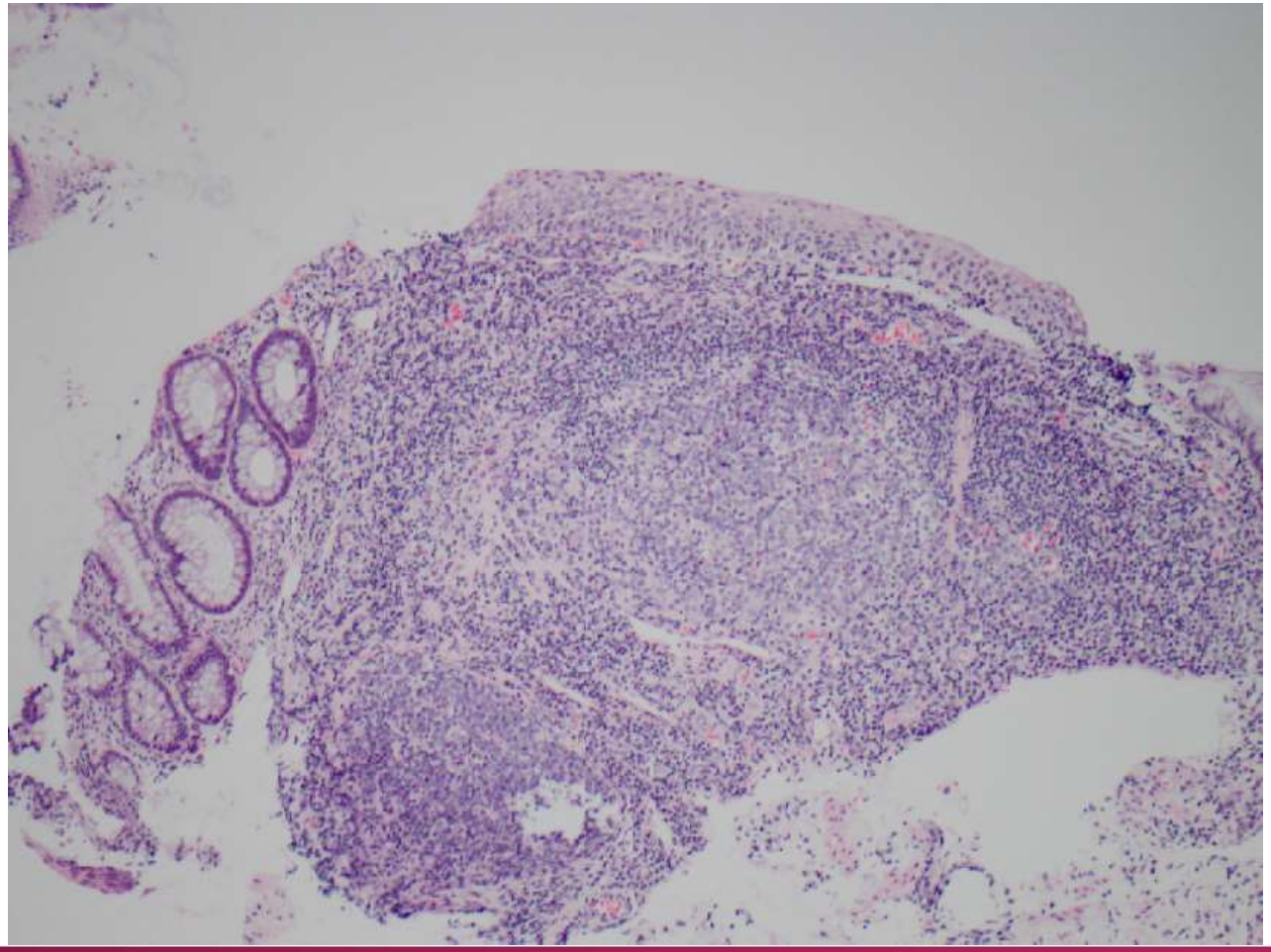


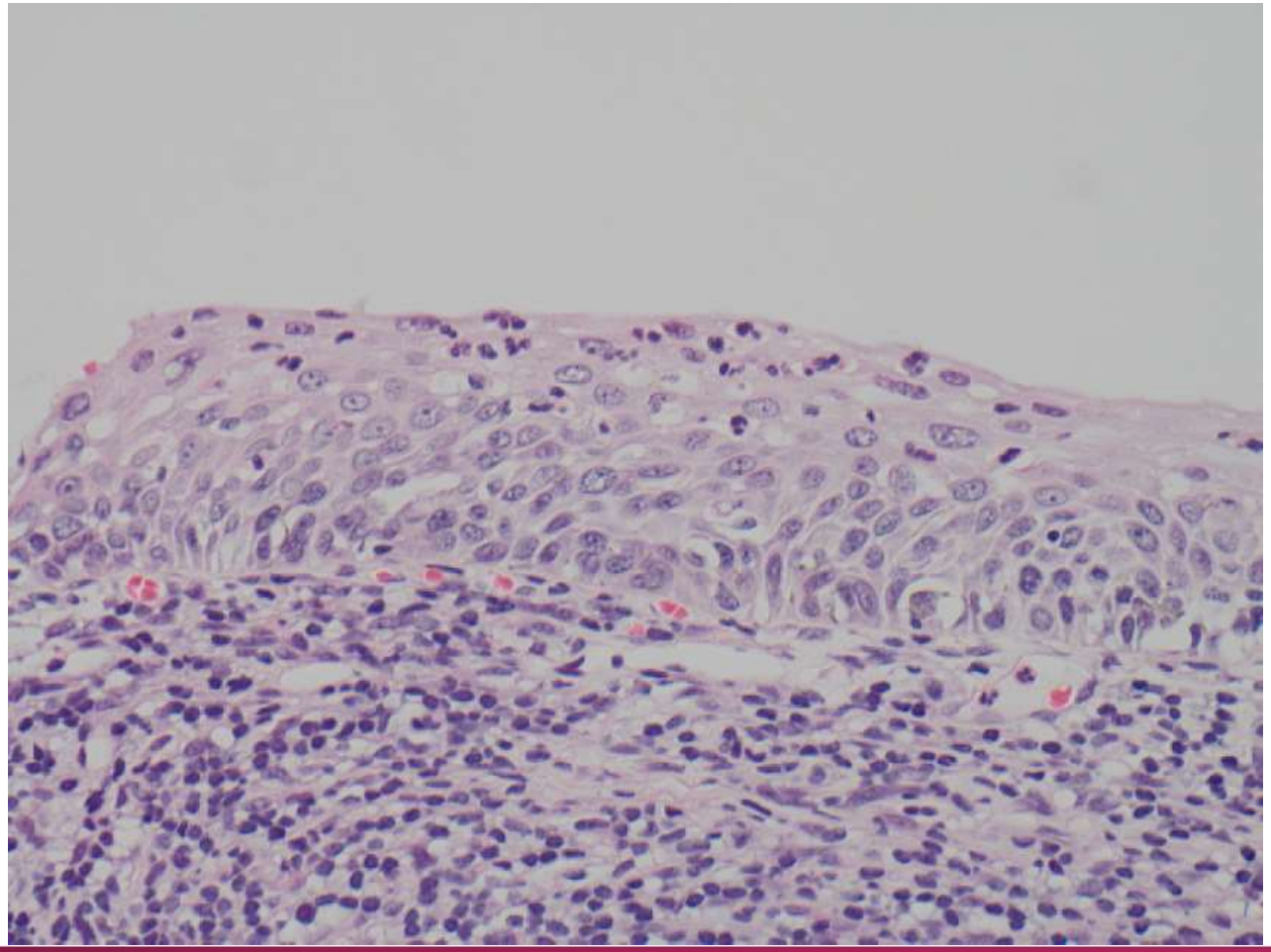


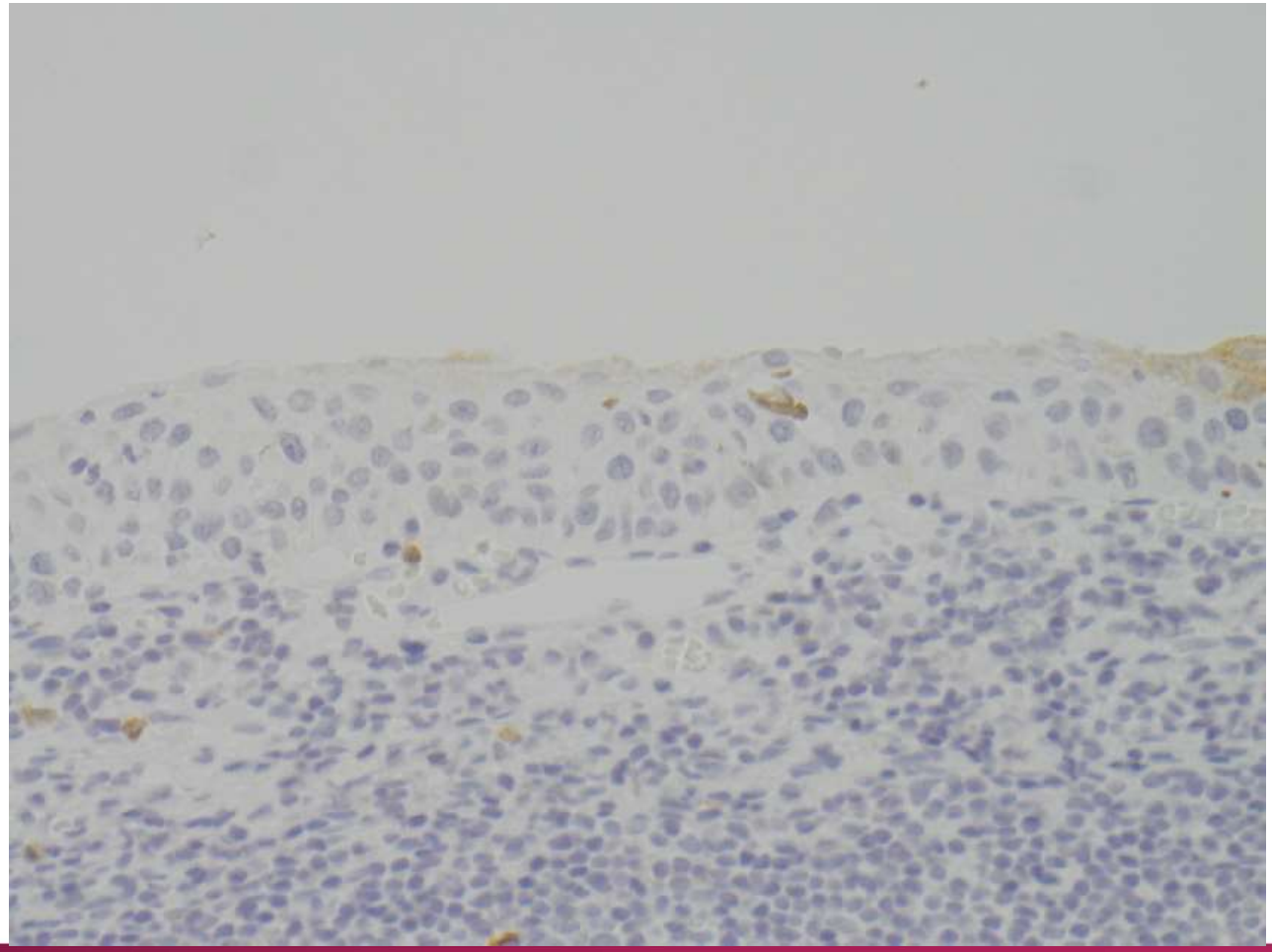


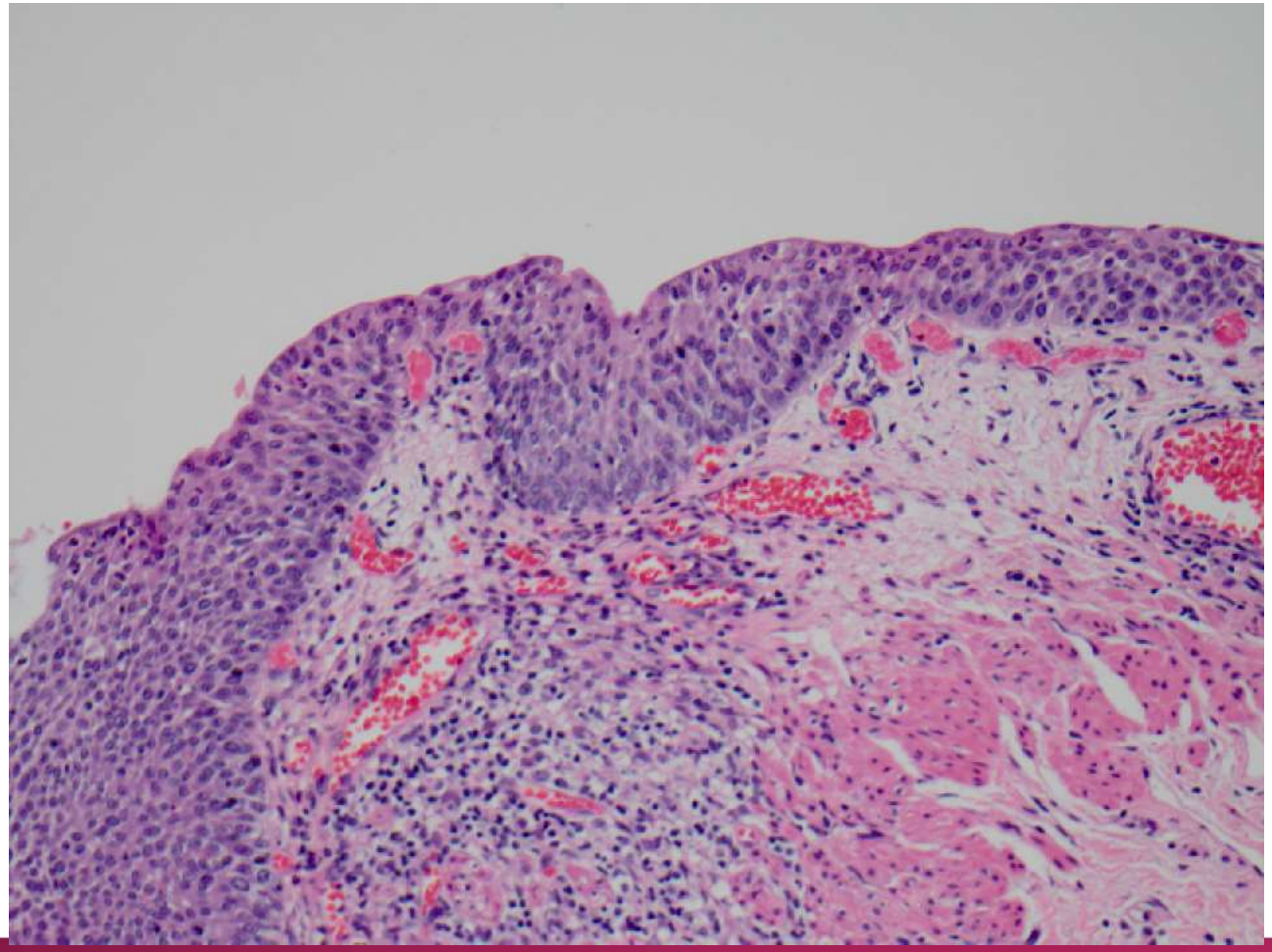


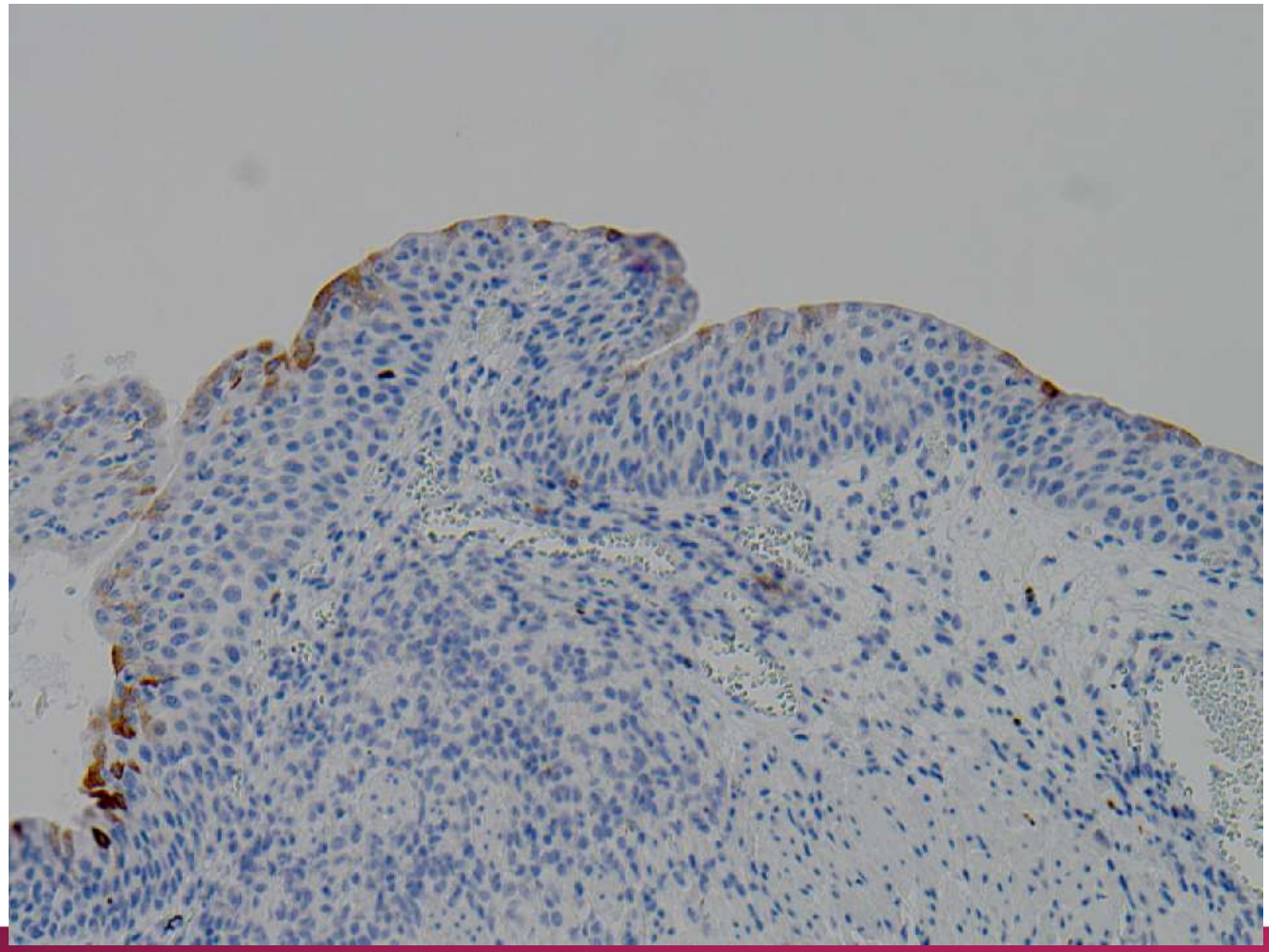
When the histologic differential diagnosis is between precancer (-IN2 or –IN3) and a mimic of precancer

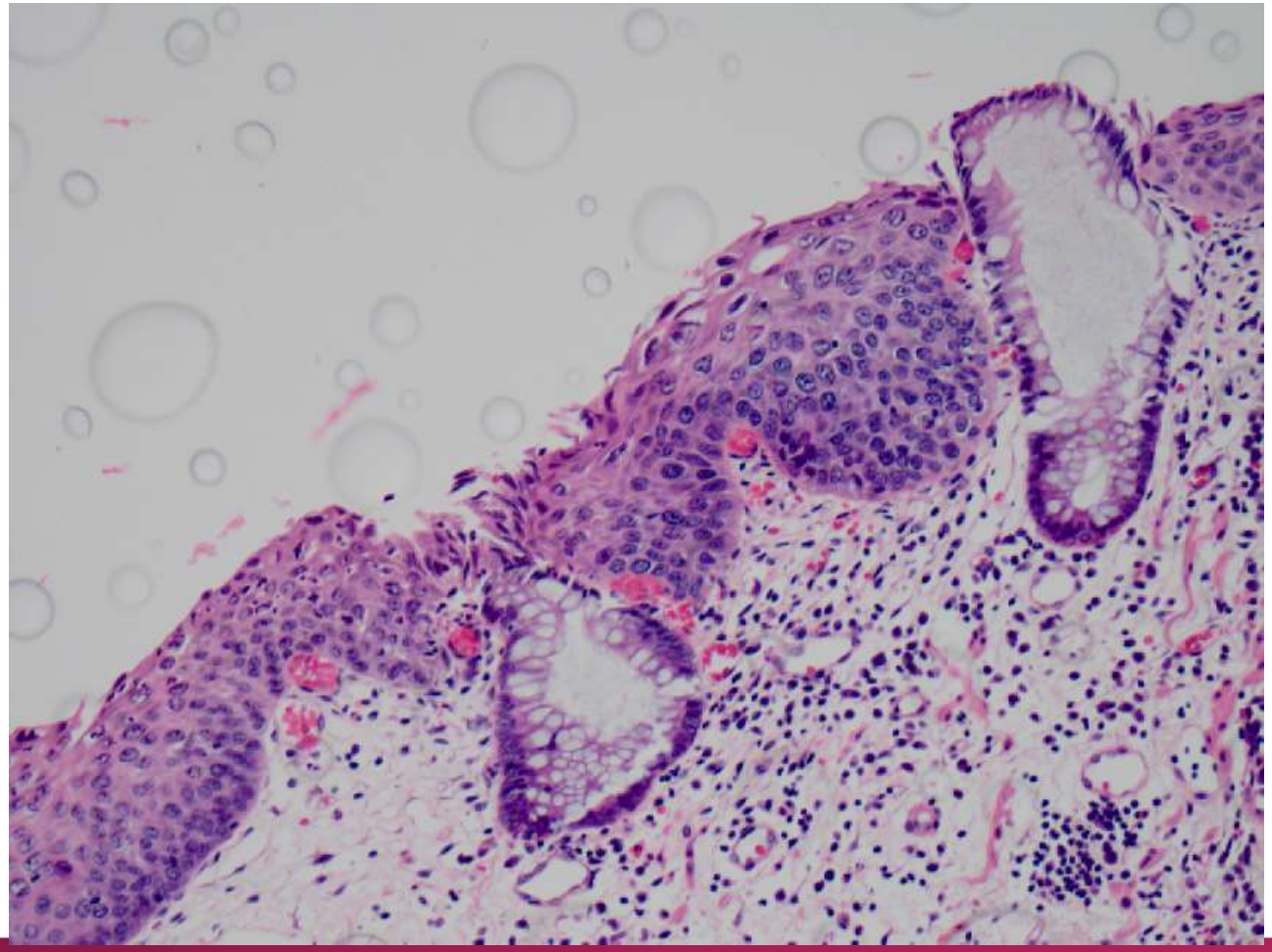


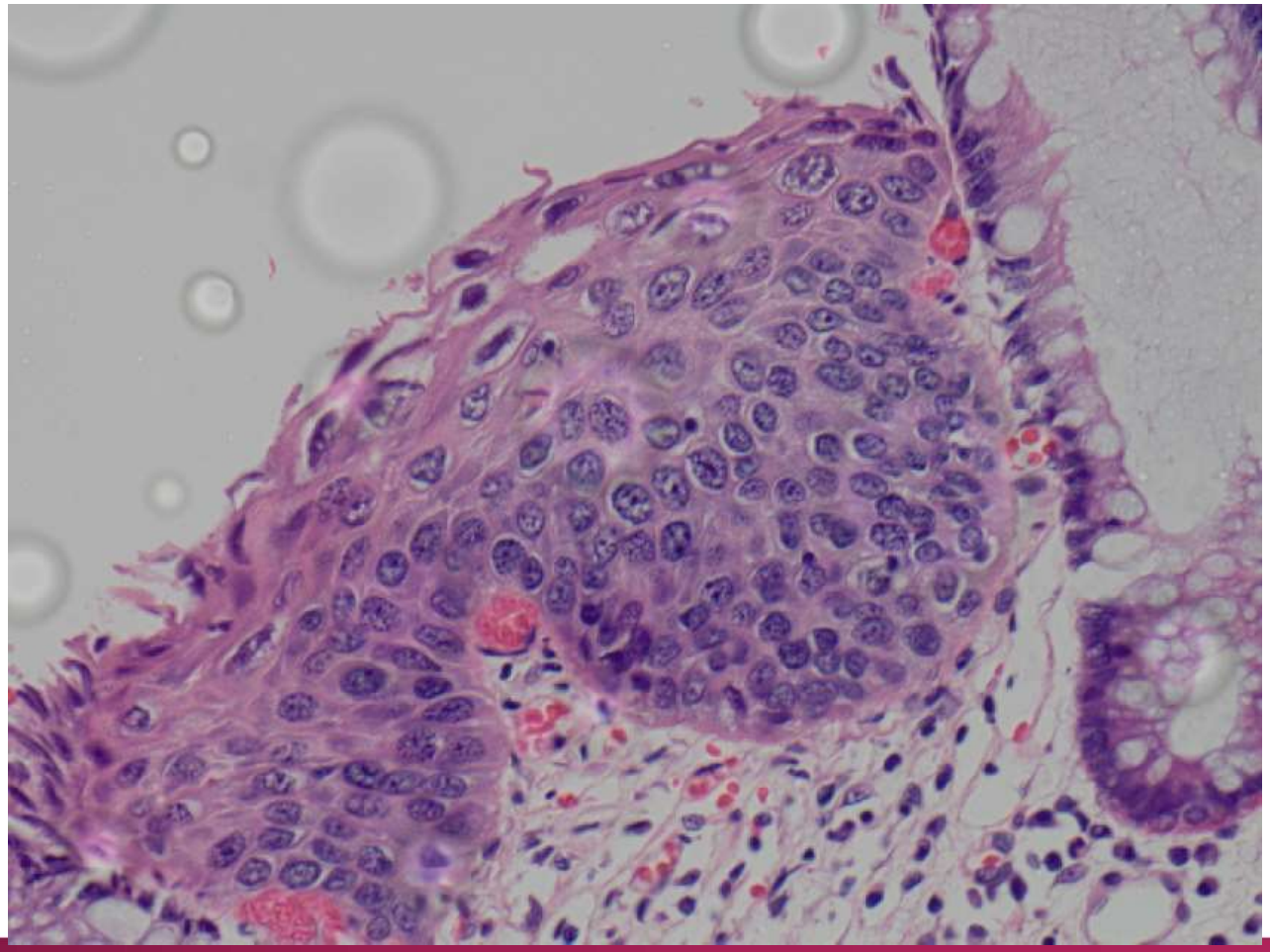


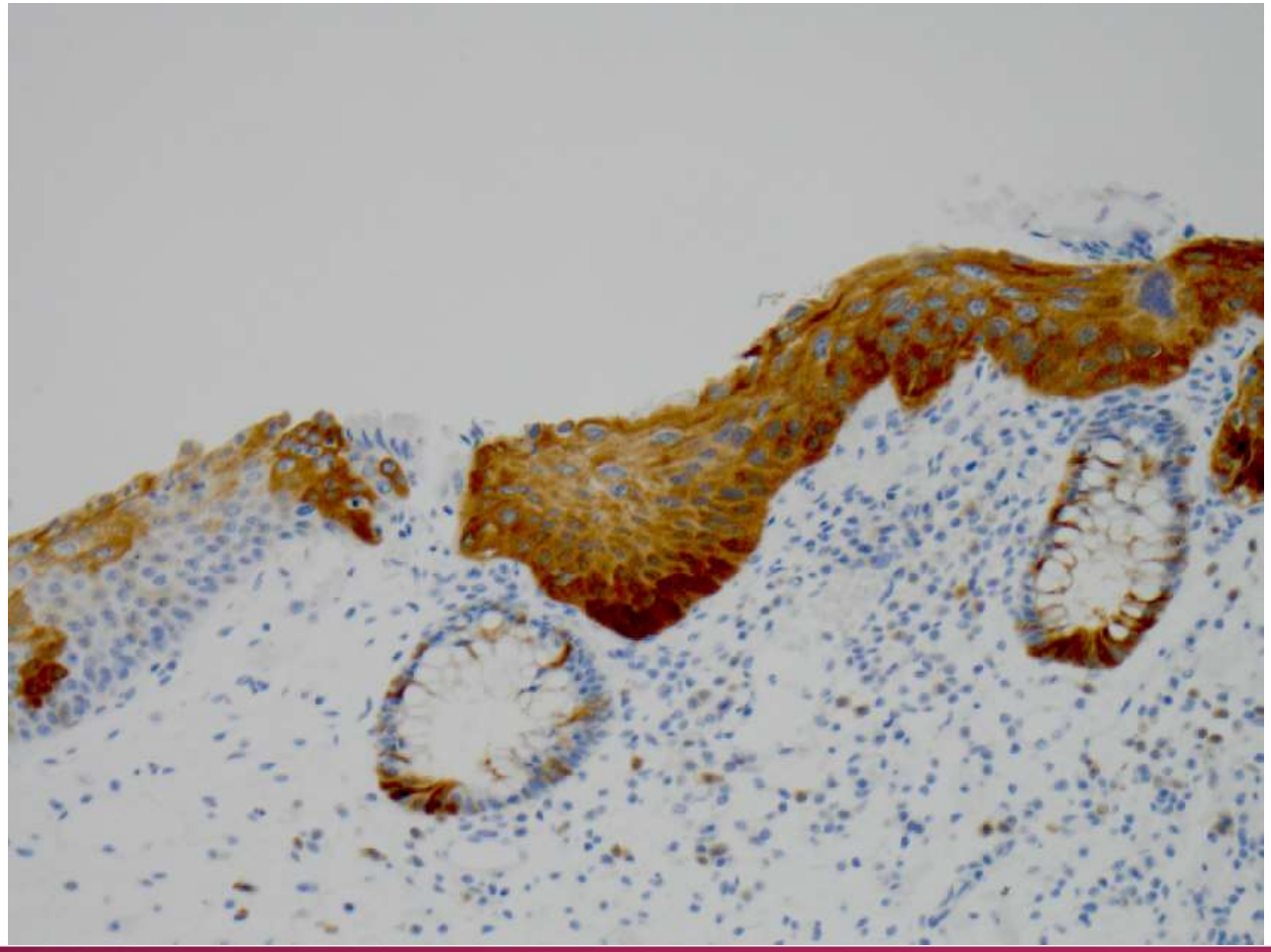


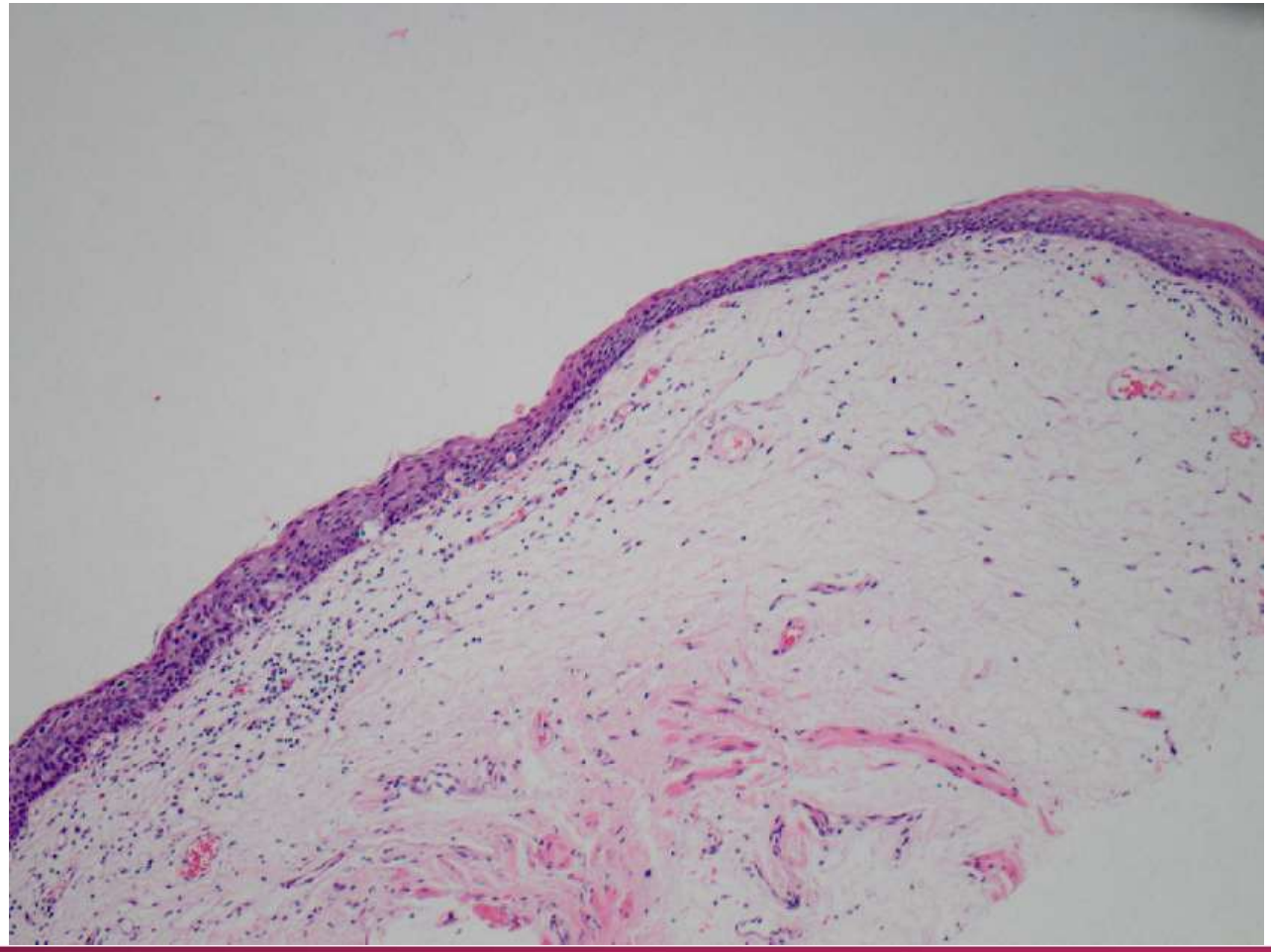


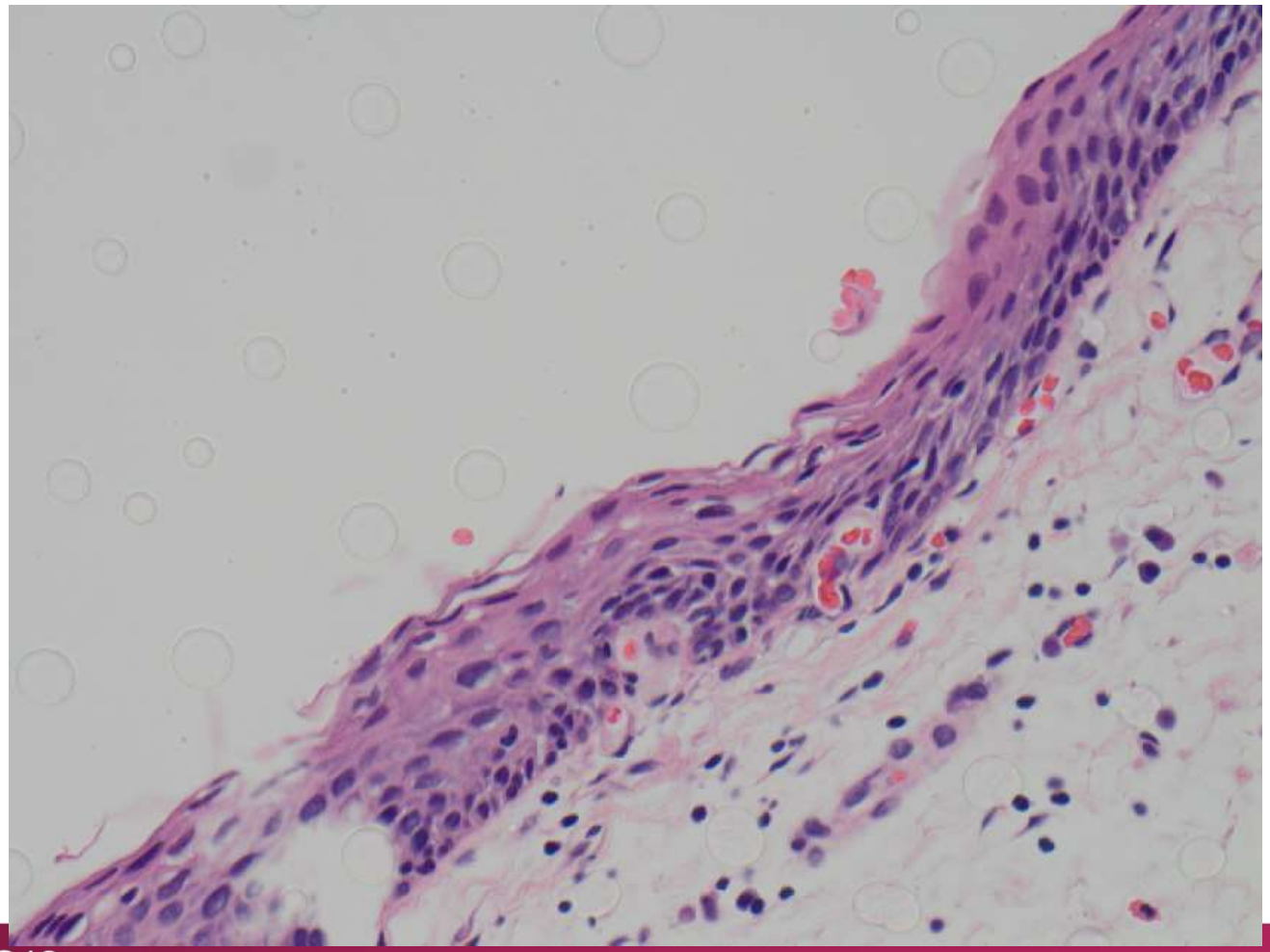


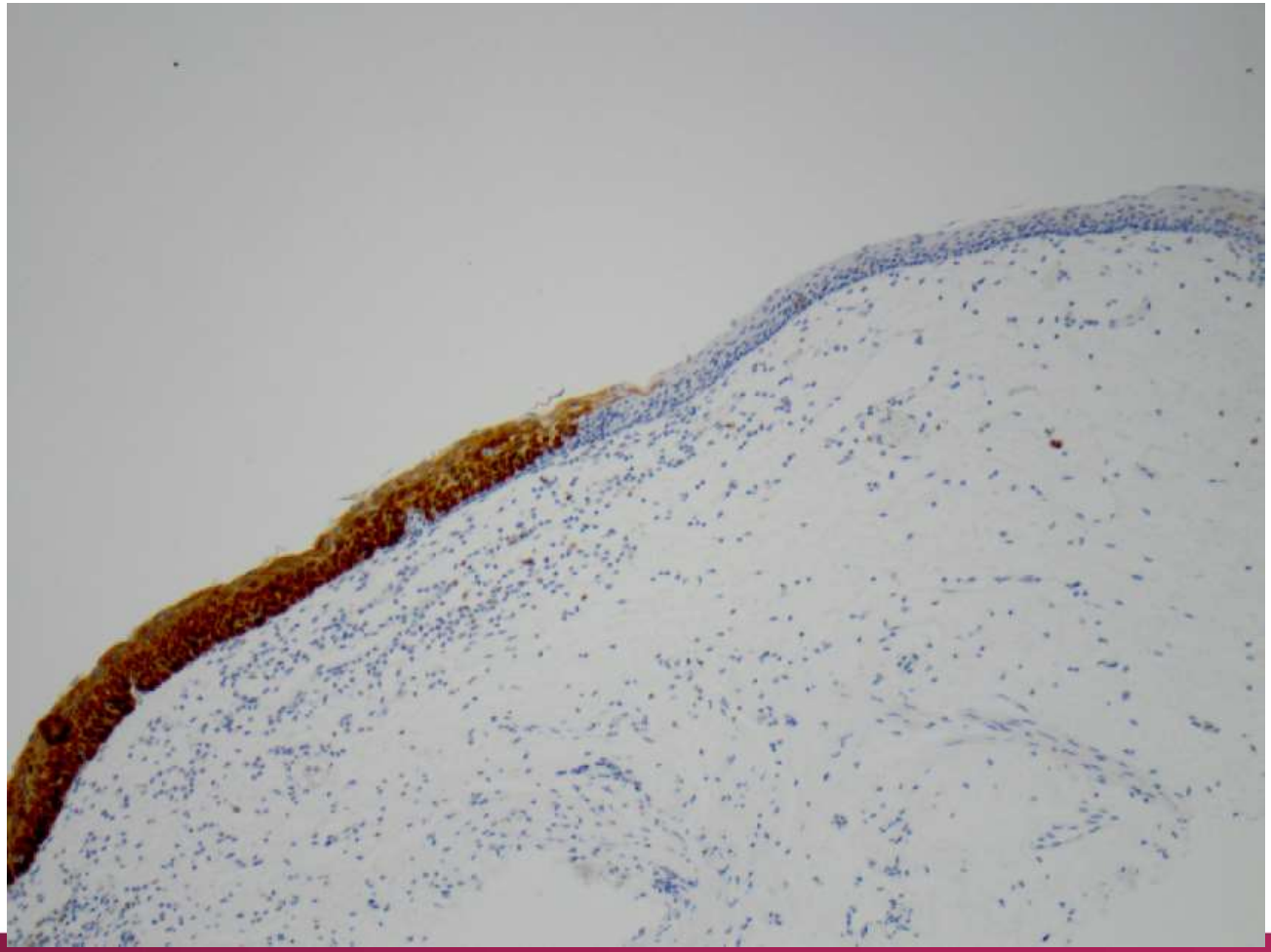


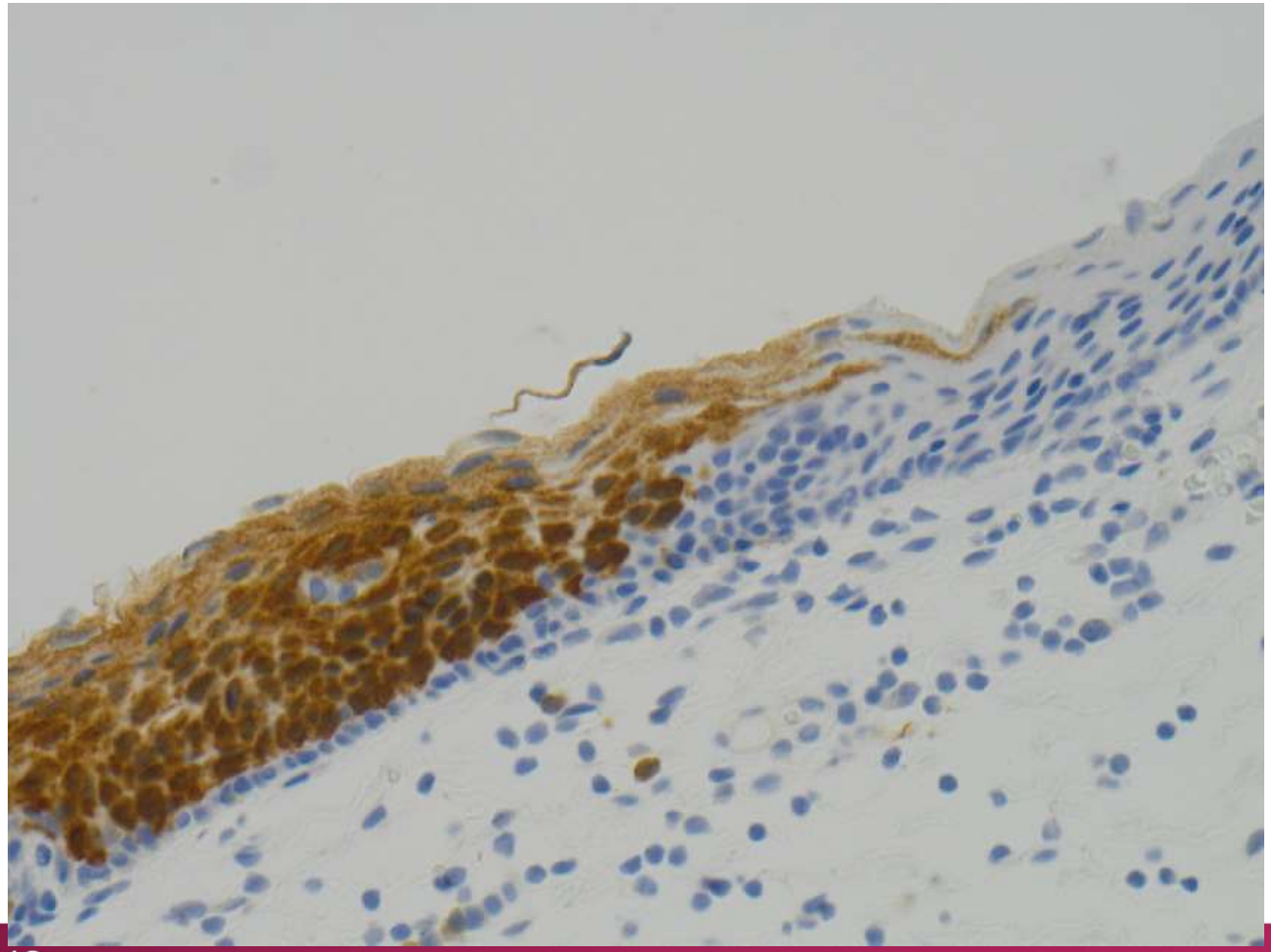




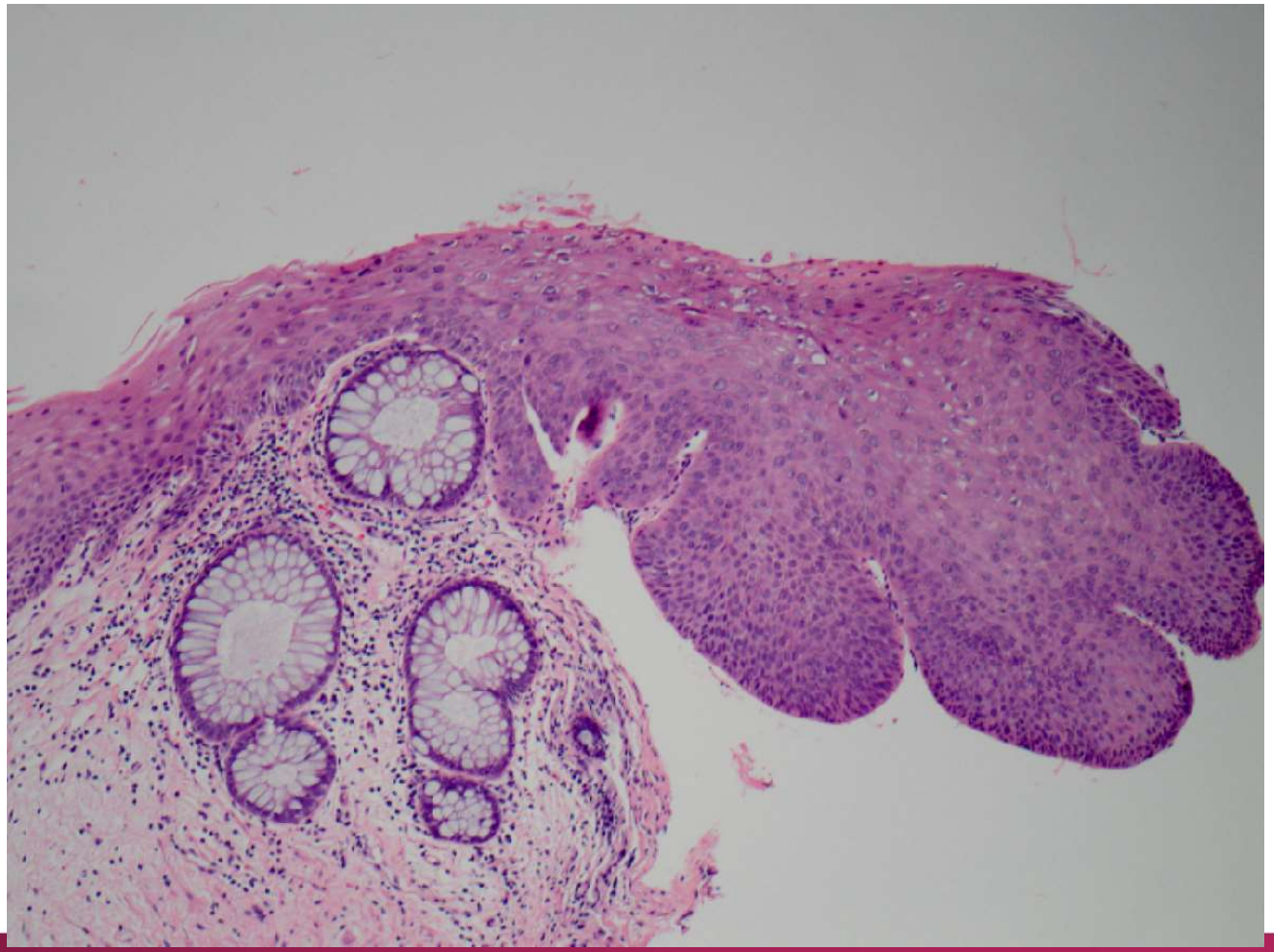


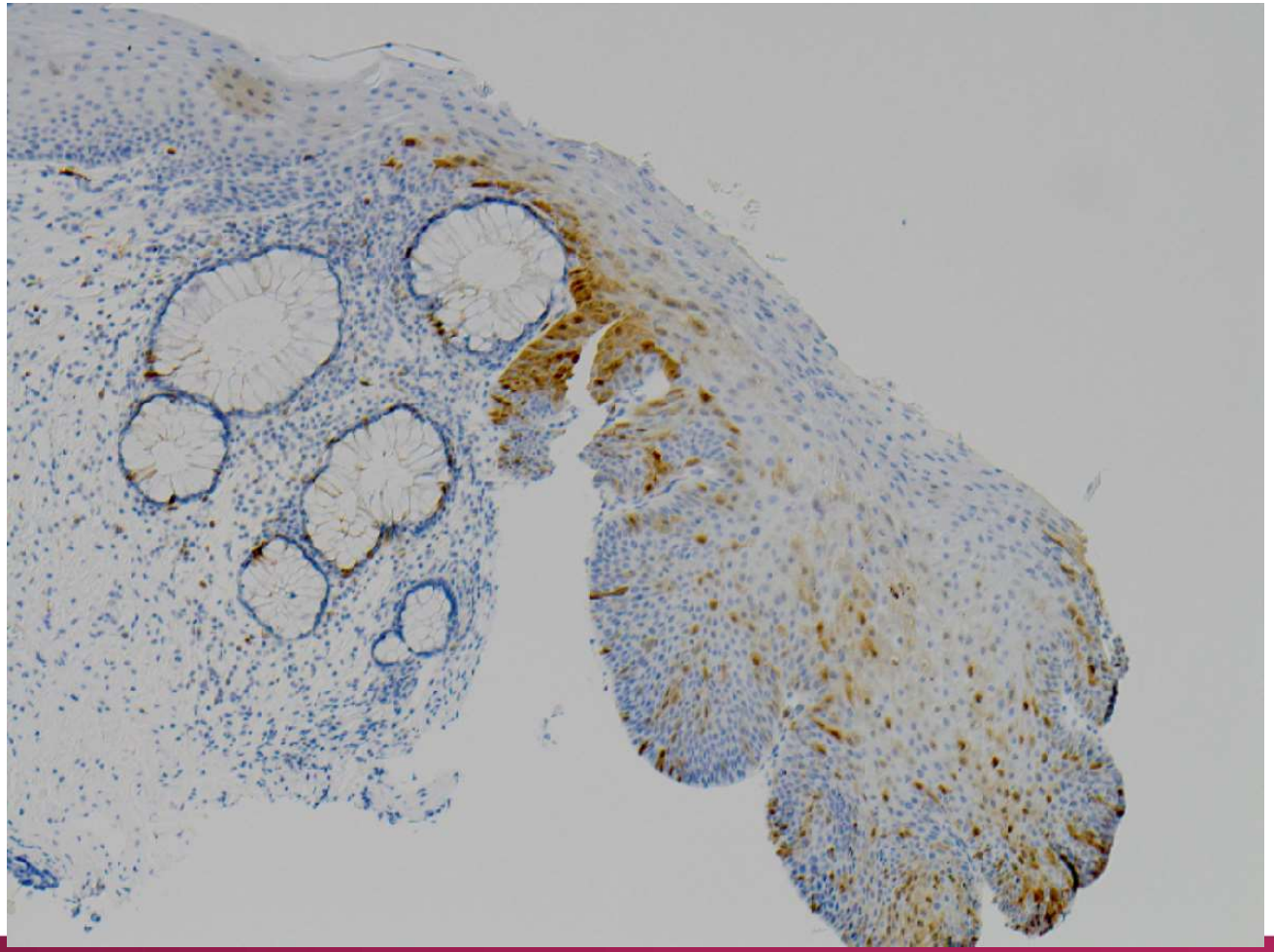


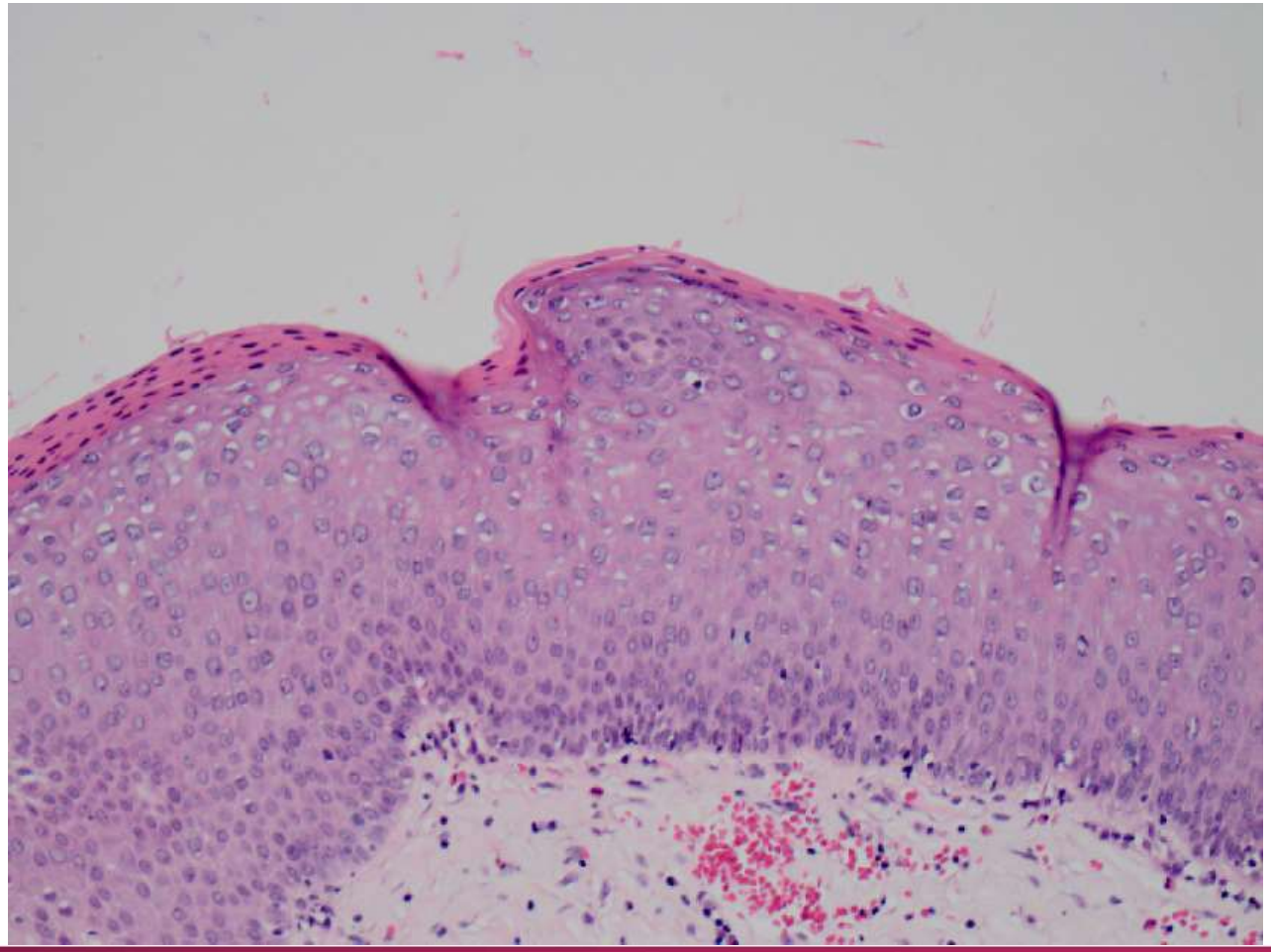


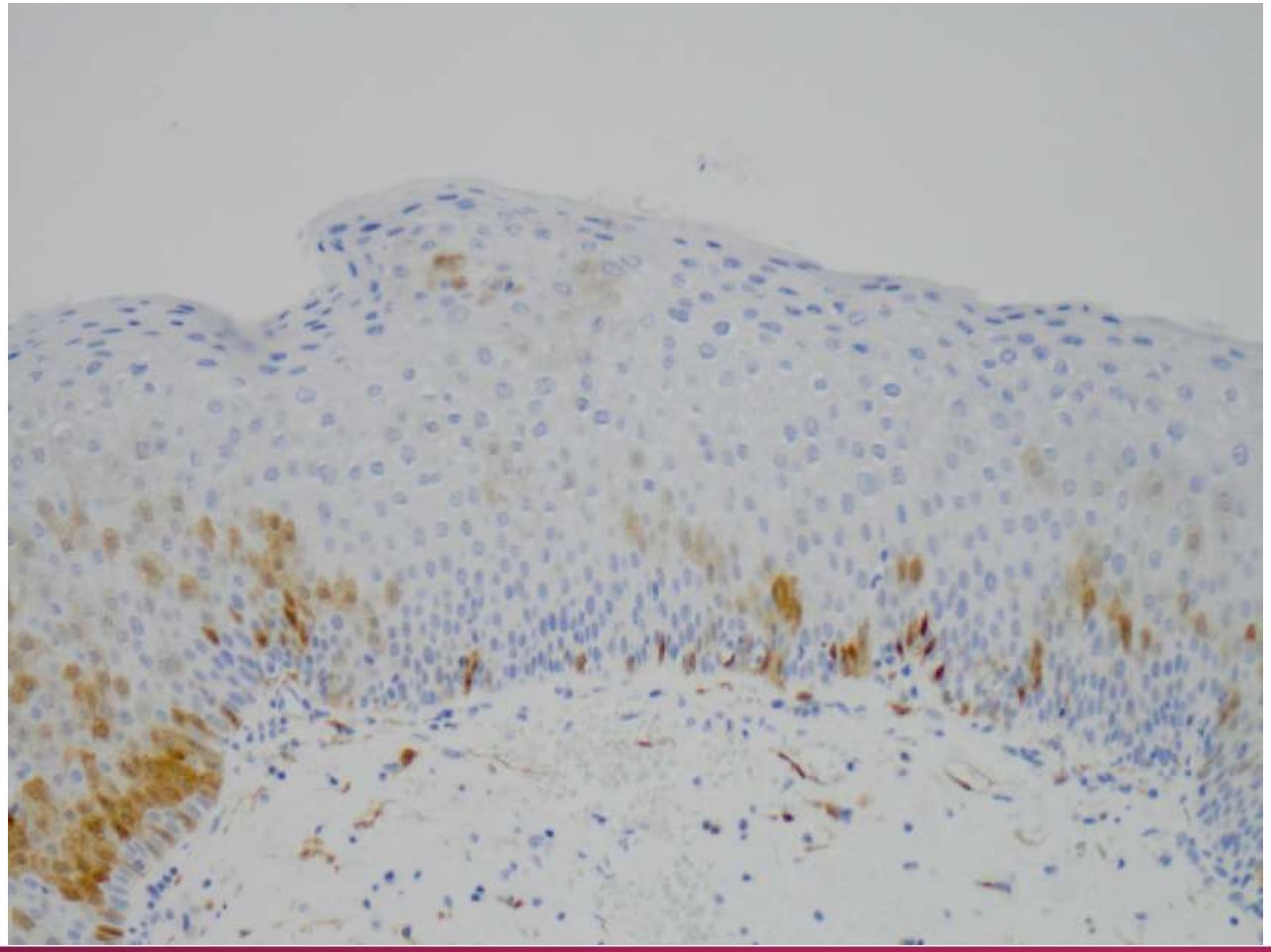


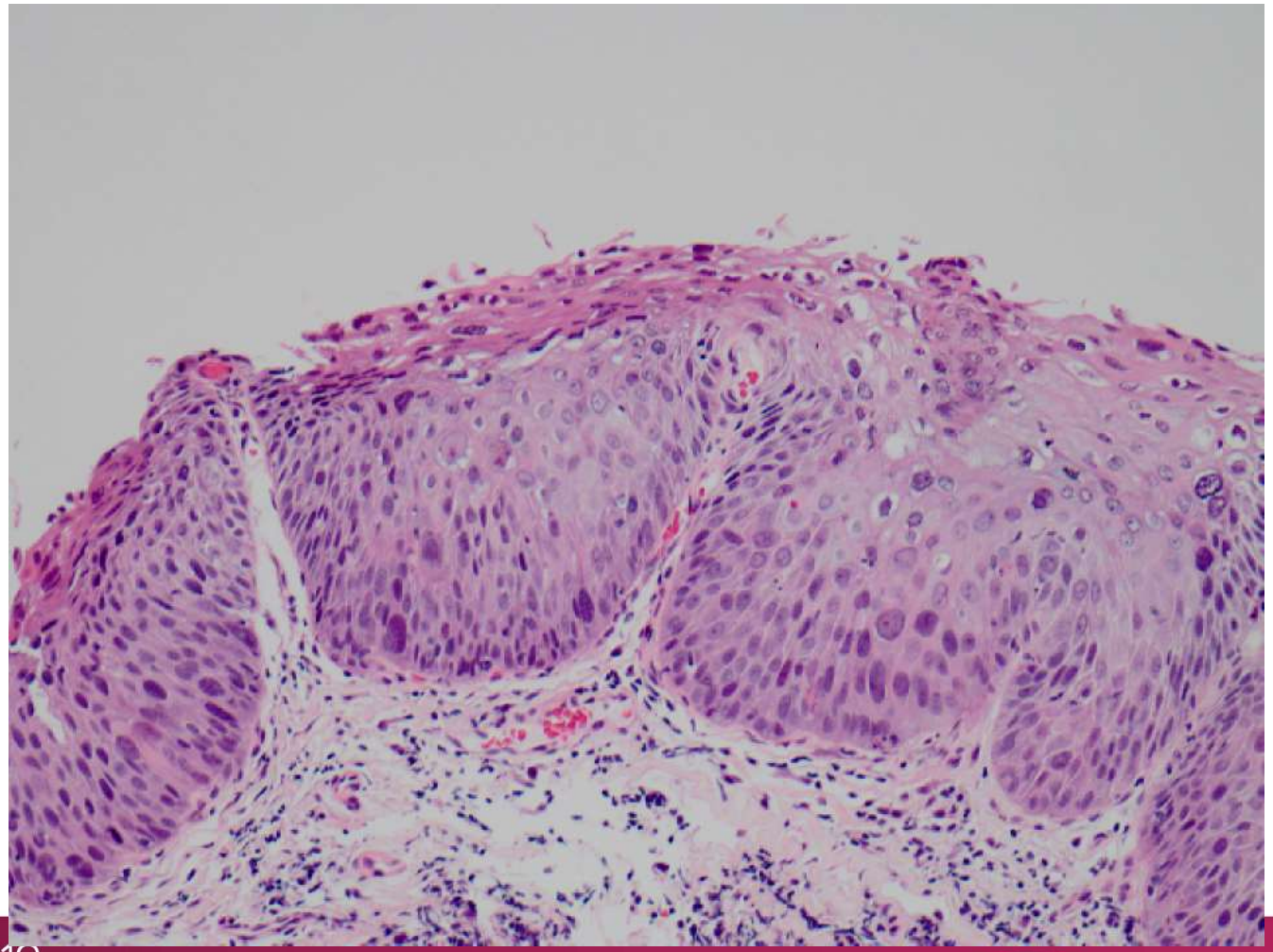
When –IN2 would be considered in the old terminology

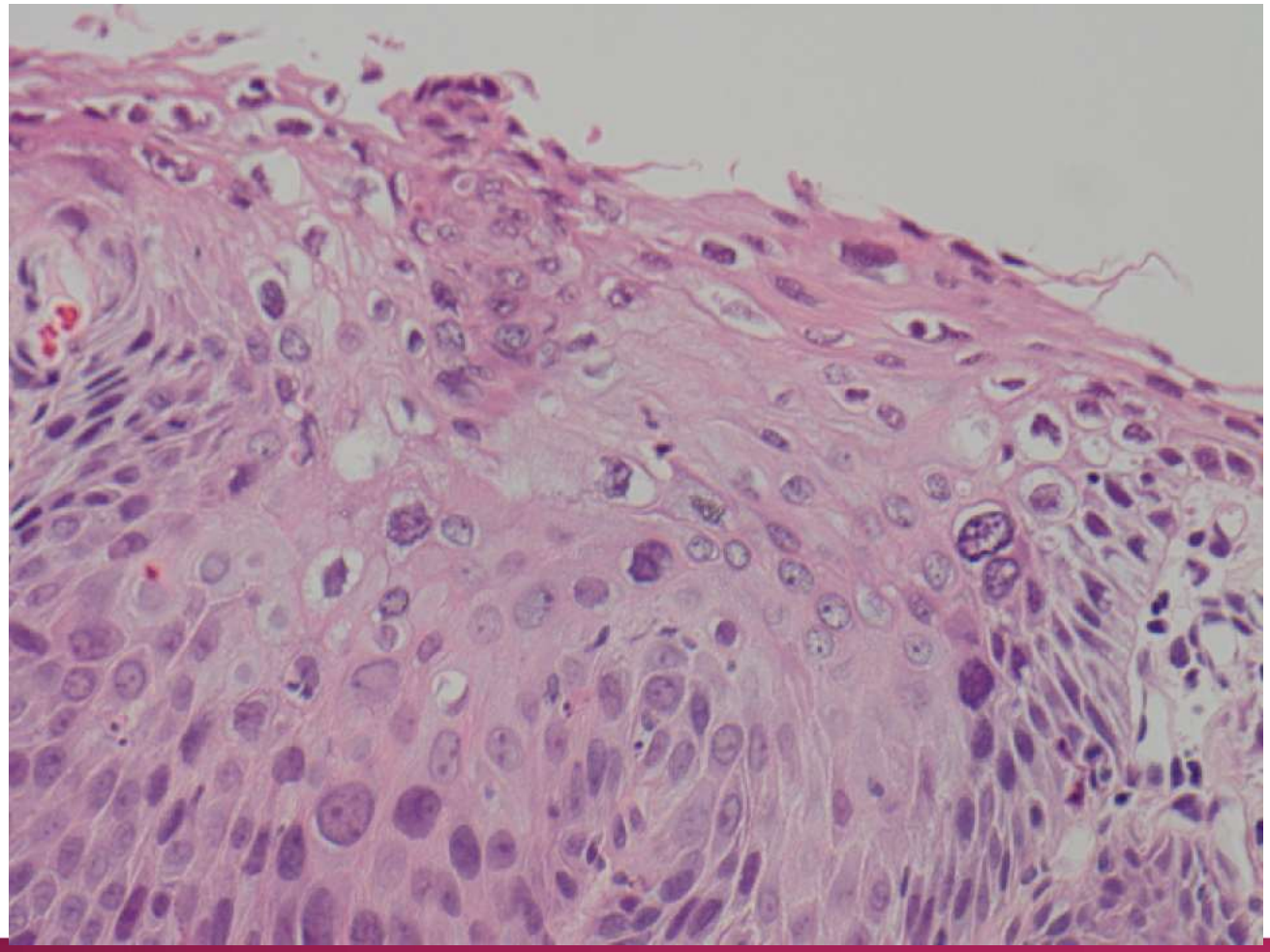


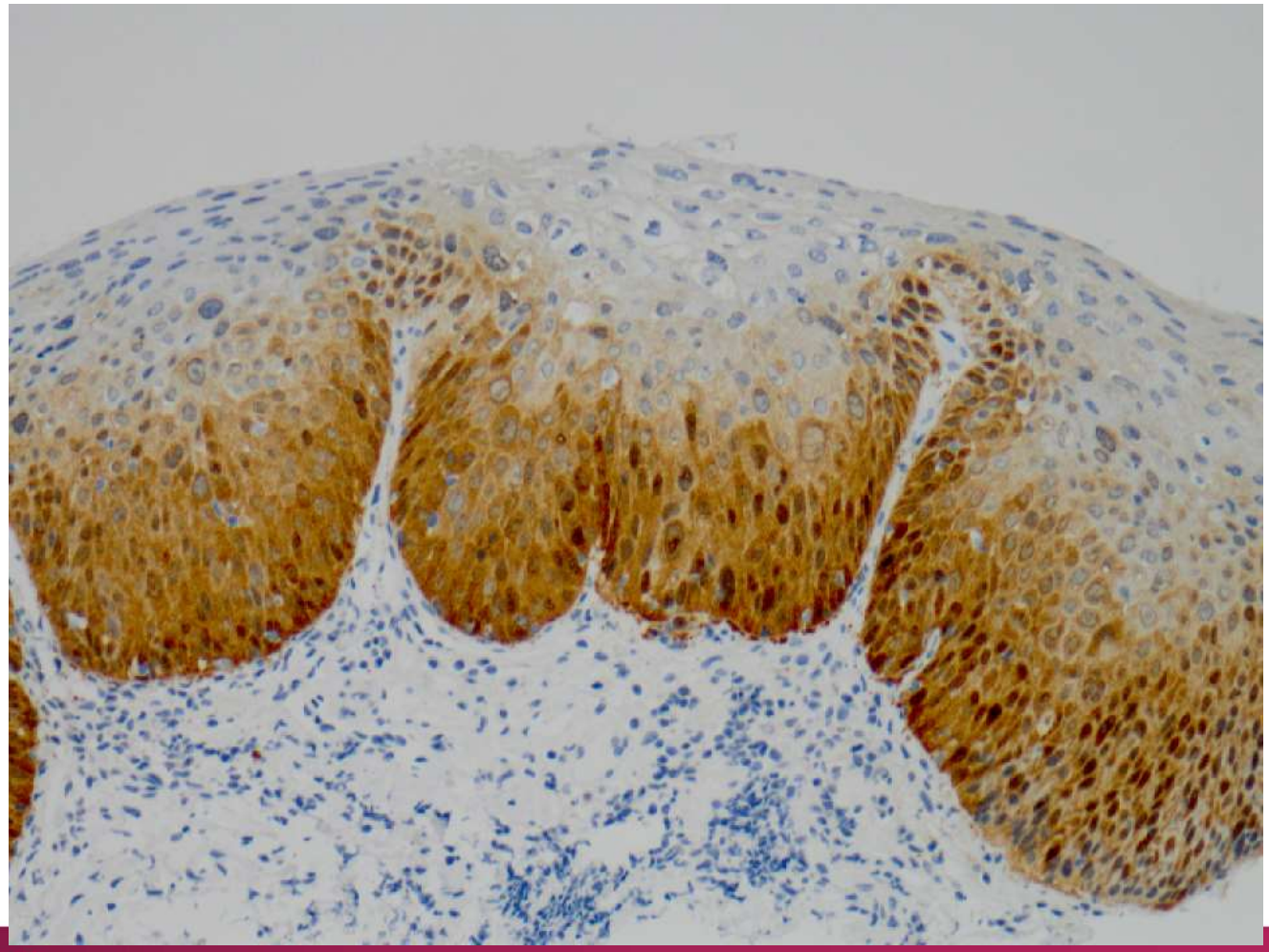


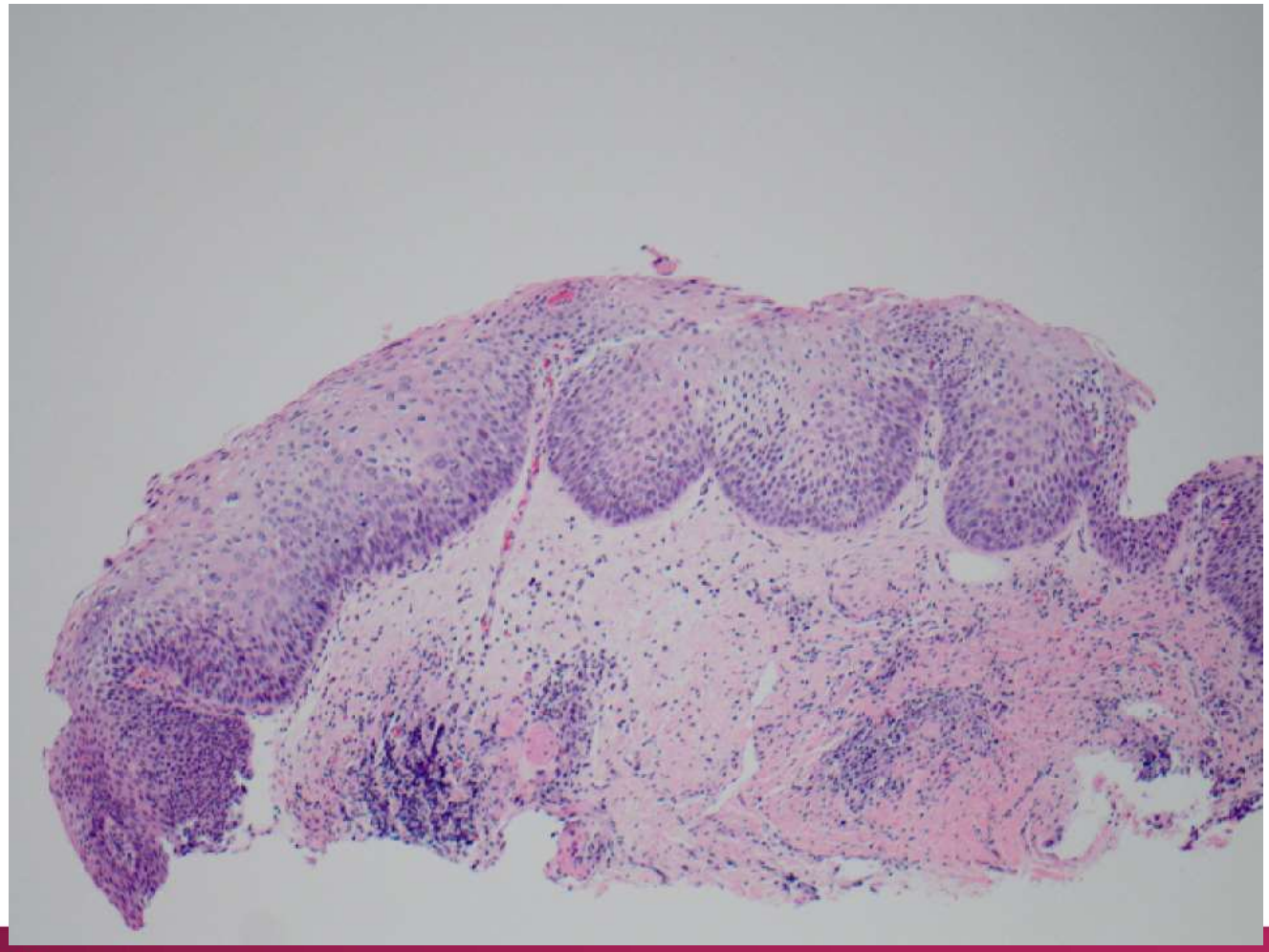


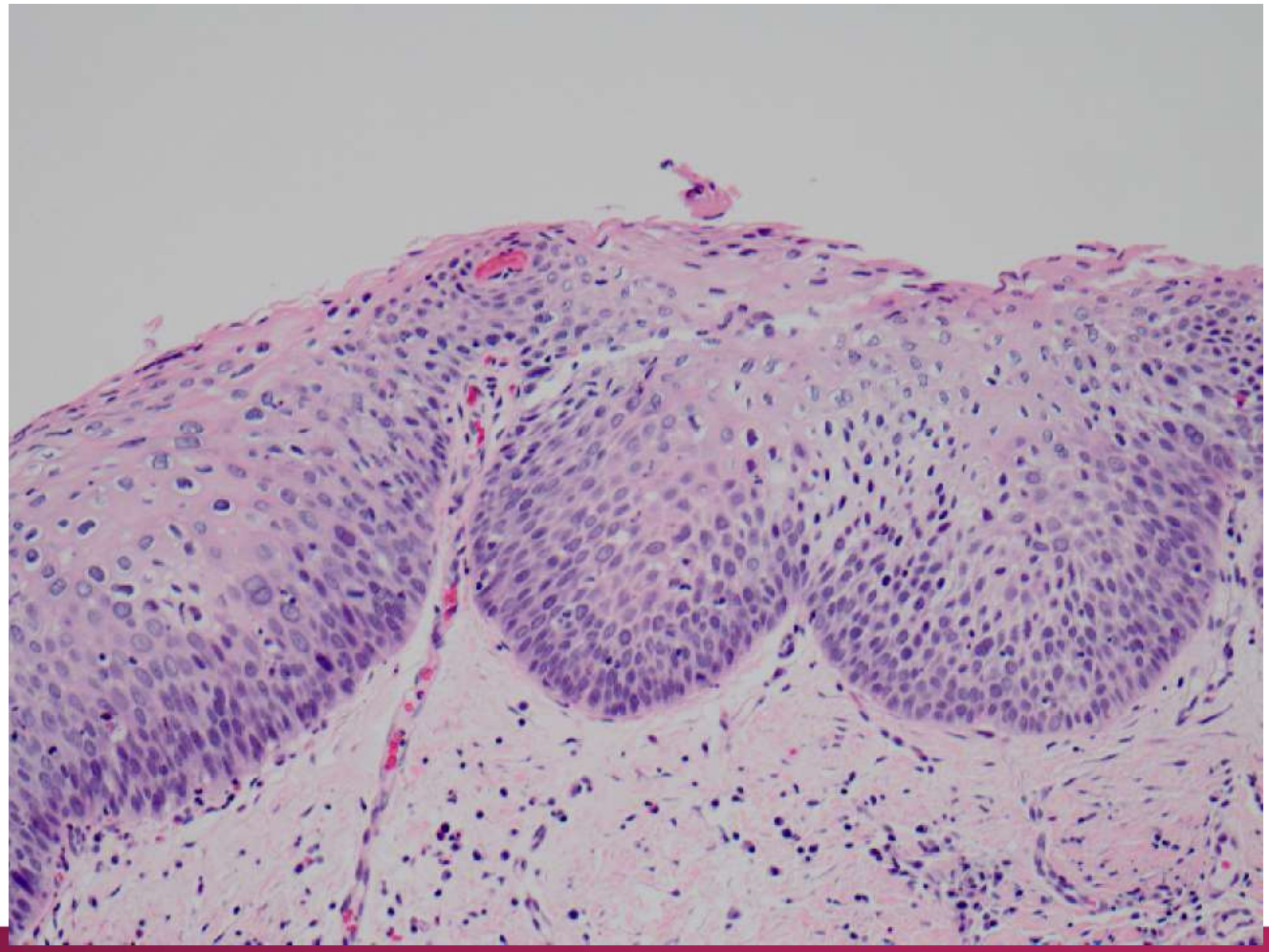


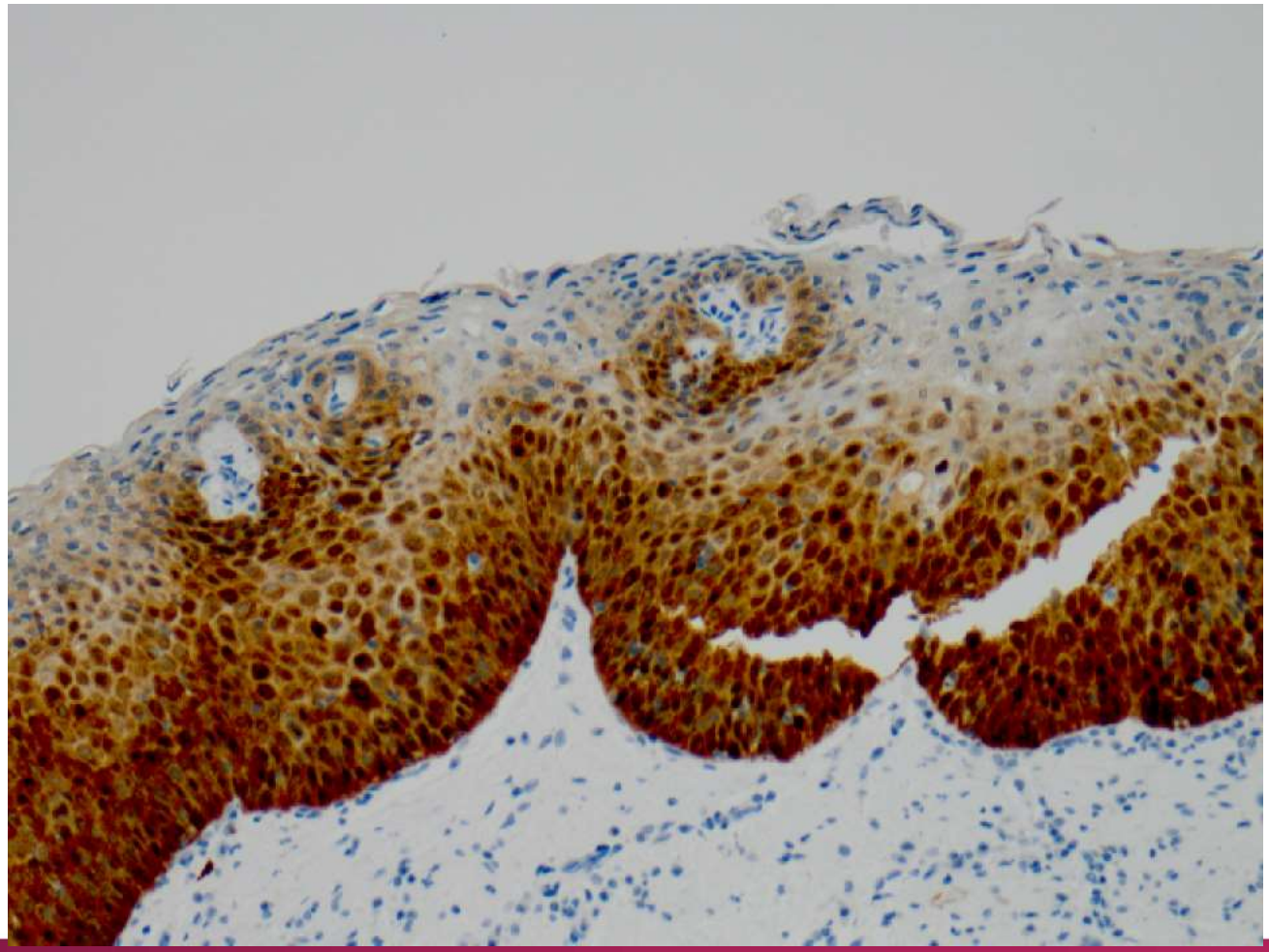




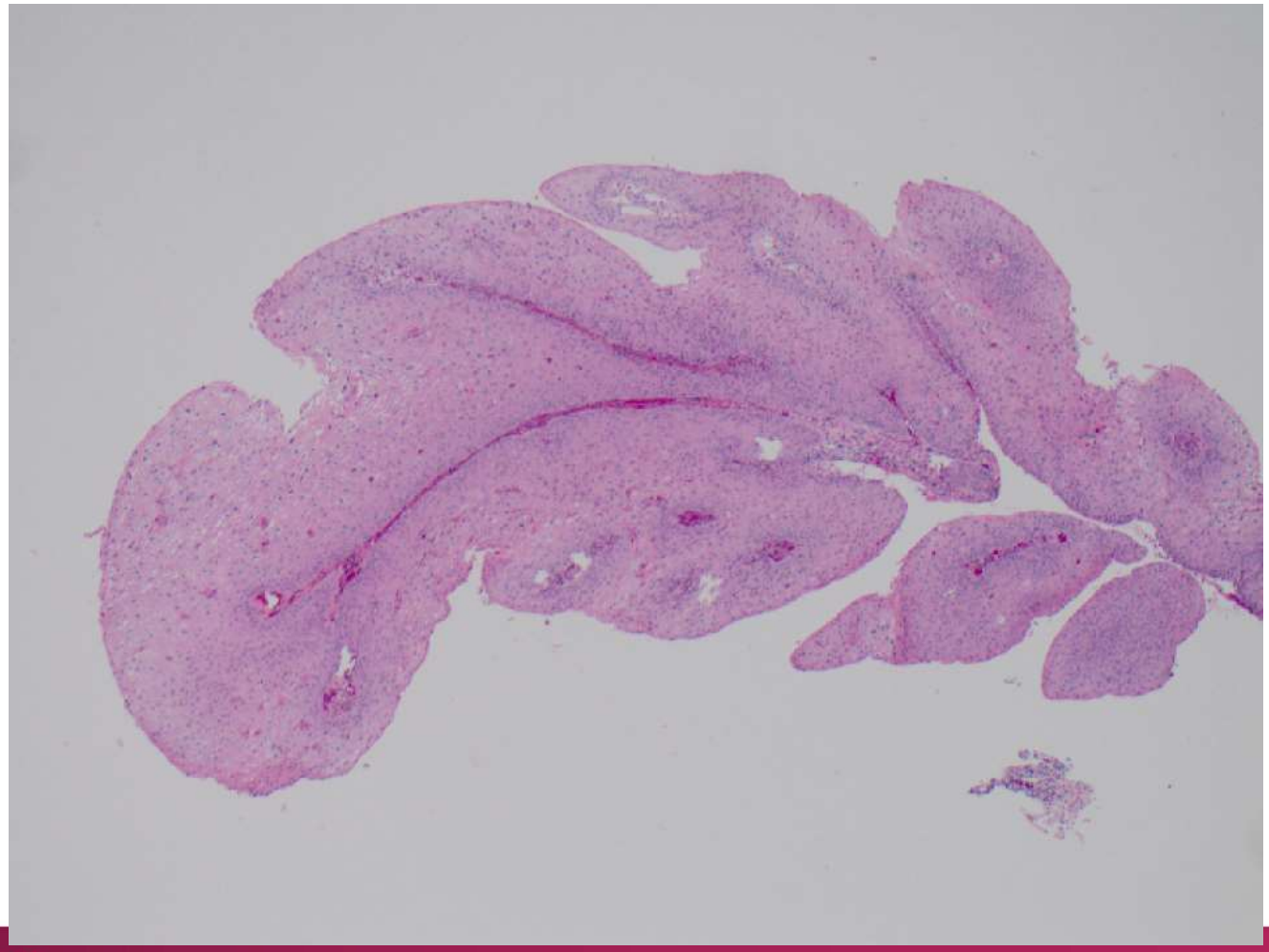


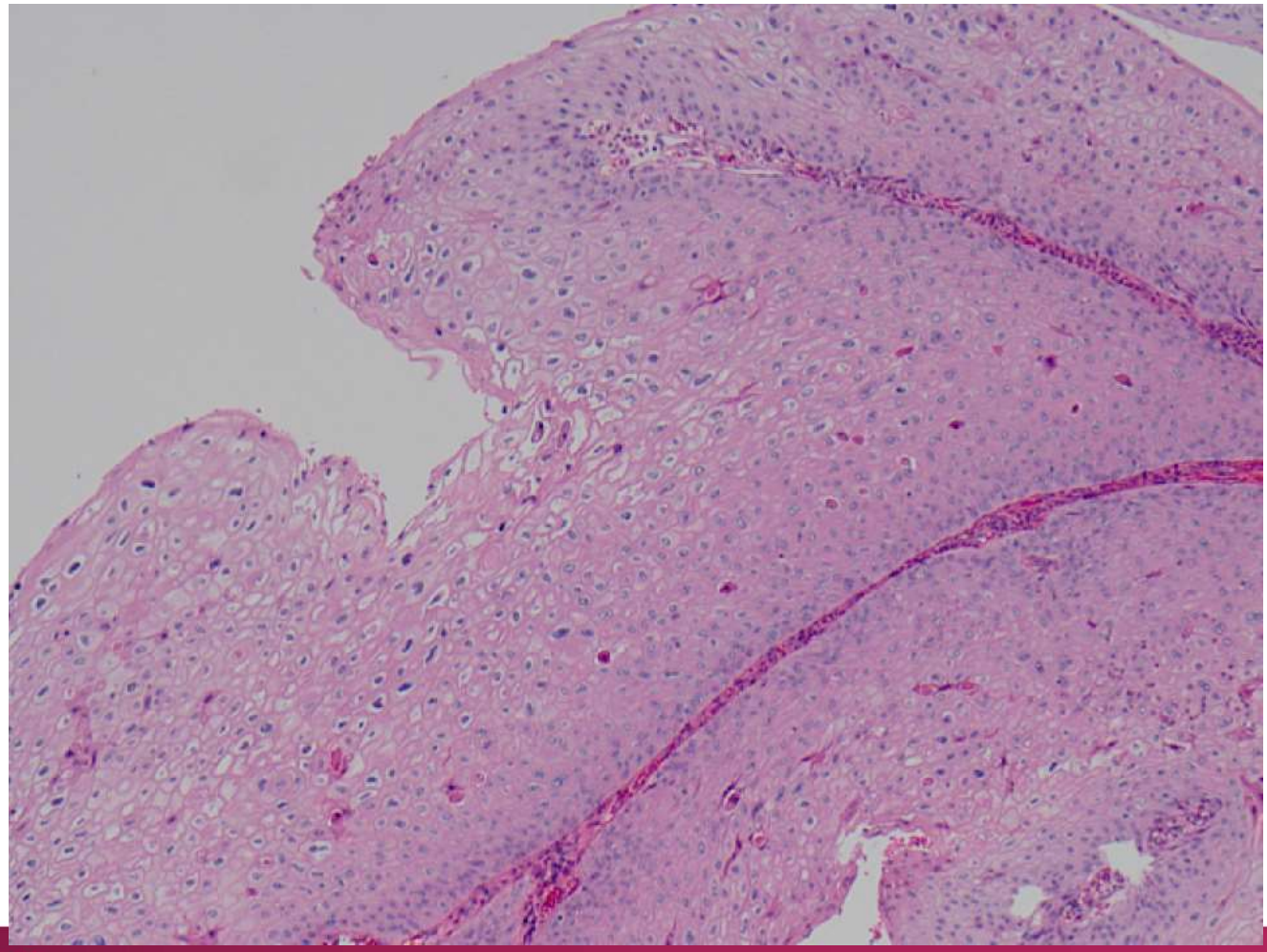


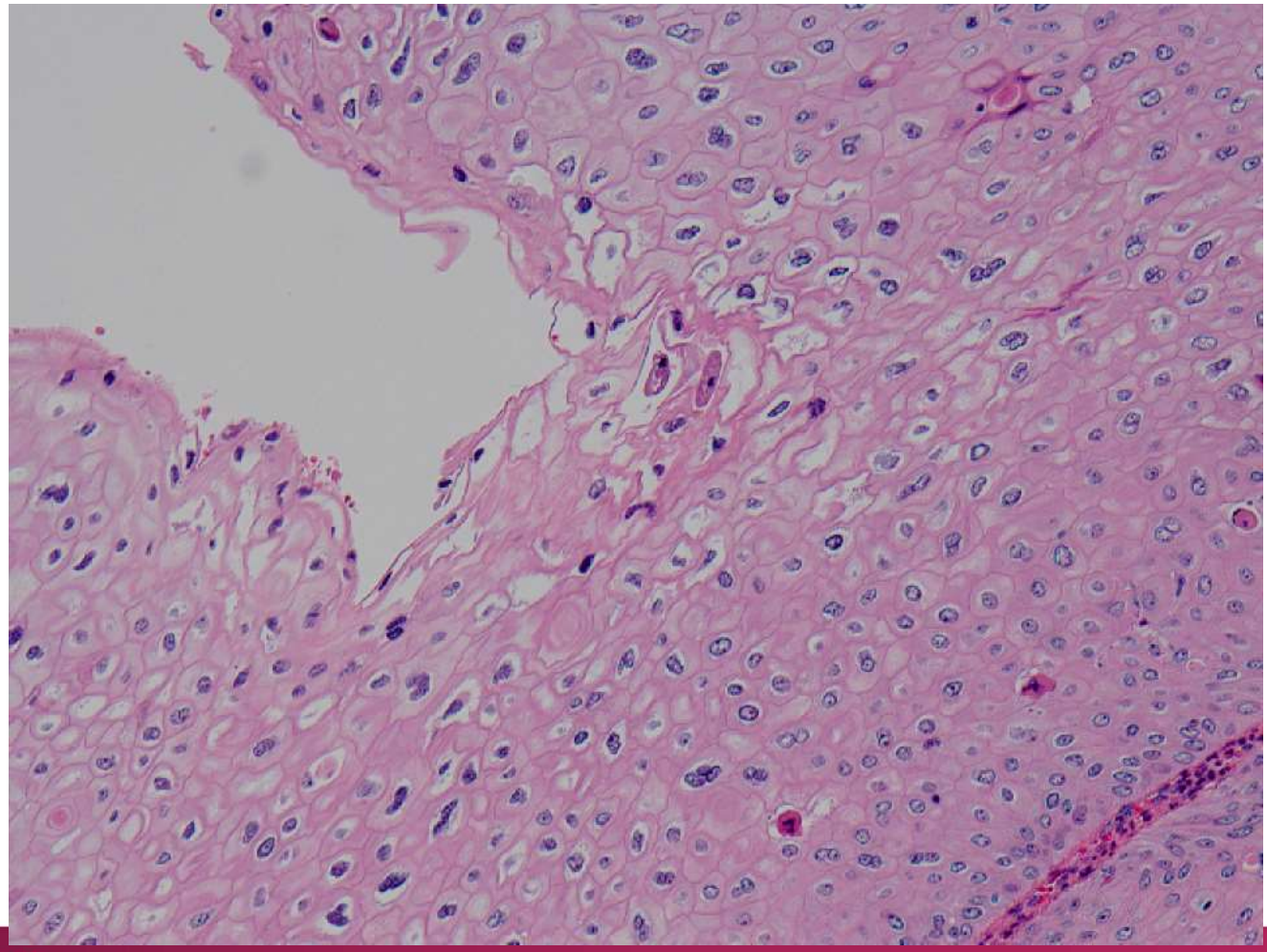


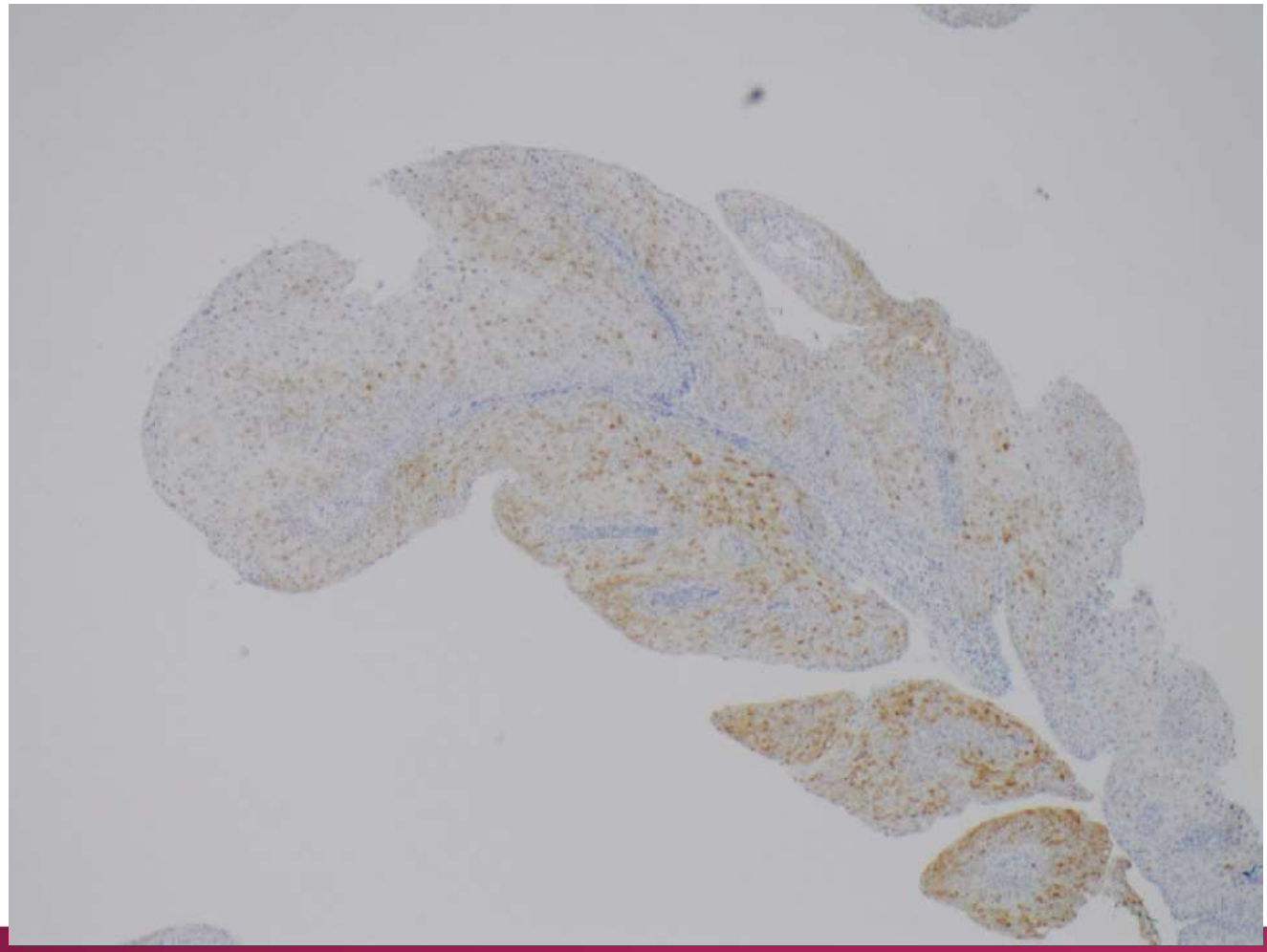


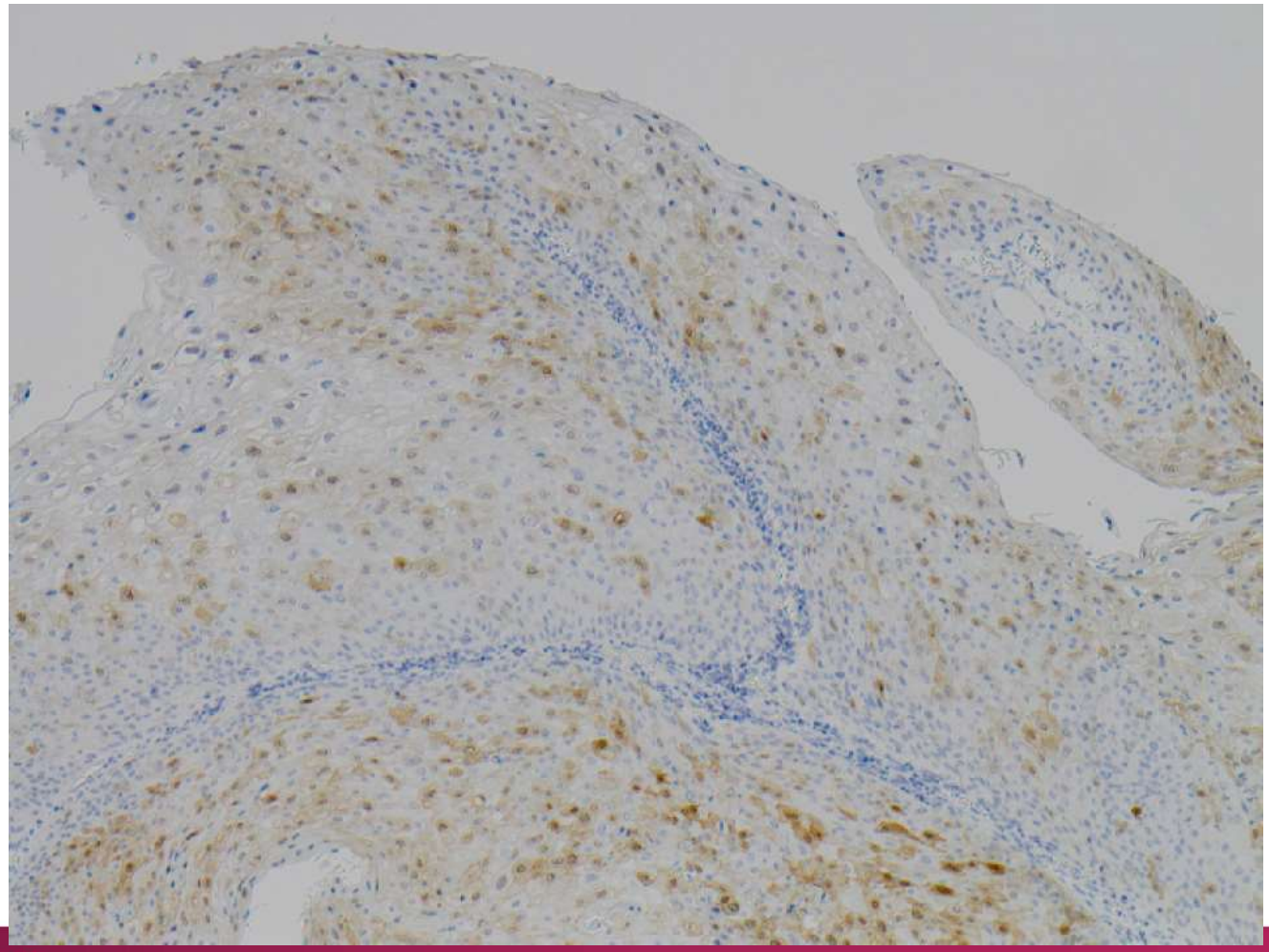
WG4 recommends AGAINST the routine use of P16 if the morphologic interpretation is NEGATIVE, -IN1, OR –IN3
SPECIAL CIRCUMSTANCE: p16 is recommended in patients that are at high risk for missed high grade disease (cytology HSIL, ASC-H, ASCUS/HPV+, OR AGC(NOS))



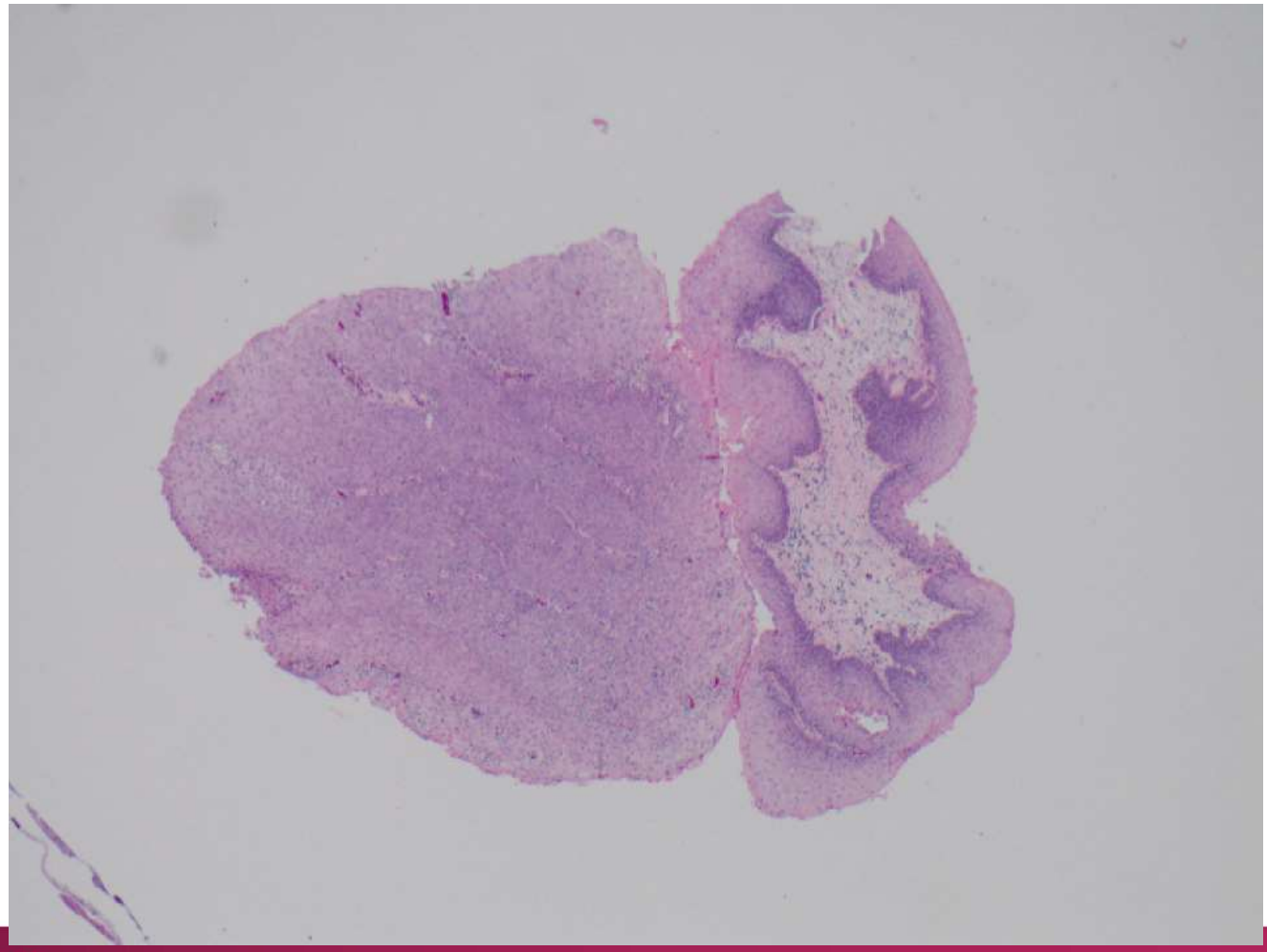


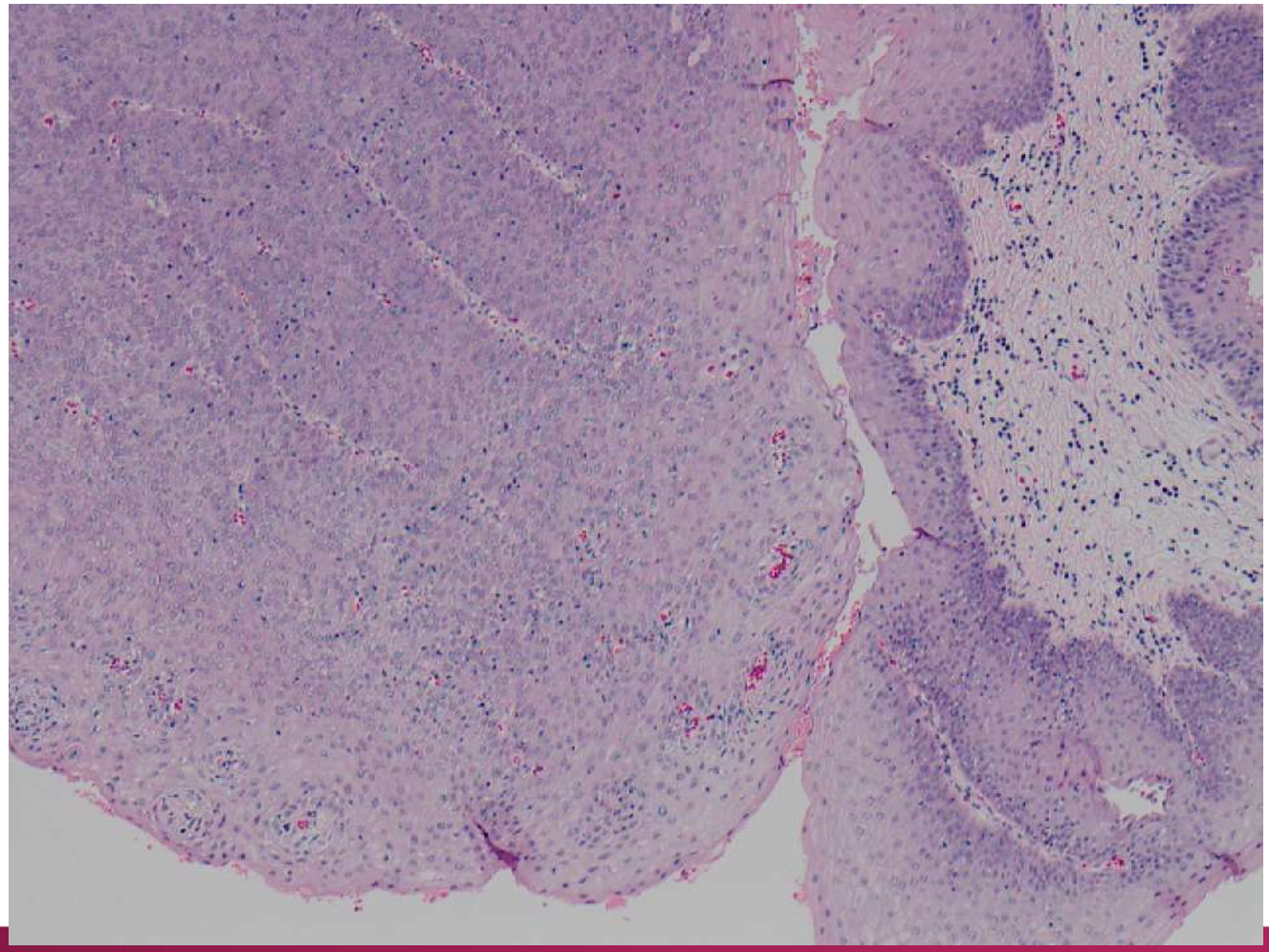


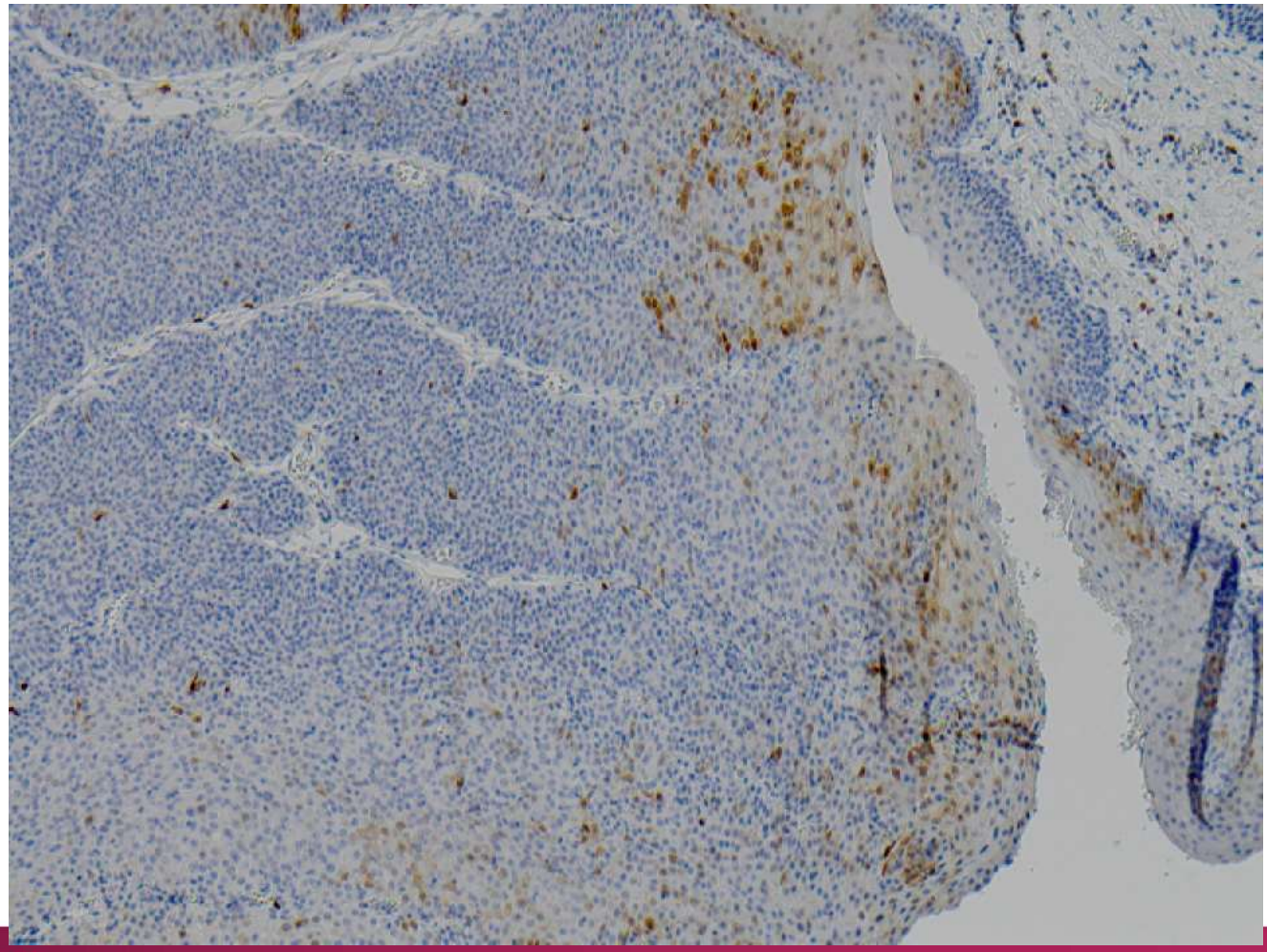


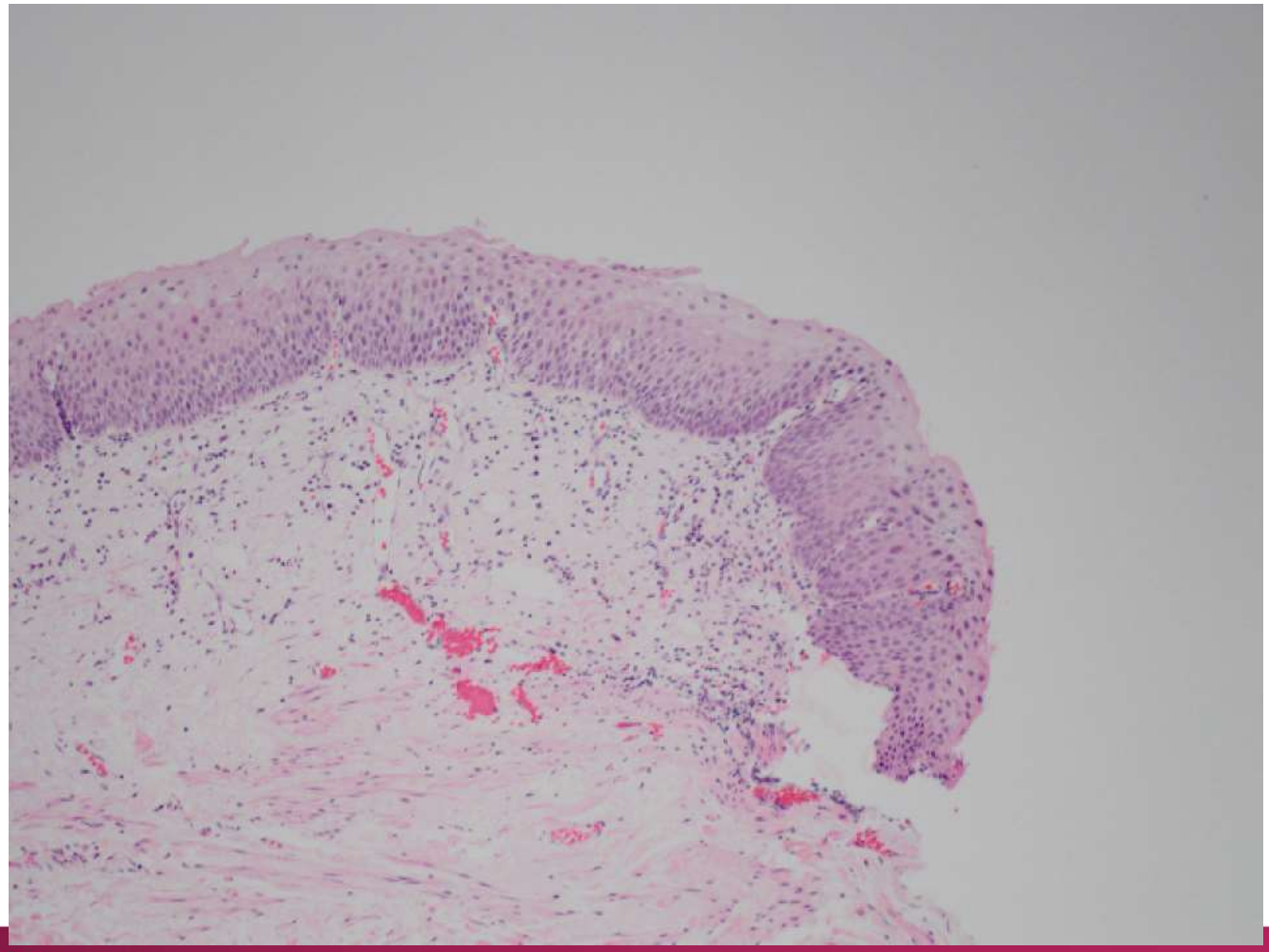


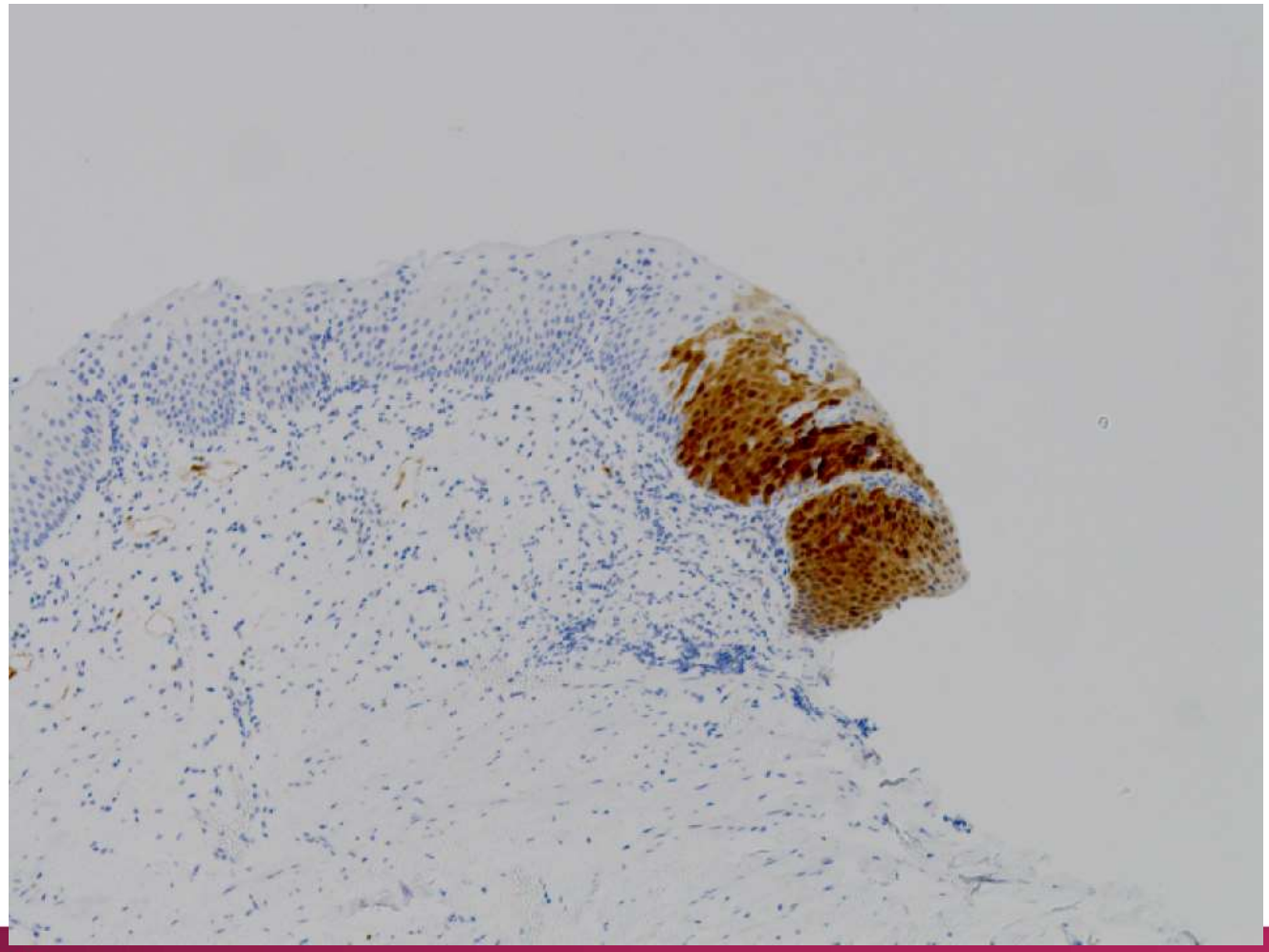
Difficult cases







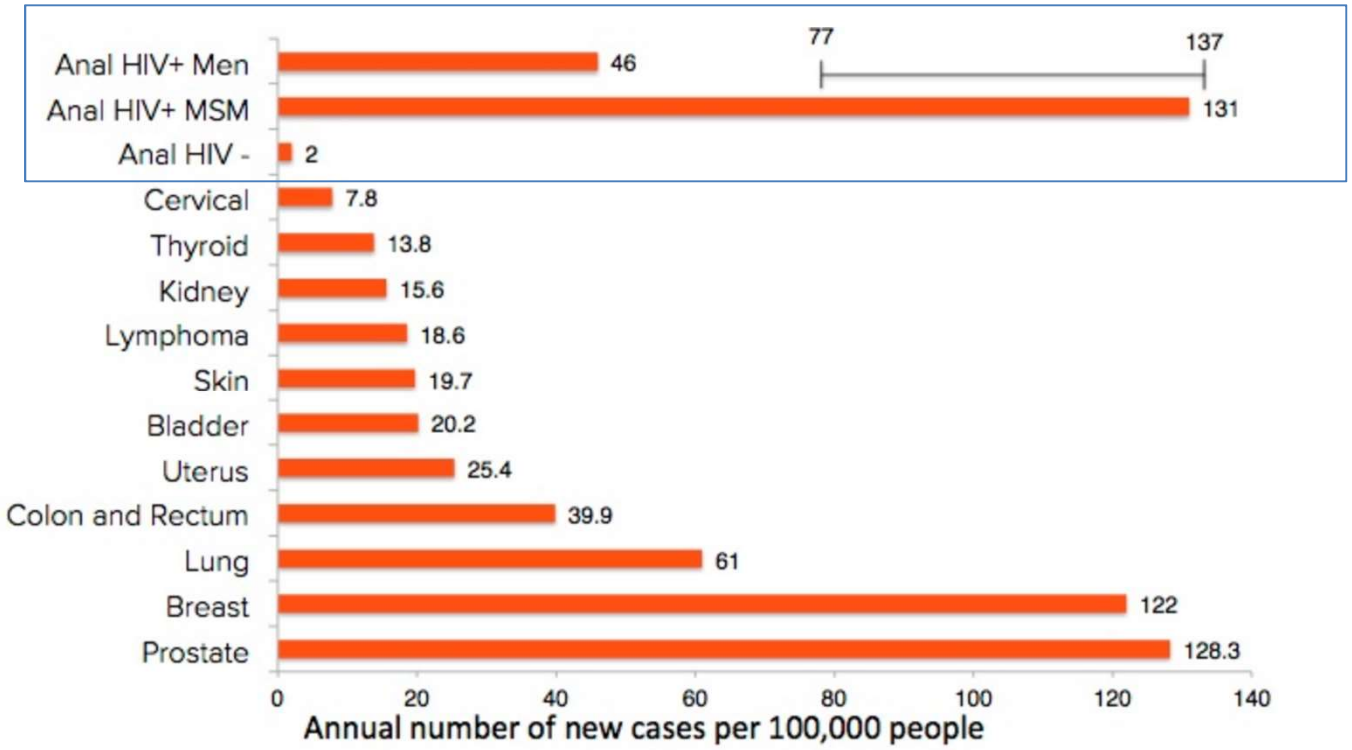




TAKE HOME MESSAGE

- **When is P16 IHC recommended?**
  1. When the histologic differential diagnosis is between precancer (-IN2 or –IN3) and a mimic of precancer - **Strong and diffuse block-positive p16 results support a categorization as a precancerous lesion**.
  2. When –IN2 would be considered in the old terminology
  3. When there is professional disagreement in a case where a precancerous lesion (-IN2 or IN3) is in the differential diagnosis
  4. WG4 recommends **AGAINST** the routine use of P16 if the morphologic interpretation is NEGATIVE, -IN1, OR –IN3

SCREENING STRATEGIES



https://anchorstudy.org/anal-cancer-risk-among-hiv-positive-men-and-women

“This is awkward….”

- DIGITAL ANAL RECTAL EXAM (DARE)
- ANAL PAP SMEARS
- HIGH RESOLUTION ANOSCOPY (HRA)

2014 Bethesda “recommendation”

“Among the high-risk populations that are the targets for anal cancer screening, those with any degree of abnormality on anal cytology are referred for HRA and biopsy, if resources allow. If resources for HRA are limited, then cytology can be used for triage: patients with HSIL or ASC-H cytology should be prioritized for HRA, followed by patients with LSIL, and finally by those with ASC-US. However anal cytology screening should only be instituted if treatment is available for individuals with HSIL. If expertise is not available to evaluate anal cytology, perform HRA and treat HSIL, then, at a minimum, high-risk patients should recieve a DARE to palpate for masses in the anal canal.”

Anal Cytology

Institutional Statistics, Correlation With Histology, and Development of Multidisciplinary Screening Program With Review of the Current Literature

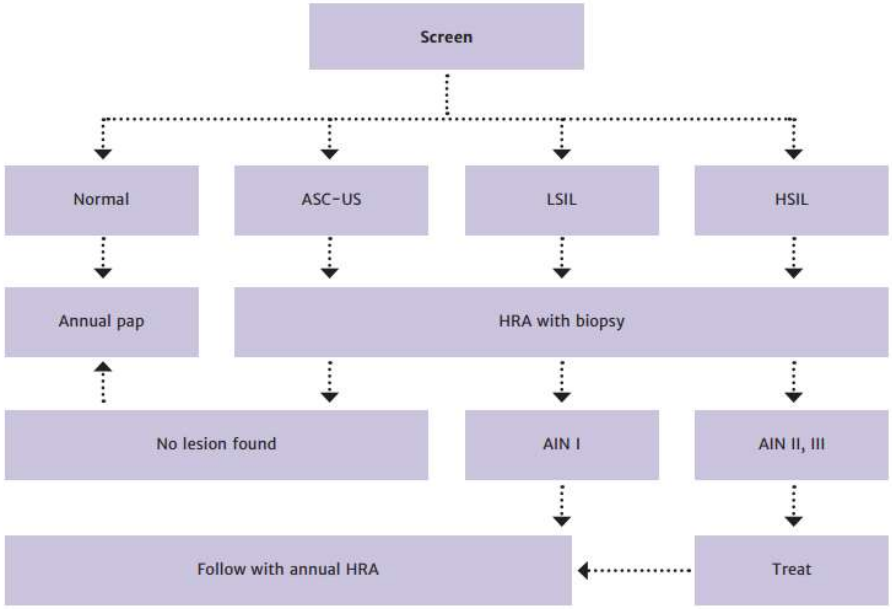
Elizabeth G. Morency, MD; Tracey Harbert, MD; Nazneen Fatima, MD; Julia Samolcyzk, BS, CT(ASCP); Kruti P. Maniar, MD; Ritu Nayar, MD

Archives of Pathology Laboratory Medicine. 2019;143:23–29

NY State Department of Health AIDS Institute Guideline

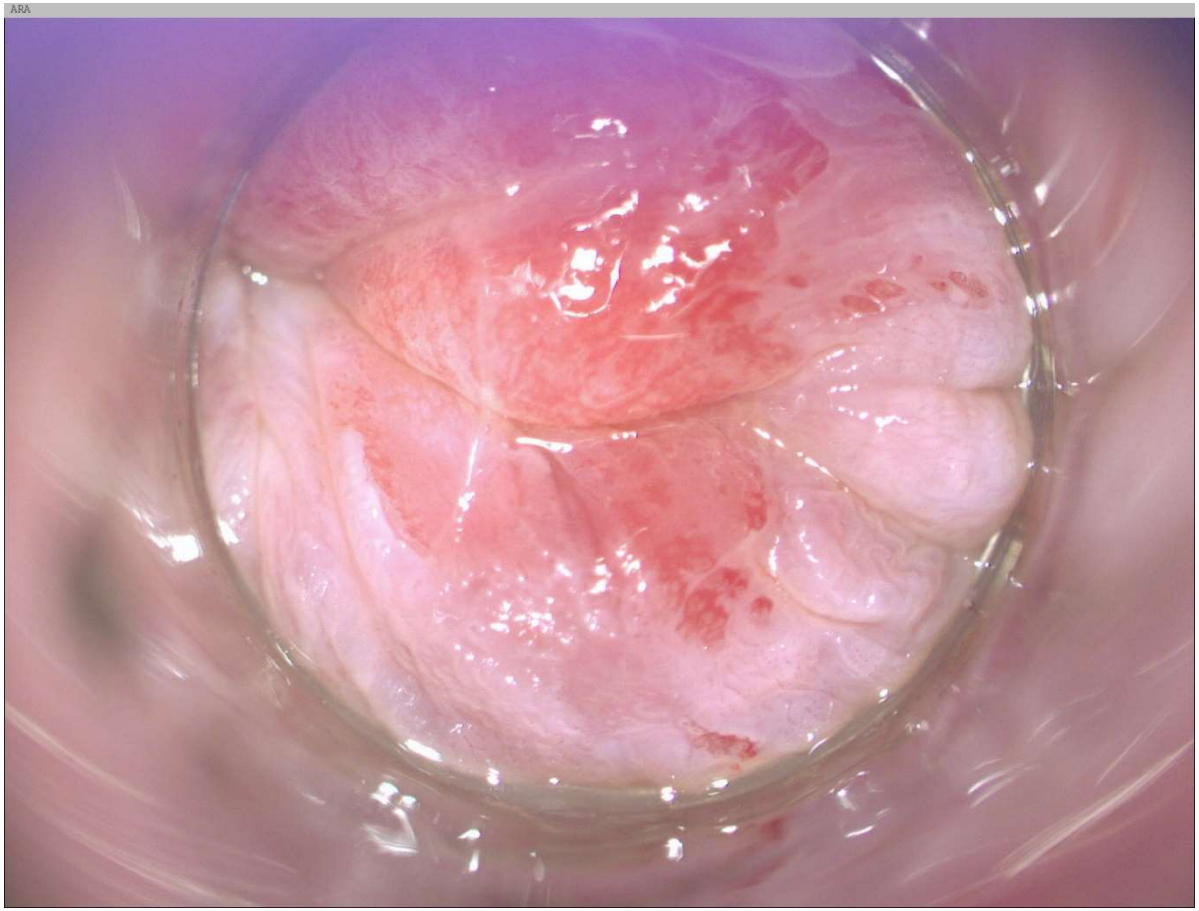
- Clinicians should obtain anal cytology at baseline and annually in the following HIV-infected populations
  - Men who have sex with men
  - Any patient with a history of anogenital condylomas
  - Women with abnormal cervical and/or vulvar histology

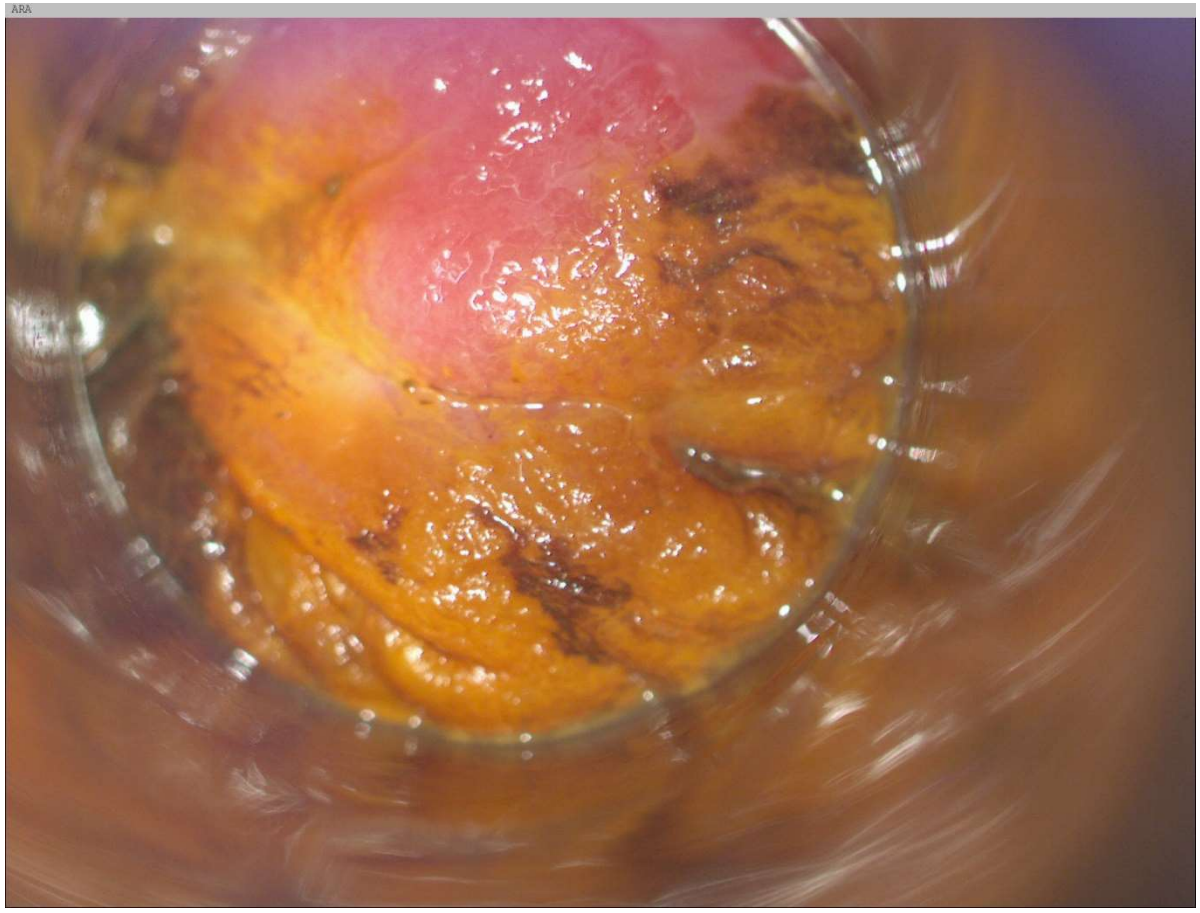
FIGURE 1. Anal Screening Evaluation

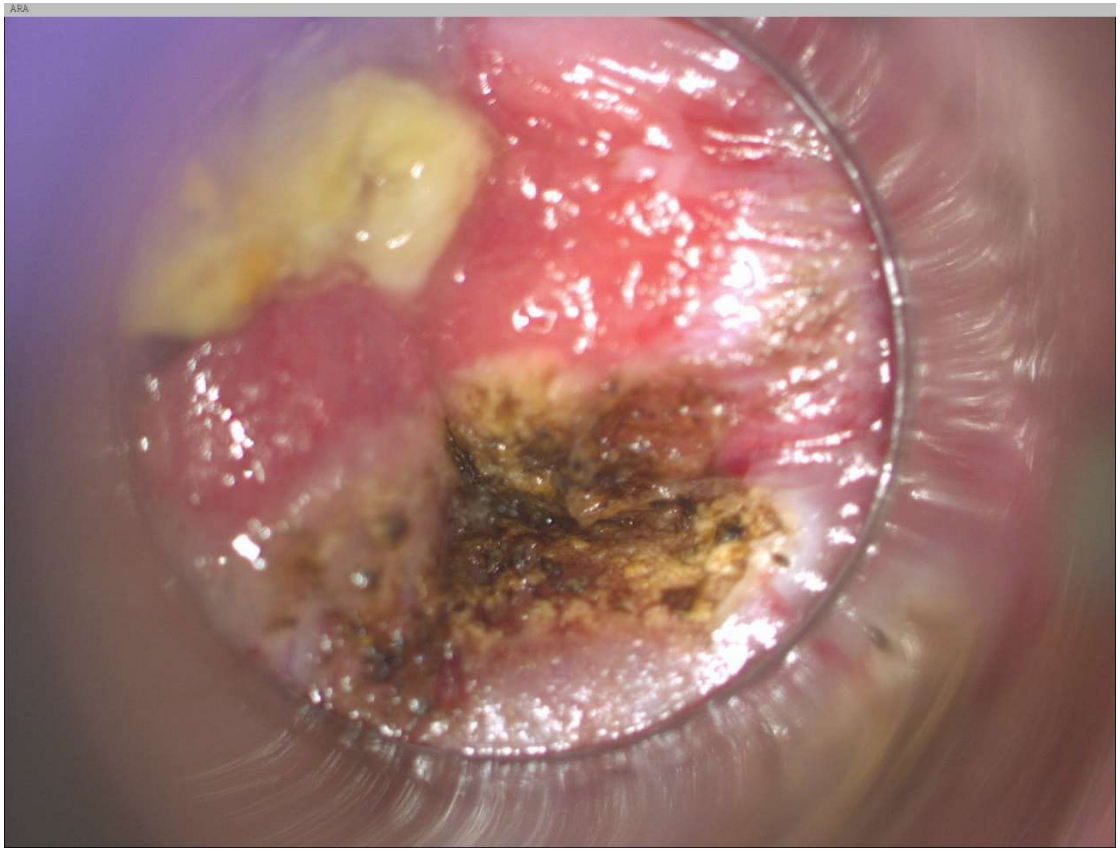


ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; AIN, anal intraepithelial neoplasia.

https://cdn.hivguidelines.org/wp-content/uploads/20180726101521/NYSDOH-AI-Anal-Dysplasia-and-Cancer-Figure-1-Anal-Screening-Evaluation_6-6-2018_HG.pdf


ARA


ARA



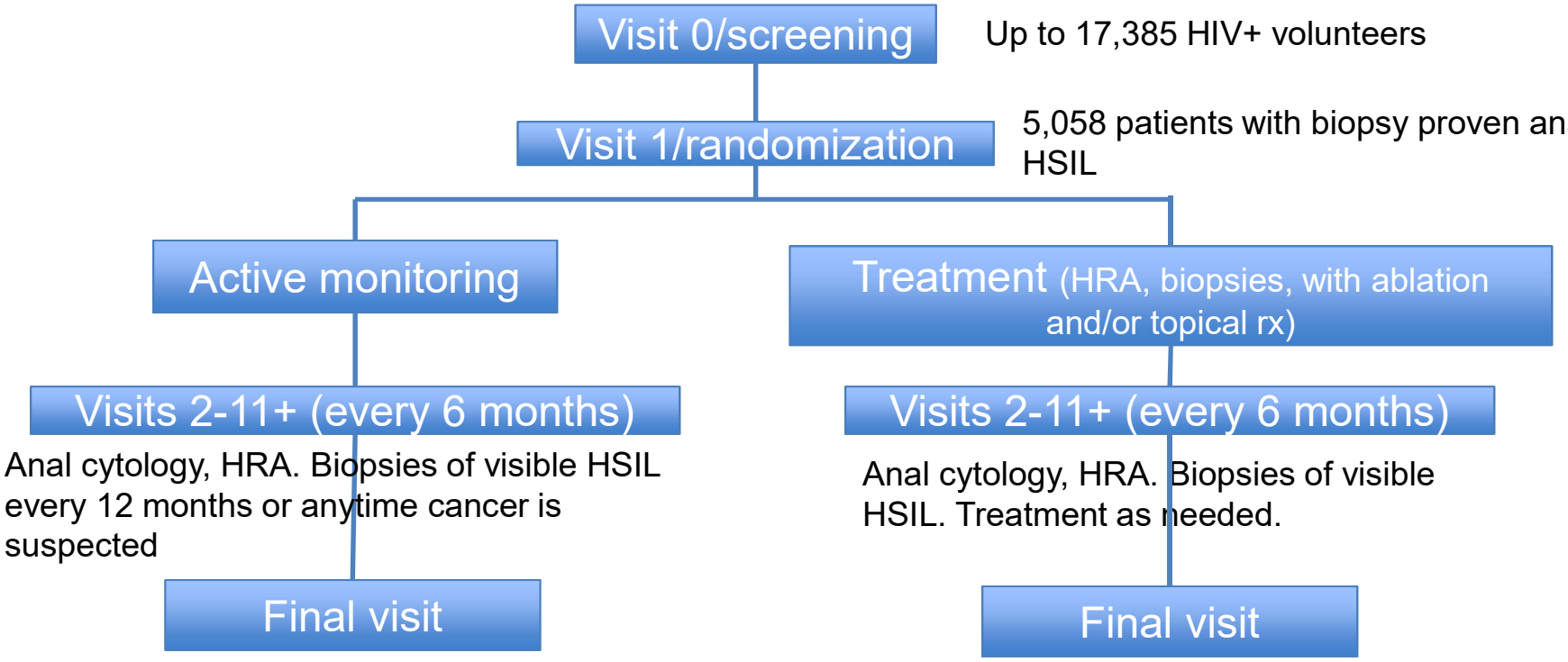
ANCHOR STUDY: Anal Cancer/HSIL Outcomes Research Study

Primary Objective

To determine whether treating anal HSIL is effective in reducing the incidence of anal cancer in HIV-infected men and women.

Secondary Objective

To determine the safety of infrared coagulation, electrocautery, imiquimod, laser, and 5-fluorouracil treatments for anal HSIL.



Adopted from ANCHOR Protocol (AMC-A01 Version 11.0) 28MAR2019
NCI Version Date 28MAR2019

References

1. @NCICancerStats. Cancer of the Anus, Anal Canal, and Anorectum - Cancer Stat Facts. 2019. Available at: https://seer.cancer.gov/statfacts/html/anus.html.
2. Albuquerque A, Sheaff M, Stirrup O, et al. Performance of Anal Cytology Compared With High-Resolution Anoscopy and Histology in Women With Lower Anogenital Tract Neoplasia. *Clin Infect Dis.* 2018;67:1262-1268.
3. Cardinal LH, Carballo P, Lorenzo MC, et al. A six-year experience with anal cytology in women with HPV in the lower genital tract: utility, limitations, and clinical correlation. *Diagn Cytopathol.* 2014;42:396-400.
4. Darragh TM, Colgan TJ, Cox JT, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med.* 2012;136:1266-1297.
5. Fenger C. Anal Canal. In: Mills S, ed. *Histology for Pathologists*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:663-683.
6. Govindarajan R, Gujja S, Siegel ER, et al. Programmed Cell Death-Ligand 1 (PD-L1) Expression in Anal Cancer. *Am J Clin Oncol.* 2018;41:638-642.
7. Lam AK, Goldblum JR. Tumors of the Anal Canal. In: Board WCoTE, ed. *Digestive System Tumours*. Lyon, France: IARC; 2019:193-212.
8. Lokko C, Turner J, Yoo W, et al. Anal Squamous Cell Carcinoma in African Americans with and without HIV: A Comparative Study. *J Cancer Epidemiol Treat.* 2015;1:6-10.
9. Meulendijks D, Tomasoa NB, Dewit L, et al. HPV-negative squamous cell carcinoma of the anal canal is unresponsive to standard treatment and frequently carries disruptive mutations in TP53. *Br J Cancer.* 2015;112:1358-1366.
10. Morency EG, Harbert T, Fatima N, et al. Anal Cytology: Institutional Statistics, Correlation With Histology, and Development of Multidisciplinary Screening Program With Review of the Current Literature. *Arch Pathol Lab Med.* 2019;143:23-29.
11. Nayar R, Wilbur DC, eds. *The Bethesda System for Reporting Cervical Cytology*. Switzerzerland: Springer INternational Publishing; 2015.
12. Oehler-Janne C, Huguet F, Provencher S, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. *J Clin Oncol.* 2008;26:2550-2557.
13. Roma AA, Liu X, Patil DT, et al. Proposed Terminology for Anal Squamous Lesions: Its Application and Interobserver Agreement Among Pathologists in Academic and Community Hospitals. *Am J Clin Pathol.* 2017;148:81-90.
14. Sendagorta E, Herranz P, Guadalajara H, et al. Prevalence of abnormal anal cytology and high-grade squamous intraepithelial lesions among a cohort of HIV-infected men who have sex with men. *Dis Colon Rectum.* 2014;57:475-481.
15. Shiels MS, Pfeiffer RM, Chaturvedi AK, et al. Impact of the HIV Epidemic on the Incidence Rates of Anal Cancer in the United States. *Jnci-Journal of the National Cancer Institute.* 2012;104:1591-1598.
16. Welton ML, Lambert R, Bosman FT. Tumours of the Anal Canal. In: Bosman FT, Carneiro F, Hruban RH, et al., eds. *WHO Classification of Tumours of the Digestive System*. Lyon: IARC; 2010:184-193.
17. Yanik EL, Kaunitz GJ, Cottrell TR, et al. Association of HIV Status With Local Immune Response to Anal Squamous Cell Carcinoma: Implications for Immunotherapy. *JAMA Oncol.* 2017;3:974-978.