Glandular lesions

Epidemiology
Cytology, Histology
Management Algorithms
Case Studies

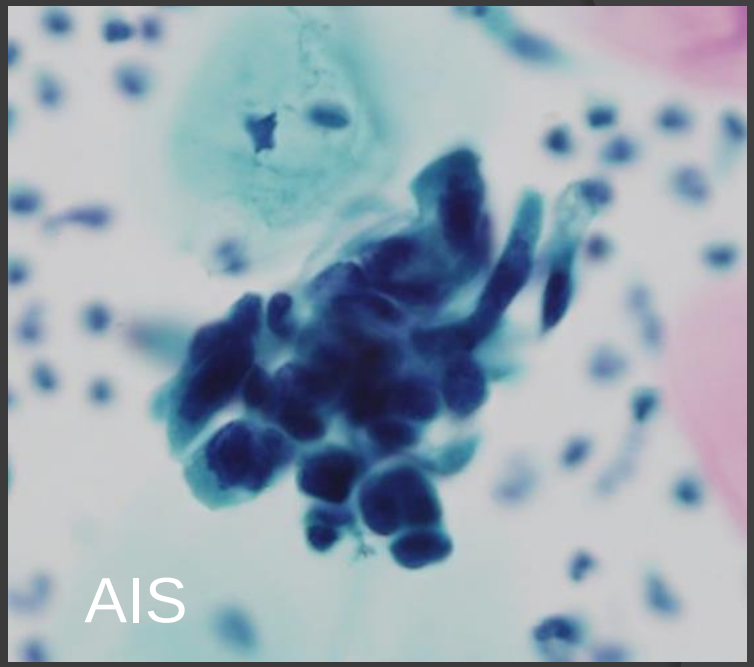
Objectives

1. Understand the epidemiology of glandular lesions.
2. Discuss the cytology, histology, and colposcopy findings of AIS and cervical adenocarcinoma.
3. Review the ASCCP guidelines and algorithms on glandular cytology and AIS.

Pap Nomenclature for Glandular Abnormalities:

Bethesda 2001

- Atypical Glandular Cells (AGC)
  - Atypical endocervical cells
  - Atypical endometrial cells
  - Atypical glandular cells not otherwise specified (NOS)
- Atypical Glandular Cells, favor neoplastic
  - Atypical endocervical cells
  - Atypical glandular cells
- Endocervical Adenocarcinoma In Situ (AIS)
- *AGC replaces prior terminology, "AGUS"*



UNM Pathology

Solomon D et al. JAMA 2002; 287: 2114-9

AGC Cytology: What does it imply?

- Makes up < 0.5% of all cervical cytology.
- Histologic diagnosis after AGC on Cytology
  - Adenocarcinoma In Situ (AIS)
  - Squamous intraepithelial lesion (any)
    - Most common pathology with AGC
    - Often coexist with glandular lesions
  - Adenocarcinoma
    - Cervix, endometrium, tube, ovary, metastatic
  - Reactive, reparative, polyps
  - Microglandular hyperplasia from OCP's
  - Adenosis

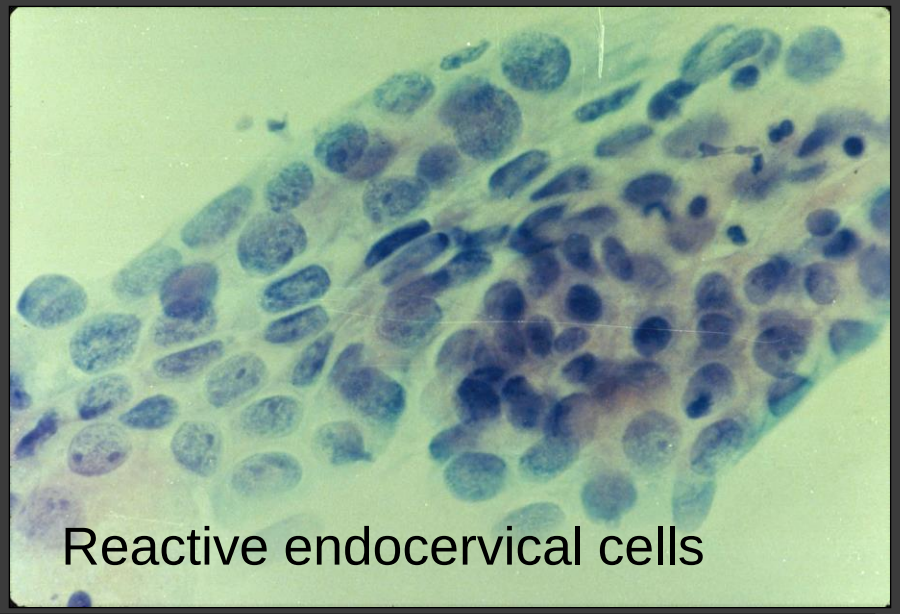
Atypical Endocervical Cells: Cytologic features

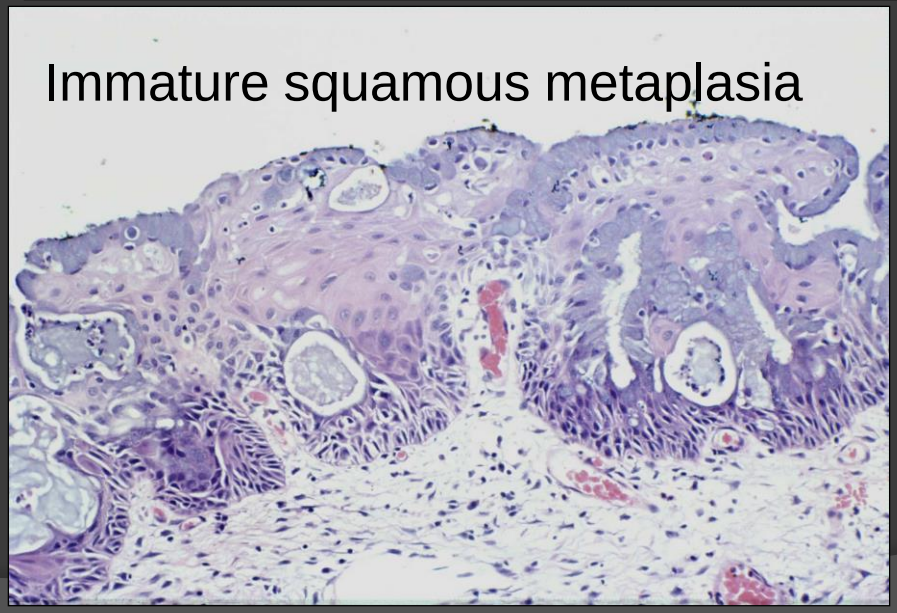
- Sheets or strips with minimal nuclear overlapping
- Enlarged nuclei (3-5 x normal endocx)
- Slight hyperchromasia
- Mild variation in size and shape
- Nucleoli may be present

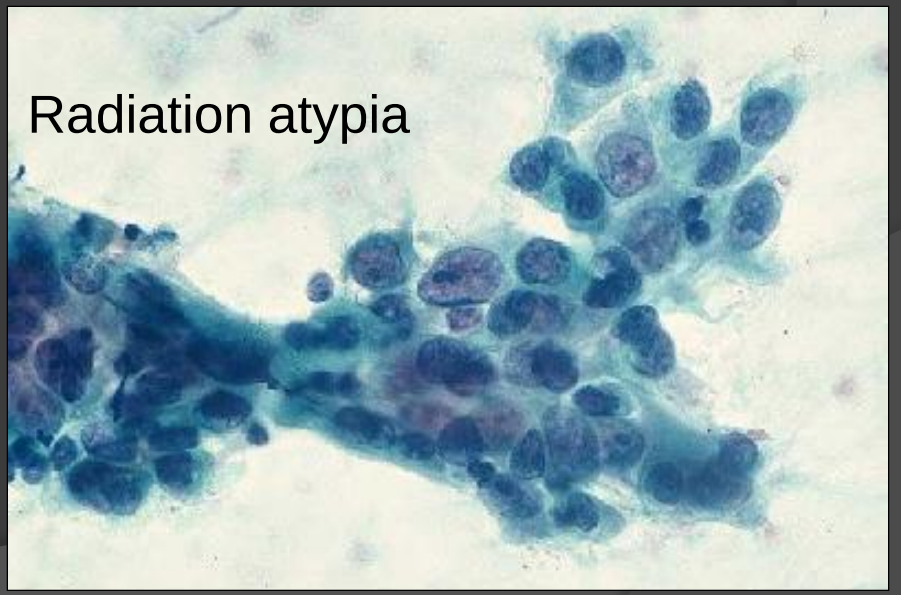
Atypical Endocervical Cells: Differential Dx

- Cervicitis / reactive endocervical cells
- Directly sampled LUS / endometrium
- Microglandular hyperplasia
- Arias-Stella change
- Tubal metaplasia
- SIL (especially HSIL)
- Endocervical AIS
- Endocervical adenocarcinoma

Atypical endocervical cells, NOS

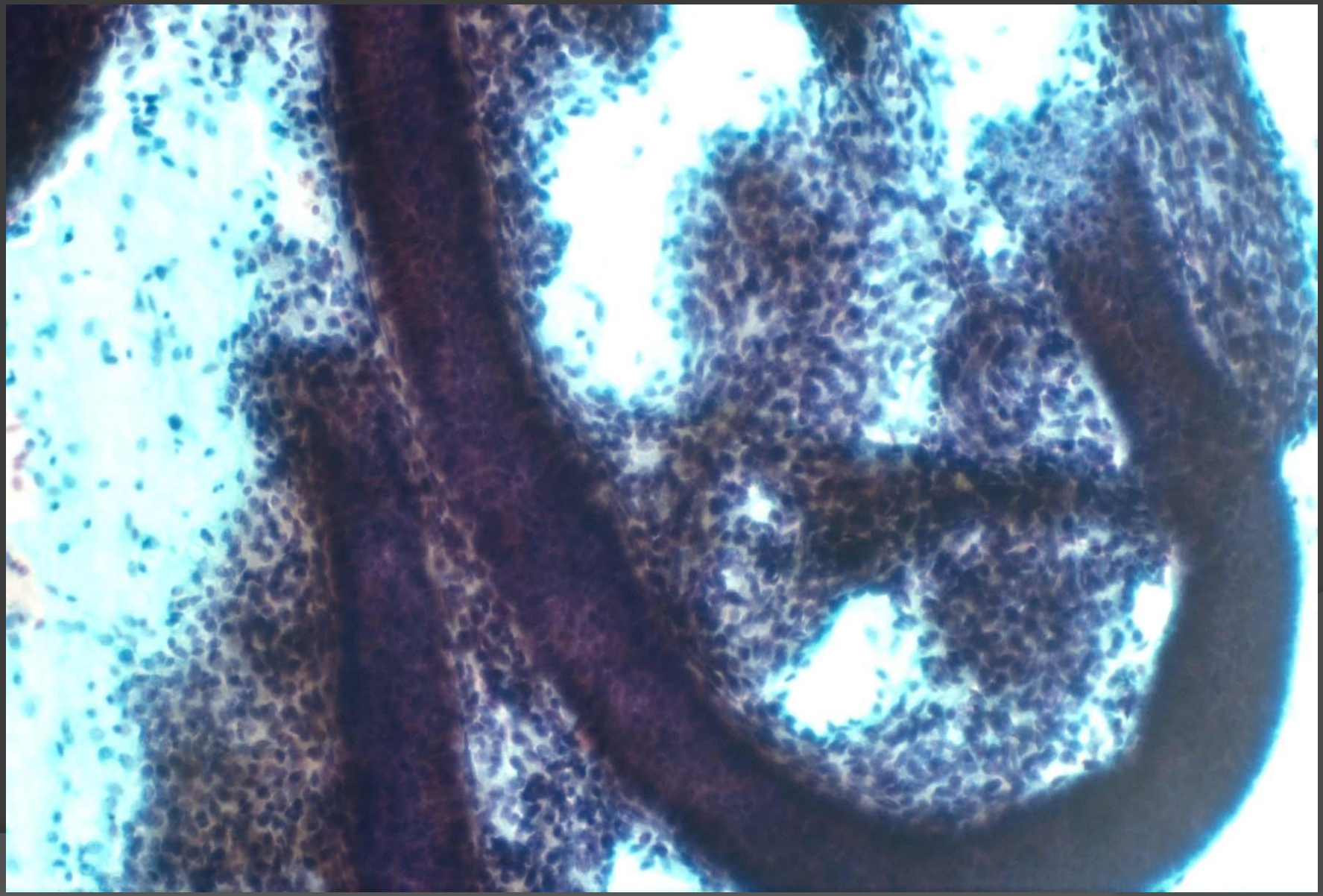




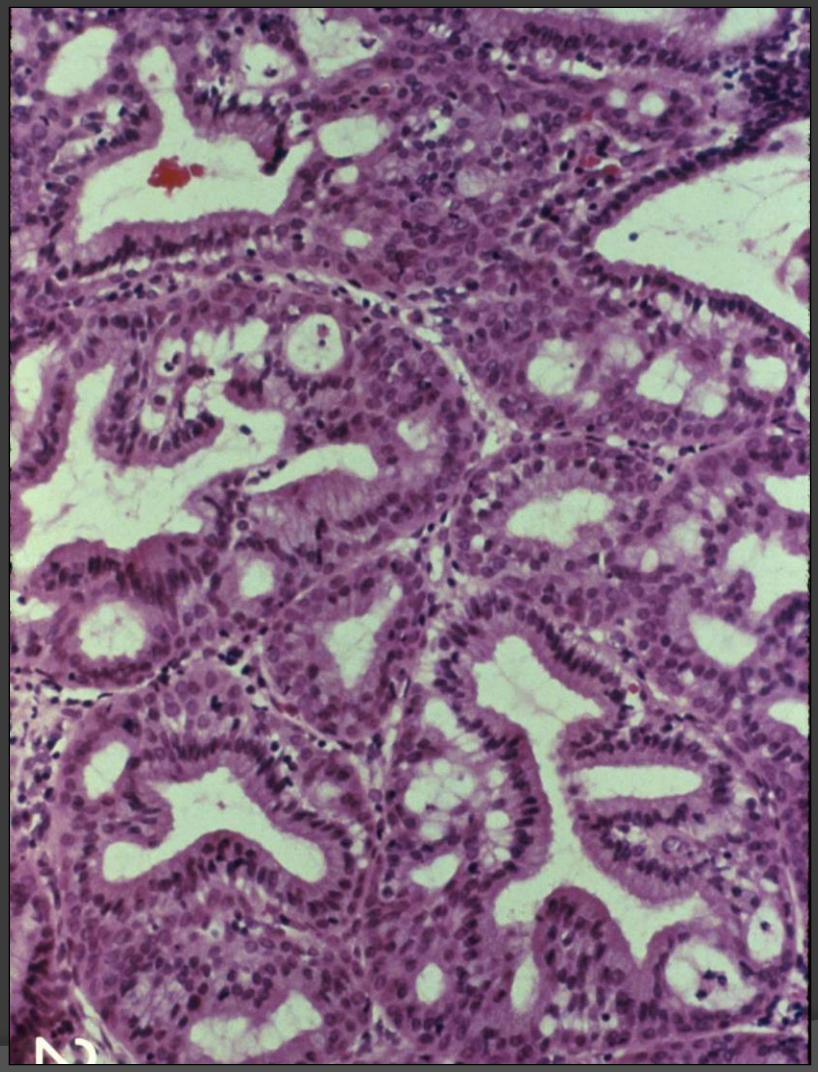


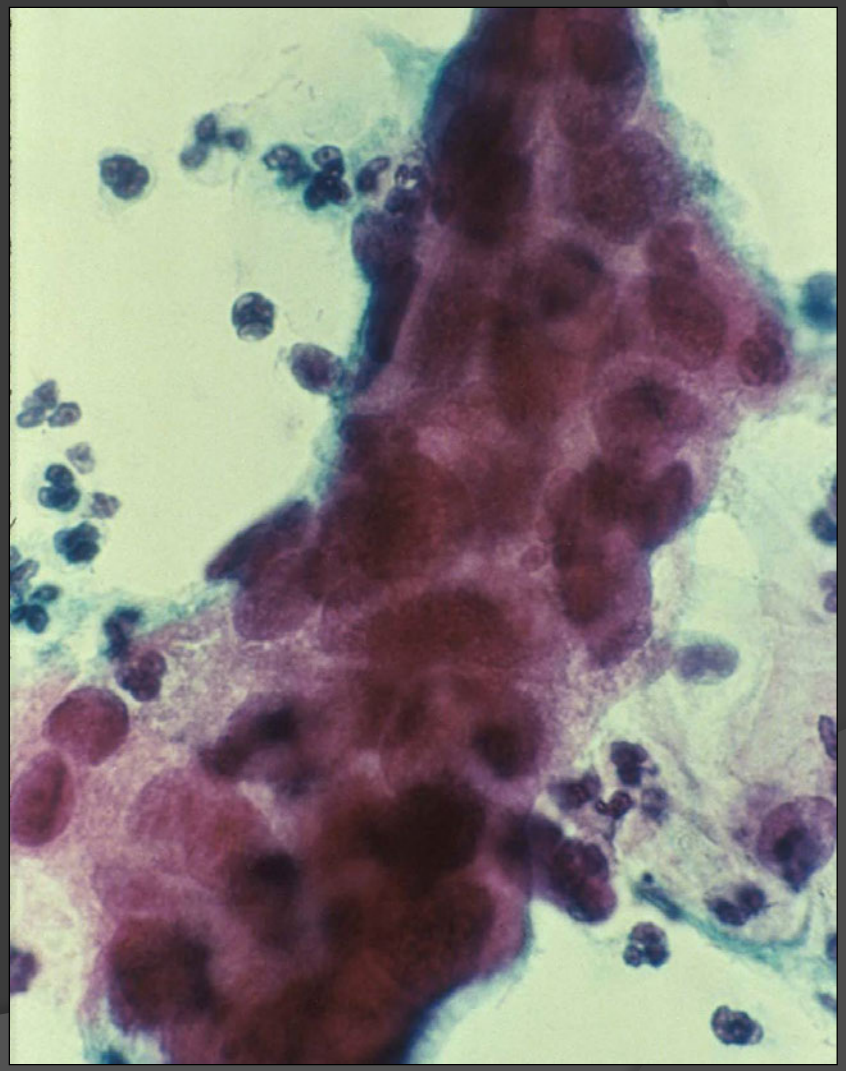
Cytology images from Bethesda Web Atlas- Thanks to Teresa Darragh, MD

Directly sampled endometrium

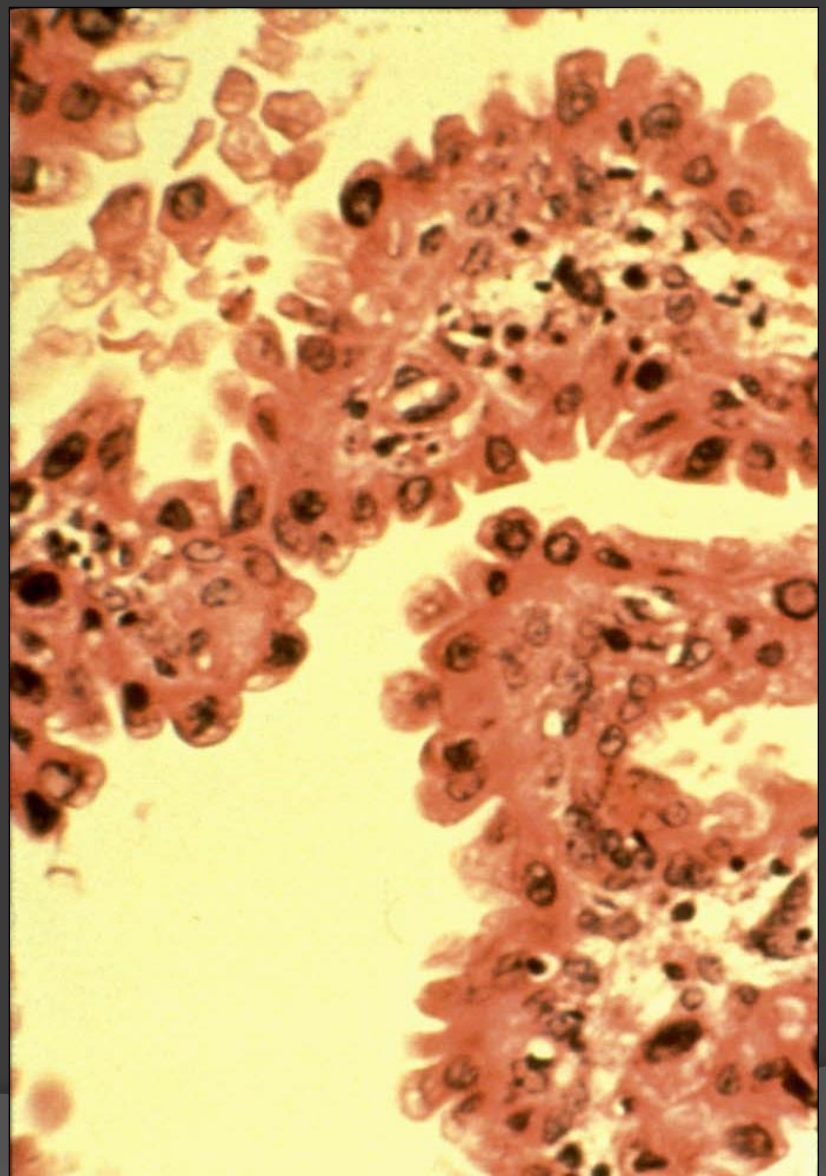


Microglandular Hyperplasia

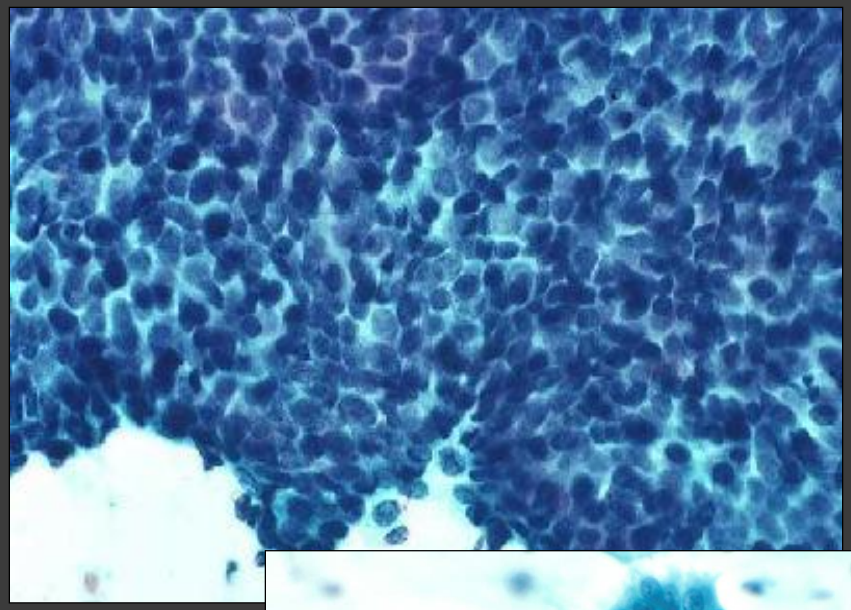


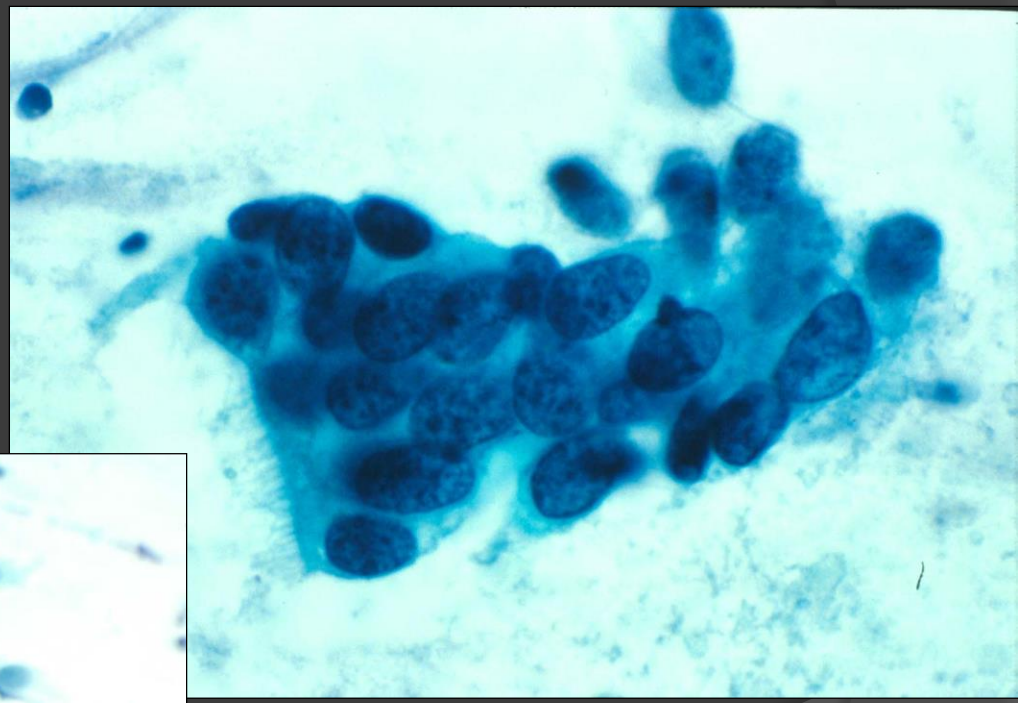


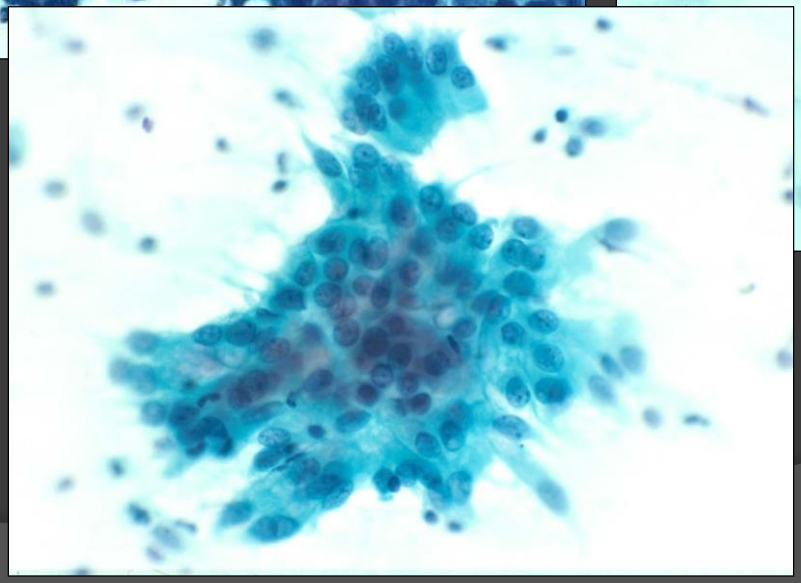
Arias-Stella Reaction



Atypical endocervical cells: Tubal metaplasia







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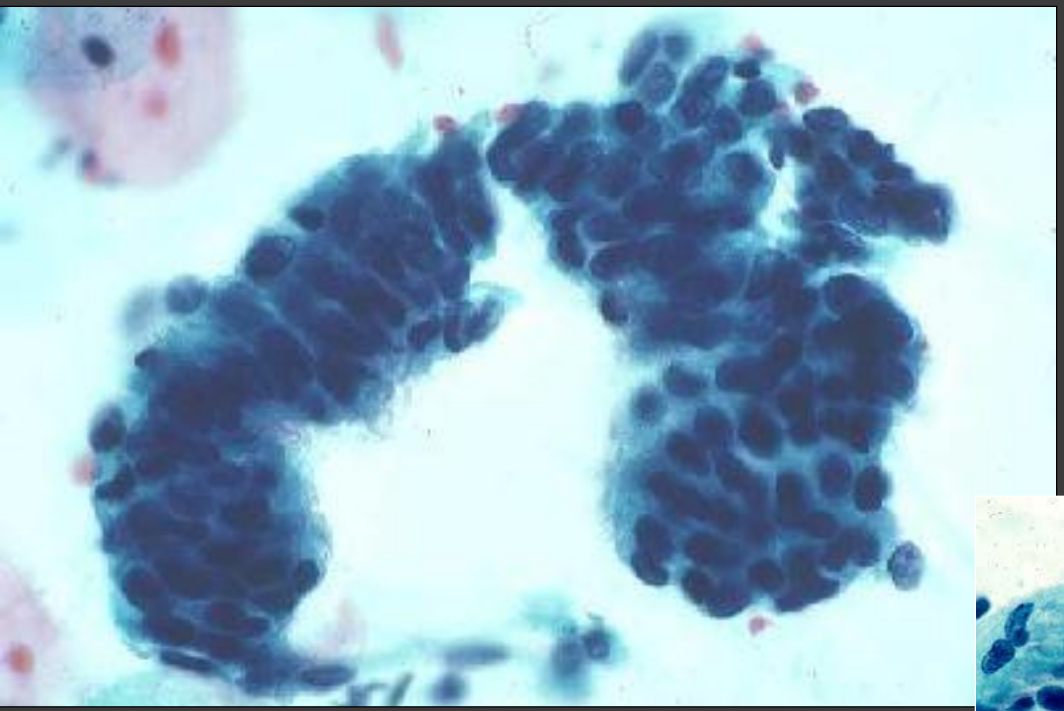
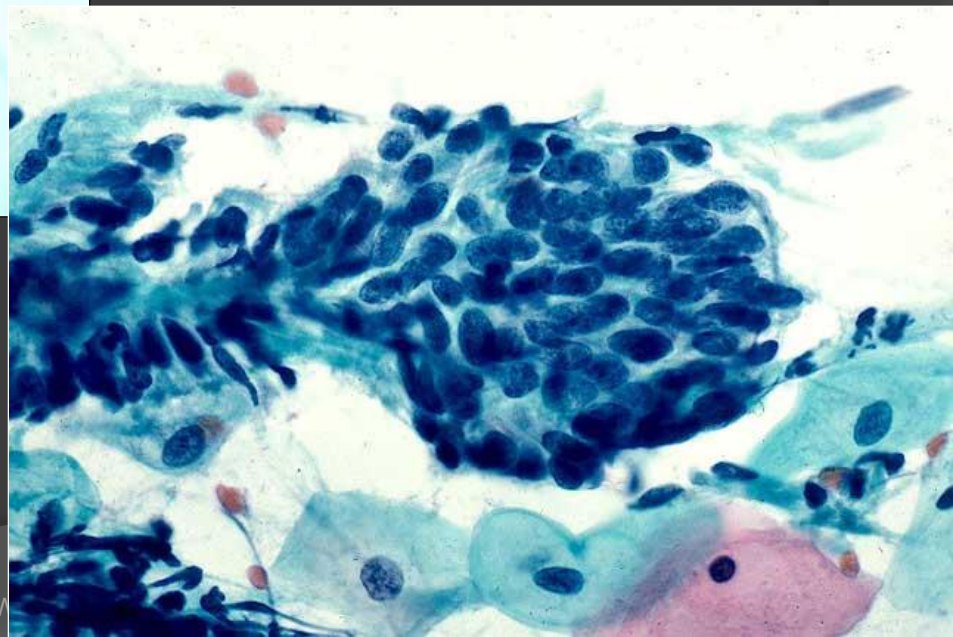
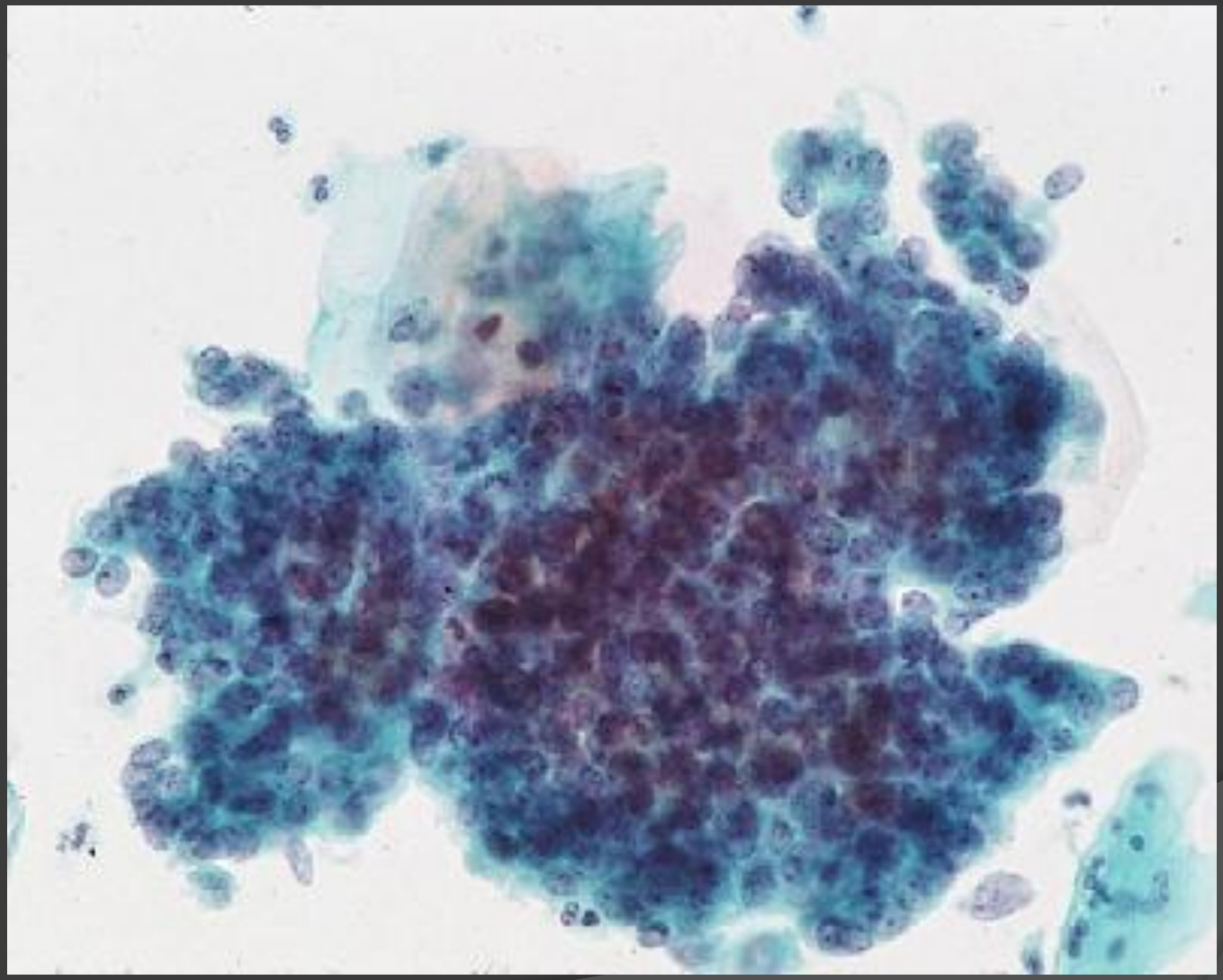


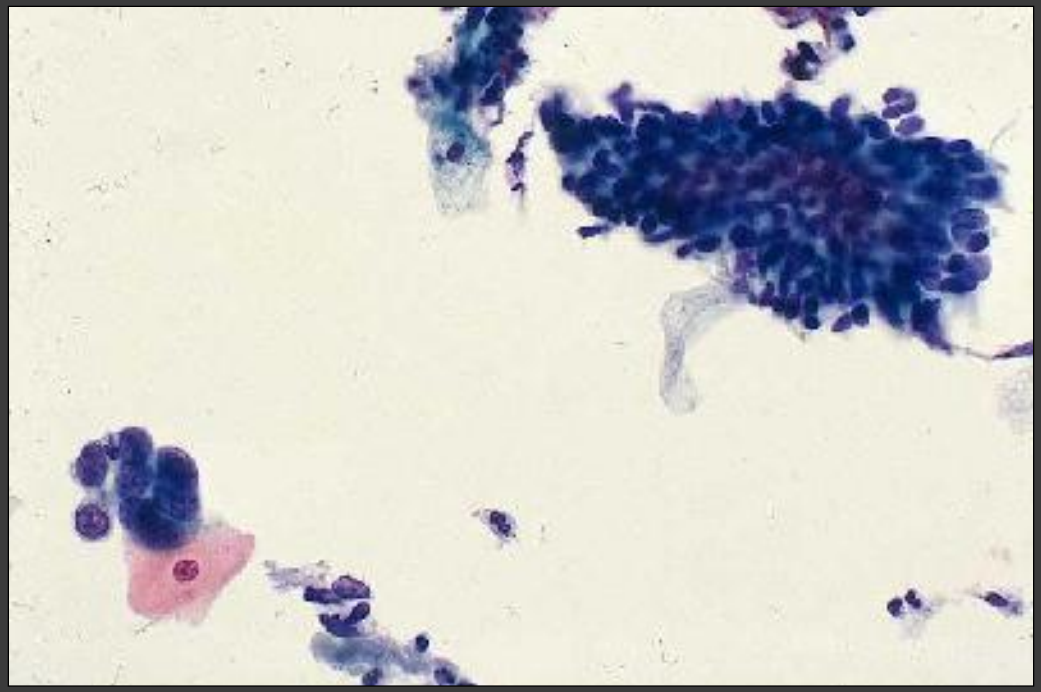
Can be very Difficult!!!

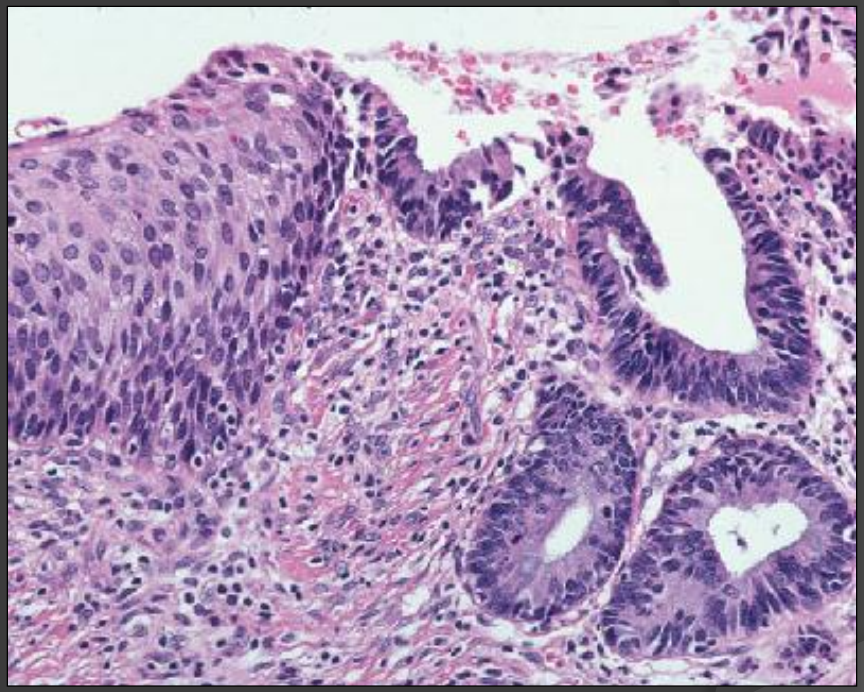


Atypical endocervical cells vs HSIL



Endocervical AIS





60 % will also have CIN 2/3

What is the Correlation of Glandular Pap Test Abnormalities to AIS and Carcinoma?

Cytology diagnosis	Likelihood of invasive CA, AIS, or CIN 2,3
AGC NOS	9 - 41%
AGC, favor neoplasia	27-96%
AIS	
Biopsy-confirmed AIS	48-69%
Invasive adenocarcinoma	38 %

Atypical Glandular Cells on Pap have higher association with cancer and pre-cancer than ASC-US

Wright et al JAMA 2002;287:2120-2129.

Significance of Atypical Glandular Cells

Schnatz et.al Obstet Gynecol 2006;107:701-8

Meta analysis of 3,890 AGC Paps +/- ASC-US

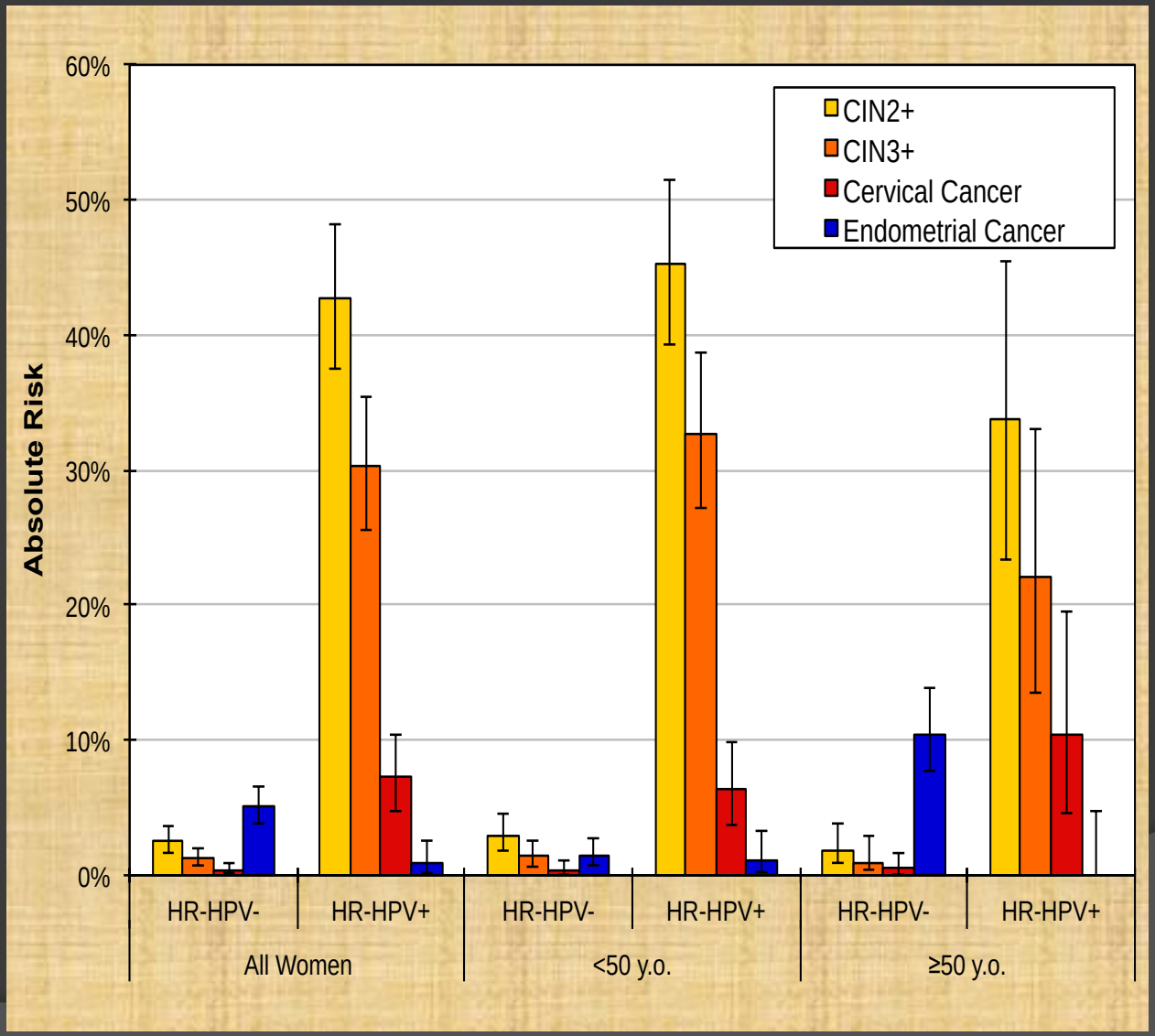
Follow-up diagnosis

- HSIL 11.1%
- AIS 2.9%
- Endometrial hyperplasia 1.4%
- Malignancy 5.2%

- AGUS favor neoplasia
  - AIS 13%
  - Malignancy 21%

Cancers found: Endometrium, endocervix, squamous cervix, ovary, fallopian tube, colon, breast

Most likely disease with AGC Pap is squamous. Cancer may be squamous or adeno. Endometrial cancer not related to HPV status and more common in older women.

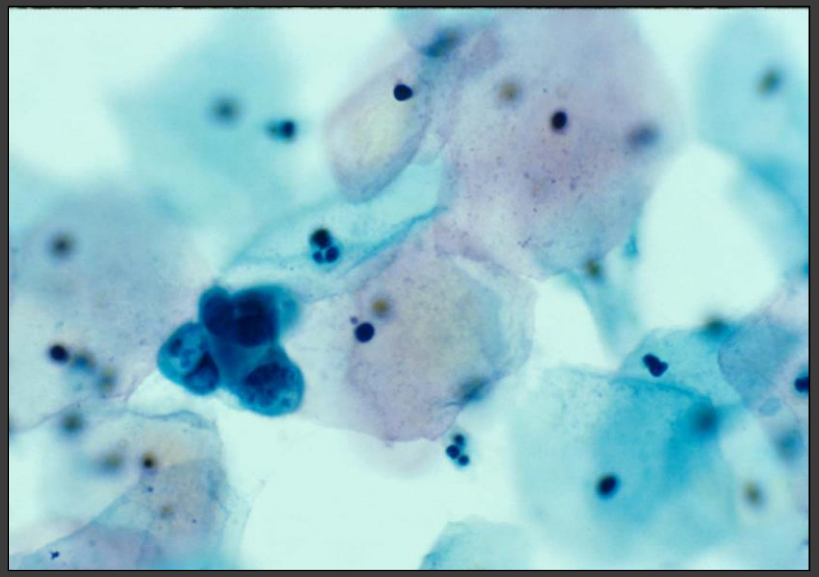


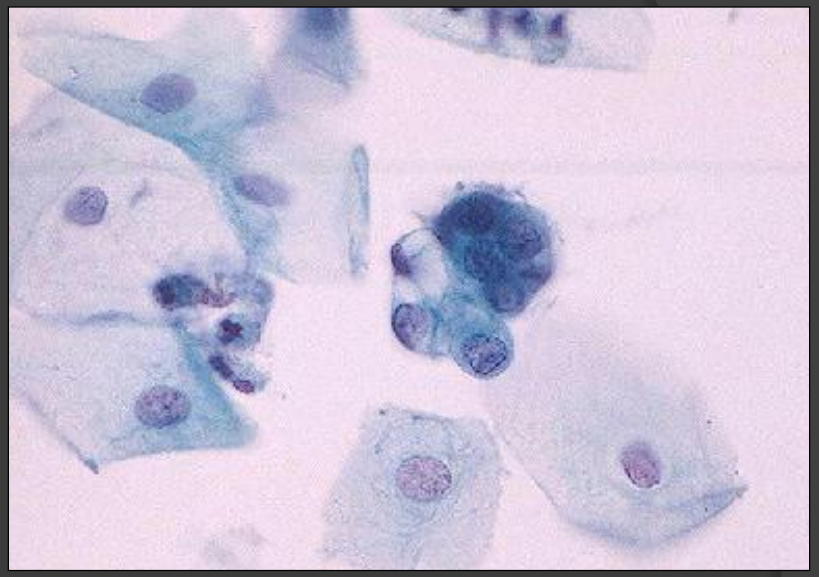
Castle et al Obstet Gynecol, 2010

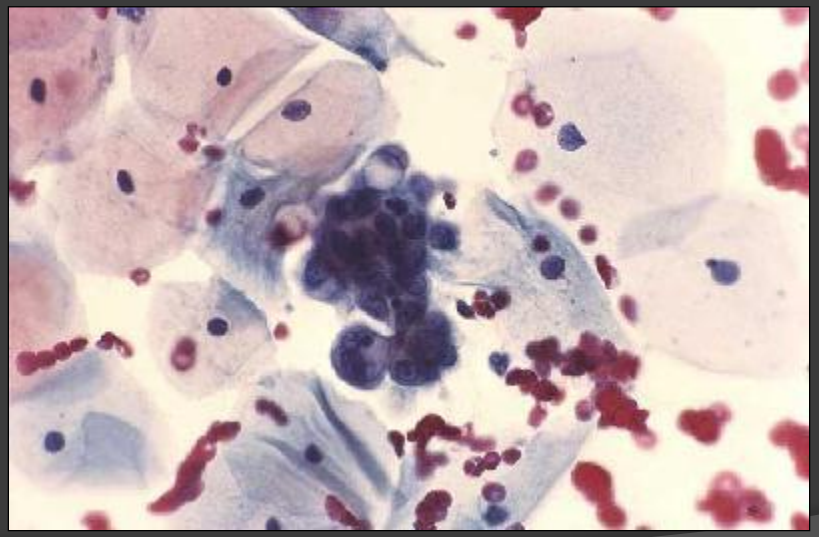
Atypical endometrial cells: Cytologic criteria

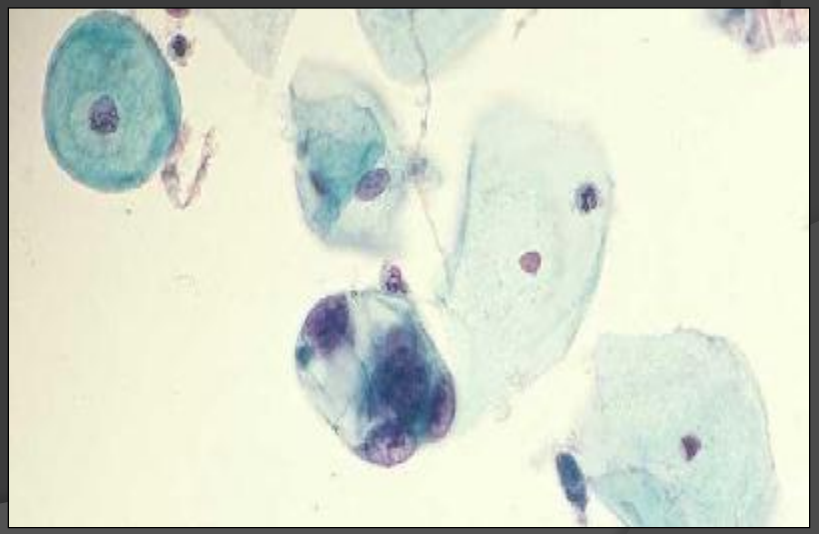
- Small cells groups (5-10 cells)
- Nuclei slightly enlarged
- Slight hyperchromasia
- Small nucleoli
- Cell borders ill-defined
- Scant cytoplasm, +/- vacuoles

Atypical endometrial cells





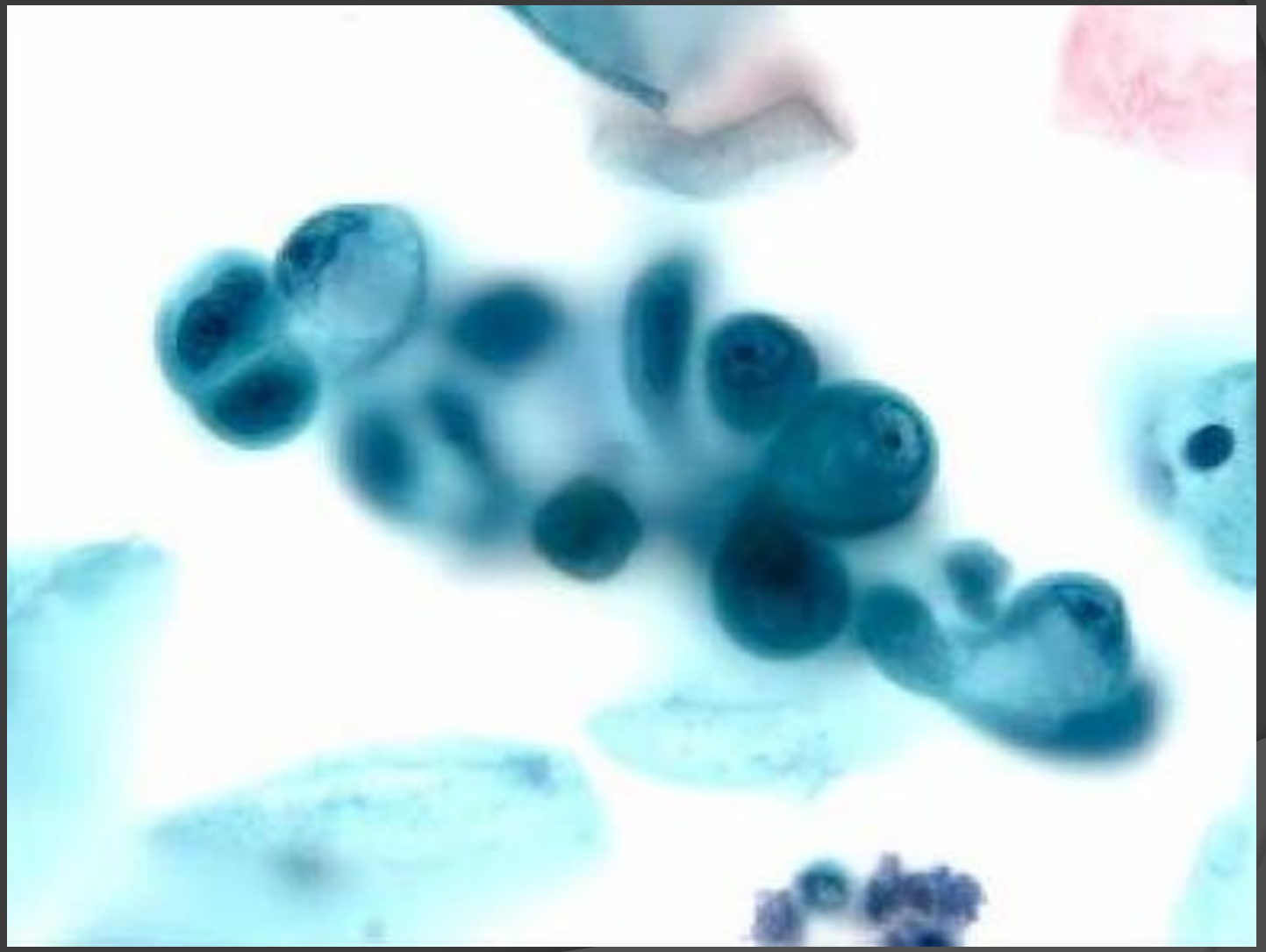




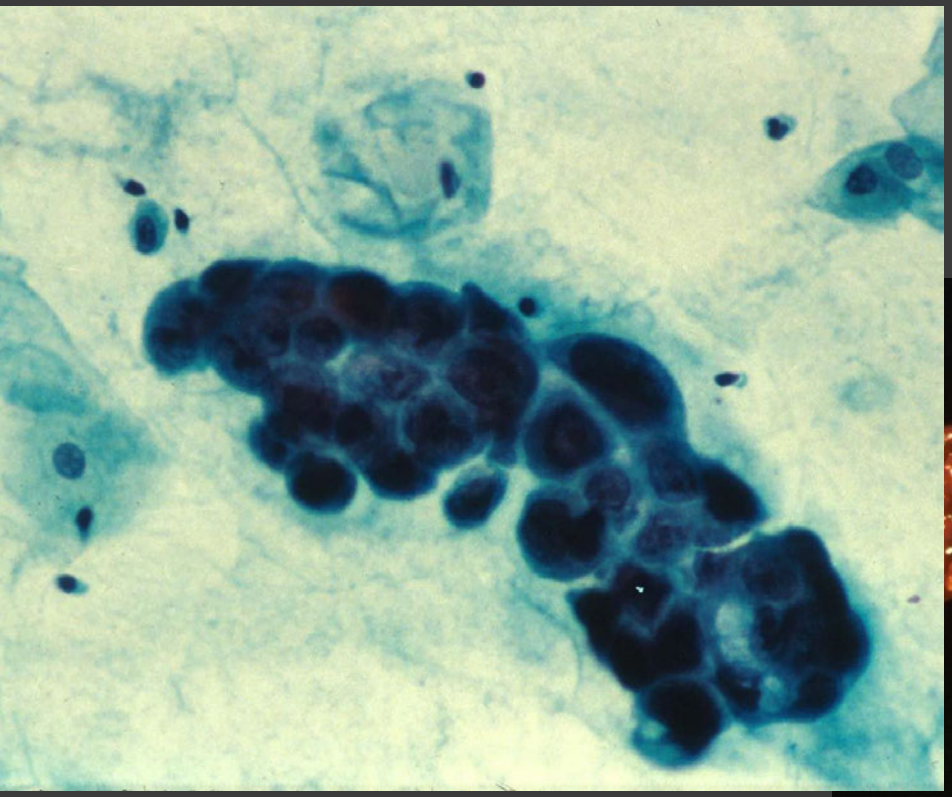
Atypical endometrial cells: Differential Dx

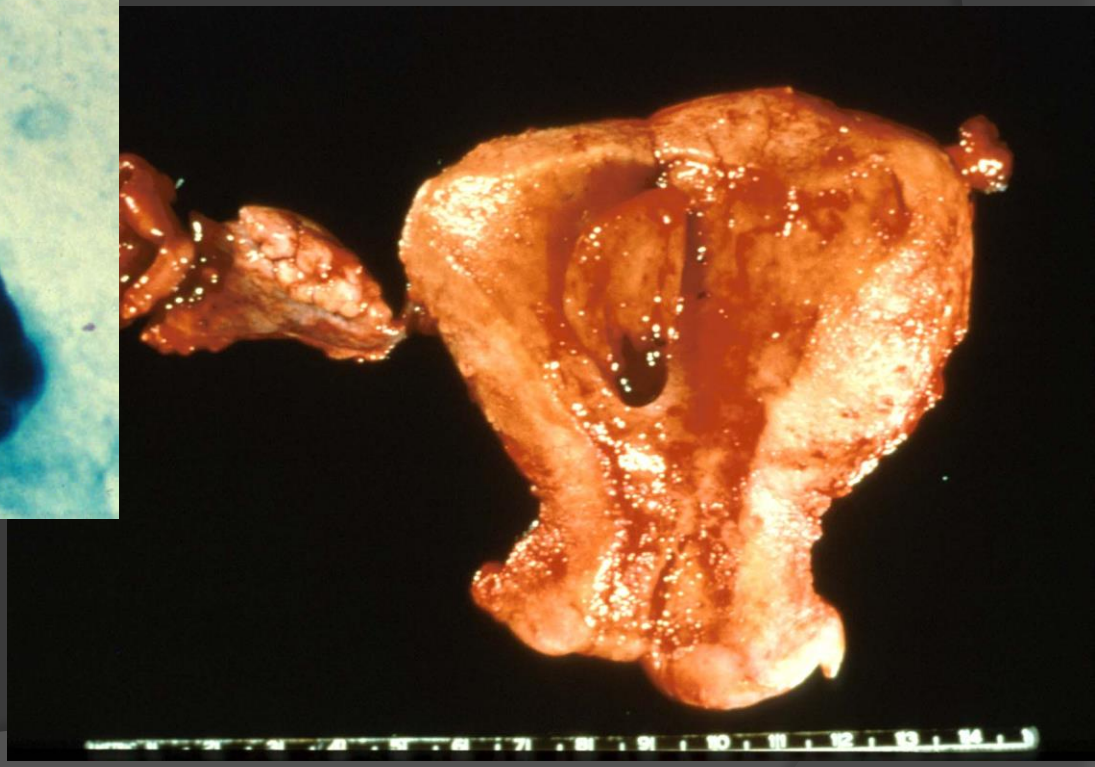
- IUD effect
- Endometrial polyps
- Chronic endometritis
- Endometrial hyperplasia
- Endometrial adenocarcinoma

Atypical glandular cells: IUD effect

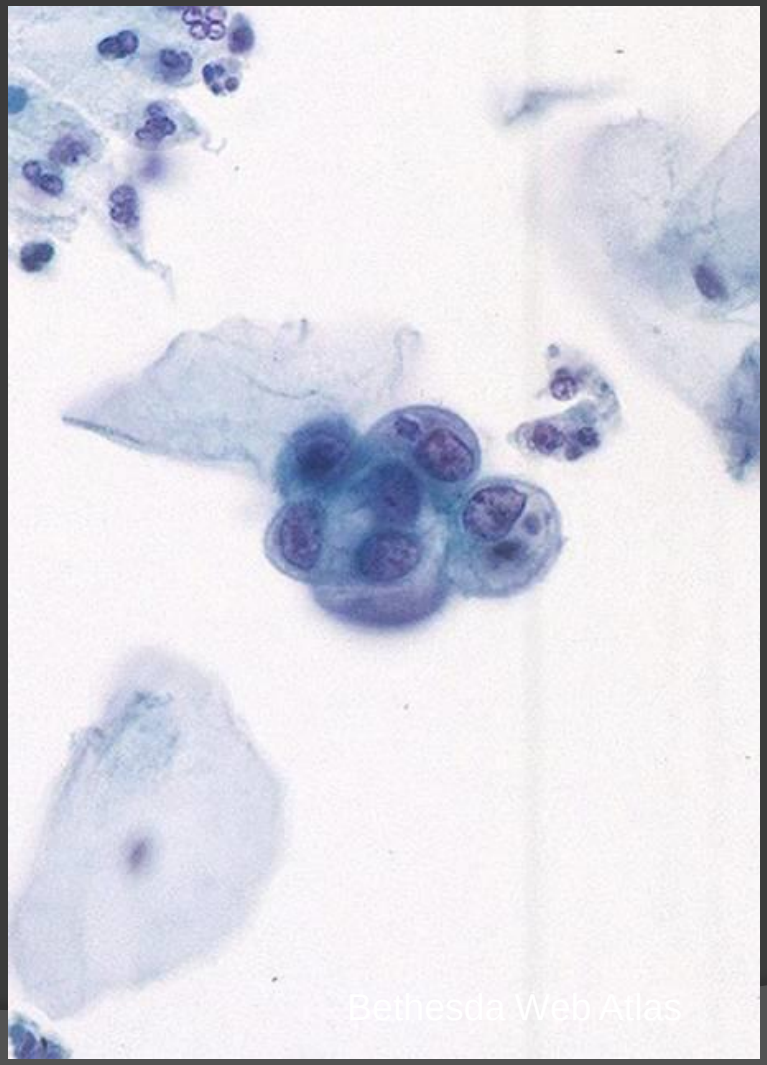


Atypical glandular cells: Endometrial Polyp

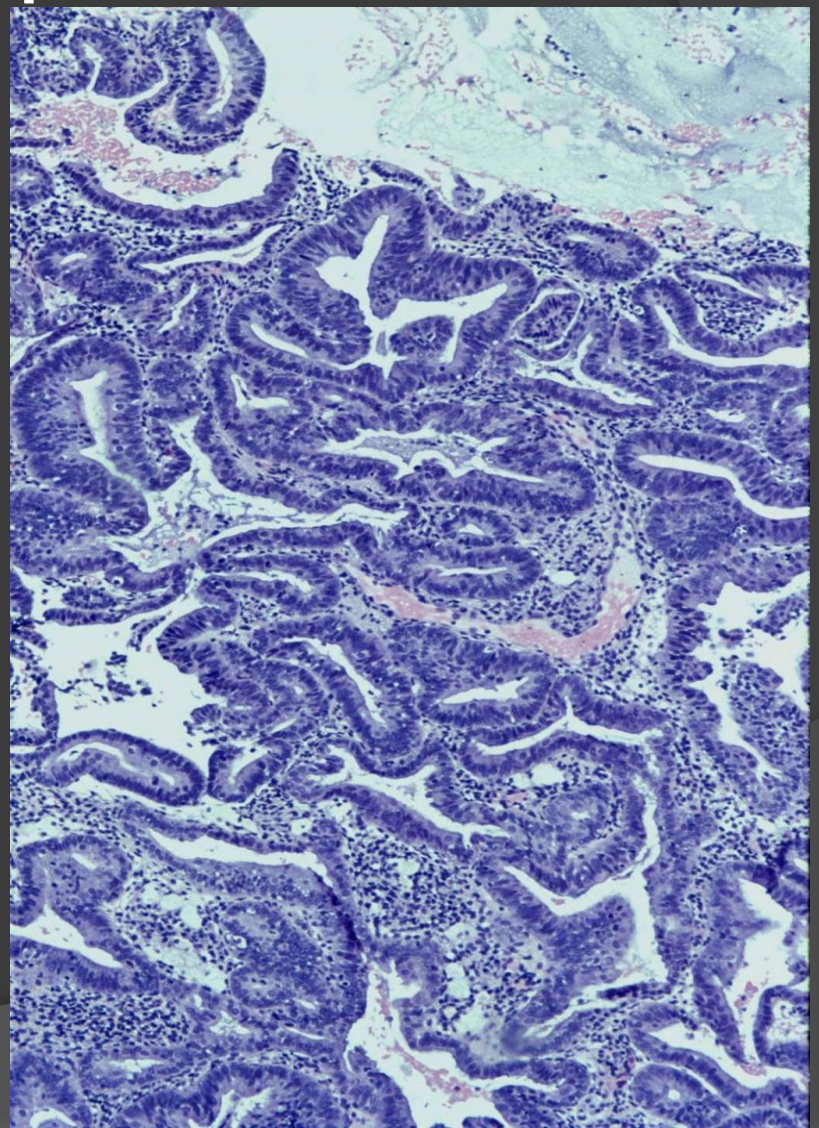




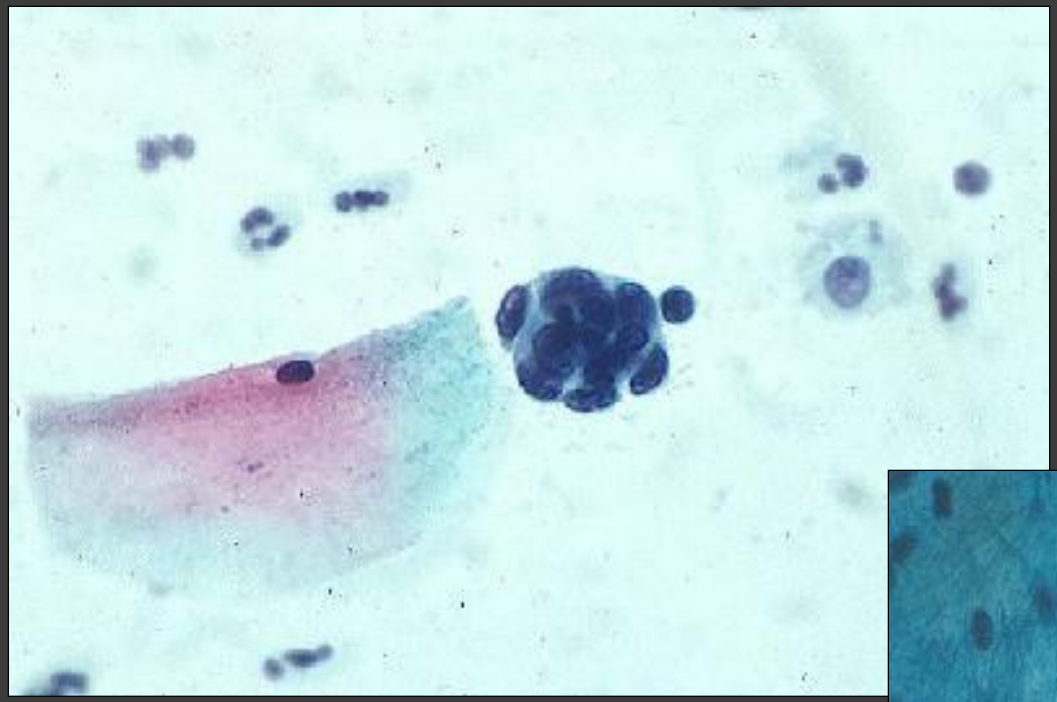
Atypical glandular cells: Endometrial Hyperplasia



Bethesda Web Atlas

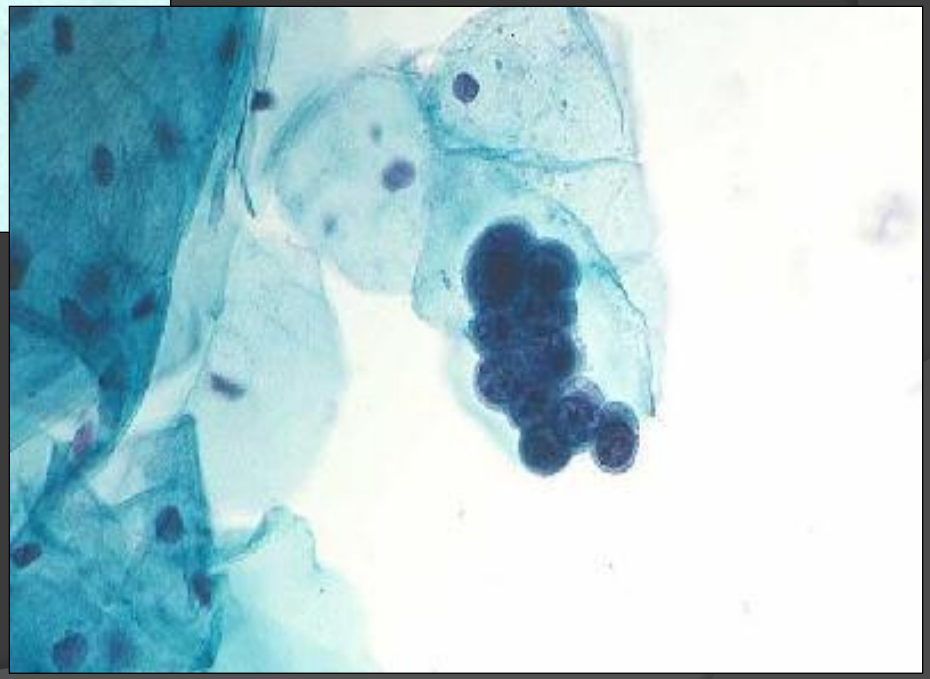


Atypical endometrial cells



Endometrial hyperplasia

Endometrial carcinom



Cervical Adenocarcinoma In Situ

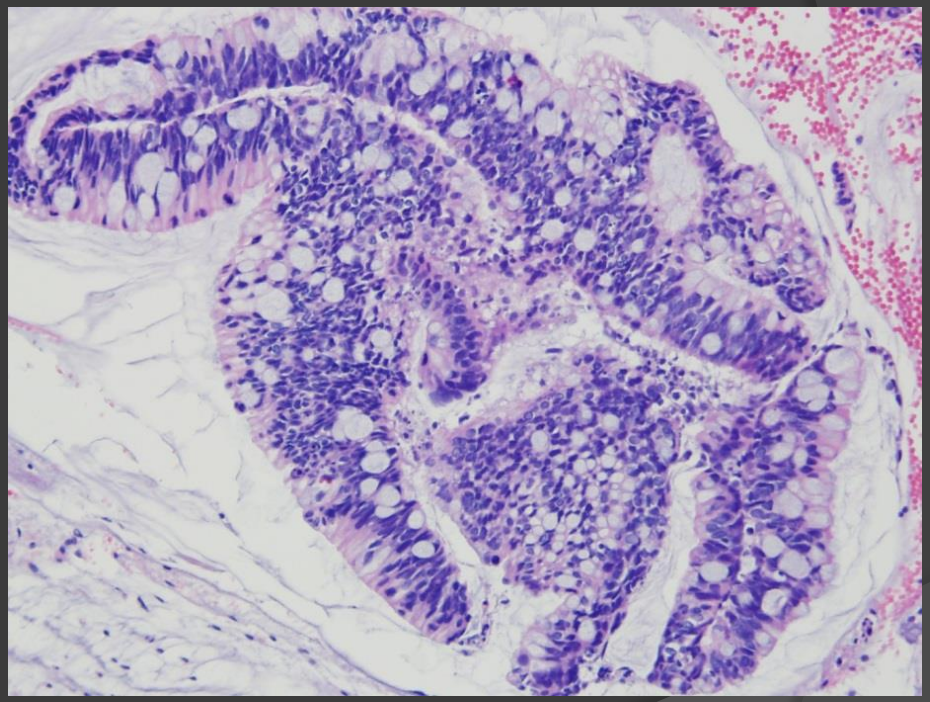
- Preinvasive lesion of the endocervical glandular cells
- Increasing incidence
- Average age: 35.8 yr
  - Range: 29-46 years
  - 10-18 years younger than adenocarcinoma
- 10% multifocal skip lesions
- Difficult to detect
  - May be missed on Pap
  - Does not obey usual colposcopy ‘rules’

Histology of AIS

- Glands lined with atypical endocervical cells,
  - Crowding, cribiform pattern
  - Confined to gland
- Multifocal disease common
- Almost half of cases of AIS have associated squamous disease.

AIS: Histology

- Gross architectural pattern “normal”
  - Cellular abnormality confined to gland
- Diagnosis depends on cellular changes
  - Loss of polarity
  - Increased nuclear size
  - Pseudostratification
  - Mitoses



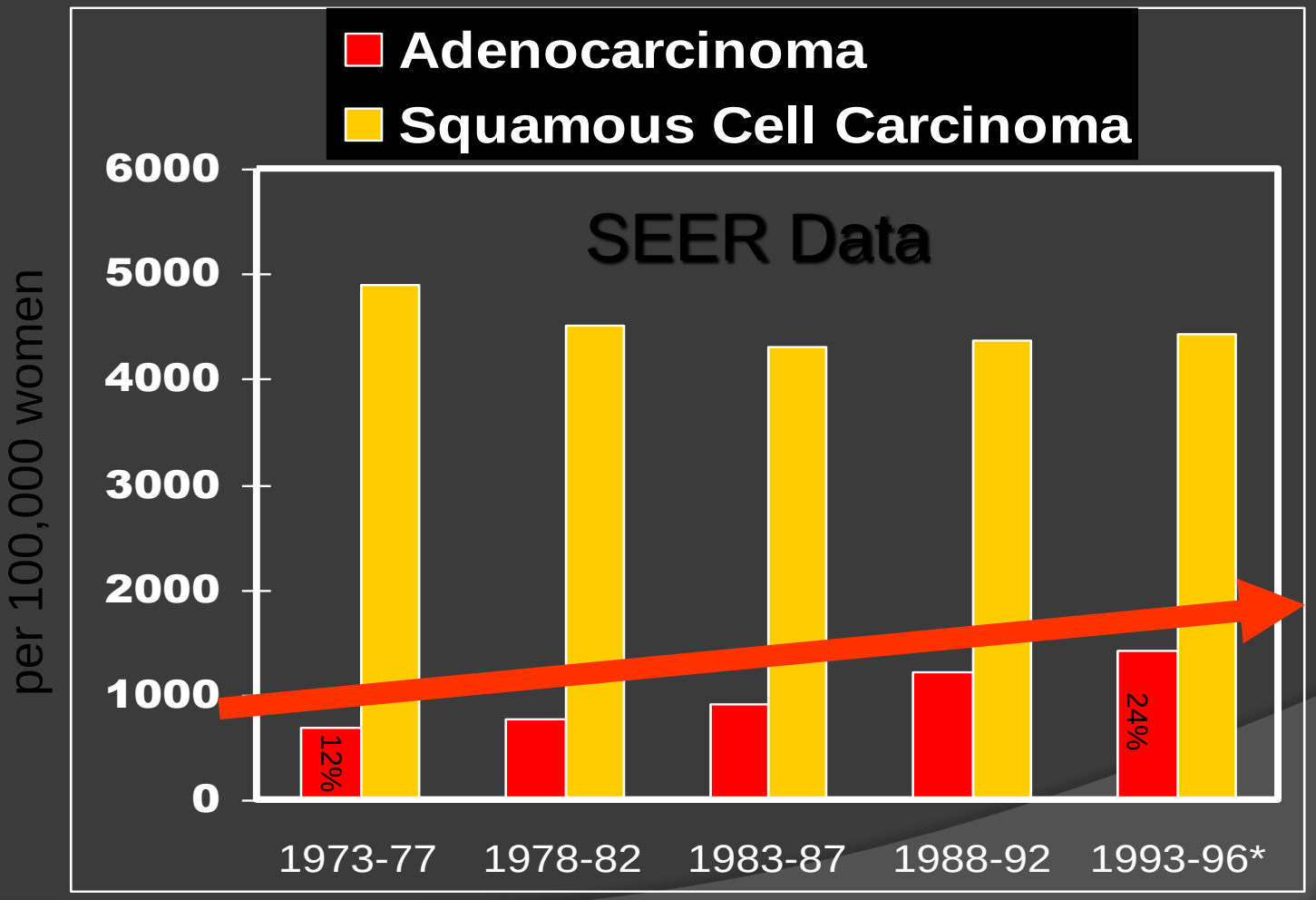
UNM Pathology

Increasing Incidence of Adenocarcinoma in Situ

- 1.25 cases per 100,000 women (compared with 44 cases of CIN 3 per 100,000).
- Increased by 6 fold since 1970.
  - Absolute increase?
  - Increased rate of detection?

Wright TC et al. *Am J Obstet Gynecol*. 2007;197:340-345.

Cervical Adenocarcinoma and Squamous Carcinoma Trends in the U.S.



Smith HO et al. Gynecol Oncol 2000;78:97-105

AIS and Adenocarcinoma are HPV mediated.

- HPV association: type 18 > type 16

	SCC	AC
HPV 16	50-60%	30%
HPV 18	10-20%	40-60%

- HPV infection can alter squamous cells, glandular cells, or both
- Concurrent squamous HSIL: 46-72%

Herzog T. Am J Obstet Gynecol 2007

Screening with HPV diagnoses more glandular lesions than Cytology alone.

331,818 women enrolled in Kaiser N. Cal

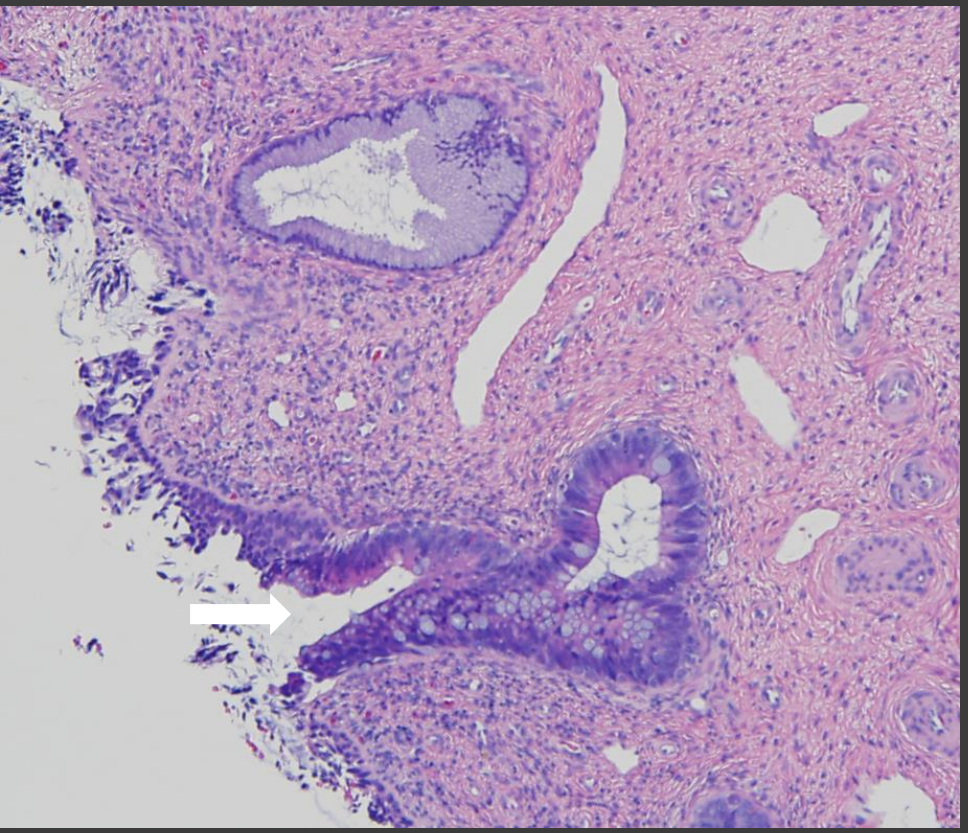
Significantly more AIS and Adenoca diagnosed over 5 yrs if initial screen:

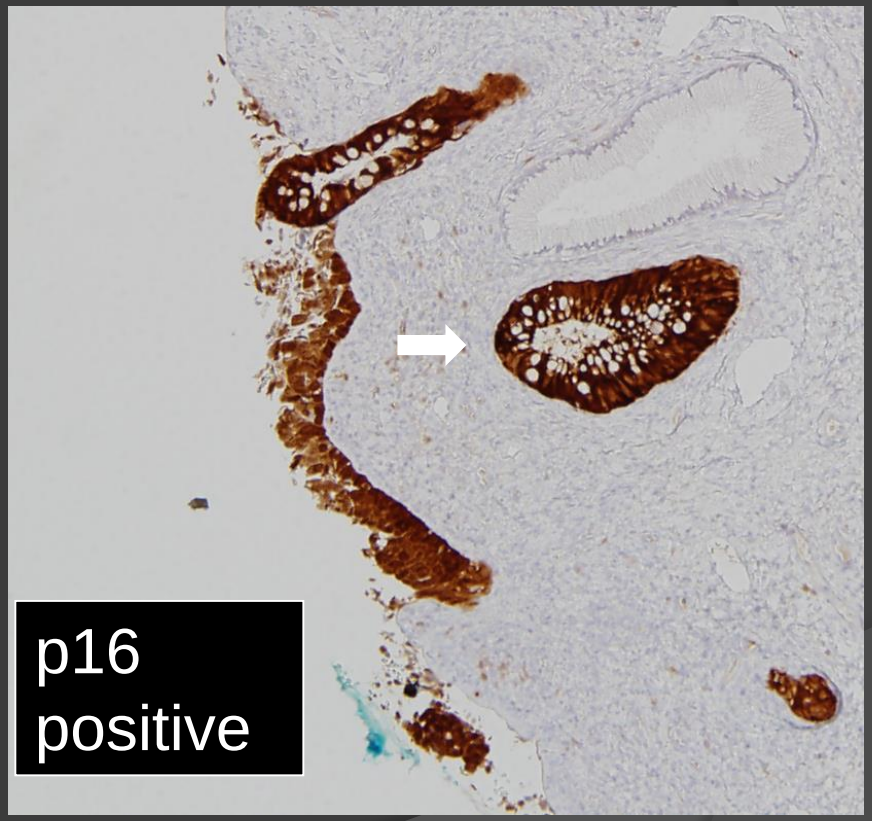
- HPV + vs Pap + ($p<0.0001$)
- HPV + / Pap – vs HPV -- / Pap + ($p<0.0001$)

	AIS	Adenocarcinoma
Total	70	27
Pap Negative	42 (60%)	23 (85%)
Pap Positive	28 (40%)	4 (15%)
HPV Positive	56 (80%)	21 (78%)
Pap -- / HPV +	31 (44%)	17 (63%)
Pap + / HPV --	3 (4%)	0

Katki, Kinney, et al Lancet oncol.2011;12:663-72

AIS is p16 positive.





UNM Pathology

Colposcopic prediction of Glandular Neoplasia

- *Prediction difficult to impossible*
- Diagnosis often serendipitous when looking for squamous disease
- Features of AIS overlap with squamous lesions and immature squamous metaplasia
- Final diagnosis made by your suspicion and histology
- Features of AIS and Adenocarcinoma may overlap.
  - Adenocarcinoma may have friability, necrosis, and surface ulceration or nodularity

Colposcopy of Glandular Neoplasia

- Most lesions lie within T-zone or close to SCJ
  - When glandular and squamous disease coexist, squamous component is more likely to be visible
- Lesions may be within the endocervical canal
  - “Skip” lesions may exist

Colposcopic Clues for Adenocarcinoma in situ

Surface Patterns

- Often looks like normal ectopy
- Coalescing papillae
  - Variable size, irregular shape
  - Often confused for immature metaplasia
- If AGC on Pap, biopsy anything that looks abnormal.

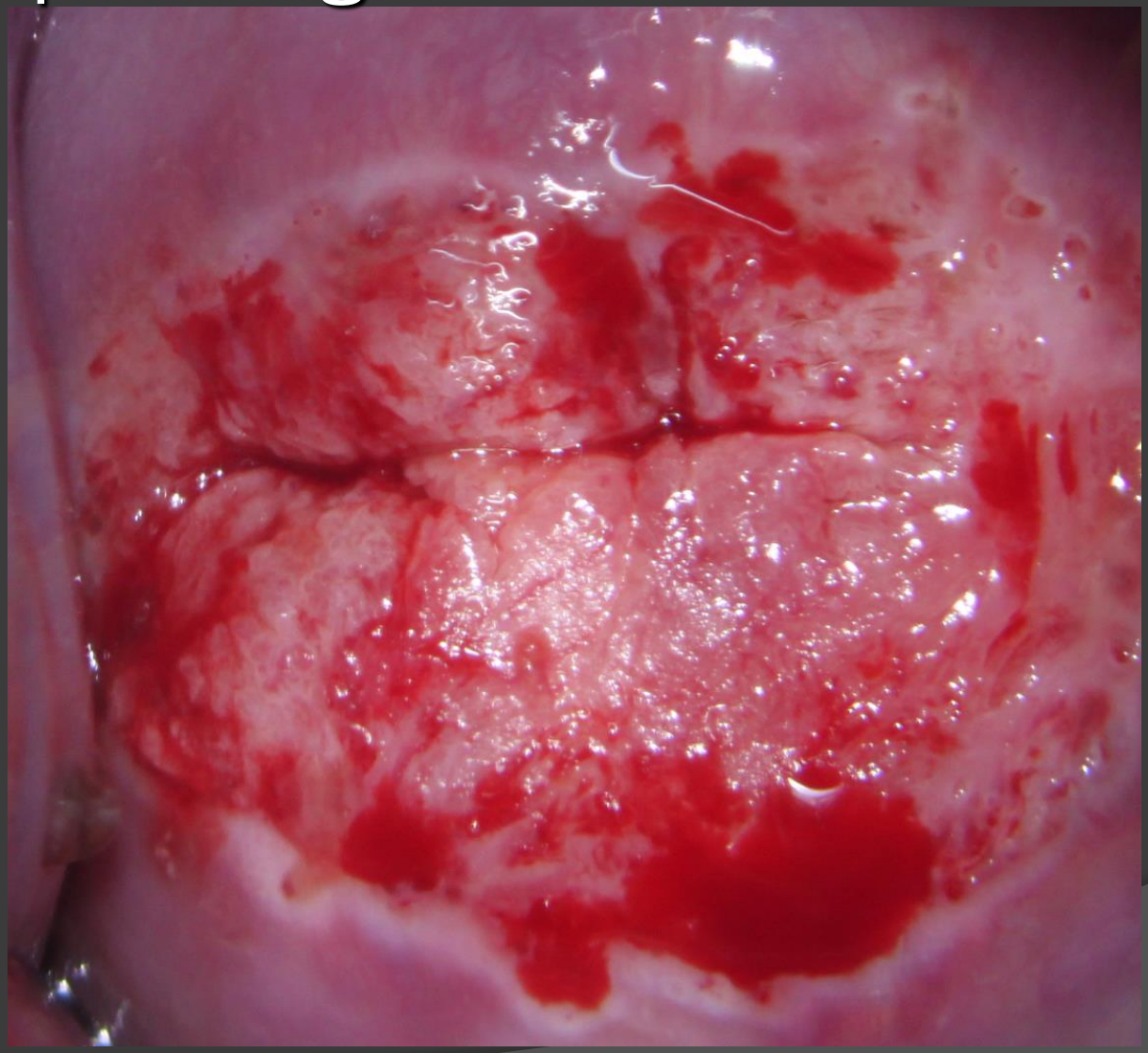
Colposcopy of AIS

- Milky white lesion surrounded by glandular epithelium
- May appear as variagated white patches on red background
- May or may not be adjacent to SCJ

- Atypical vessels
  - Root-like vessels, hairpin vessels
  - Easily mistaken for cervicitis

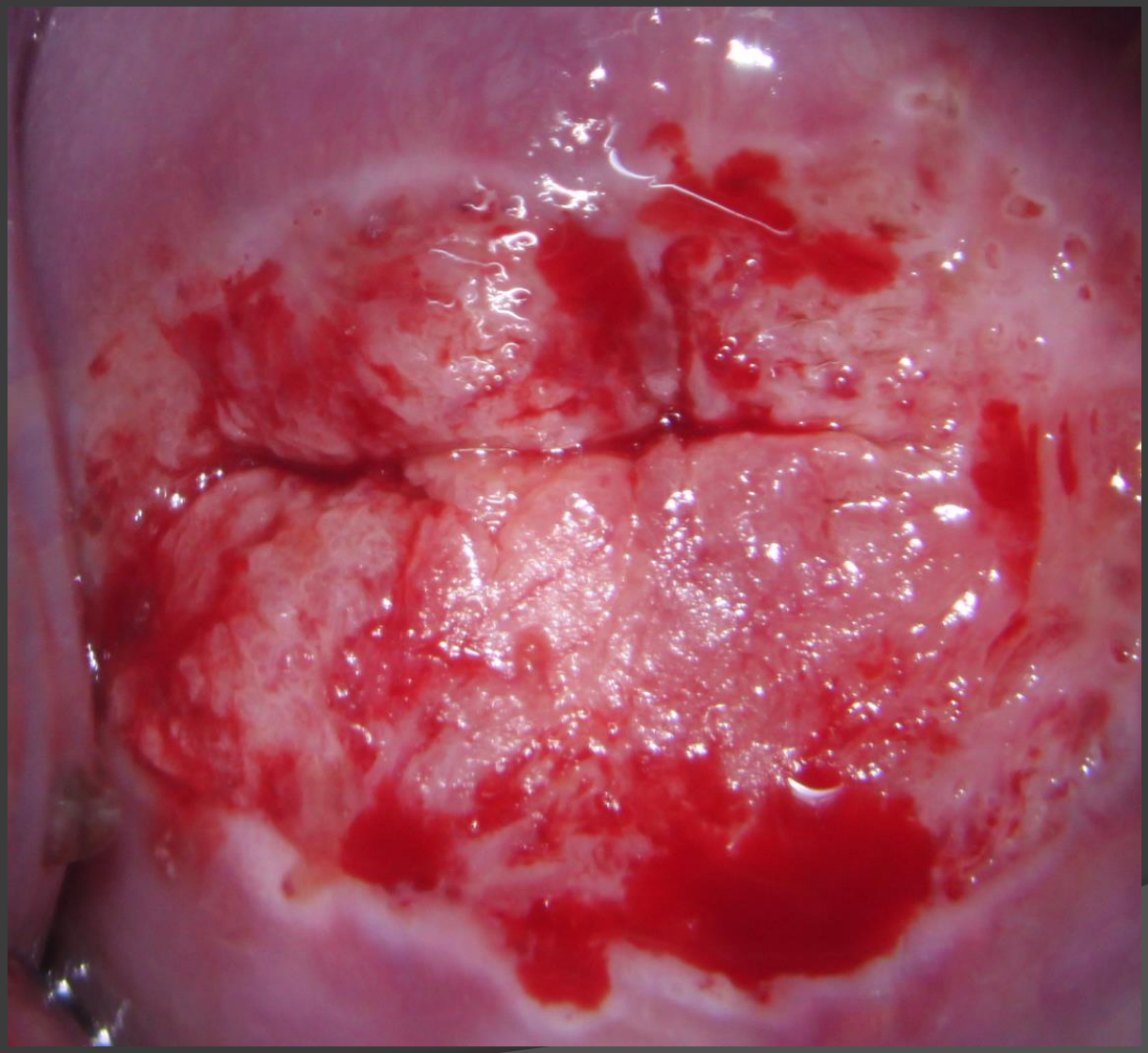
- Large gland openings
  - May not have rim of acetowhite
  - “Cuffed” gland openings

29 y.o. with AGC on Pap
Ectropion or glandular lesion?



Richard Lieberman, MD

Variegated red and white lesion



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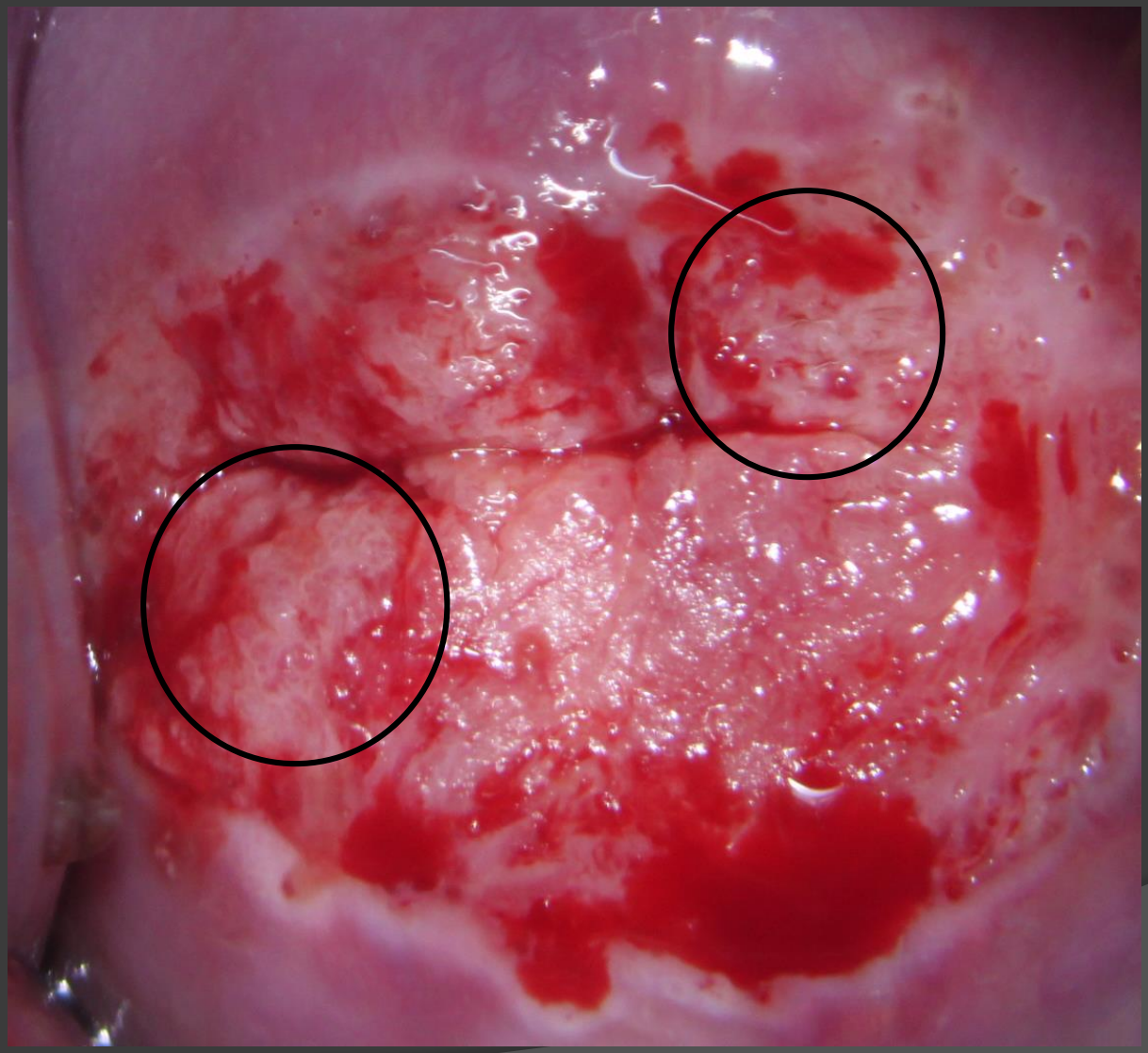
Atypical coalescence of Papillae



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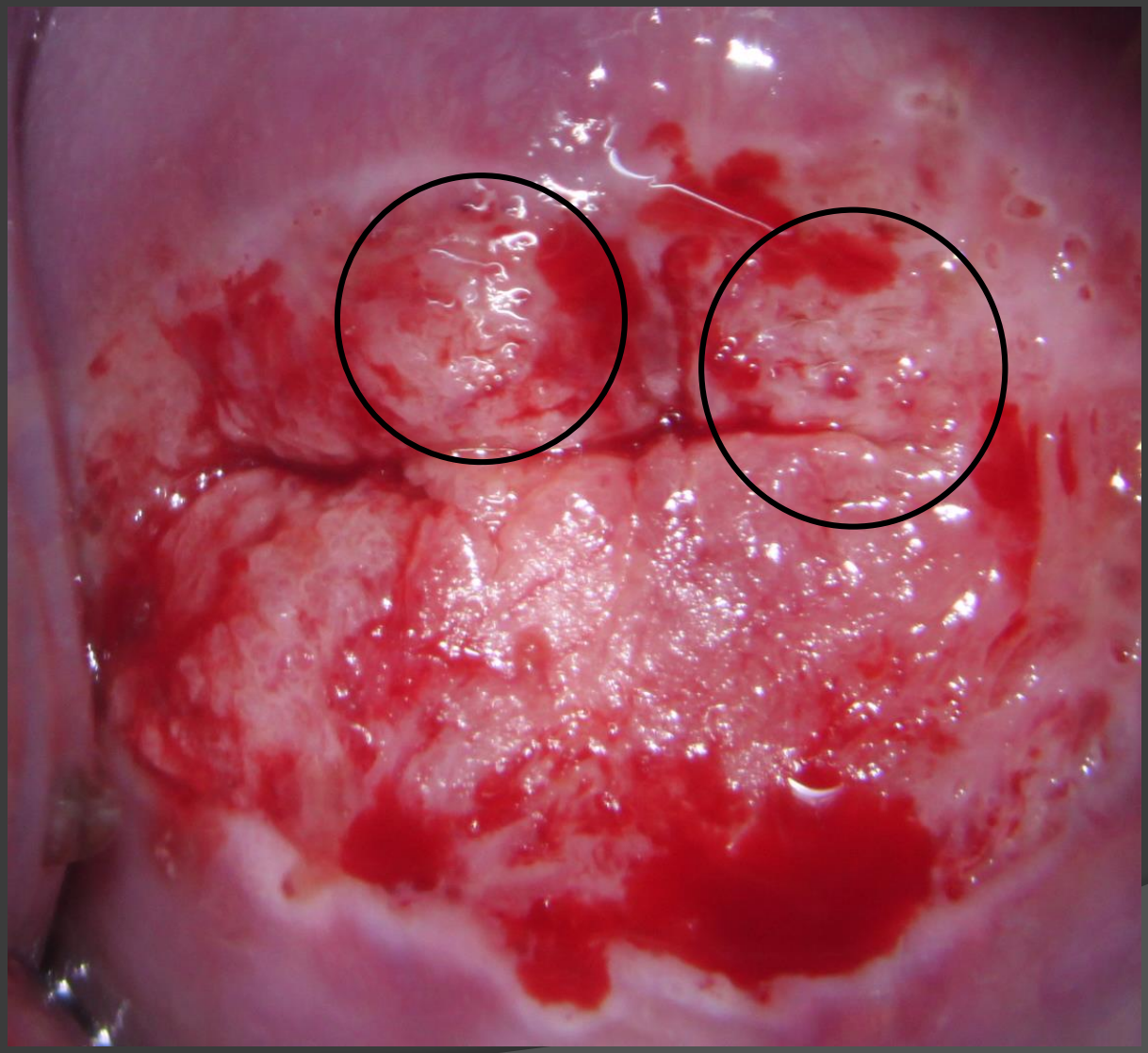
Note also root-like and hairpin vessels!



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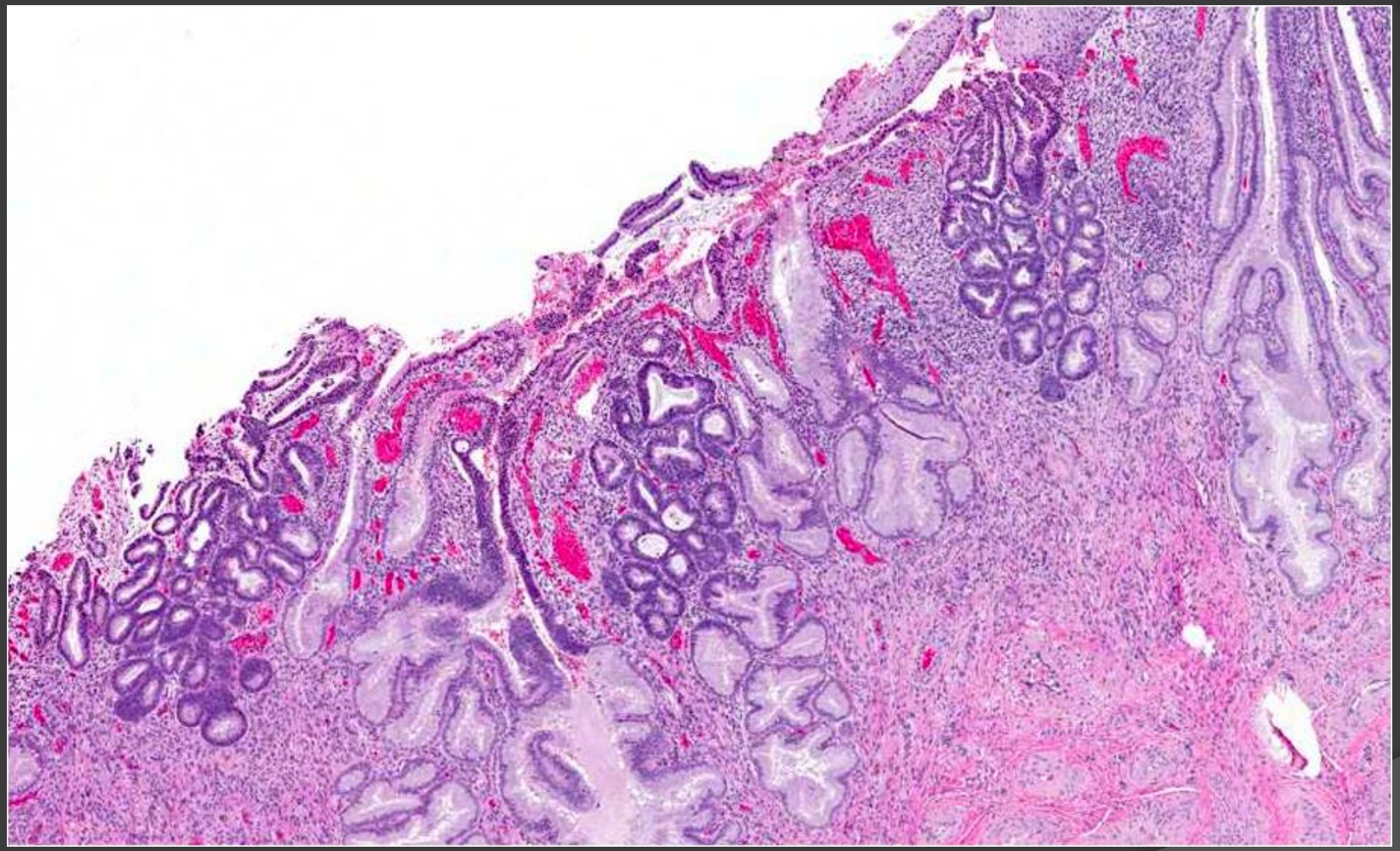
Histology: AIS



Richard Lieberman, MD

AIS - Milky white lesion, superficial ulceration

Photo: Lisa Flowers, MD

Milky White Lesion Extends Into Canal

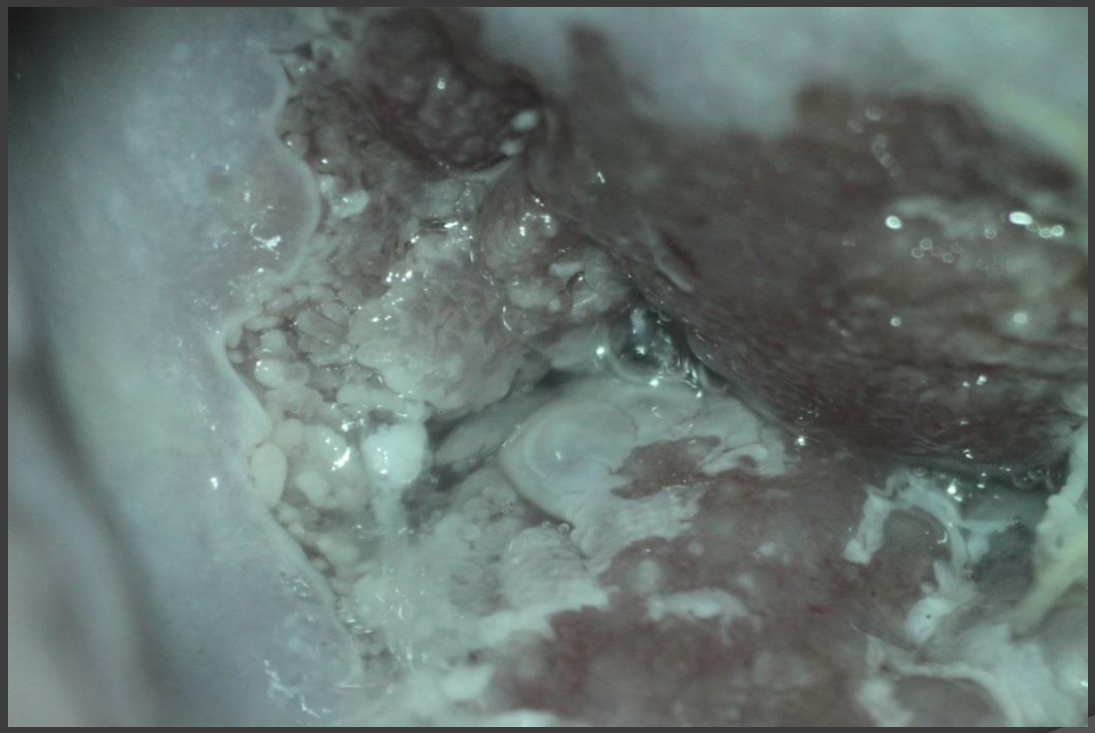


Photo: Alan Waxman, MD

Root-like vessels

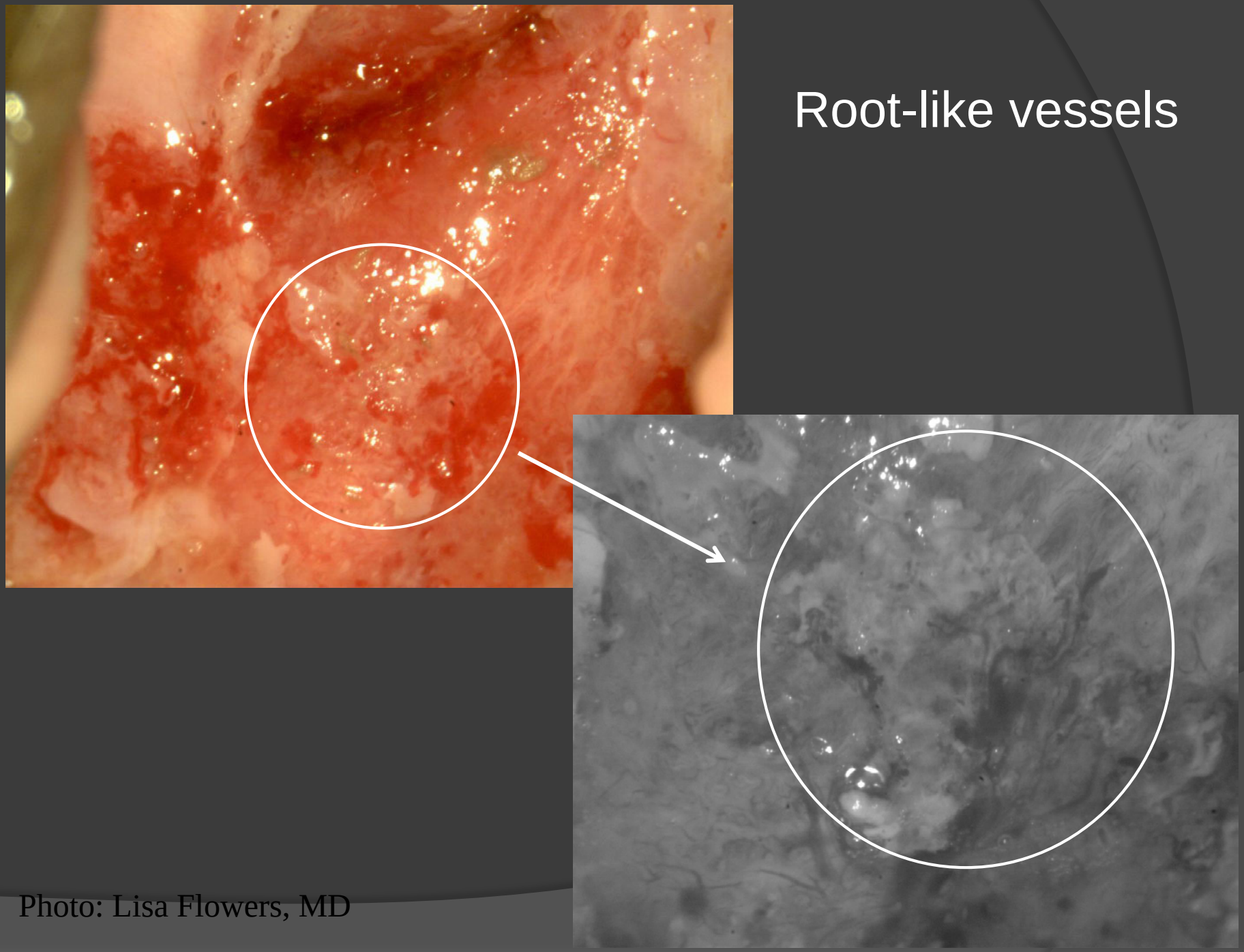


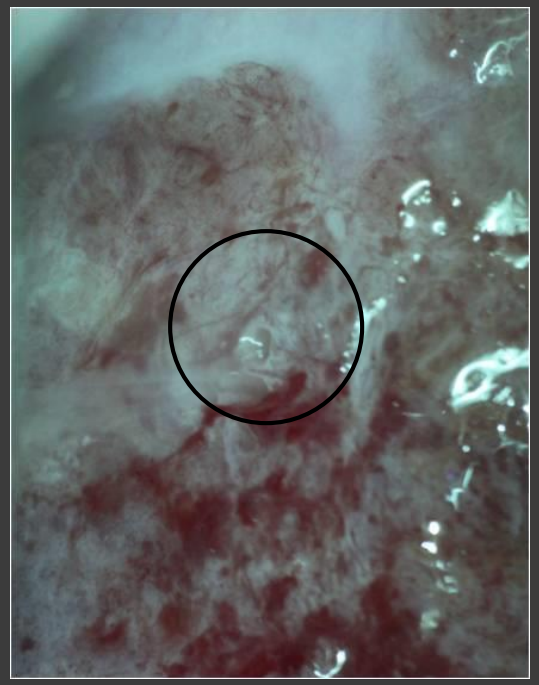
Photo: Lisa Flowers, MD

AIS Prominent atypical surface vessels Copious mucus

Photo: Alan Waxman, MD

AIS : Copious mucus, large ectopic gland openings

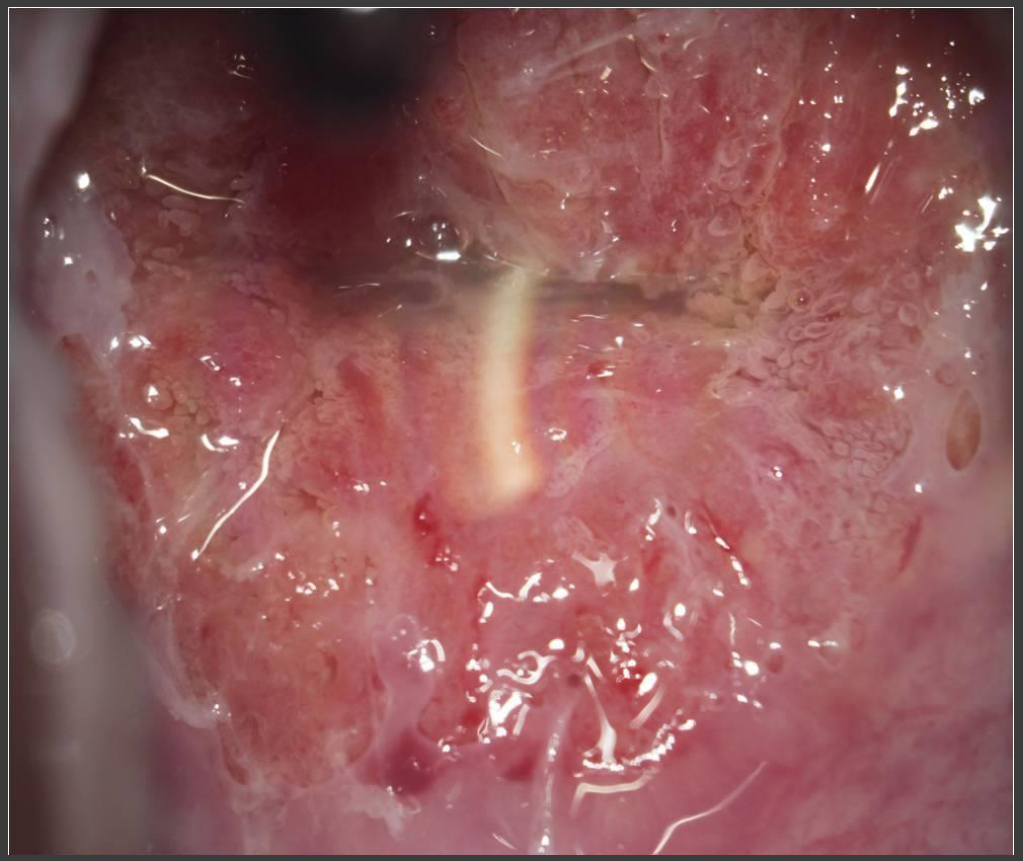
Ectopic plug of mucus



Gland opening, mucus plug removed

Same without blue filter

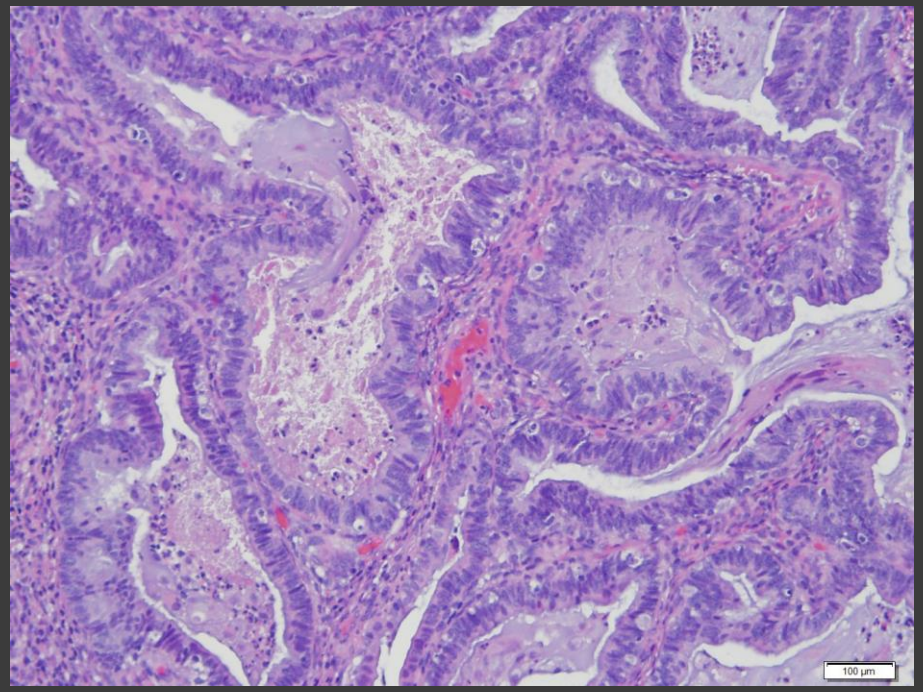
Photo: Alan Waxman, MD

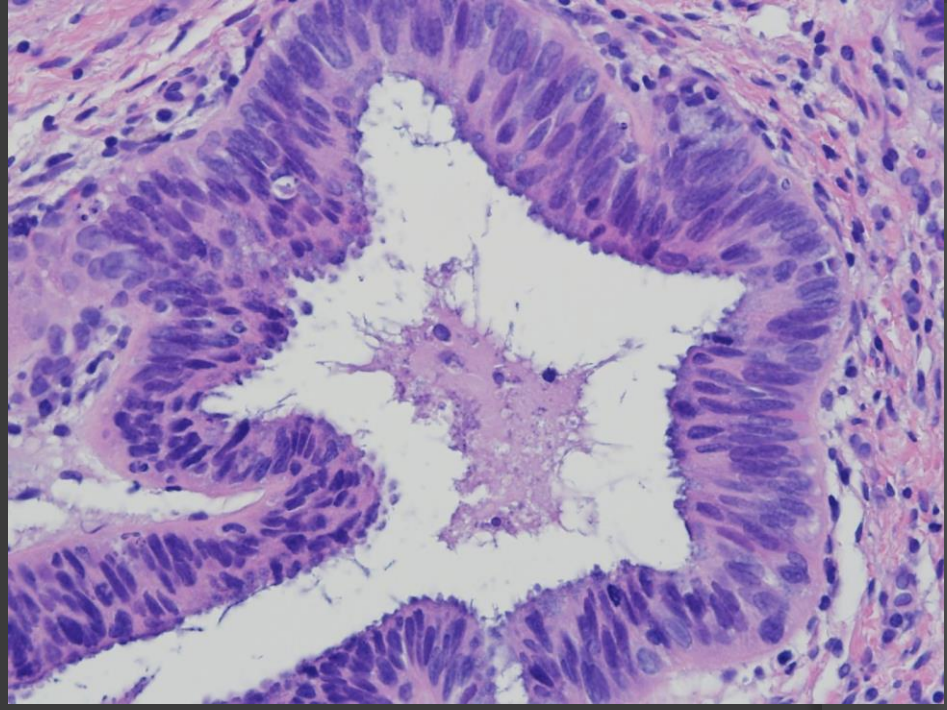


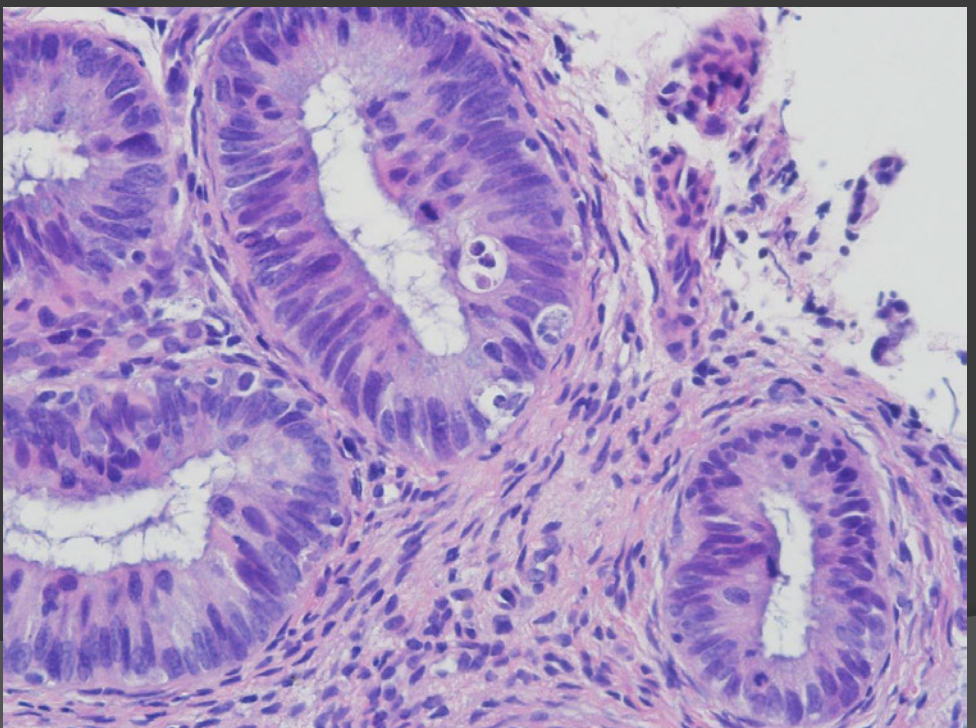
43 y.o.
Pap: atypical endocervical cells favor neoplasia

Wide ectropion with root like vessels

Photo: Alan G. Waxman, MD







Histology: Adenocarcinoma in situ

Photo: UNM Pathology

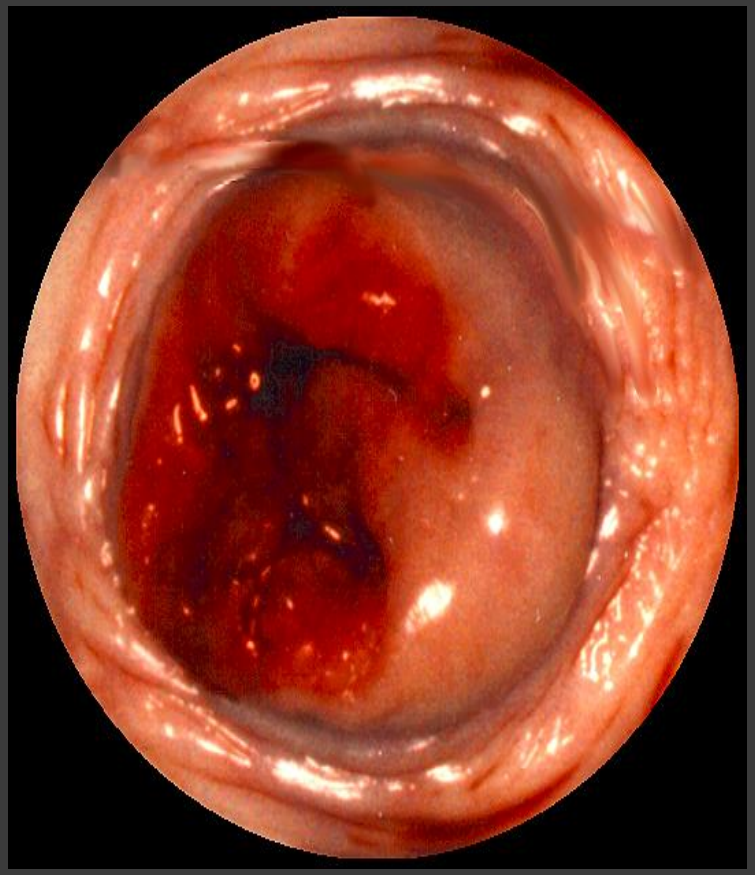
Cervical Adenocarcinoma: Colposcopic Features Similar to AIS, but More Pronounced

- Color
  - Milky to densely white after acetic acid
  - Patches of red and white in ectropion
  - Yellow to orange color
- Papillae of various sizes; may be large, fused
- Columnar epithelium may surround lesion
- Atypical Vessels: hairpin vessels, inconsistent caliber, root-like
- Gland openings: large, irreg., may lack white outlines
- Copious mucus production
- Hemorrhage and necrosis on surface

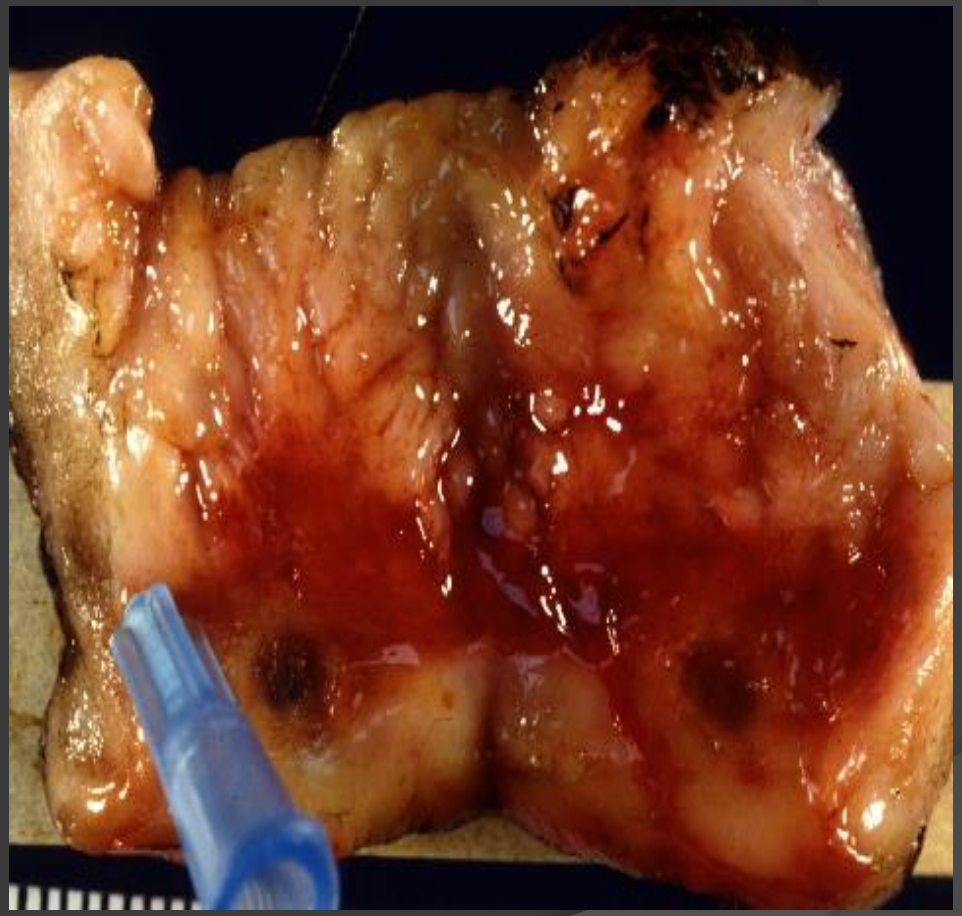
Cervical Adenocarcinoma: Exophytic

Richard Lieberman, MD

Adenocarcinoma
Endophytic (Barrel Shaped)

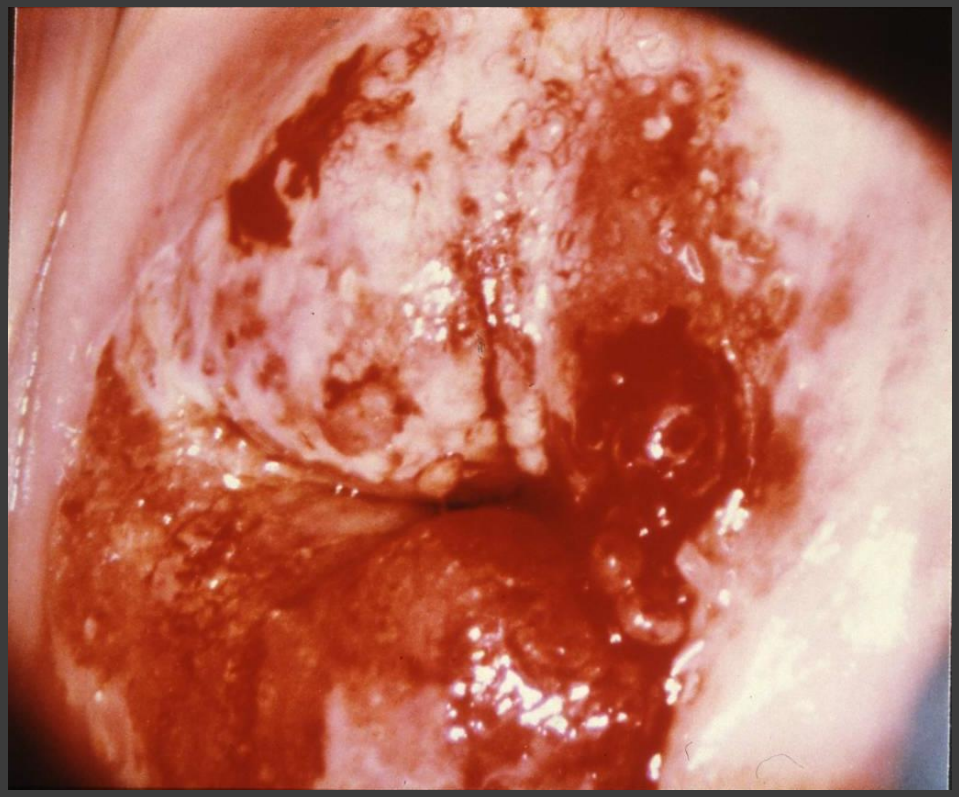


Richard Lieberman, MD



Don’t forget to do a bimanual exam!

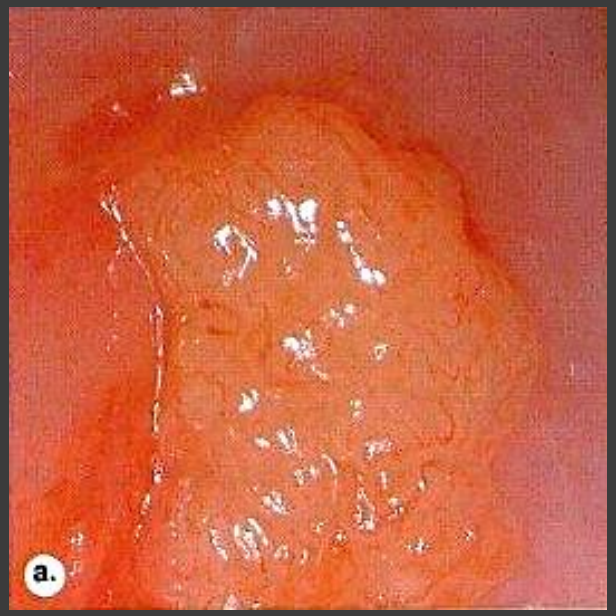
Characteristic features of adenocarcinoma



- Densely acetowhite
- Overlies columnar epithelium
- Patchy red and white lesions
- Atypical vessels

Apgar, Brotzman, Spitzer

Adenocarcinoma: abnormal papillary coalsecence



Before acetic acid

After acetic acid

Adenocarcinoma: Milky white abnormal papillae Atypical, Root-like and Hairpin vessels

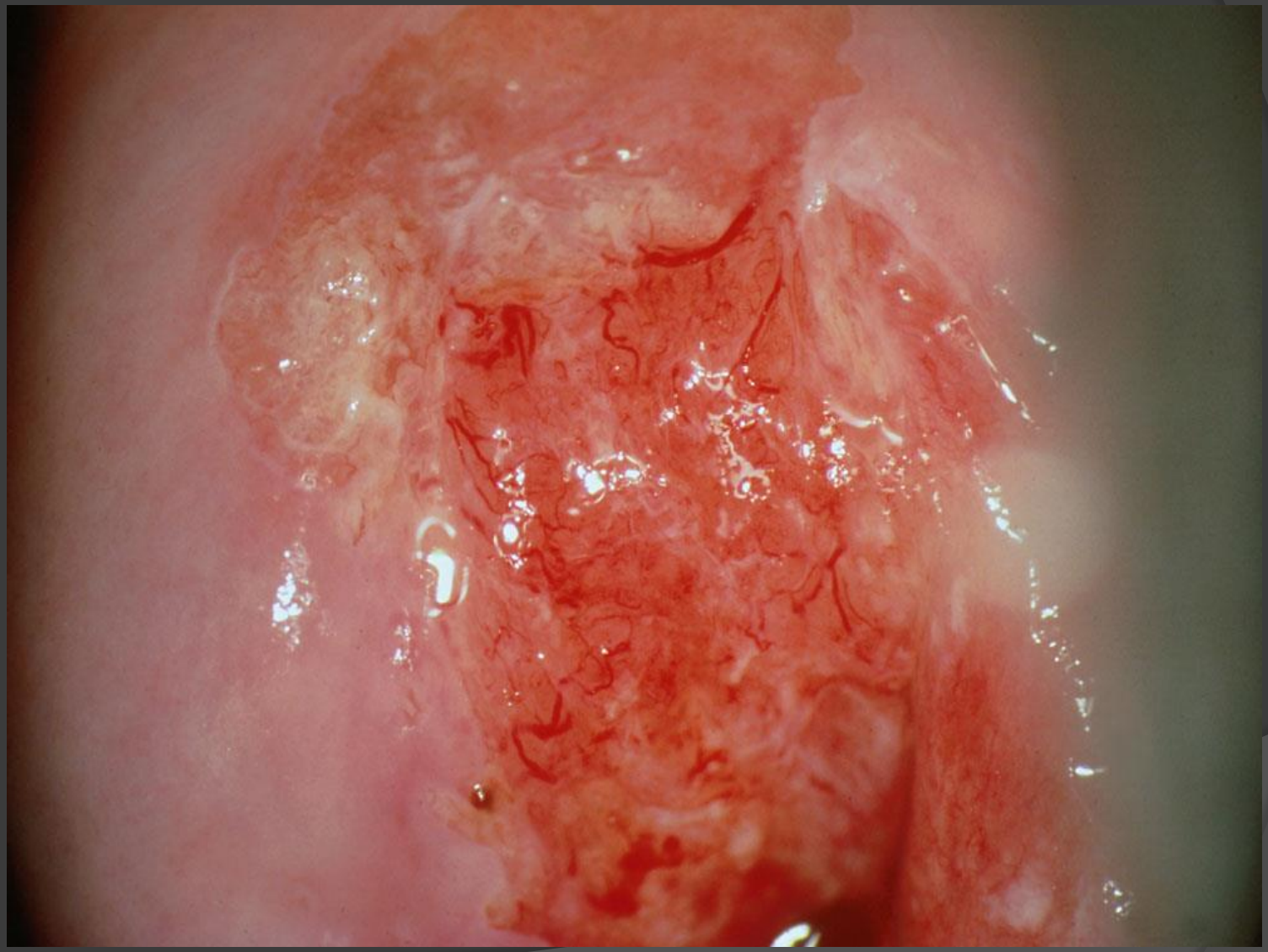


Photo: Richard Lieberman, MD

Milky white abnormal papillae surrounded by columnar epithelium

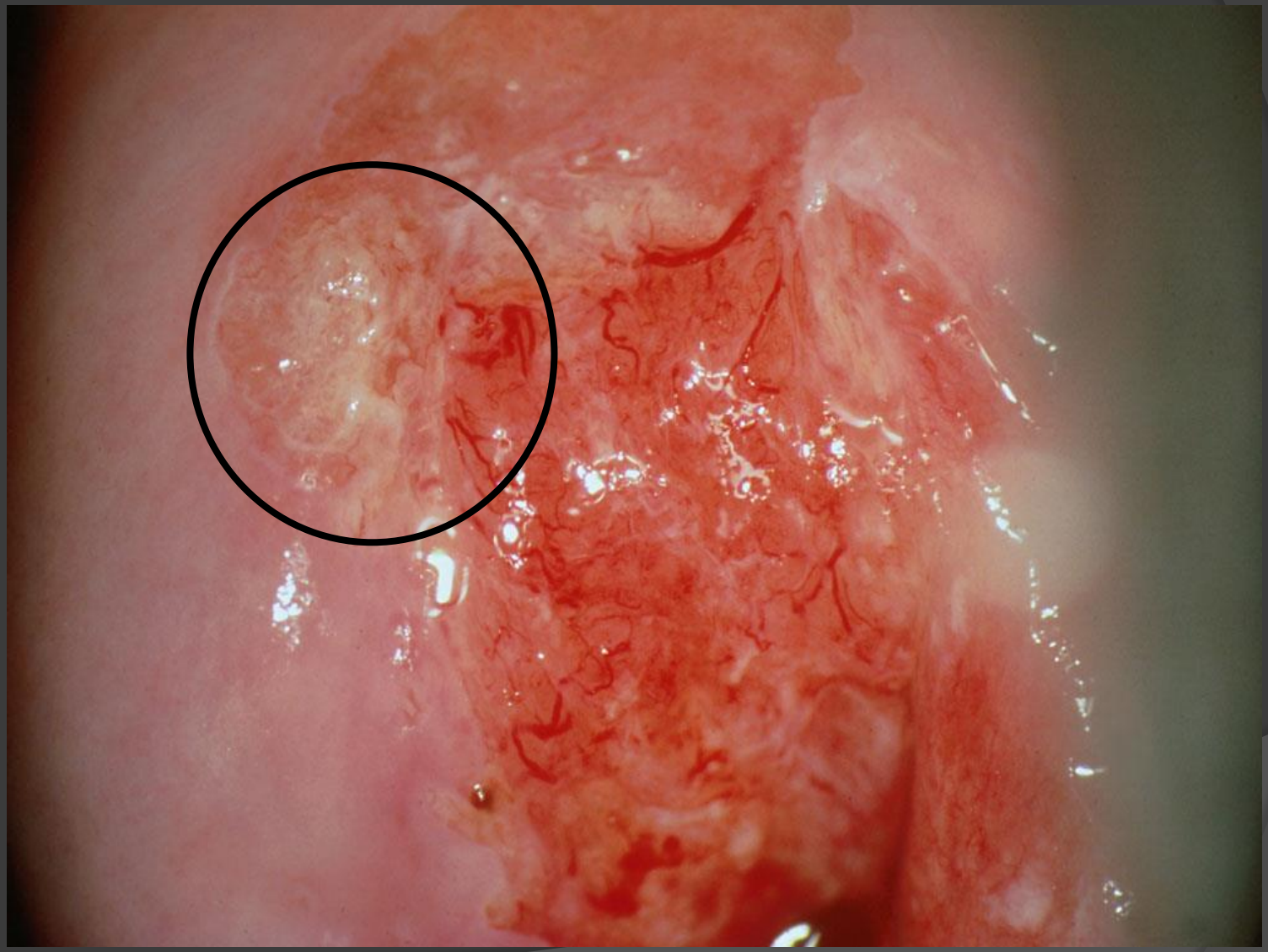


Photo: Richard Lieberman, MD

Atypical, Root-like and Hairpin Vessels

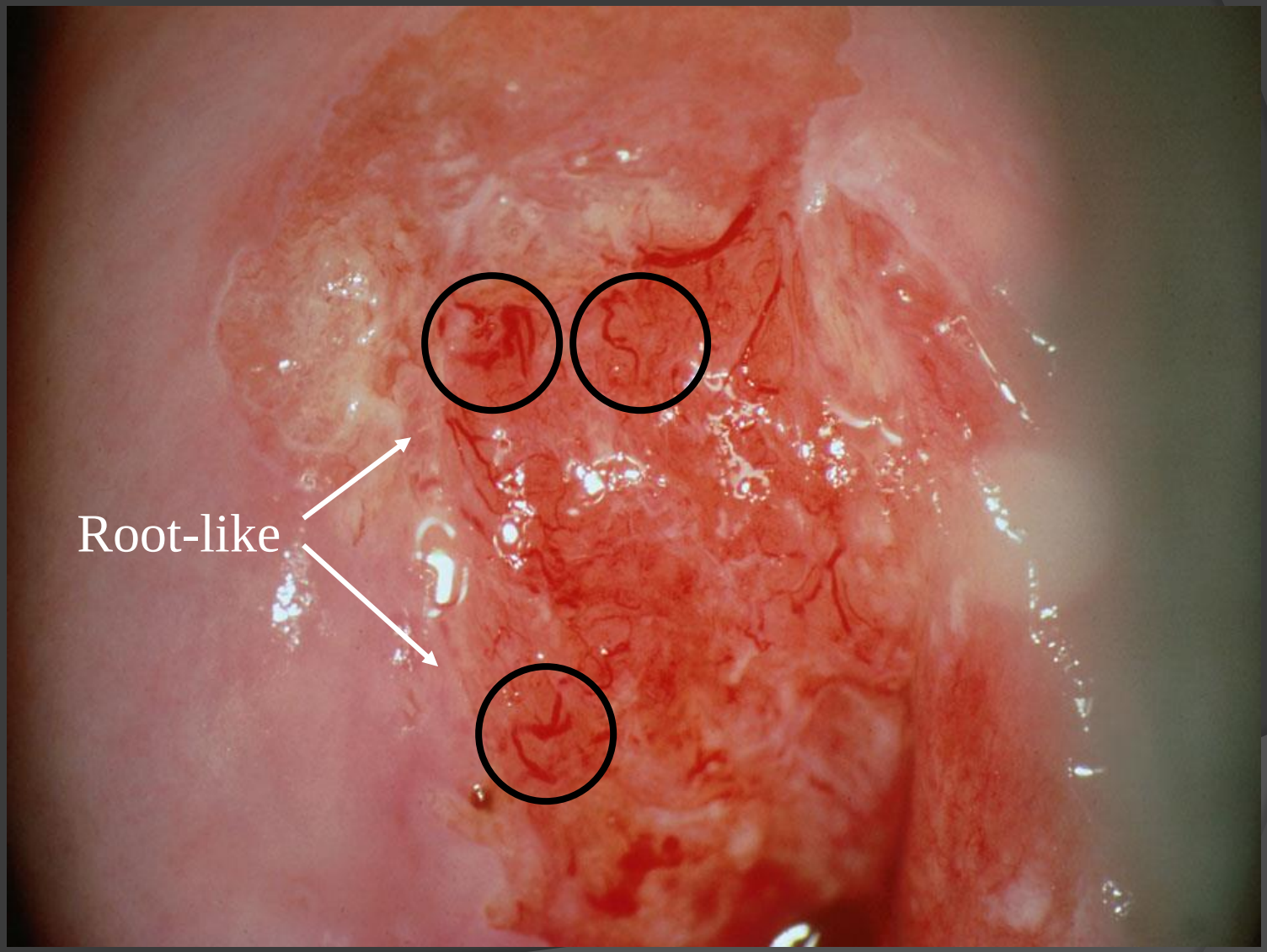


Photo: Richard Lieberman, MD

Atypical, Root-like and Hairpin Vessels

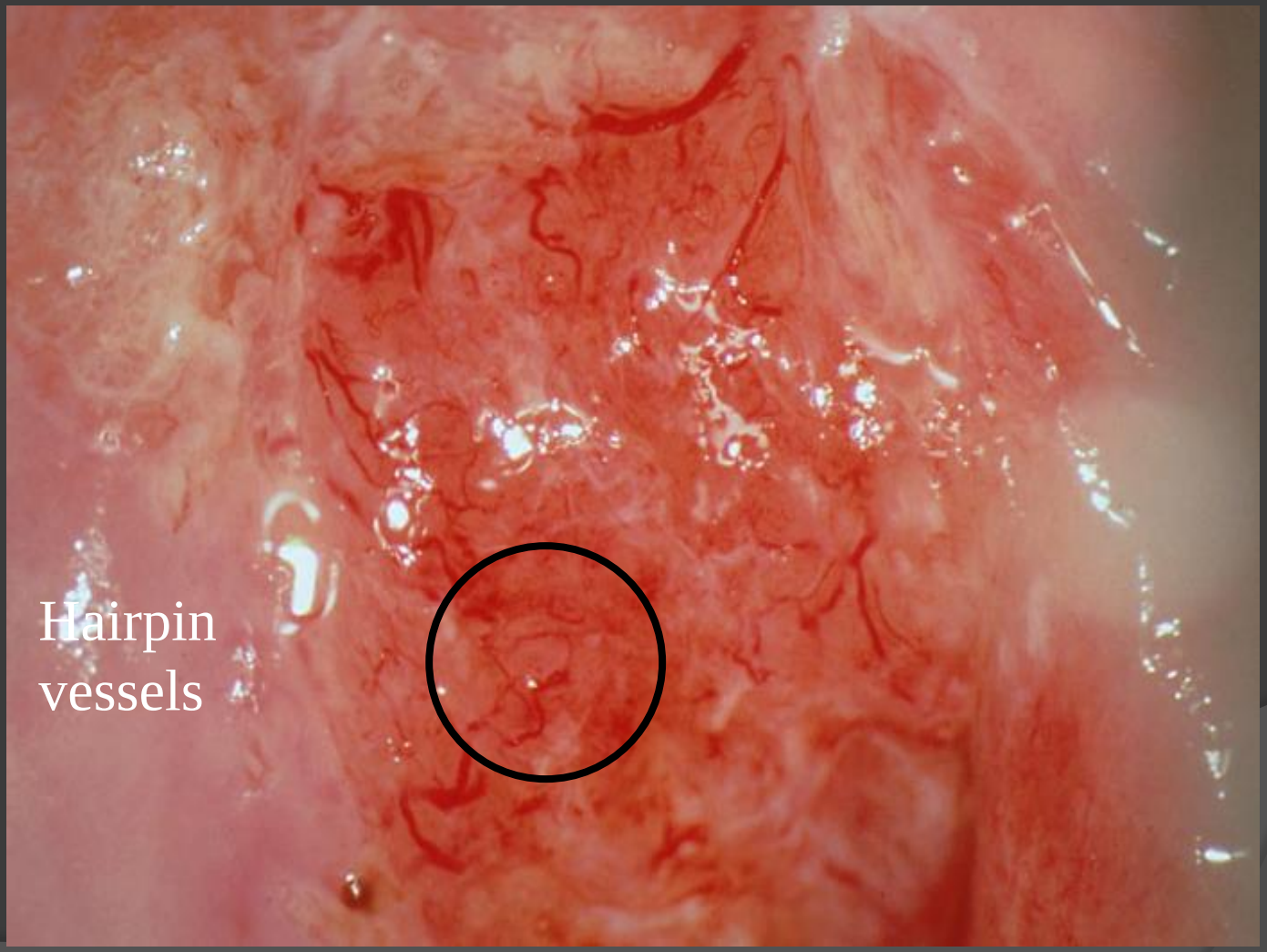
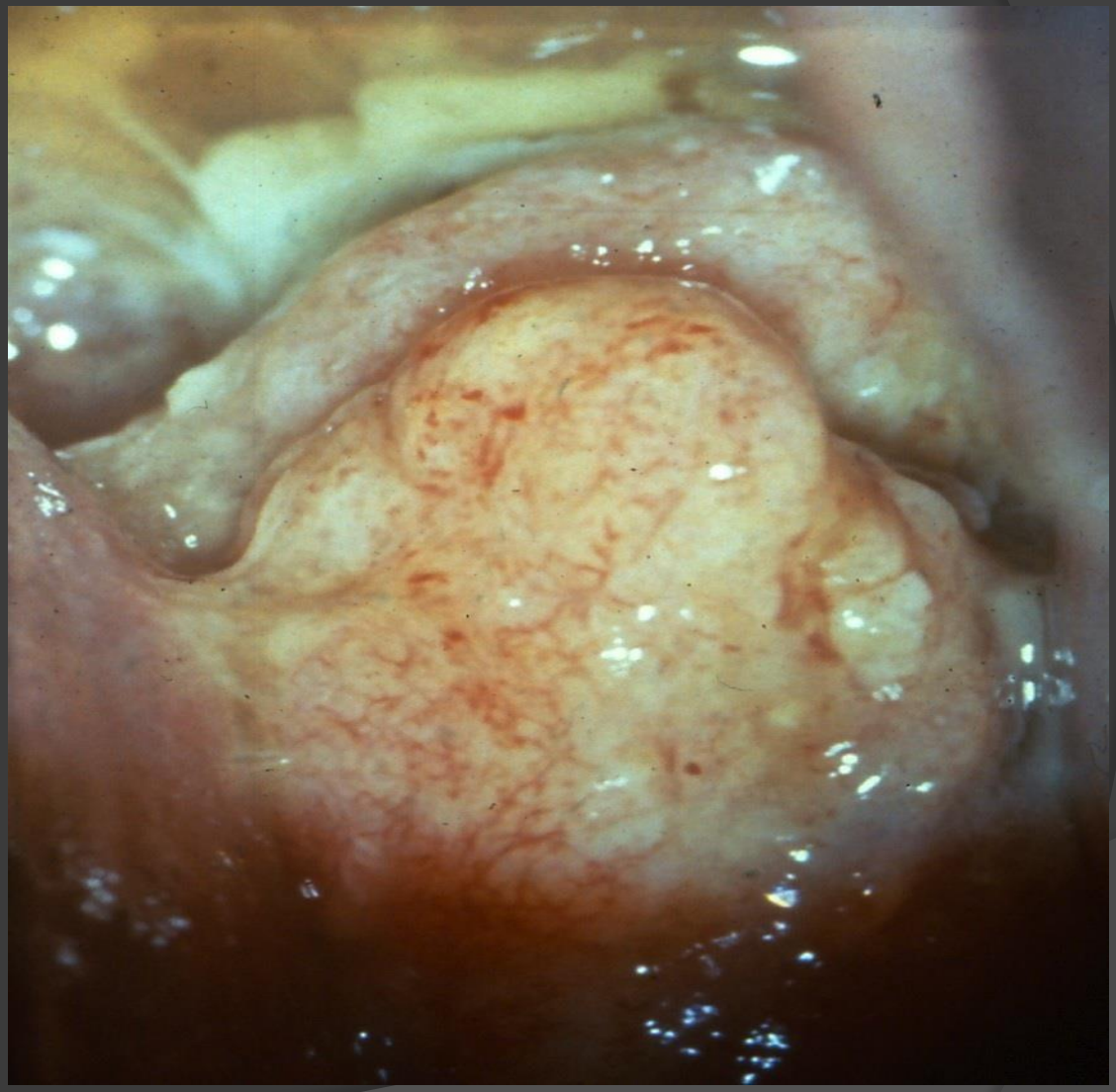


Photo: Richard Lieberman, MD

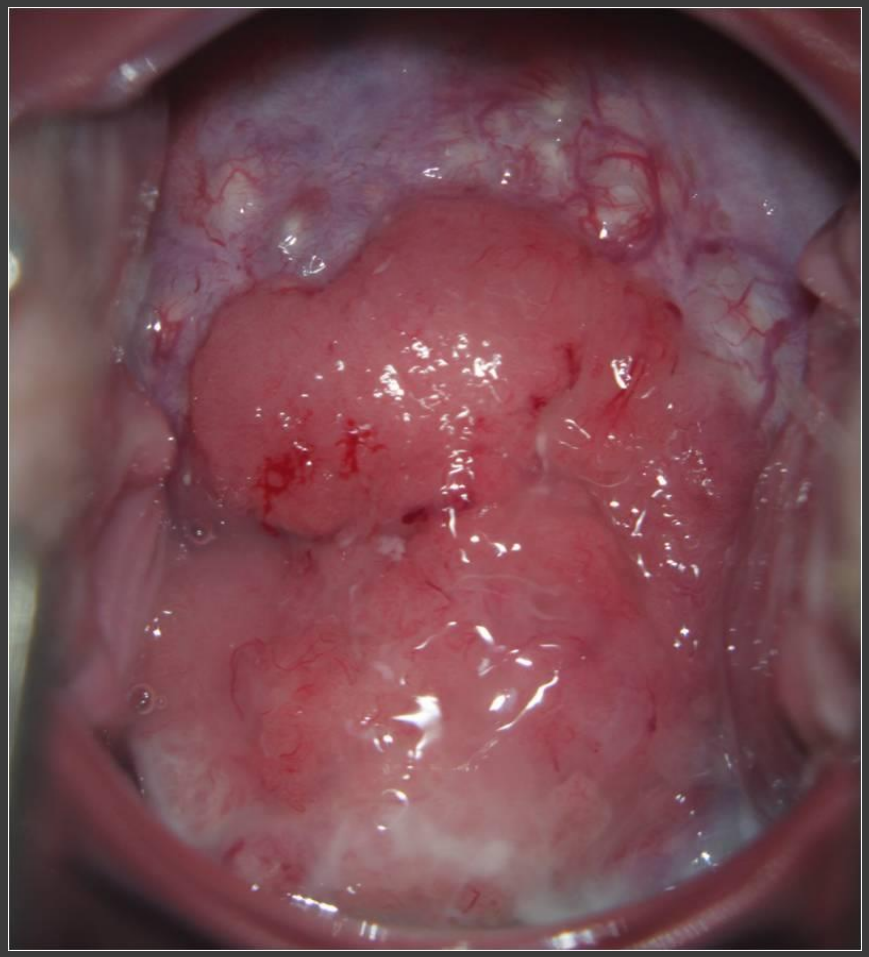
Cervical Adenocarcinoma

Milky white, exophytic, Ulceration and necrosis, atypical vessels

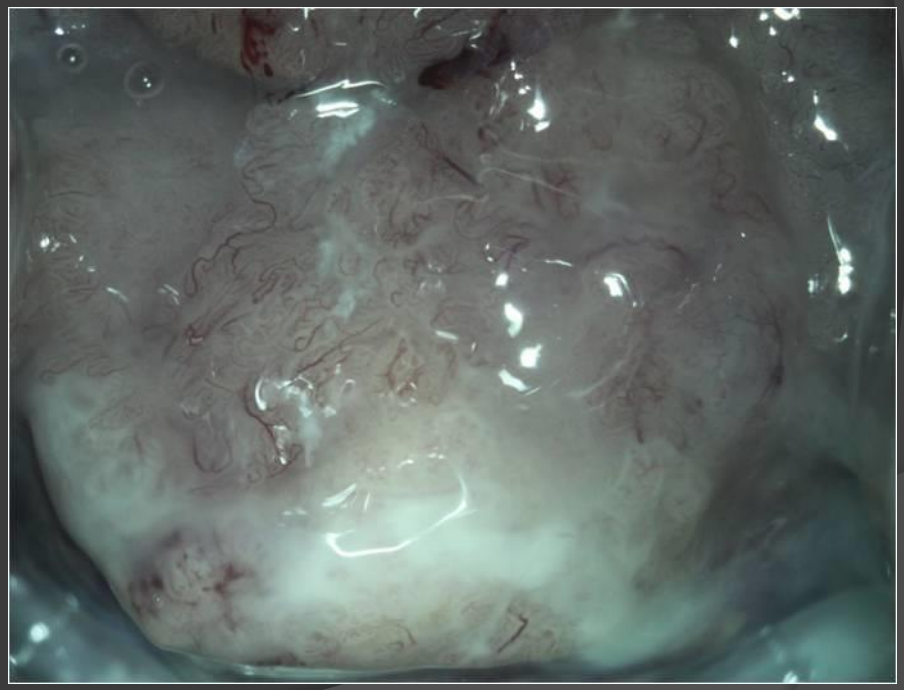


Candice Tedeschi, OGNP

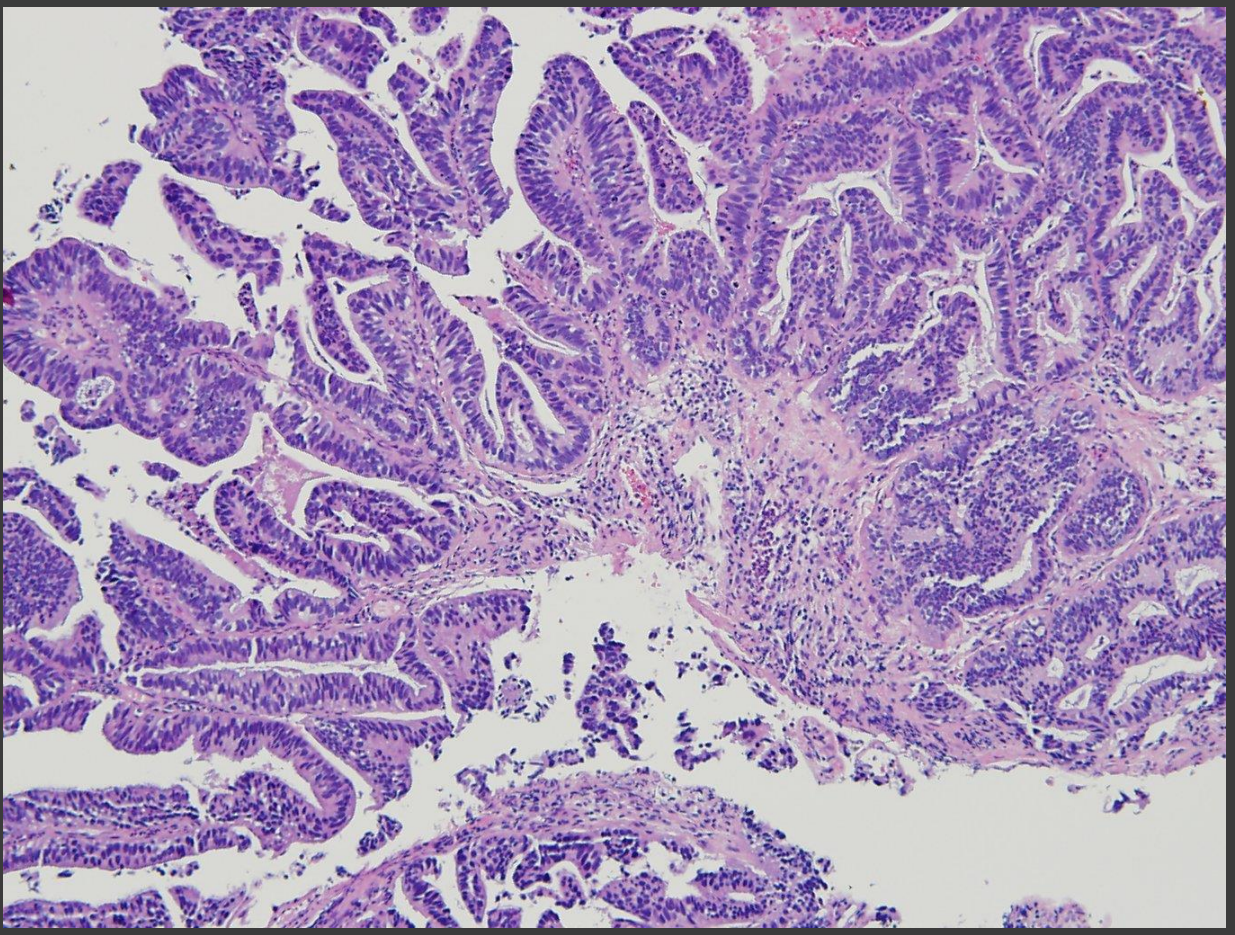
Endocervical Adencarcinoma - Villoglandular Type



Before Acetic Acid



Photos: Alan G. Waxman, MD

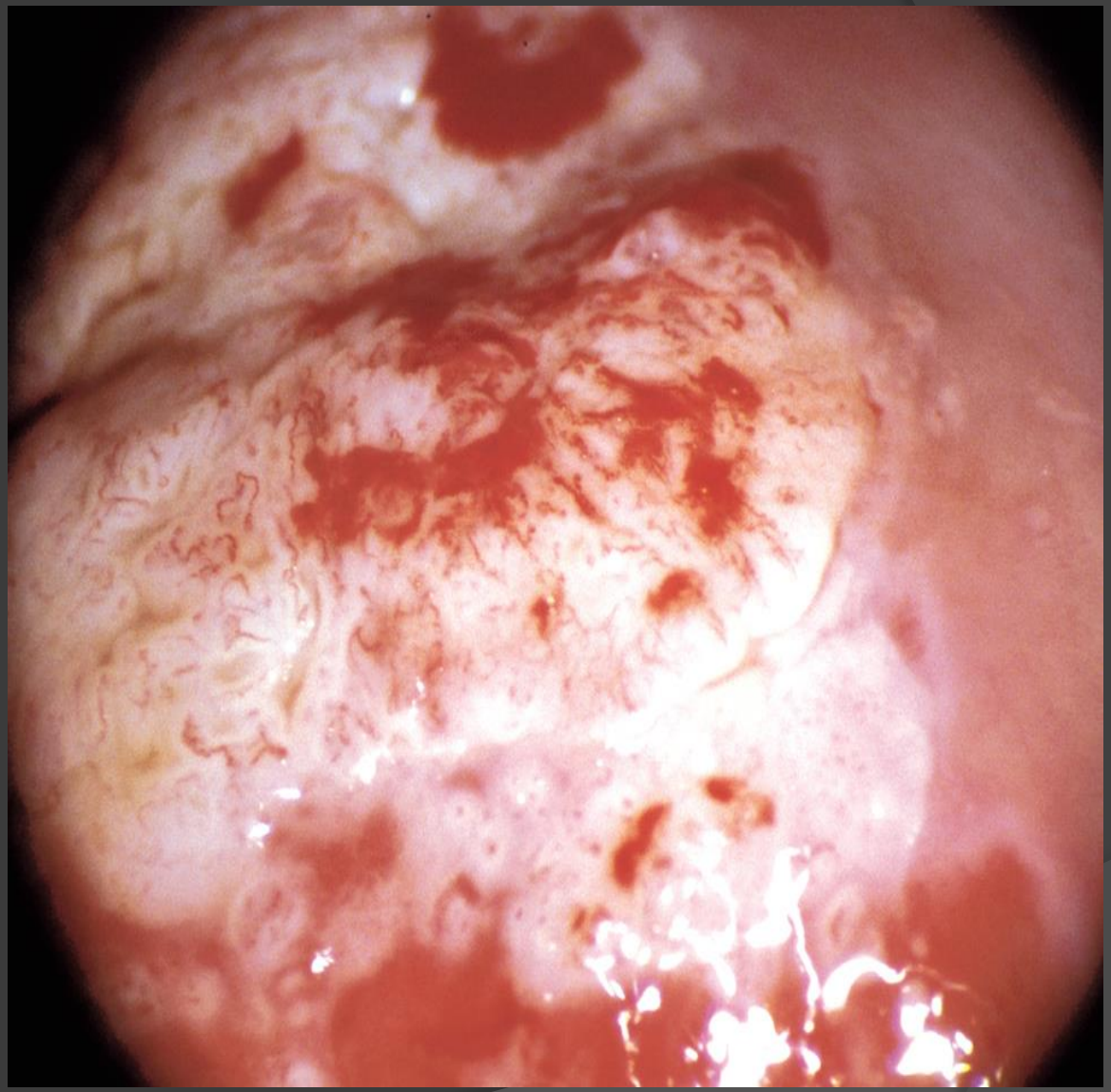


Endocervical Adencarcinoma Villoglandular Type

Photo: UNM Pathology

Vessel pattern: Adenocarcinoma

Note hairpin and root-like vessels



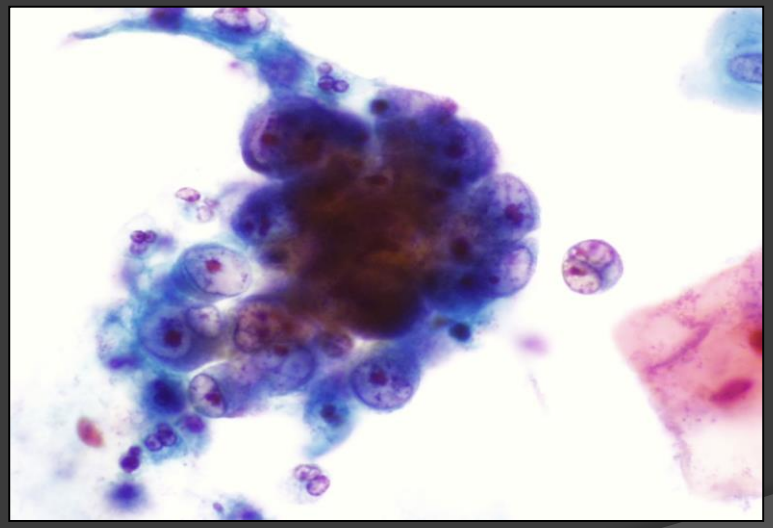
Apgar, Brotzman, Spitzer

Squamous vs adenocarcinoma?

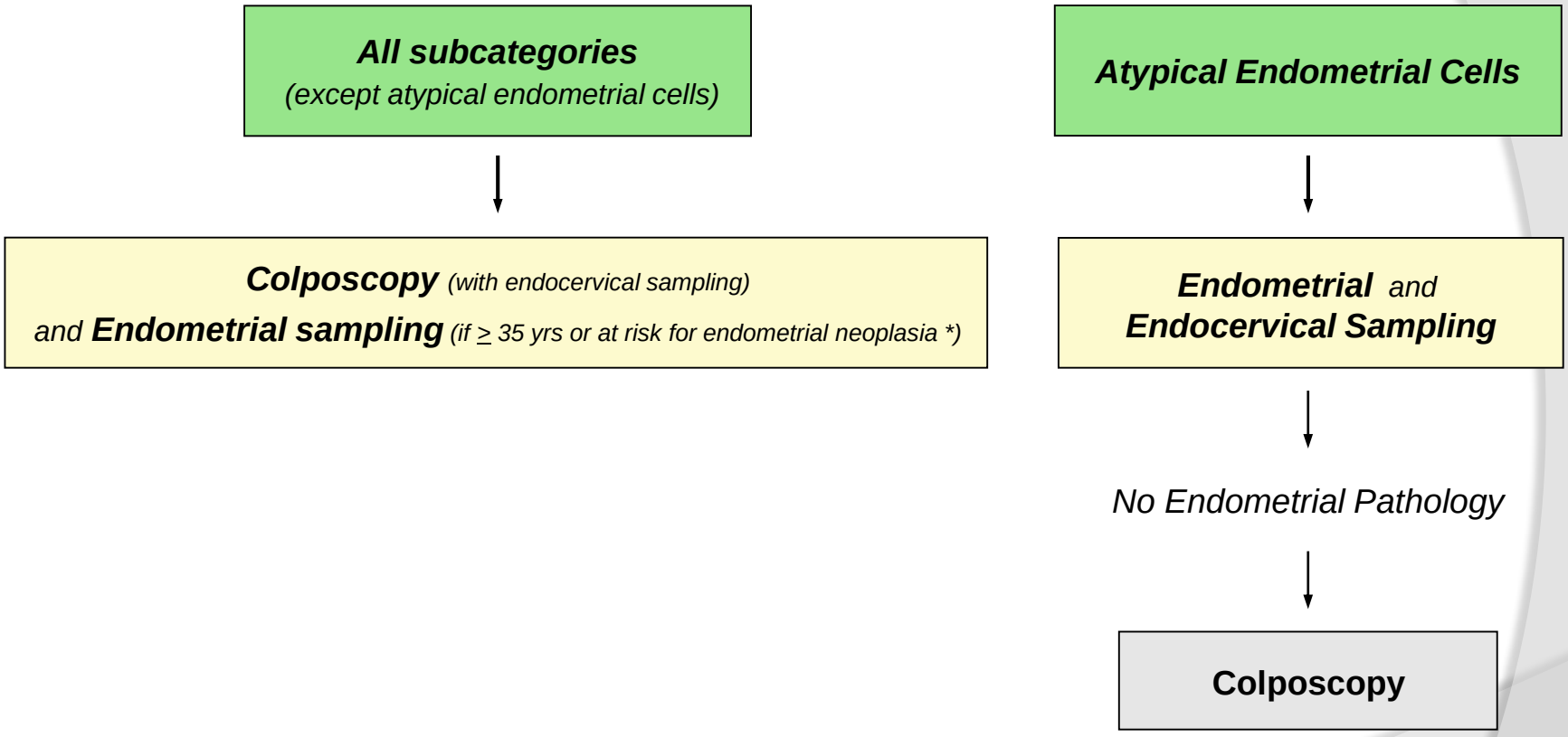
It’s cancer!
Biopsy needed to confirm histologic type

Management Algorithms

Updated Consensus Guidelines



Initial Workup of Women with Atypical Glandular Cells (AGC)



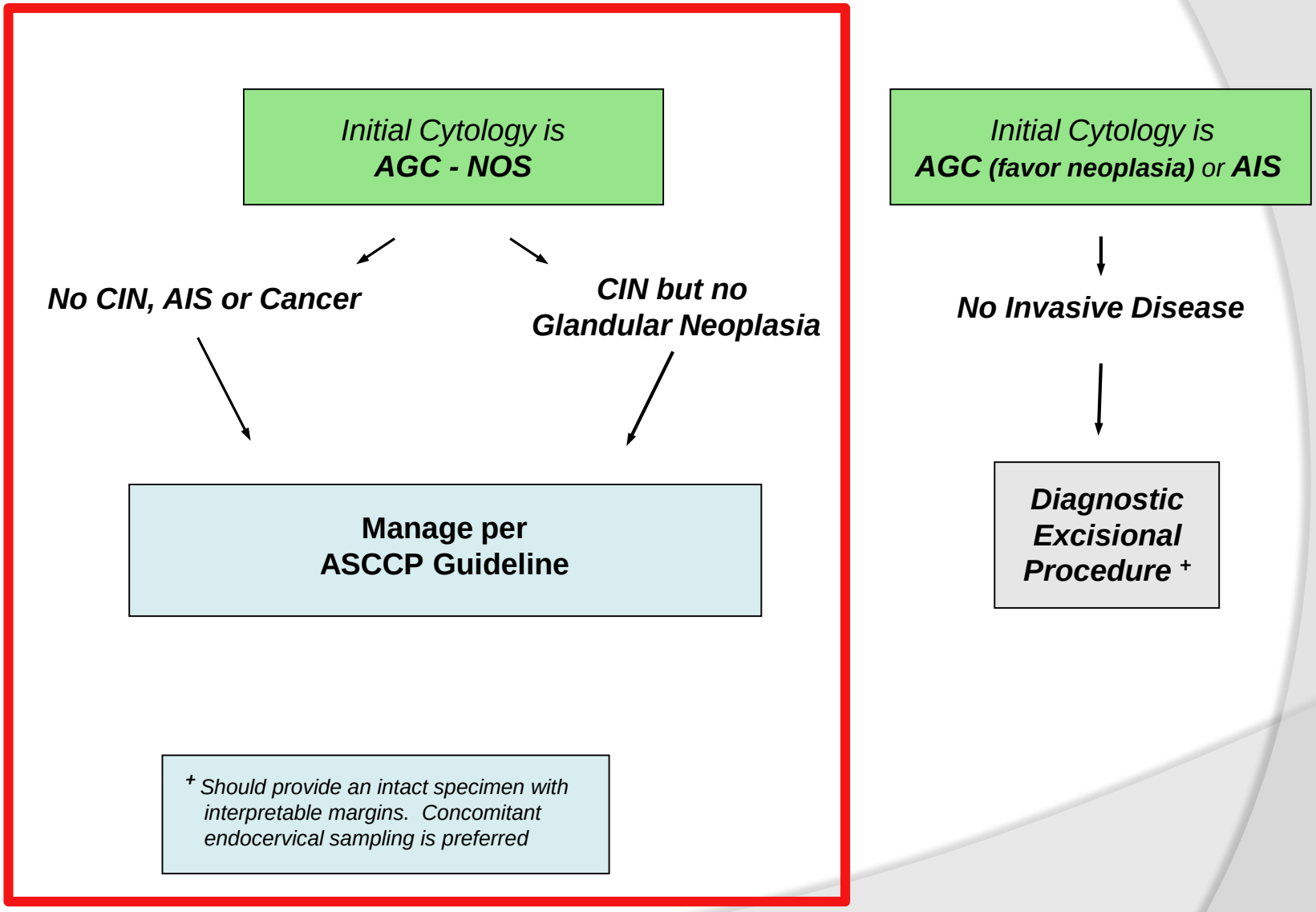
* Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation.

Atypical Glandular Cells

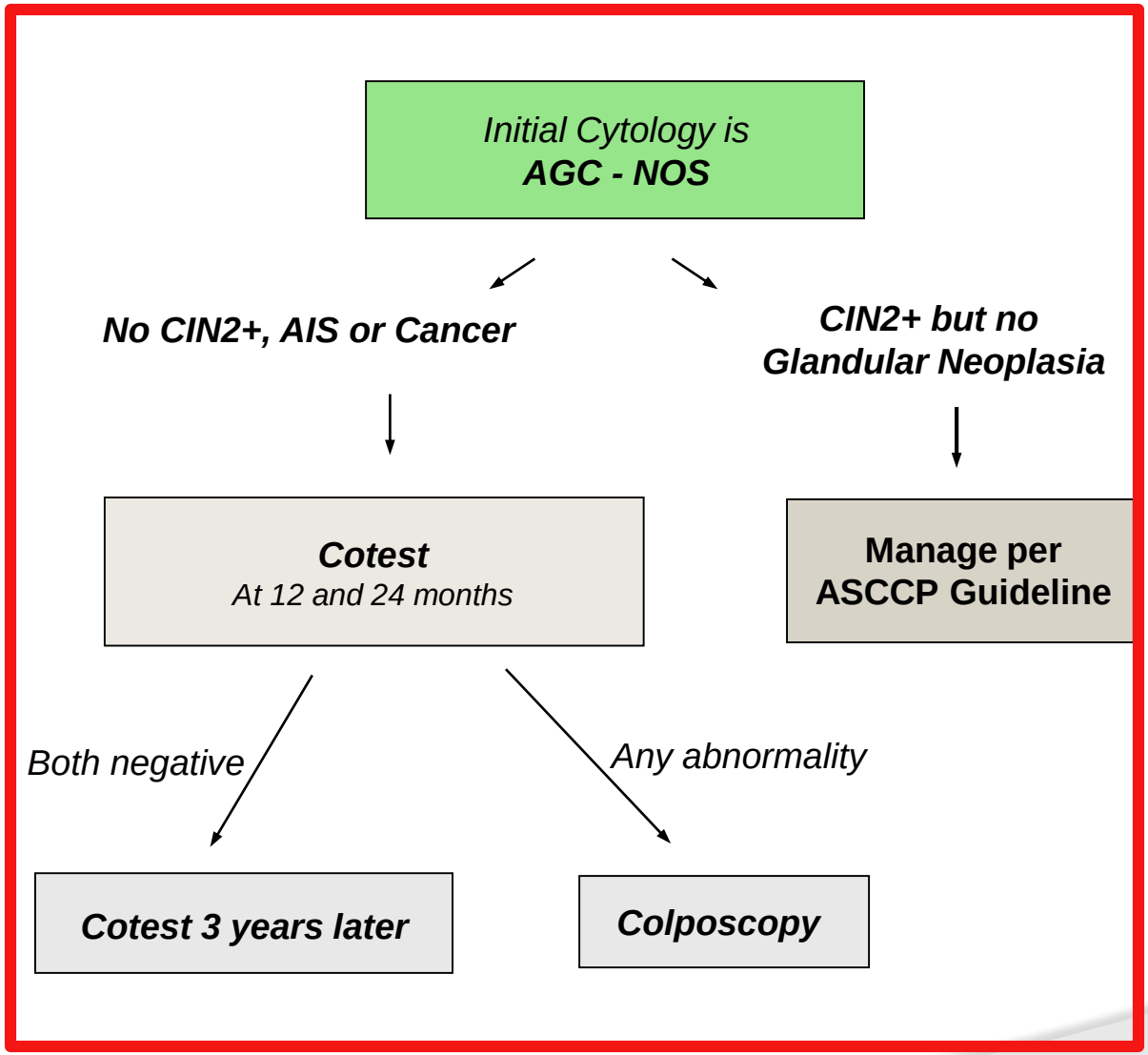
- Neither HPV testing nor repeat cervical cytology sensitive enough to be used alone as *triage test.*

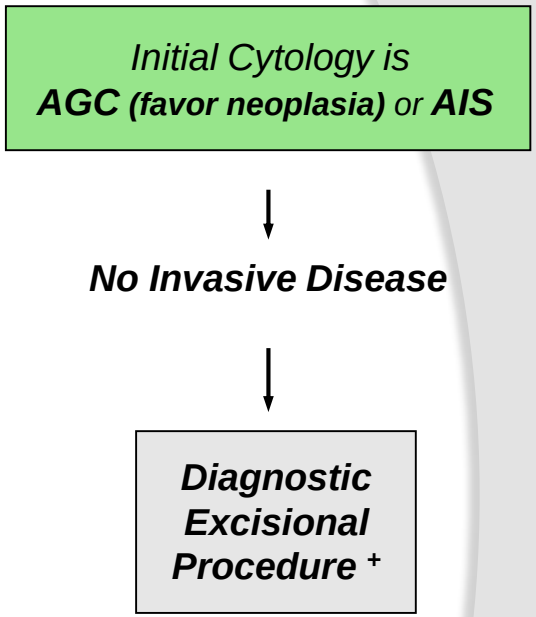
- Initial evaluation includes multiple modalities:
  - Colposcopy
  - Endocervical assessment and sampling
  - Endometrial evaluation if indicated.

Subsequent Management of Women with Atypical Glandular Cells (AGC)



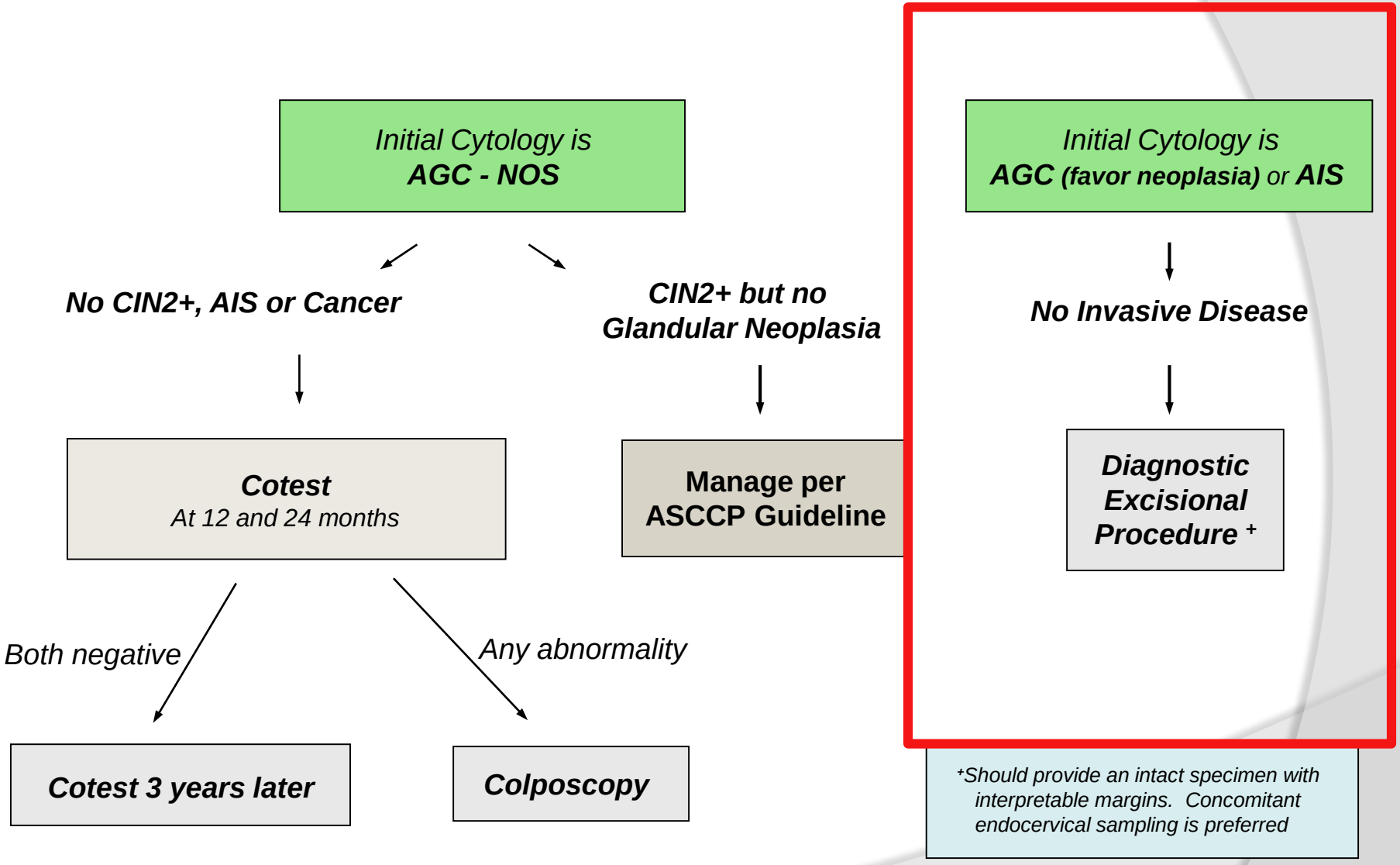
Subsequent Management of Women with Atypical Glandular Cells (AGC)





+Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred

Subsequent Management of Women with Atypical Glandular Cells (AGC)

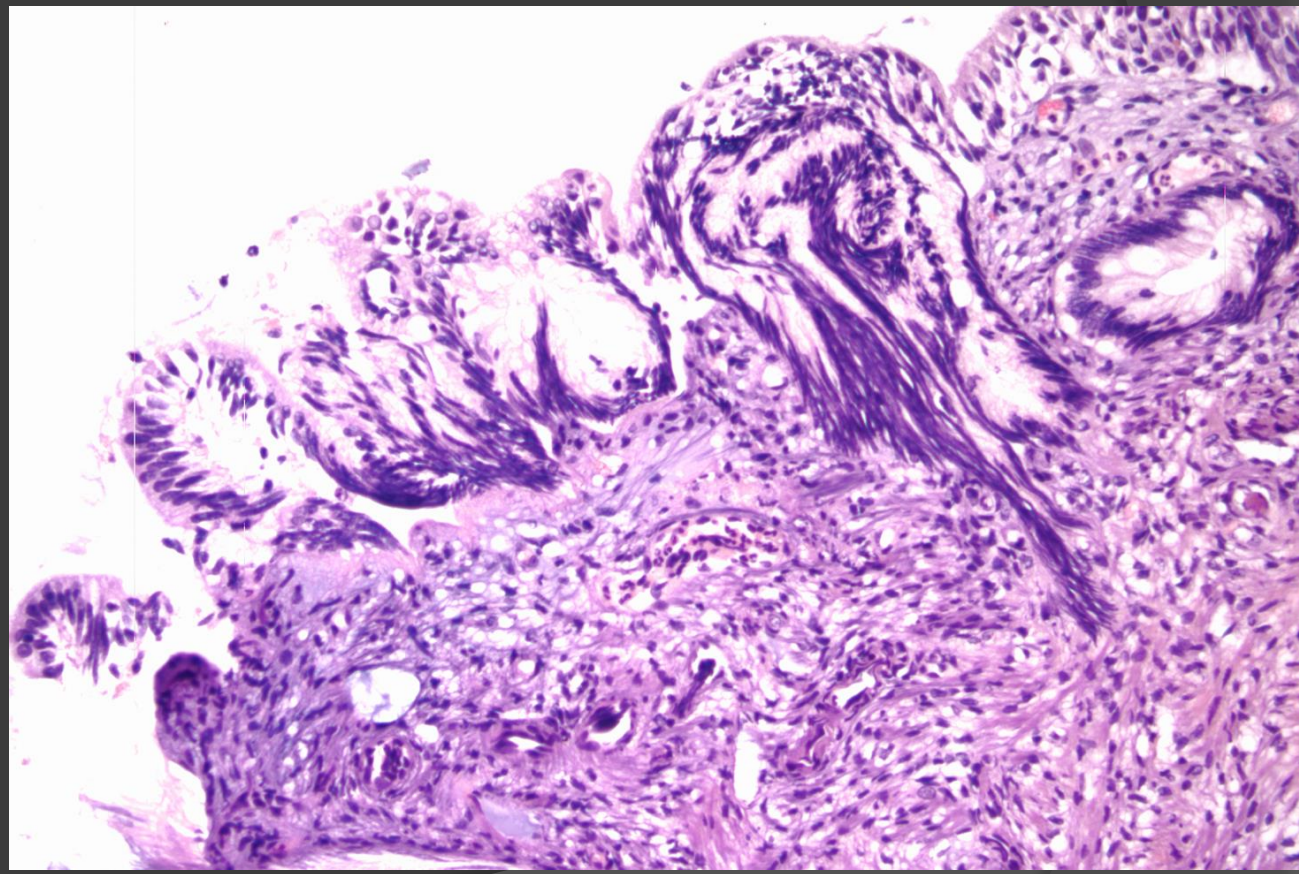


Treatment of glandular lesions

- *An intact specimen with interpretable margins is key to direct therapy in glandular abnormalities*.
- Therefore clinicians should choose the modality most likely to *yield the best pathologic specimen*.
- Endocervical curettage is recommended at the time of excisional biopsy in suspected glandular abnormalities.

Thermal Effect on Endocervical Glands

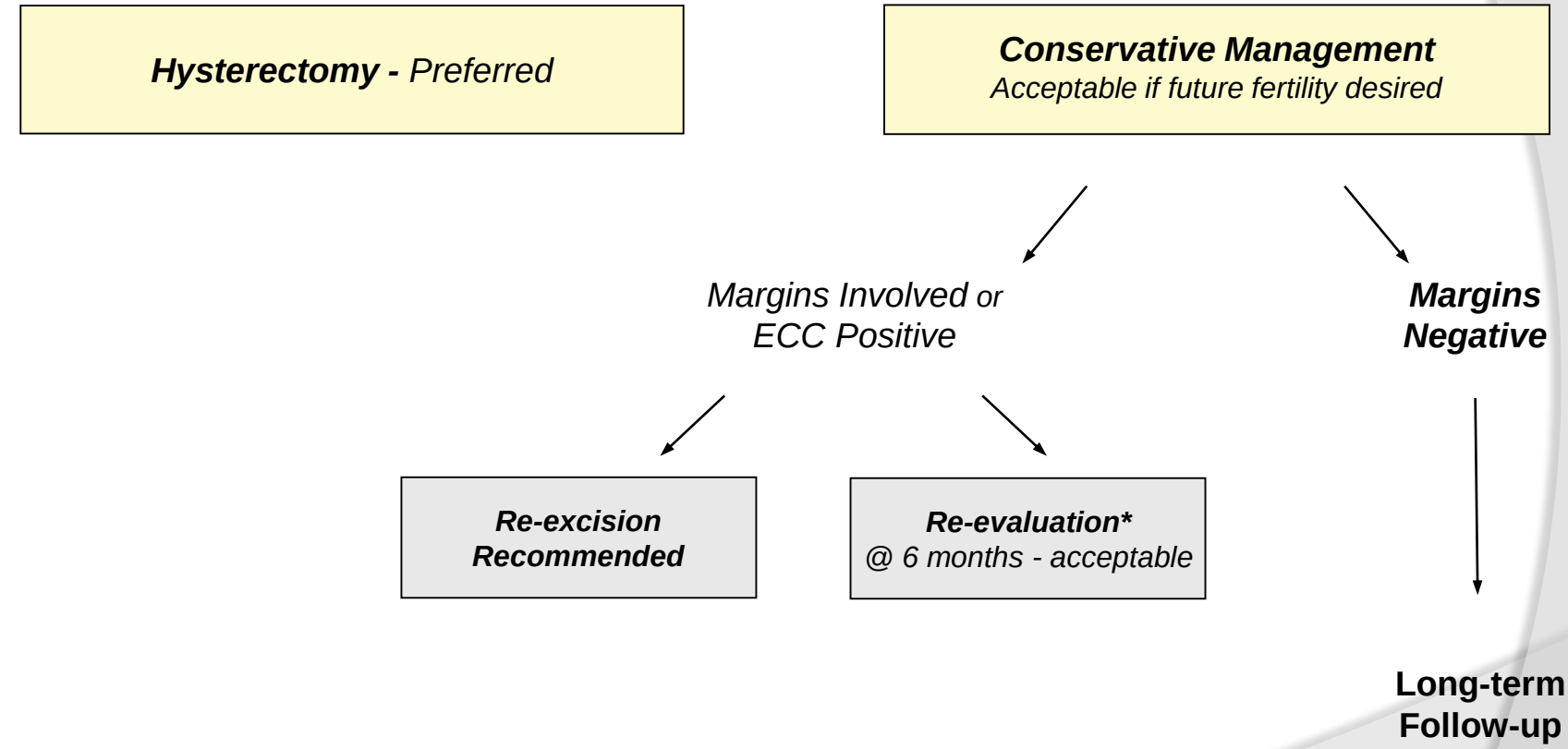
Mucus conducts electricity very efficiently



Conization versus large loop electrosurgical excision for adenocarcinoma in situ Positive margins more likely with LEEP

Author	Cone Biopsy	Positive Margins	Large Loop Electrosurgical Excision	Positive Margins
Wolf et al. (21)	43	18 (42%)	7	5 (71%)
Widrich et al. (8)	18	6 (33%)	14	7 (50%)
Denehy et al. (20)	24	8 (33%)	13	9 (69%)
Azodi et al. (32)	25	6 (24%)	8	6 (75%)
Totals	110	38 (38%)	42	27 (62%)

Management of Women Diagnosed with Adenocarcinoma in-situ (AIS) during a Diagnostic Excisional Procedure



** Using a combination of cotesting and colposcopy with endocervical sampling*

AIS, Implications of Conization Margin Status

Salani et al Am J Obstet Gynecol 2009;200:182 e1-5

- Meta-Analysis, 33 studies / 1278 patients
  - Mean follow-up 39.2 months

607 pts. had second excision

93 repeat conization / 499 hysterectomy

Residual AIS based on margins of first conization

Negative margins: 20.3%

Positive margins: 52.8%

RR: 4 (CI 2.62-6.33) p<.001

671 followed conservatively after excision

Recurrent AIS based on margins of first conization

Negative margins: 2.6%

Positive margins: 19.4%

Rr:2.5 (CI1.05-6.22) p<.001

AIS, Implications of Conization Margin Status

Salani et al Am J Obstet Gynecol 2009;200:182 e1-5

29 patients in 13 studies developed invasive adenocarcinoma

- 5.2% with positive margins/ 0.7% with negative margins

Of 607 patients who underwent second excision

21 (3.5%) had adenocarcinoma on hysterectomy

Positive margins on initial conization: 17 patients

Negative margins on initial conization: 4

Of 671 patients followed conservatively

8 (1.2%) subsequently developed adenocarcinoma

Positive margins on initial conization: 6 patients

Negative margins on initial conization: 2

Histologic AIS Conservative management

- **When future fertility is desired**
- **Re-evaluation at 6 months using a combination of *cervical cytology, HPV DNA testing, and colposcopy with endocervical sampling* is acceptable in this circumstance.**
- **Long-term follow up is recommended for women who do not undergo hysterectomy.**

Massad LS et al. J Lower Genital Tract Dis. 2013. 17(5):S1-27

AIS is hard to diagnose on colposcopicy. If the Pap test shows *AGC*, biopsy anything that looks abnormal.

Thank you!