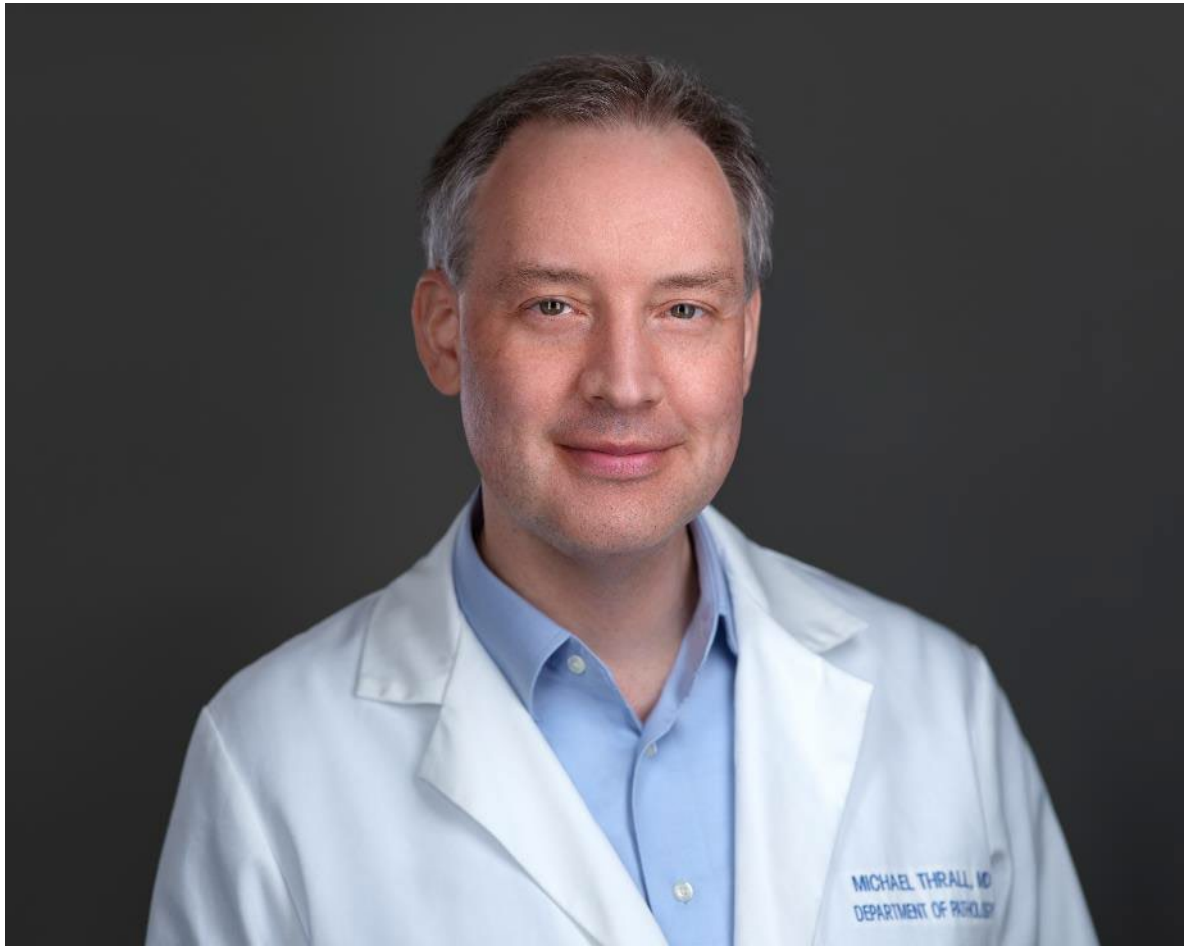
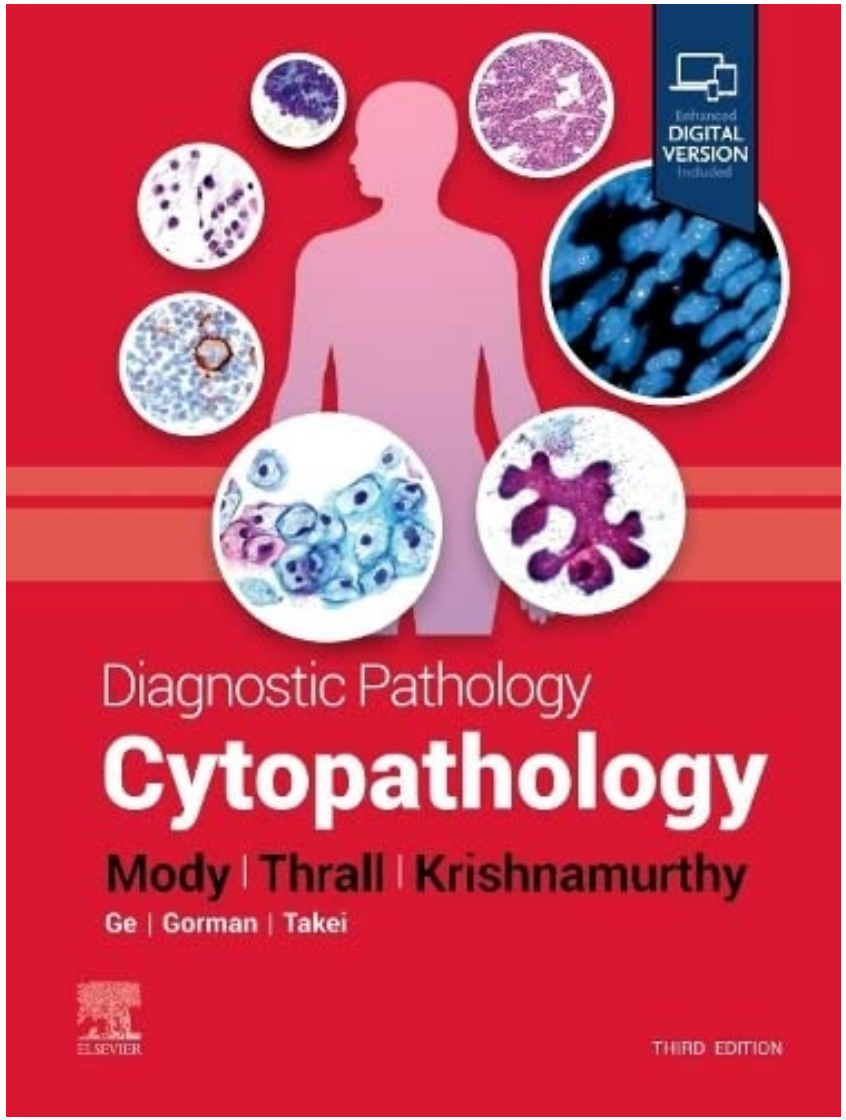
Essentials in Gynecologic Cytology

HOUSTON Methodist®
LEADING MEDICINE

- Michael J. Thrall M.D.
- Director of Cytopathology Fellowship and Digital Pathology
  - Department of Pathology and Genomic Medicine
  - Houston Methodist Hospital in Houston, TX, USA
- Professor, Houston Methodist Hospital Academic Institute and Weill-Cornell College of Medicine



- Co-editor of 2022 textbook Diagnostic Pathology: Cytopathology, 3rd Edition Publisher: Amirsys/Elsevier



Glandular Lesions

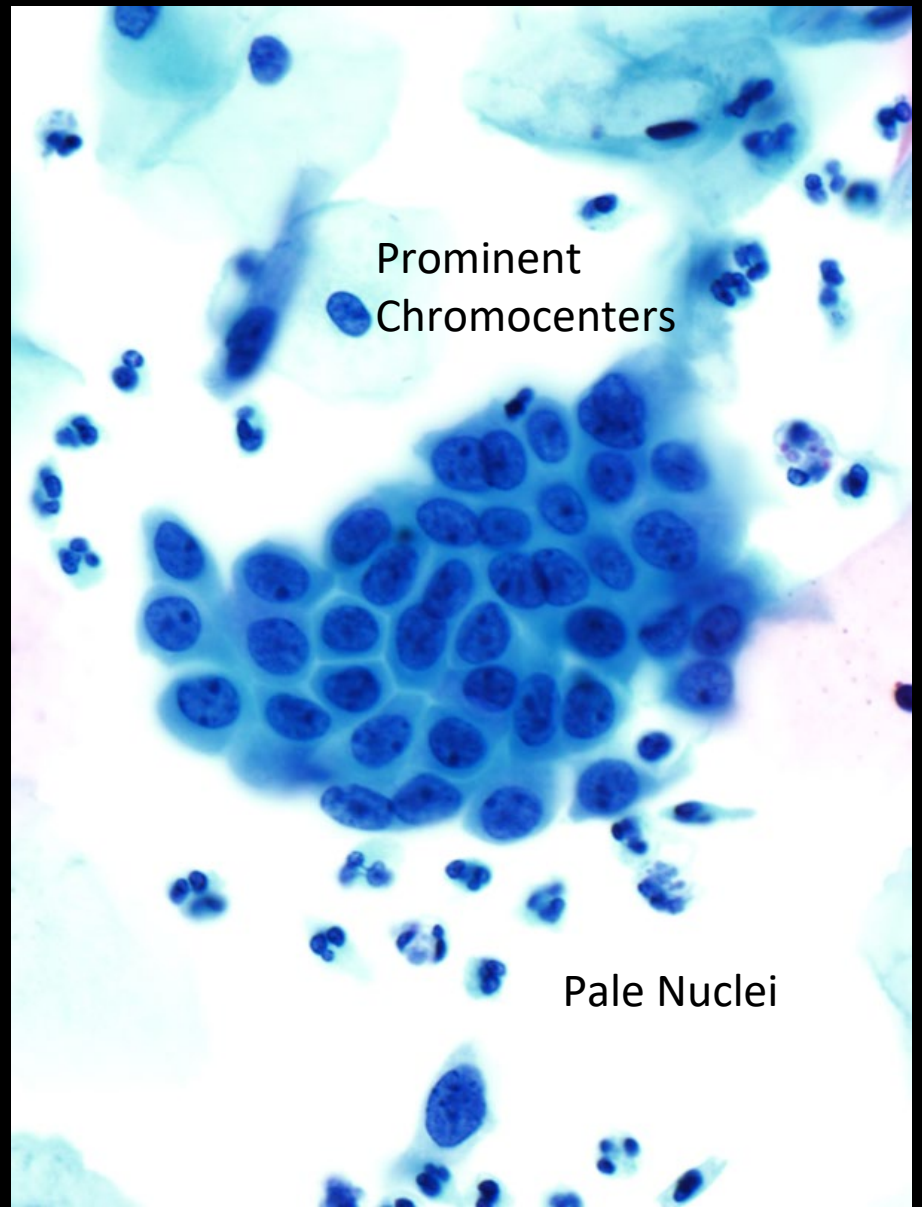
HOUSTON Methodist
LEADING MEDICINE

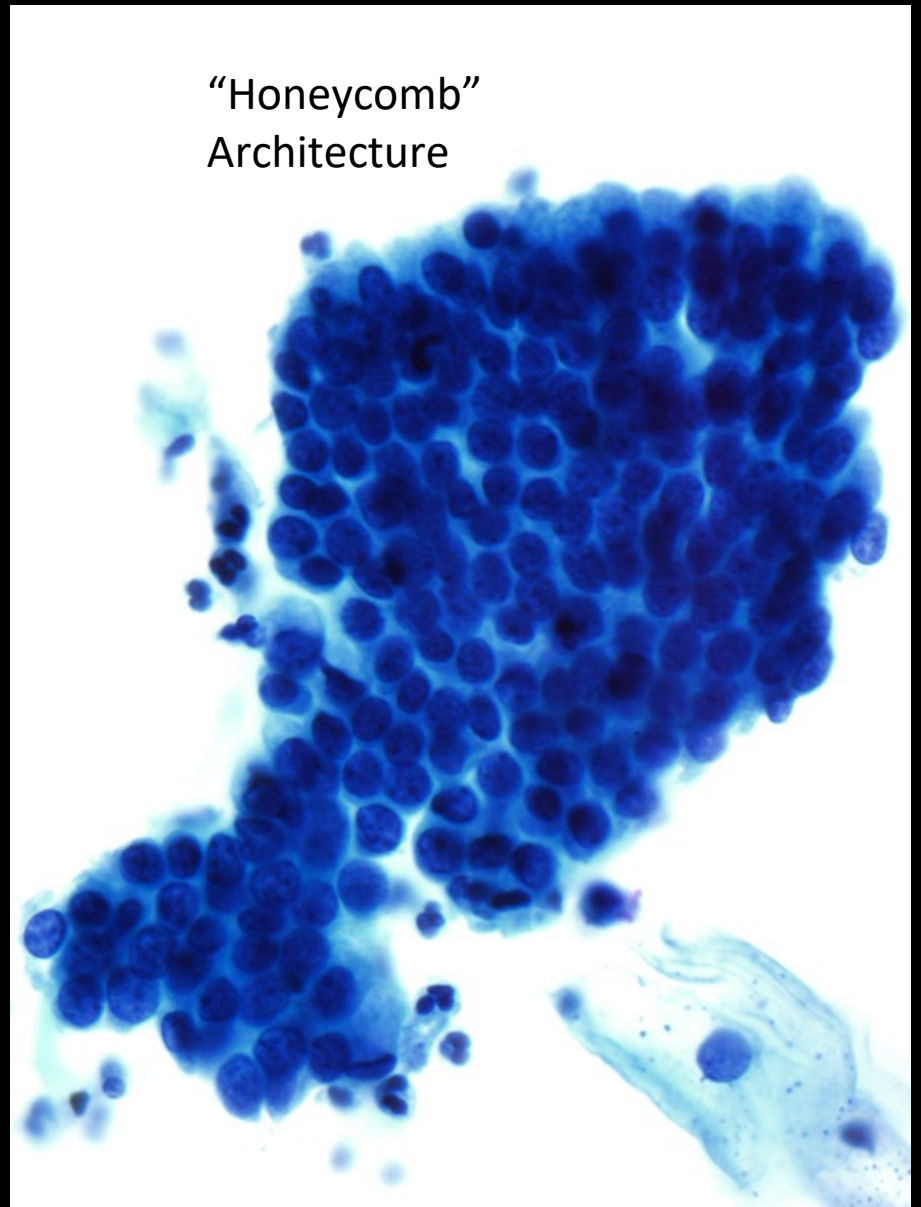
Glandular Cells

- Glandular cells are a perennial problem in Papanicolaou tests
- The Pap test is designed to find squamous dysplasia and carcinoma
- Glandular lesions are a “bonus”
- The sensitivity of Pap tests for adenocarcinoma is much less than for squamous dysplasia
- Liquid-based Pap tests appear to perform slightly better than conventional smears*

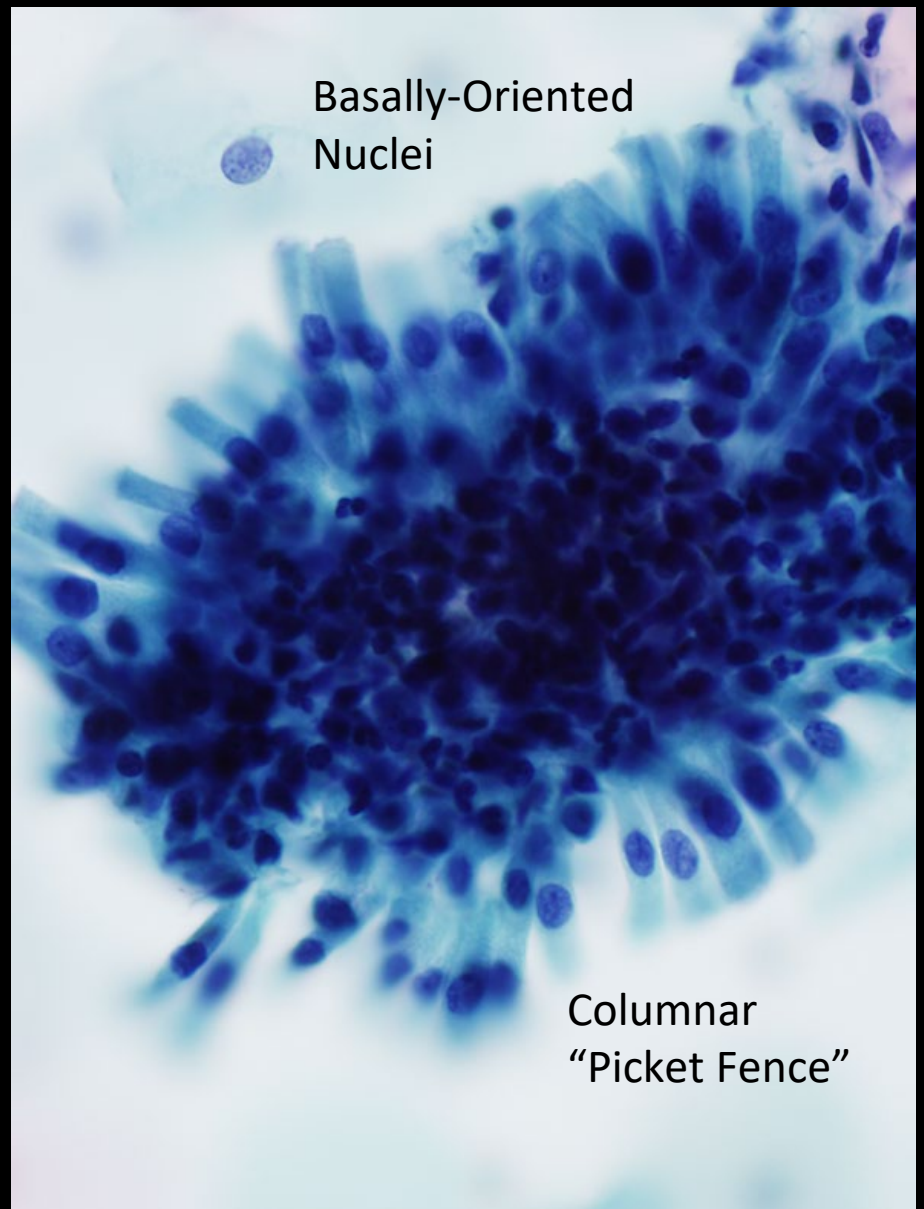
*Burnley *et al.* Diagn Cytopathol 2011; 39: 869.

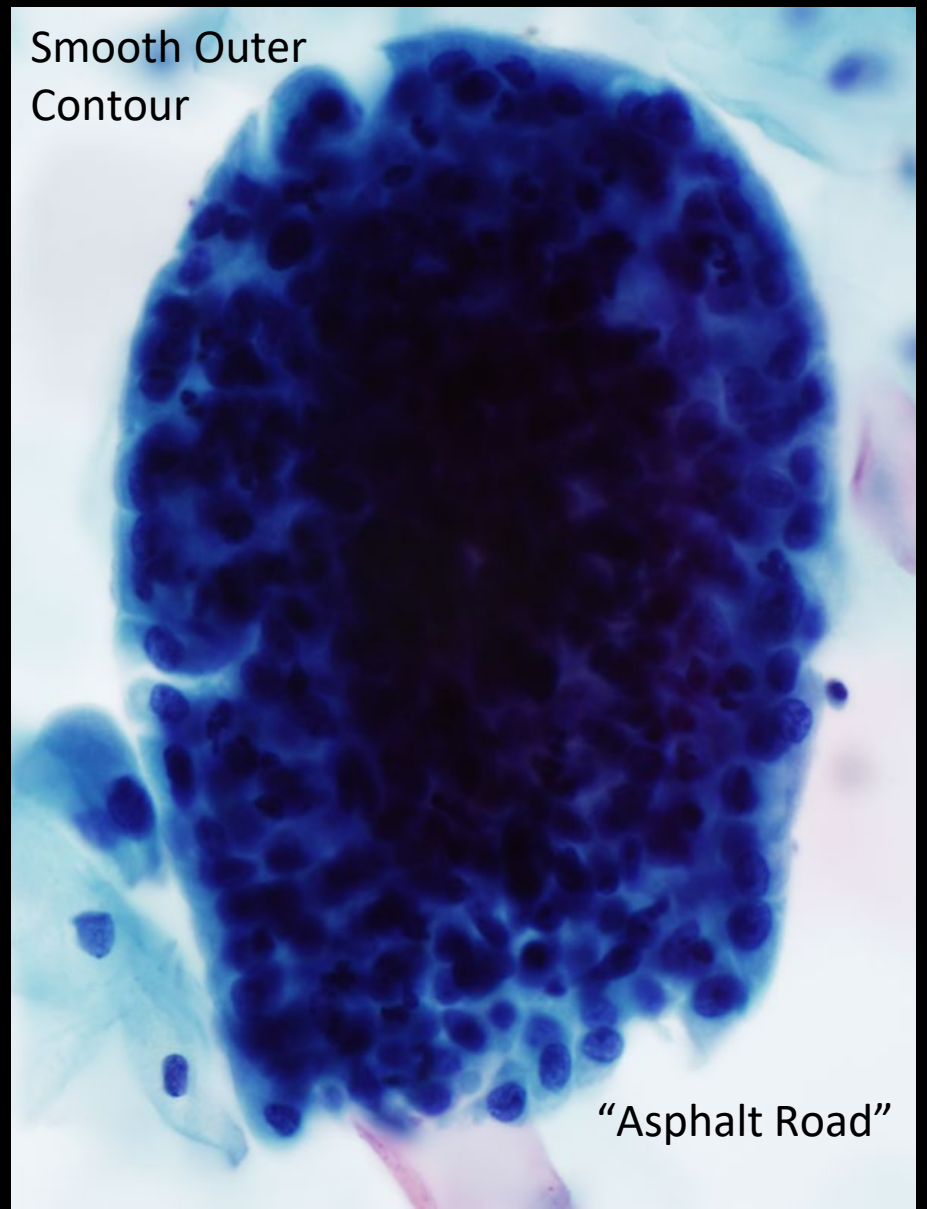
Endocervical cells



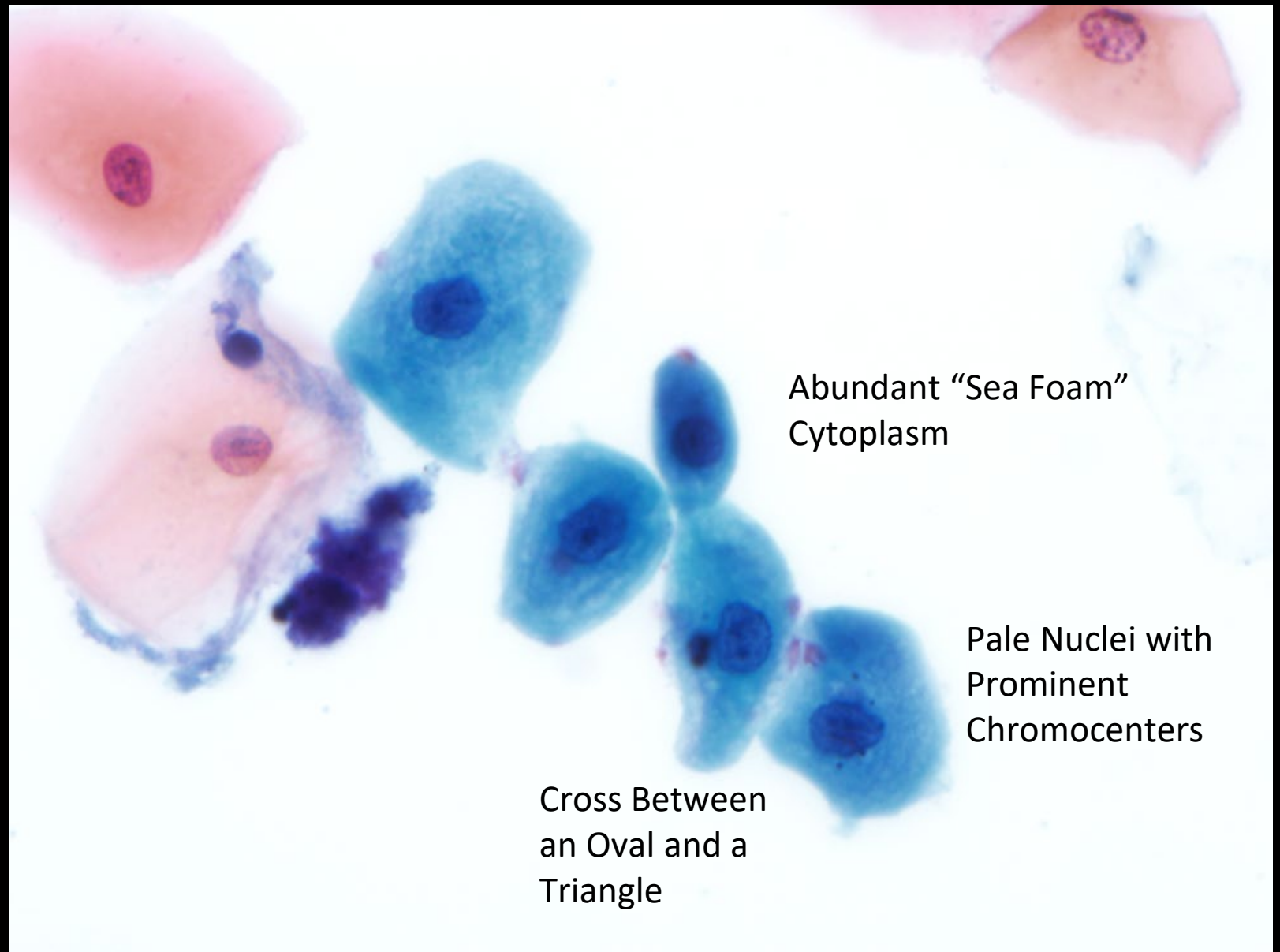


Columnar Cells, Smooth Contour





Squamous Metaplastic Cells



Adequacy

- The Bethesda System includes the presence or absence of endocervical cells in the adequacy assessment
- These cells are more likely to be absent in older women
- Counterintuitively, Pap tests without endocervical cells are not more likely to be false negative*

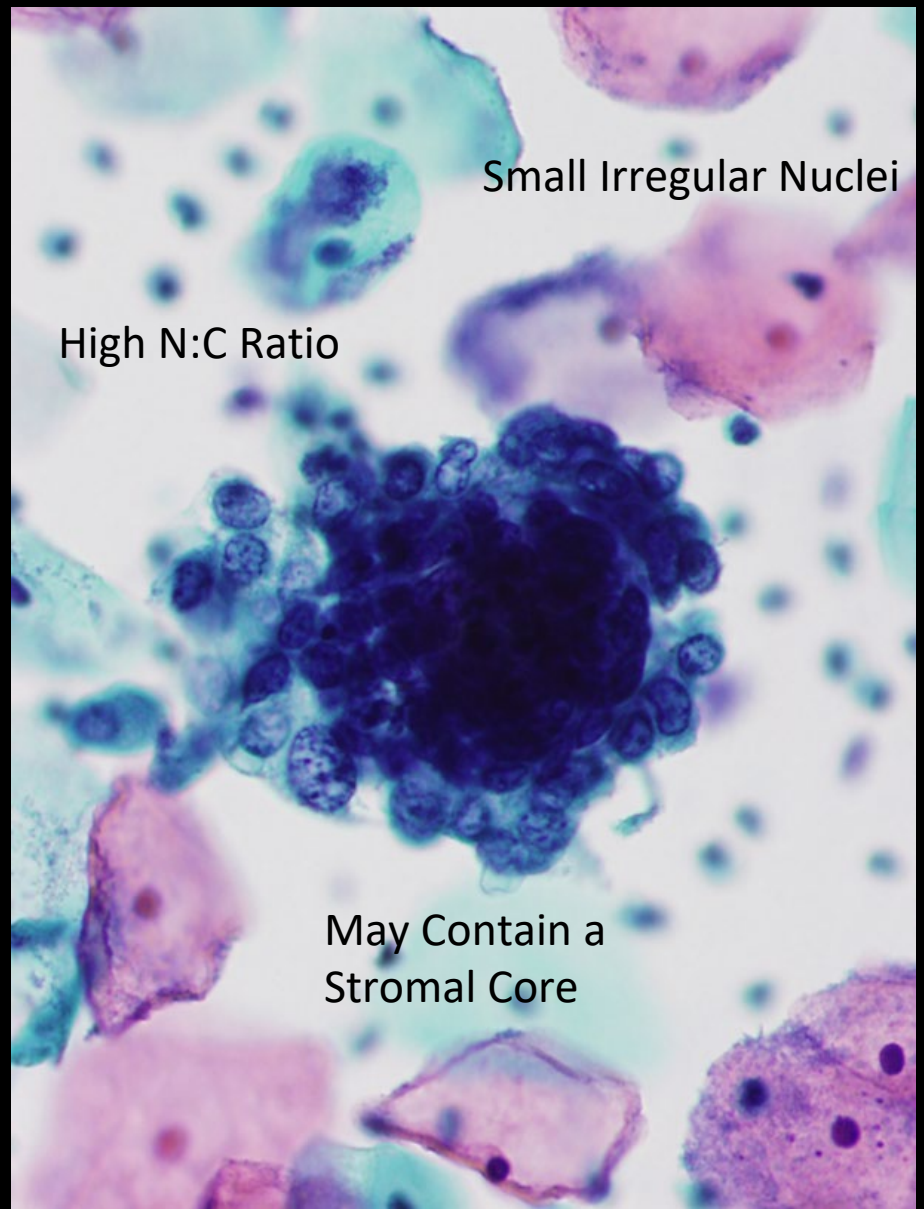
* Zhao and Austin Obstet Gynecol 2007; 107: 231.

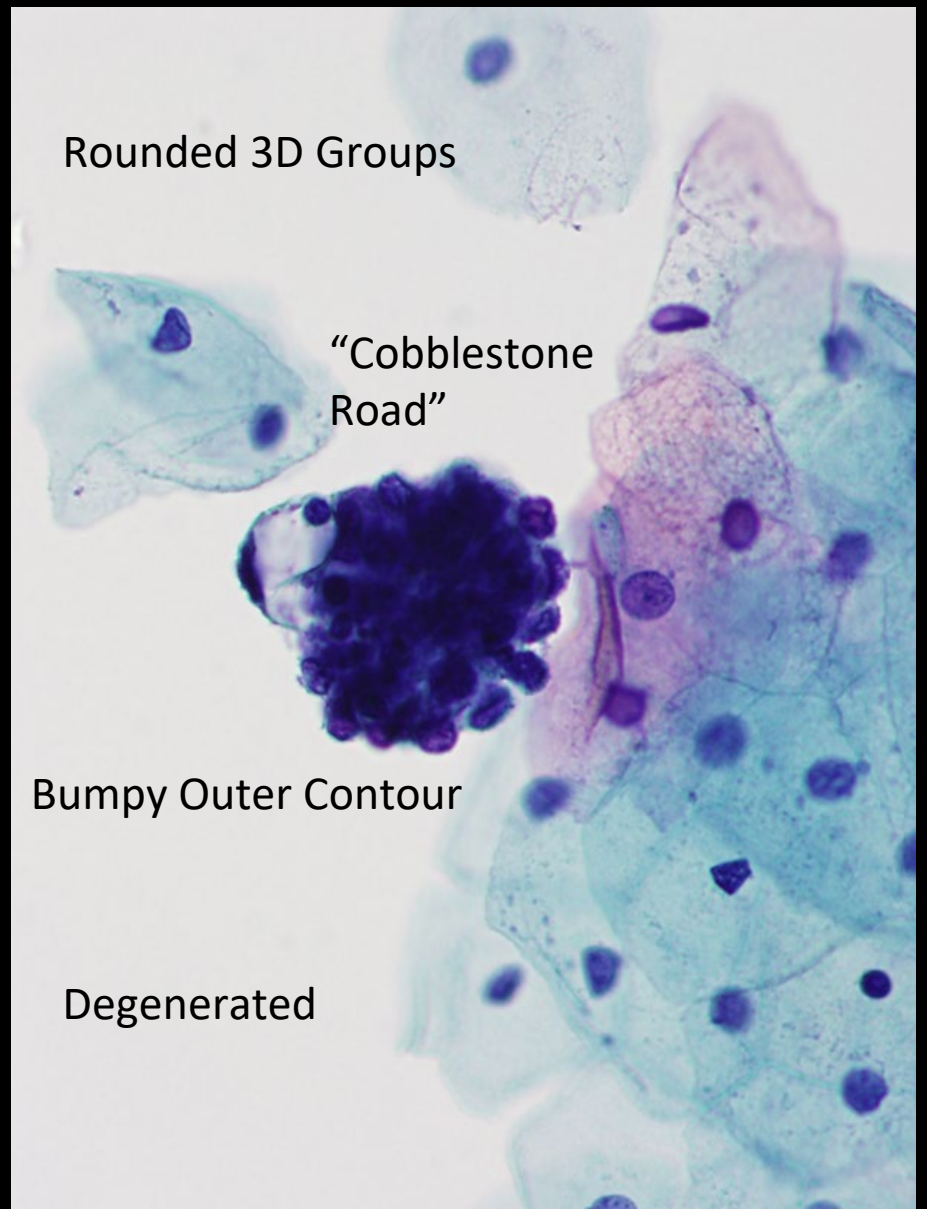
Benign-Appearing Glandular Cells Post-Hysterectomy

- Reporting the presence of glandular cells after a hysterectomy is optional if the cells appear benign
- Benign-appearing glandular cells do not imply recurrence after hysterectomy for an adenocarcinoma*
- The cells are probably of vaginal or paravaginal origin
- Sometimes there is an unreported history of supracervical hysterectomy

* Tambouret *et al.* Acta Cytol 1998; 42: 1403.

Endometrial Cells





Endometrial Cells Over Age 45

- There is a special Bethesda System category of “Other” for endometrial cells in women aged 45 years or more
- These cells have low positive predictive value for endometrial hyperplasia or malignancy
- Biopsy follow-up is only recommended for post-menopausal or symptomatic women*

*Fadare et al. Adv Anat Pathol 2005; 12: 274.

Bathesda Categories

- The classification of glandular abnormalities is very complex:
- Atypical glandular cells (AGC)
  - Multiple sub-categories
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma
  - Multiple sub-categories

- “Reversing the order” makes the system easier to understand
  - Once you recognize malignancy, “atypical” is more meaningful

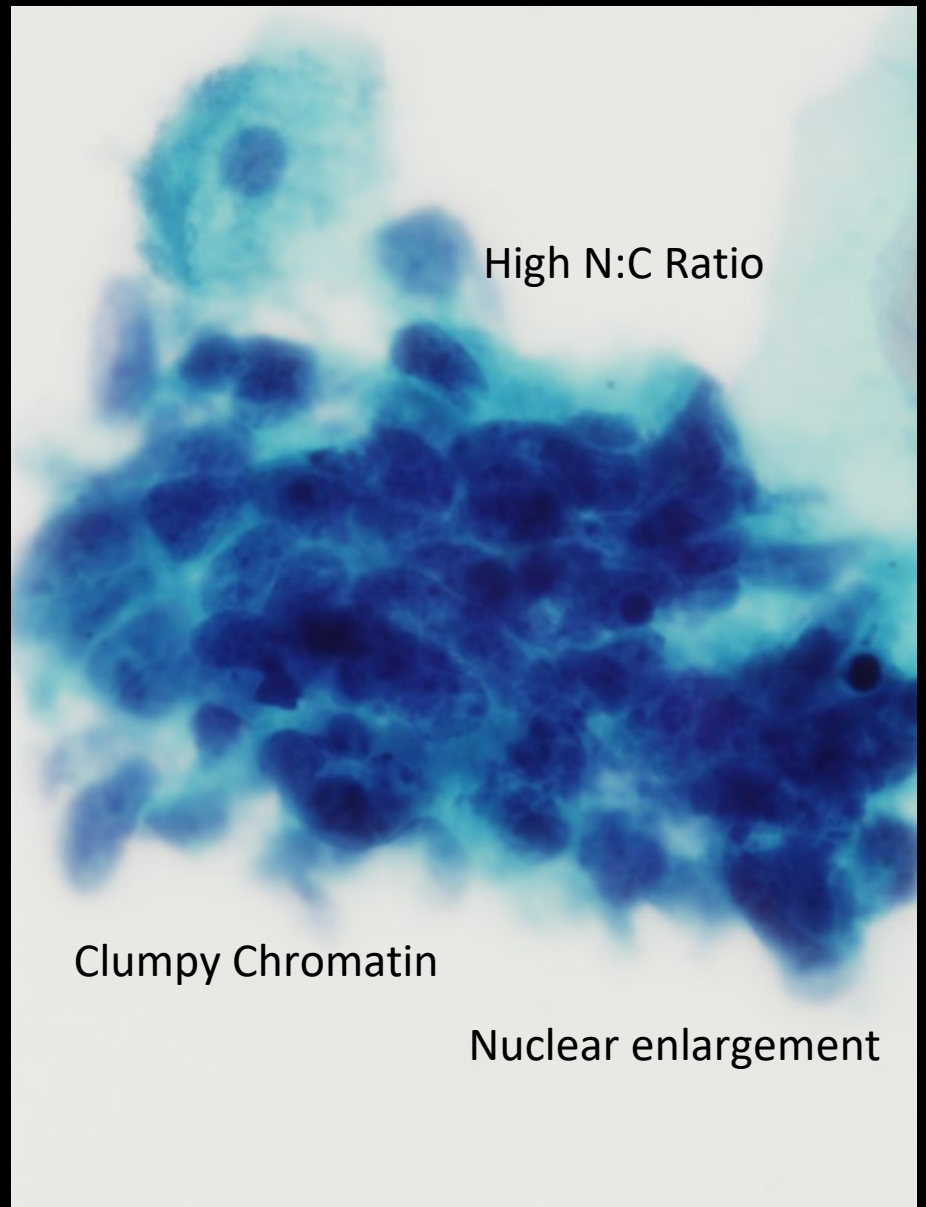
Adenocarcinoma

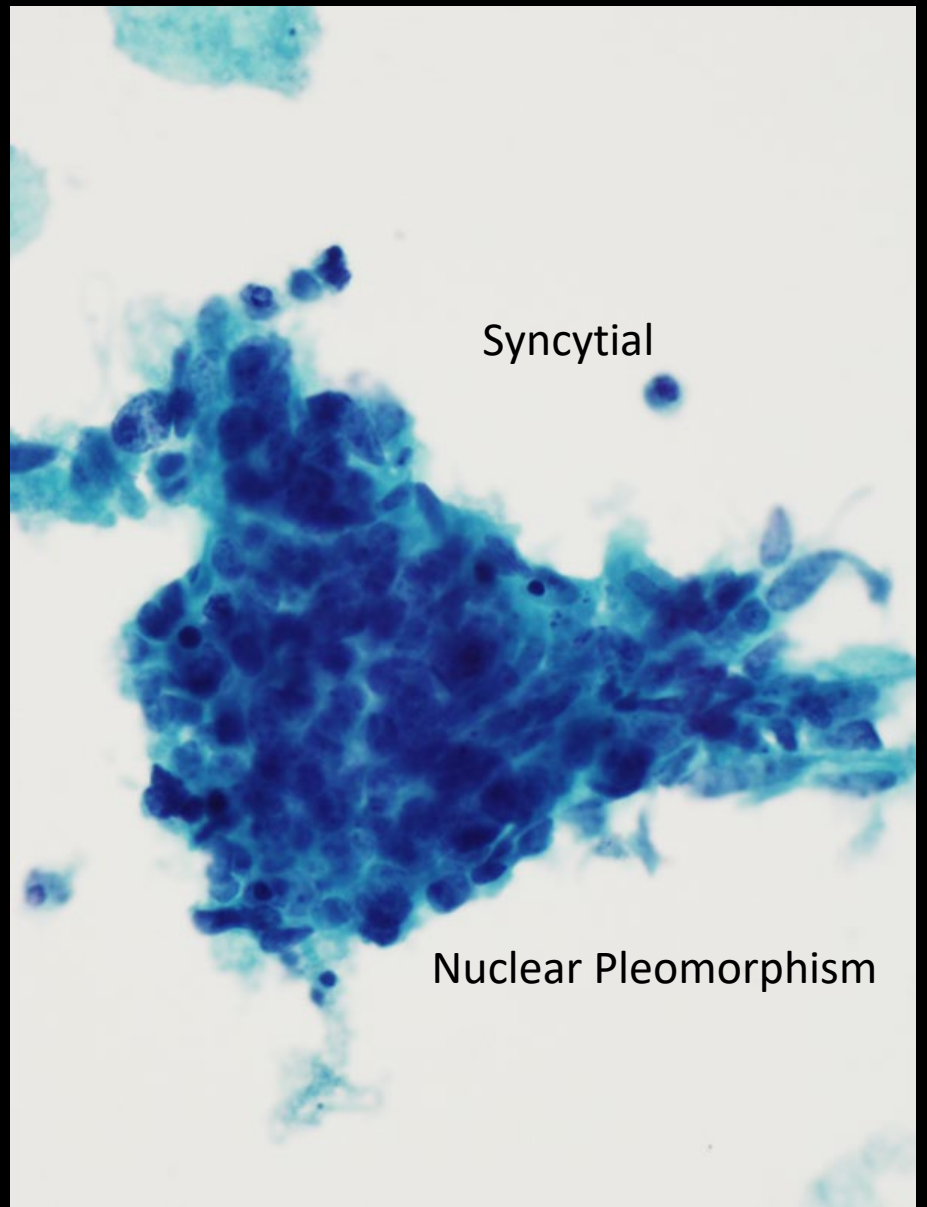
HOUSTON Methodist
LEADING MEDICINE

Adenocarcinoma

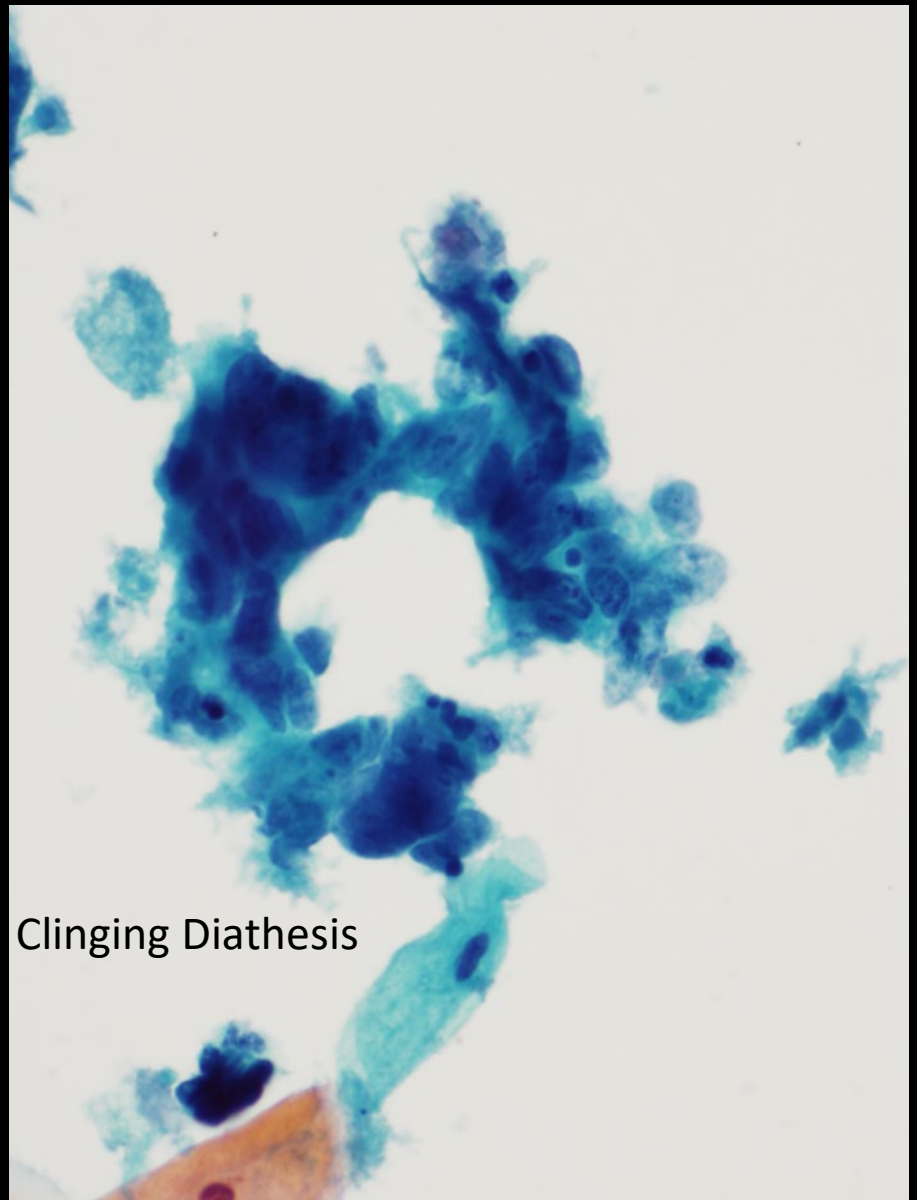
- Adenocarcinoma:
  - Endocervical
  - Endometrial
  - Extra-uterine
  - Not otherwise specified (NOS)

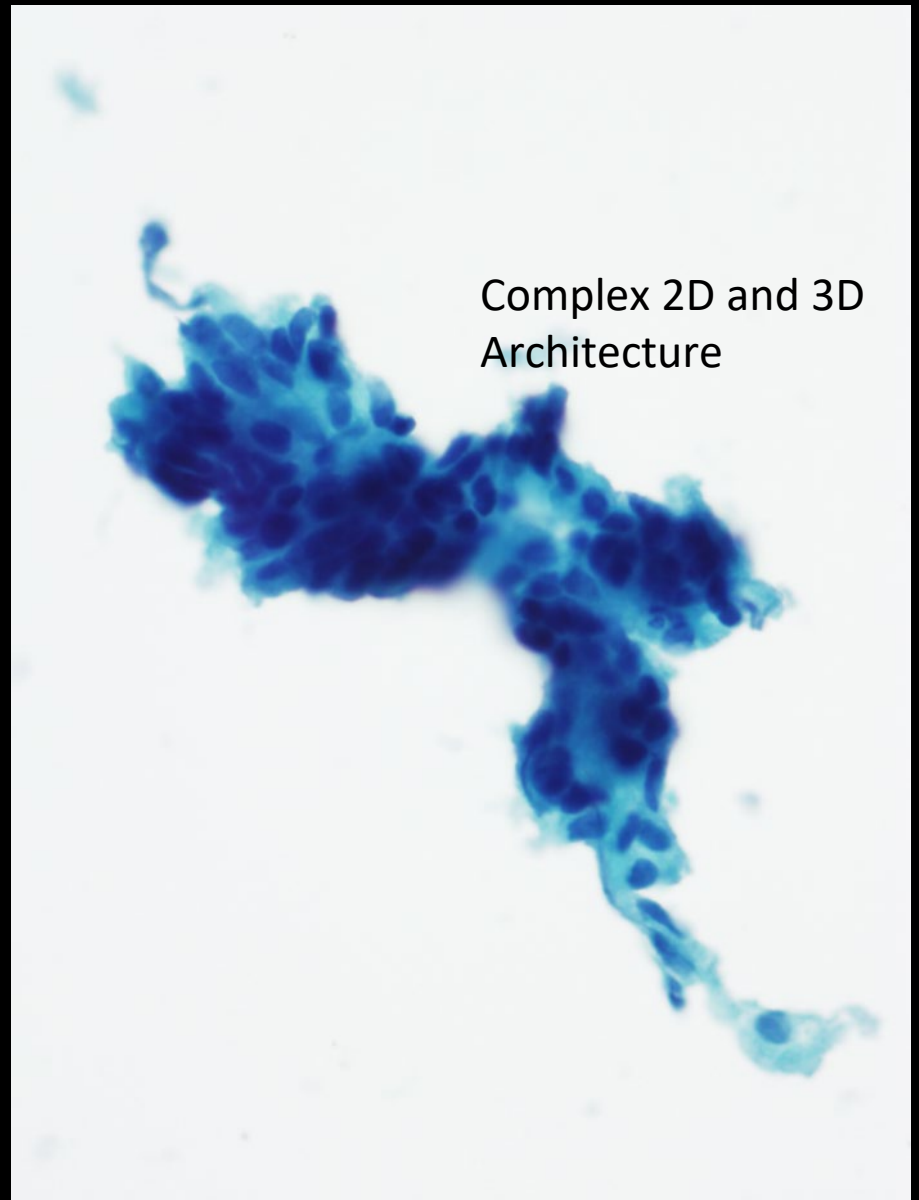
Endocervical Adenocarcinoma



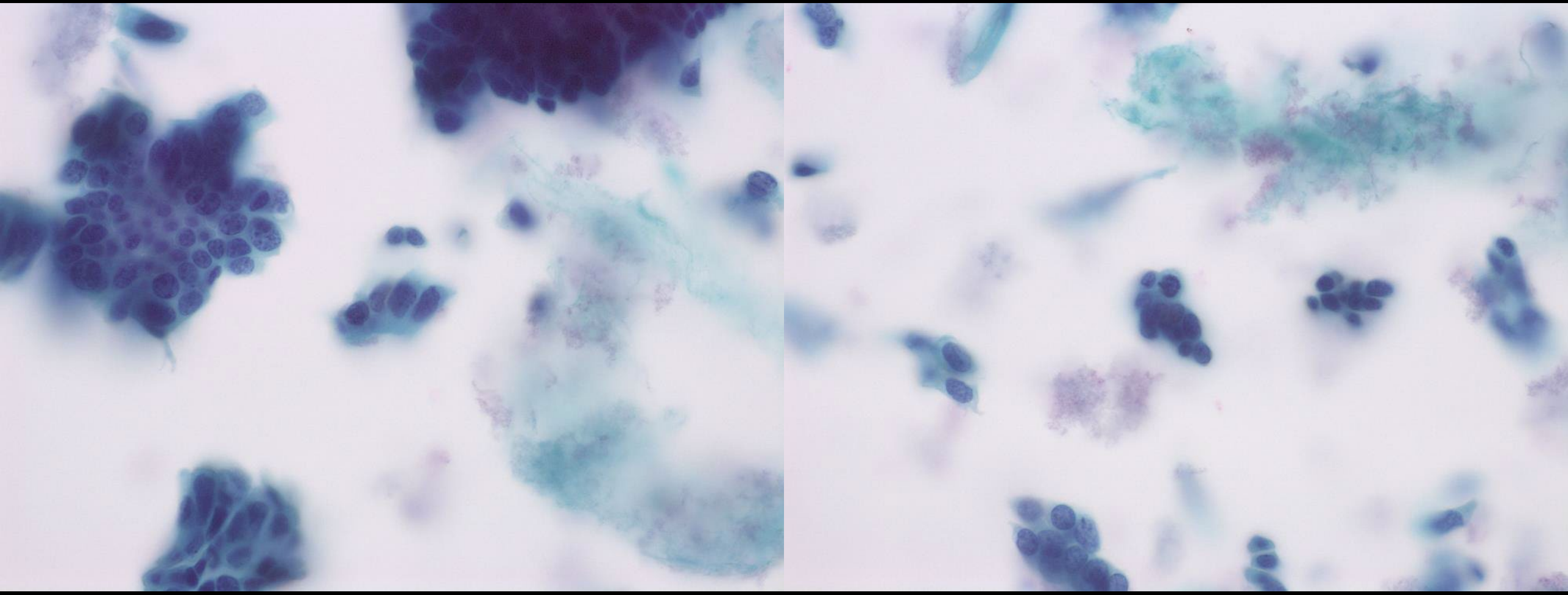


Endocervical Adenocarcinoma





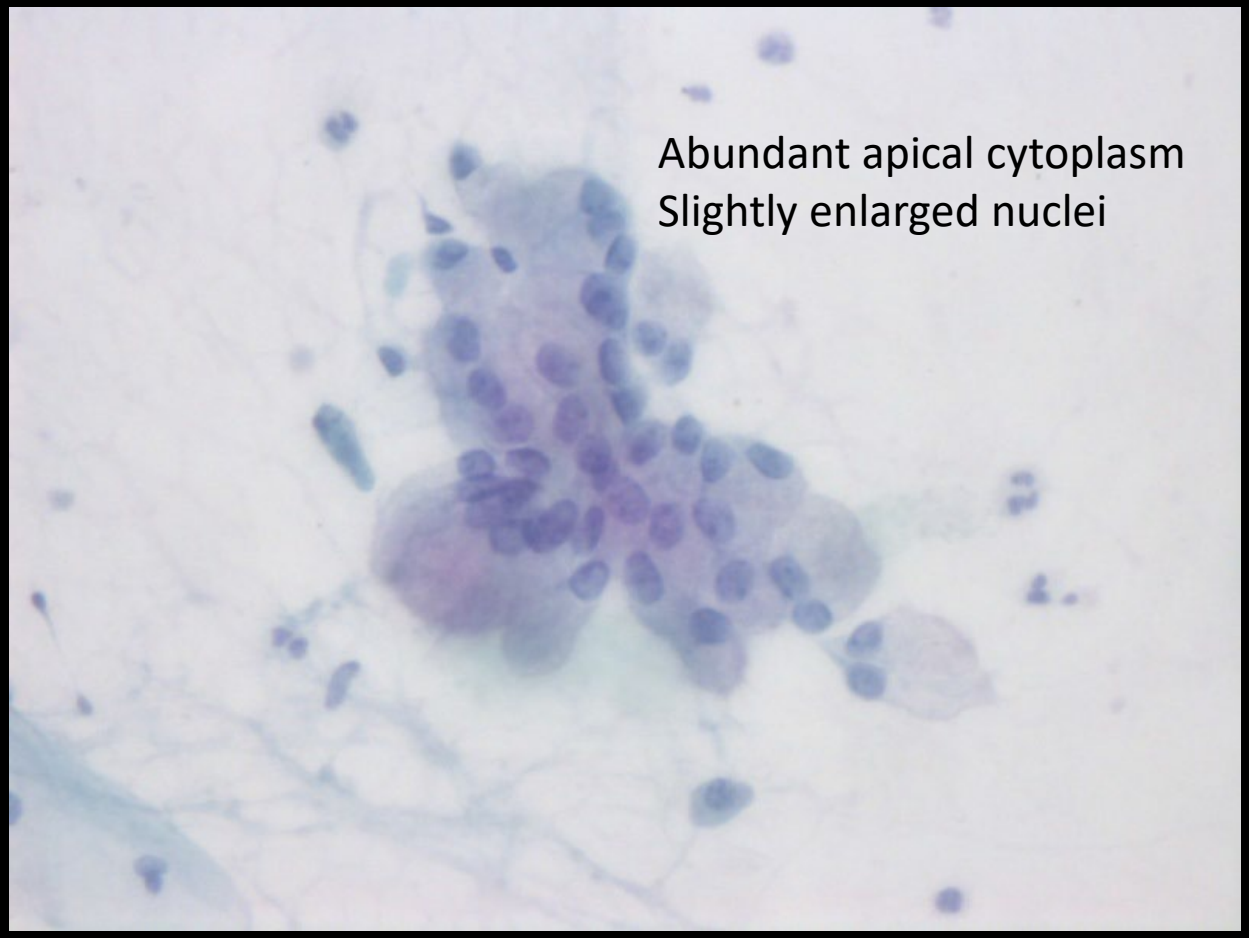
Endocervical Adenocarcinoma Diathesis



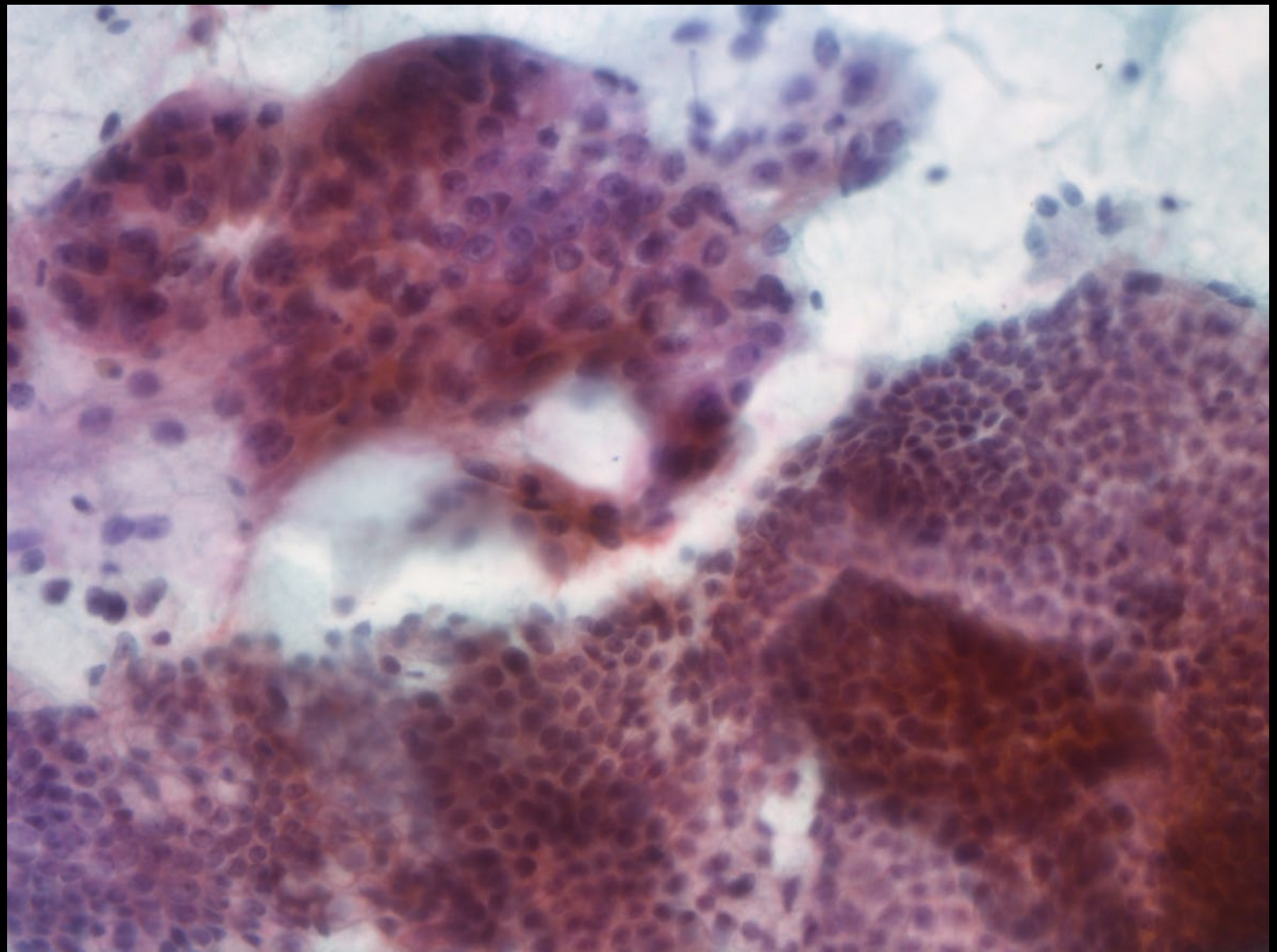
Endocervical Adenocarcinoma

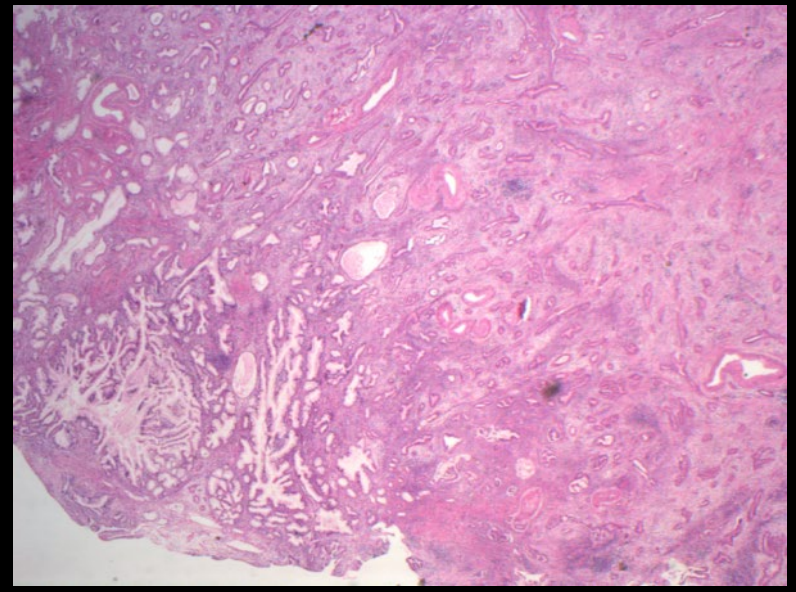
- Abundant abnormal cells, typically columnar
- Enlarged, pleomorphic nuclei with irregular chromatin, parachromatin clearing, and nuclear membrane irregularities
- Single cells, 2D sheets, 3D clusters, and syncytial aggregates are commonly seen
- Macronuclei may be present
- Cytoplasm is usually finely vacuolated
- Tumor diathesis may be present
- Abnormal squamous cells may be present

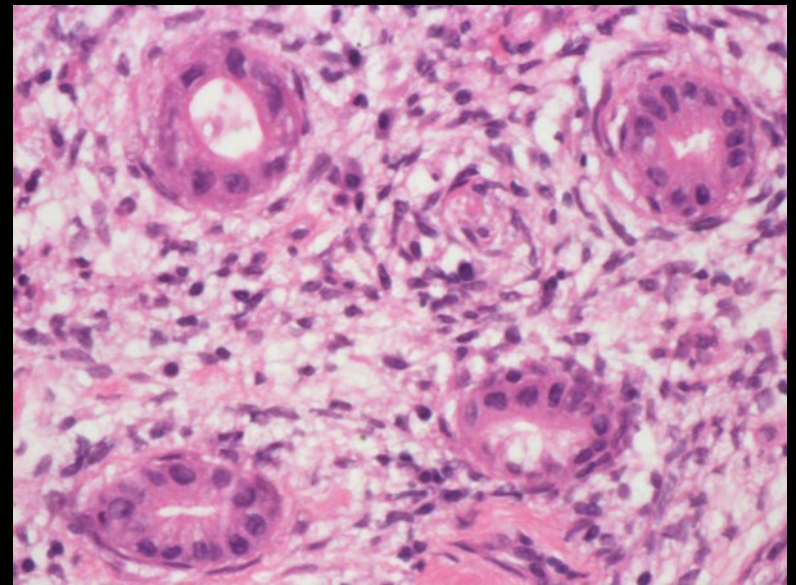
Gastric-Type Endocervical Adenocarcinoma



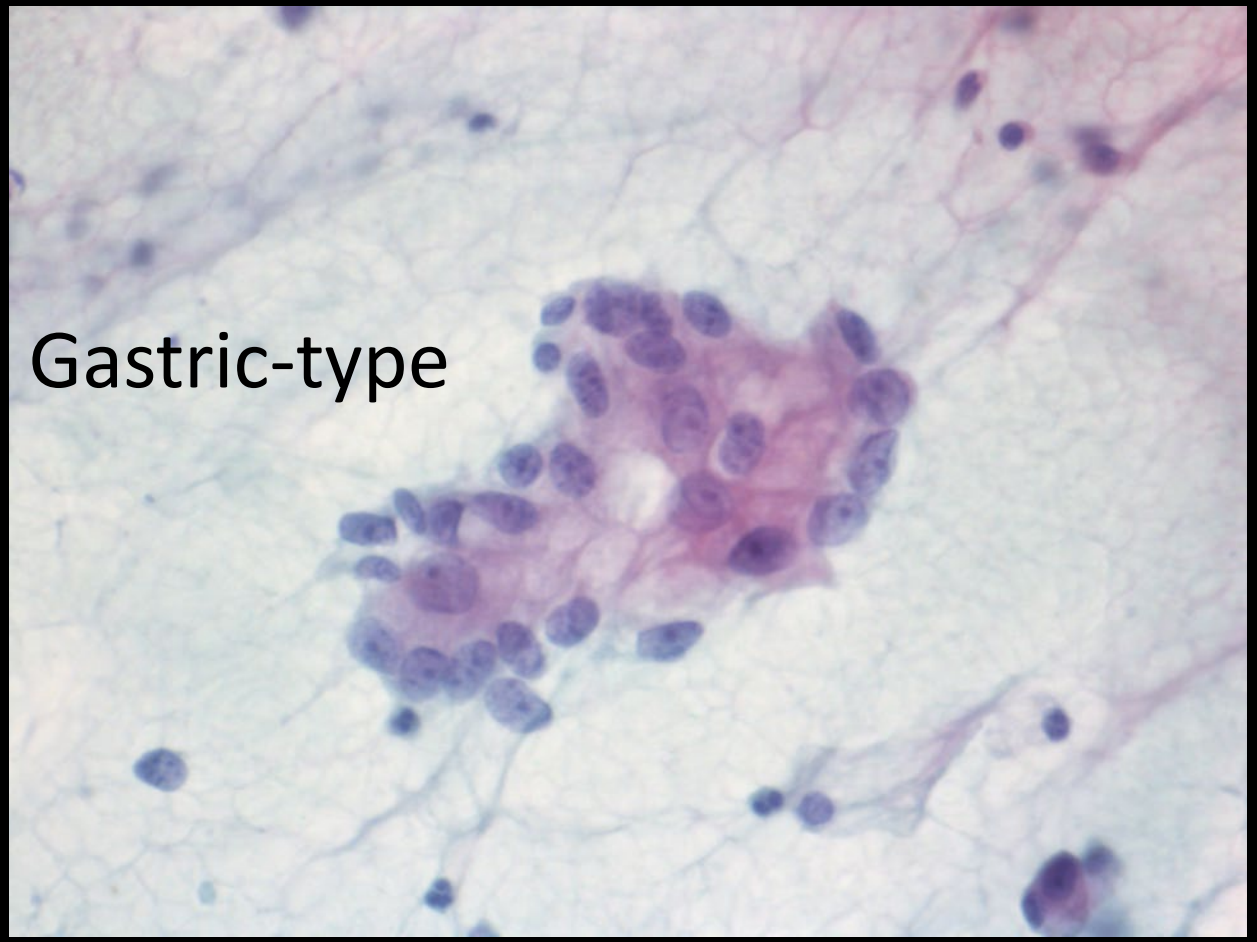
Endocervical Gastric-Type Adenocarcinoma







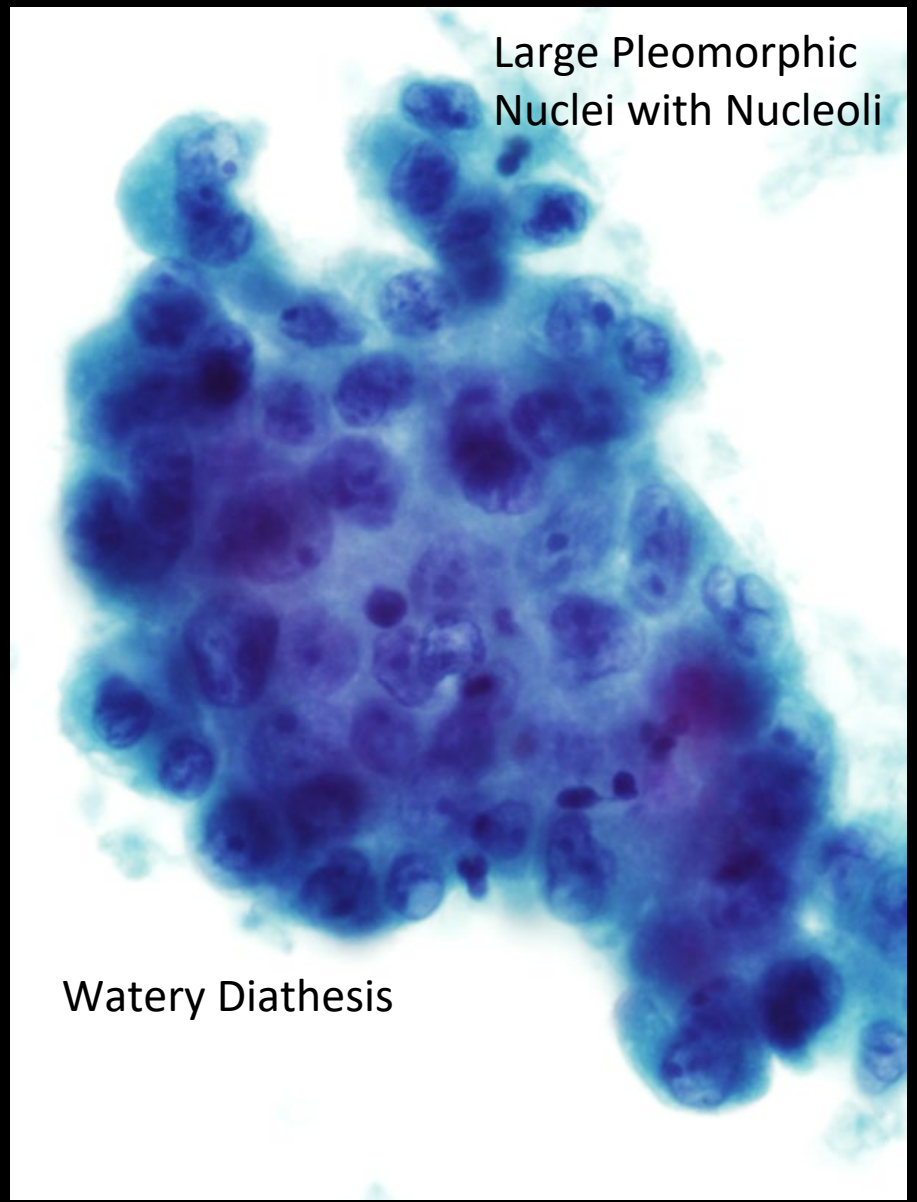
Comparison With HPV-Driven AIS

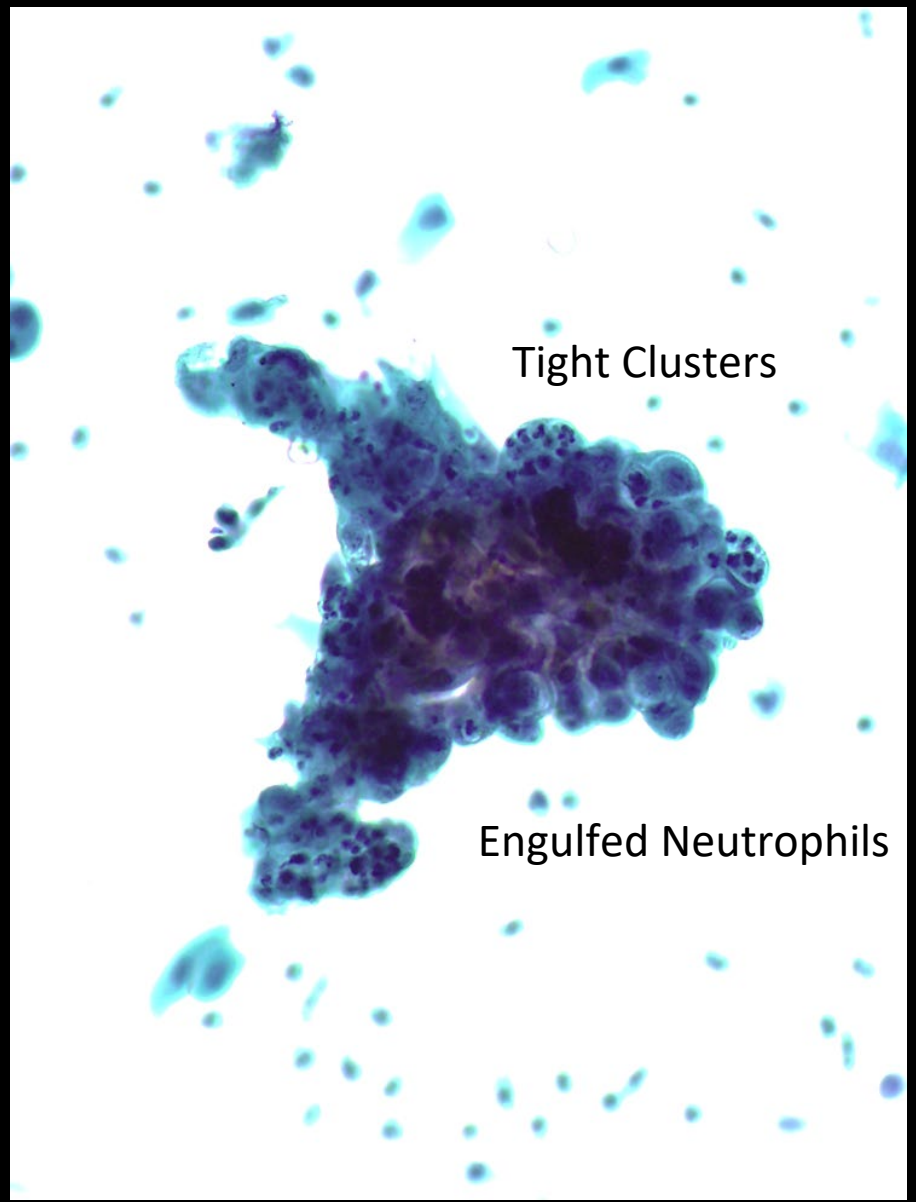


Gastric-Type Neoplasia

- Arises from gastric (or pyloric) metaplasia that is usually not discernable by H&E (yellow-tinged mucus may be seen on Pap tests)
- HIK 1083 stain can identify as a research tool
- Spectrum includes lobular endocervical glandular hyperplasia (LEGH) and adenoma malignum/minimal deviation adenocarcinoma as well as high-grade adenocarcinoma
- This process is not HPV-driven; negative for p16 and HR-HPV testing
- *STK11* mutations and Peutz-Jeghers association
- Significant minority of adenocarcinomas, up to 25% in Japan

Endometrial Adenocarcinoma

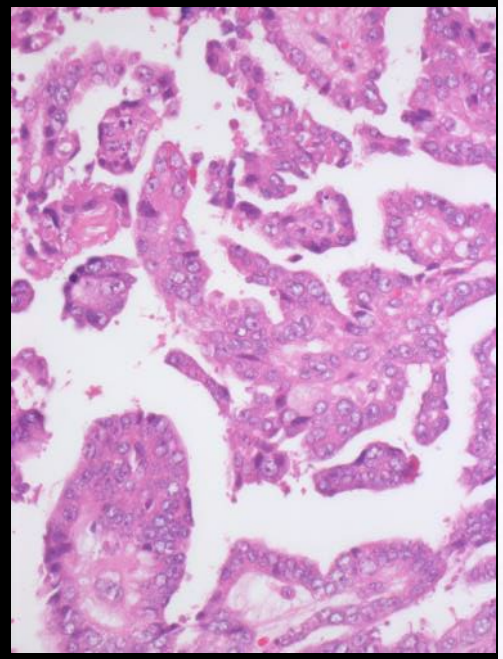


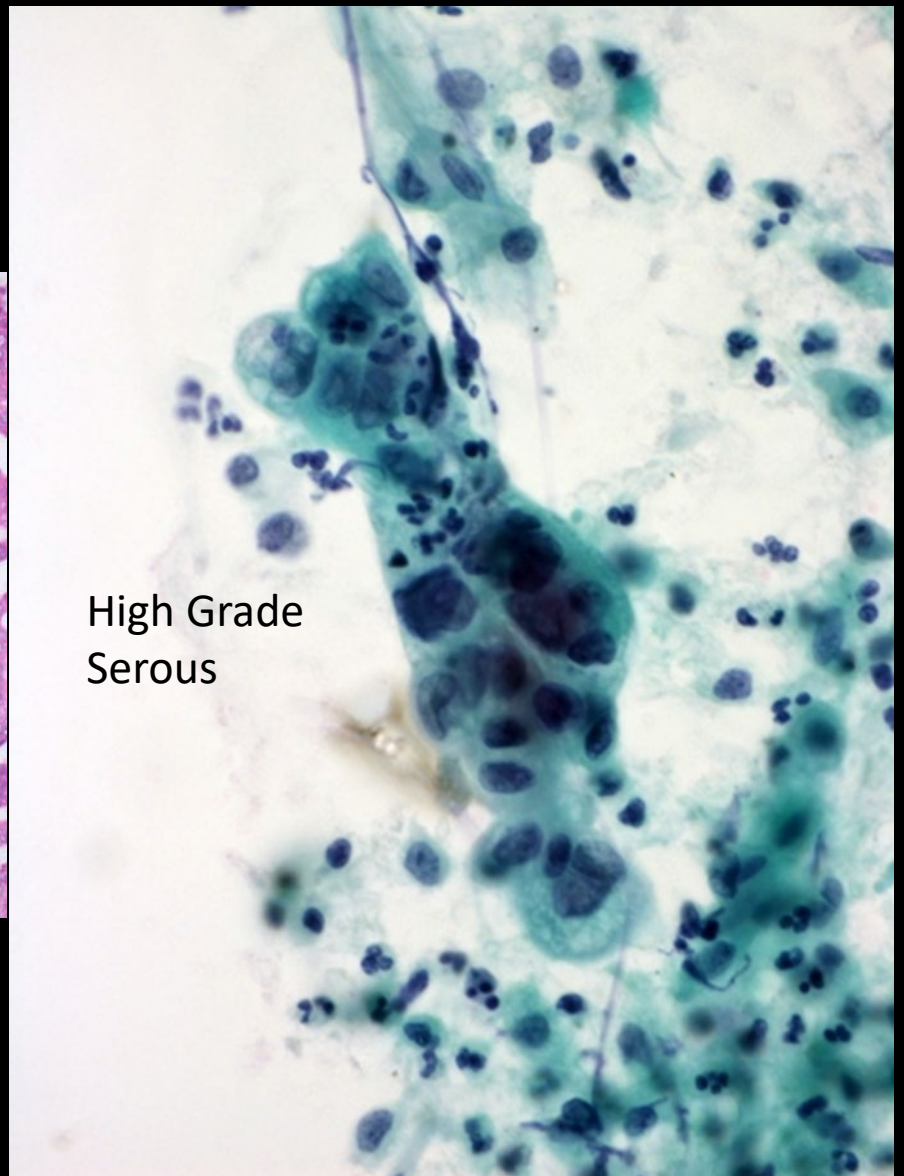


Endometrial Adenocarcinoma

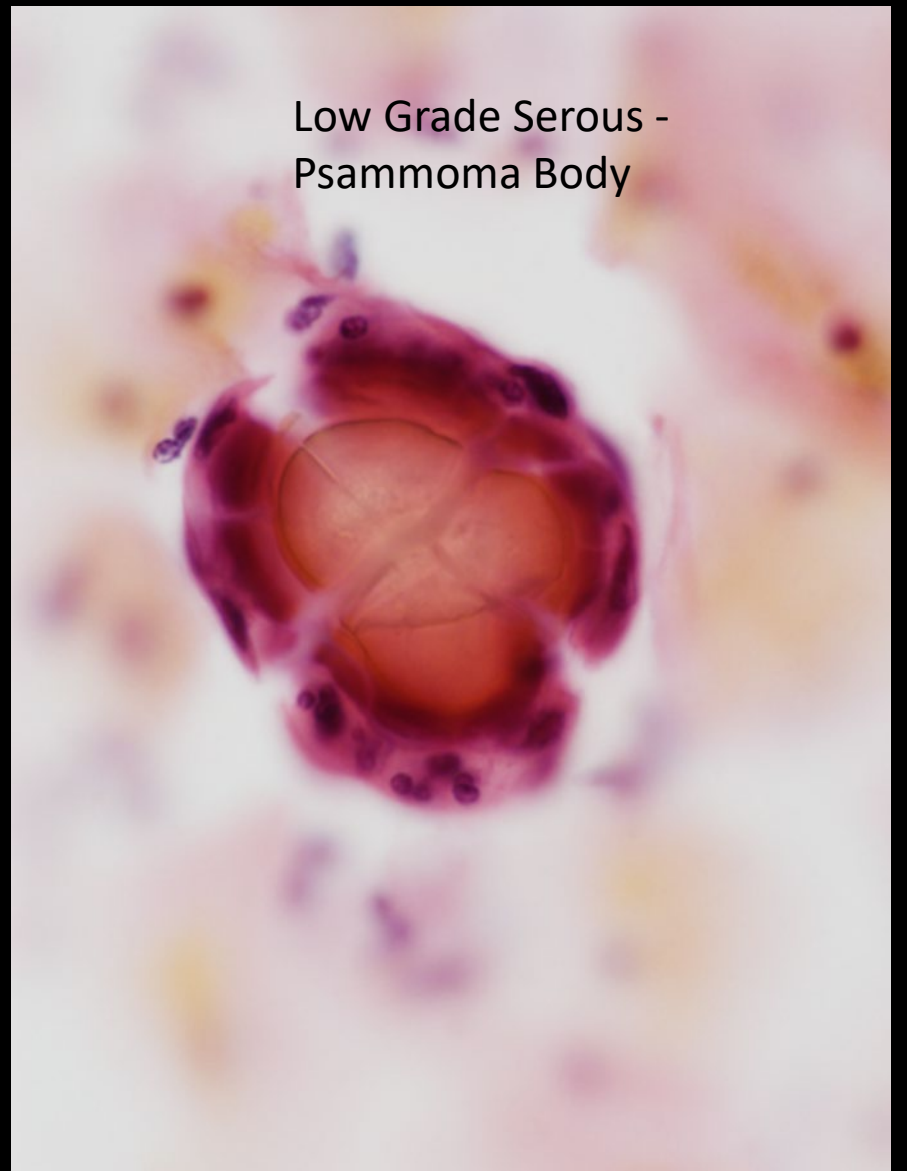
- Cells occur singly or in small, tight clusters
- Nuclear enlargement (varies by grade)
- Variation in nuclear size and loss of polarity
- Nuclear hyperchromasia with irregular chromatin and parachromatin clearing
- Nucleoli
- Scant cytoplasm that may be vacuolated or contain engulfed neutrophils
- Watery (finely granular) diathesis may be present

Serous Carcinoma



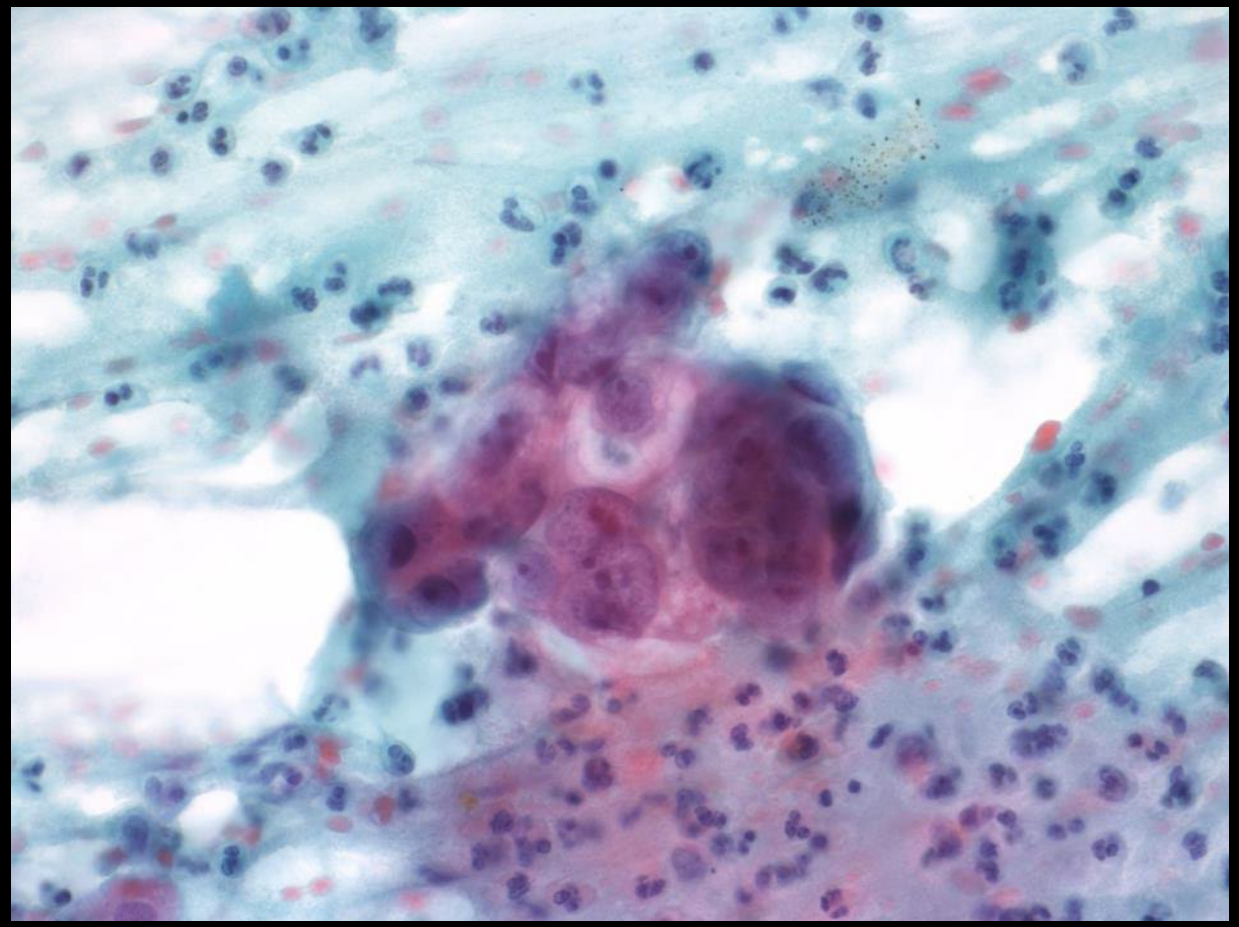


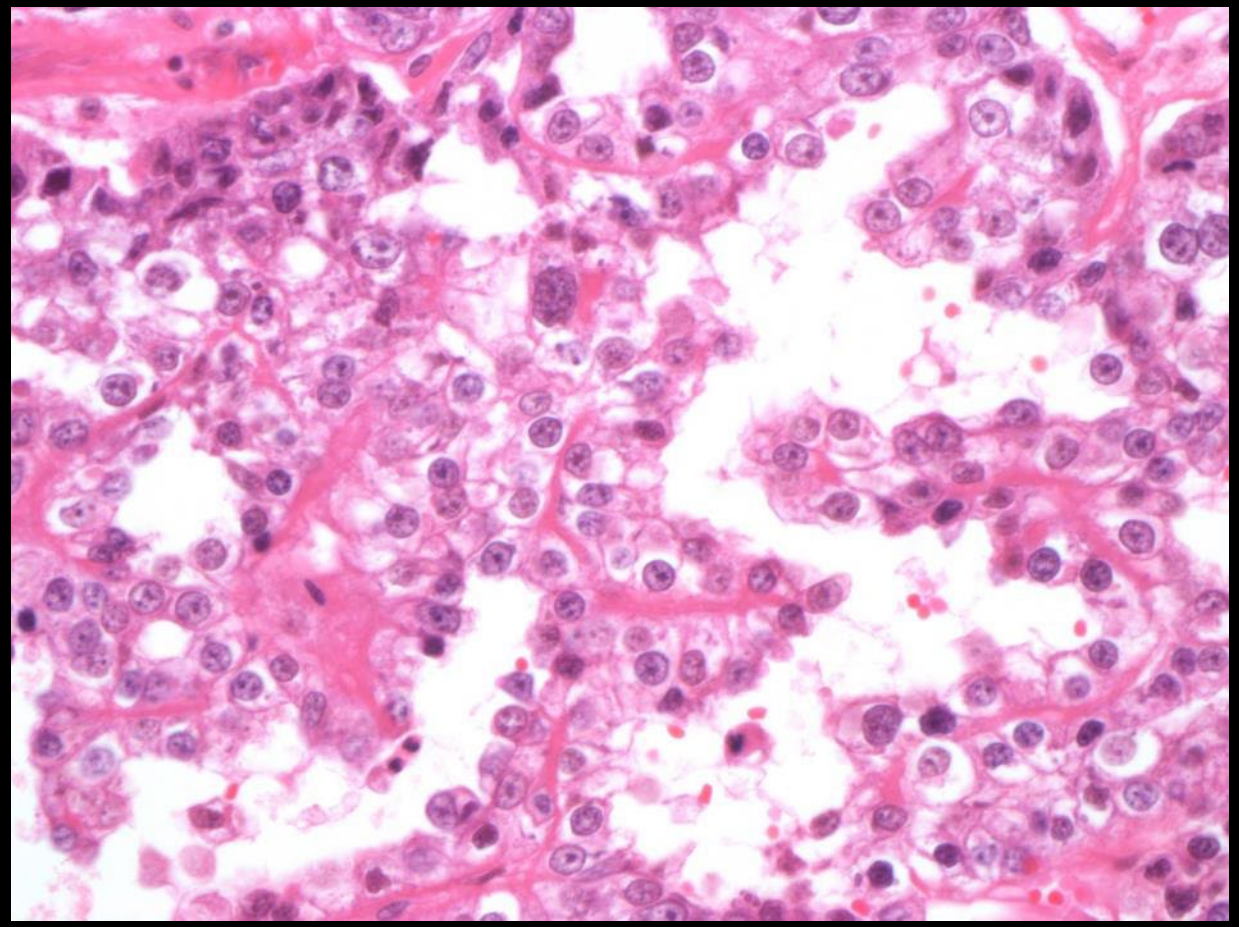
High Grade
Serous



Low Grade Serous -
Psammoma Body

Clear Cell Carcinoma





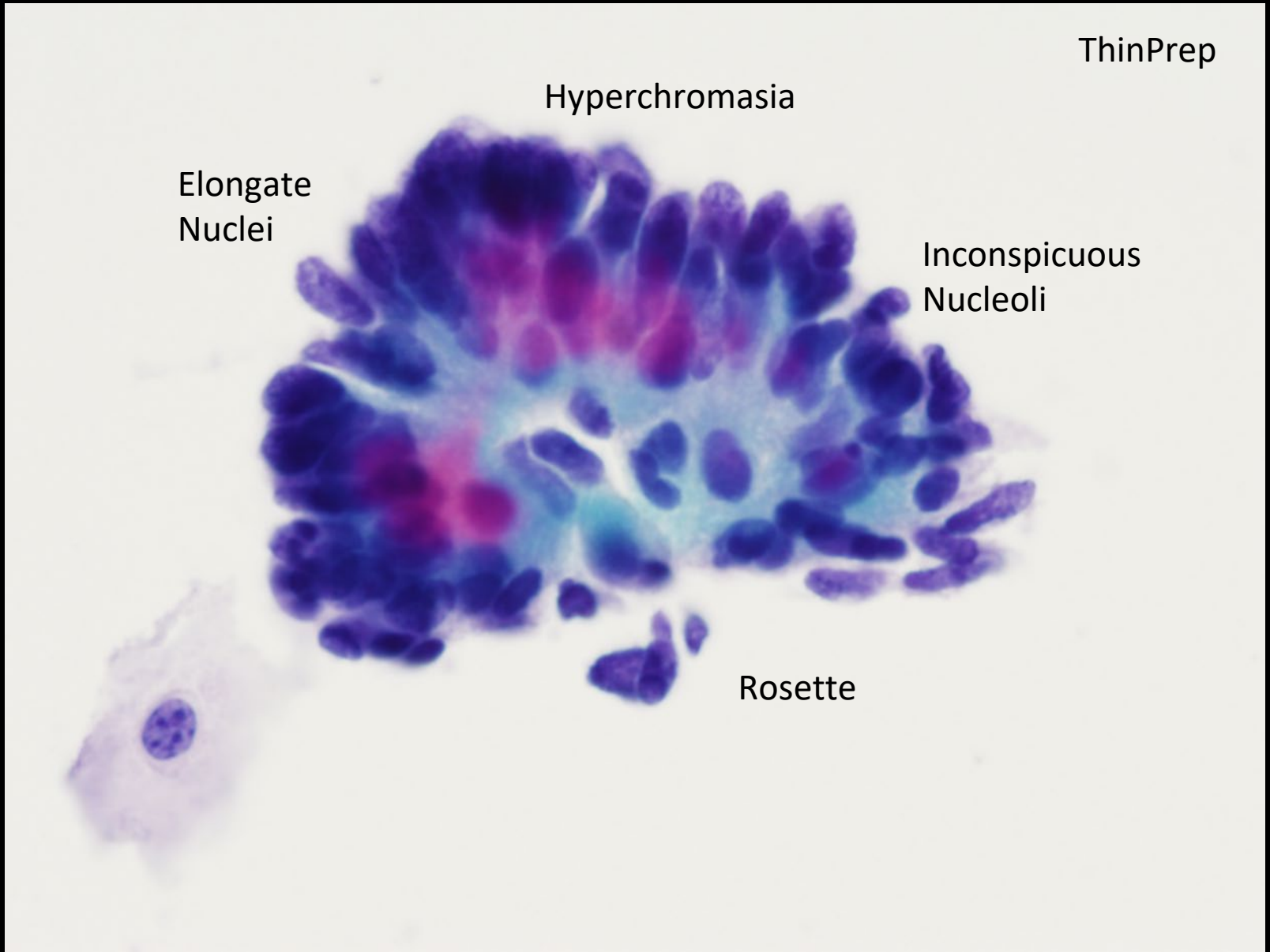
Adenocarcinoma In Situ (AIS)

HOUSTON Methodist
LEADING MEDICINE

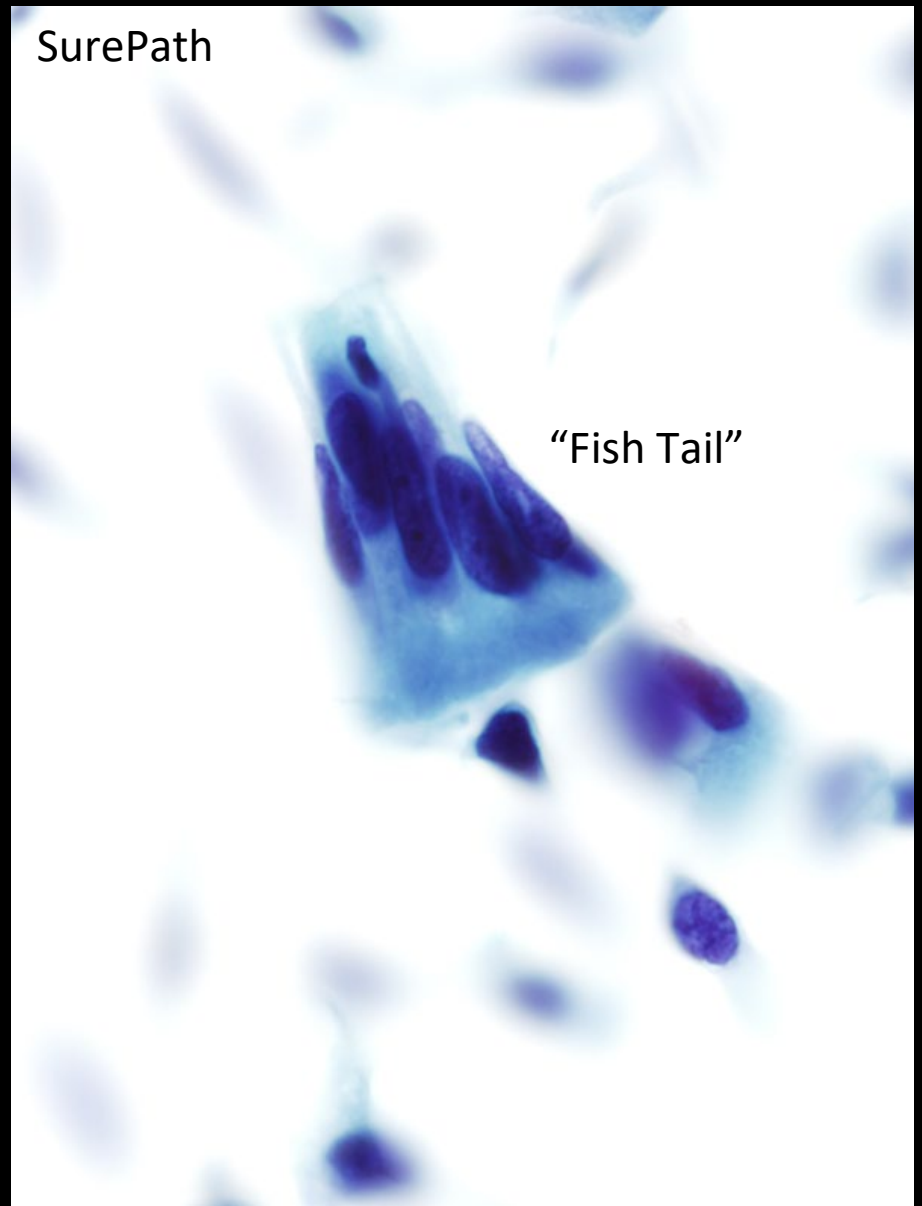
Adenocarcinoma In Situ

- Sheets, clusters, strips, or rosettes with nuclear crowding and overlap
- Feathering
- Nuclear enlargement with anisonucleosis, elongation, and stratification
- Nuclear hyperchromasia with evenly dispersed coarse chromatin
- Mitosis and apoptotic bodies
- Some cells show a definite columnar arrangement
- Inconspicuous or small nucleoli
- Increased N:C with decreased cytoplasm and mucin
- Clean background
- Abnormal squamous cells may also be present

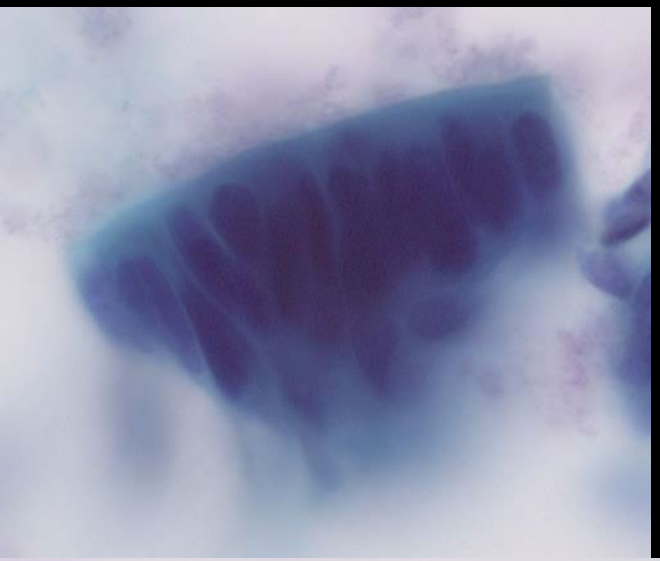
Adenocarcinoma In Situ

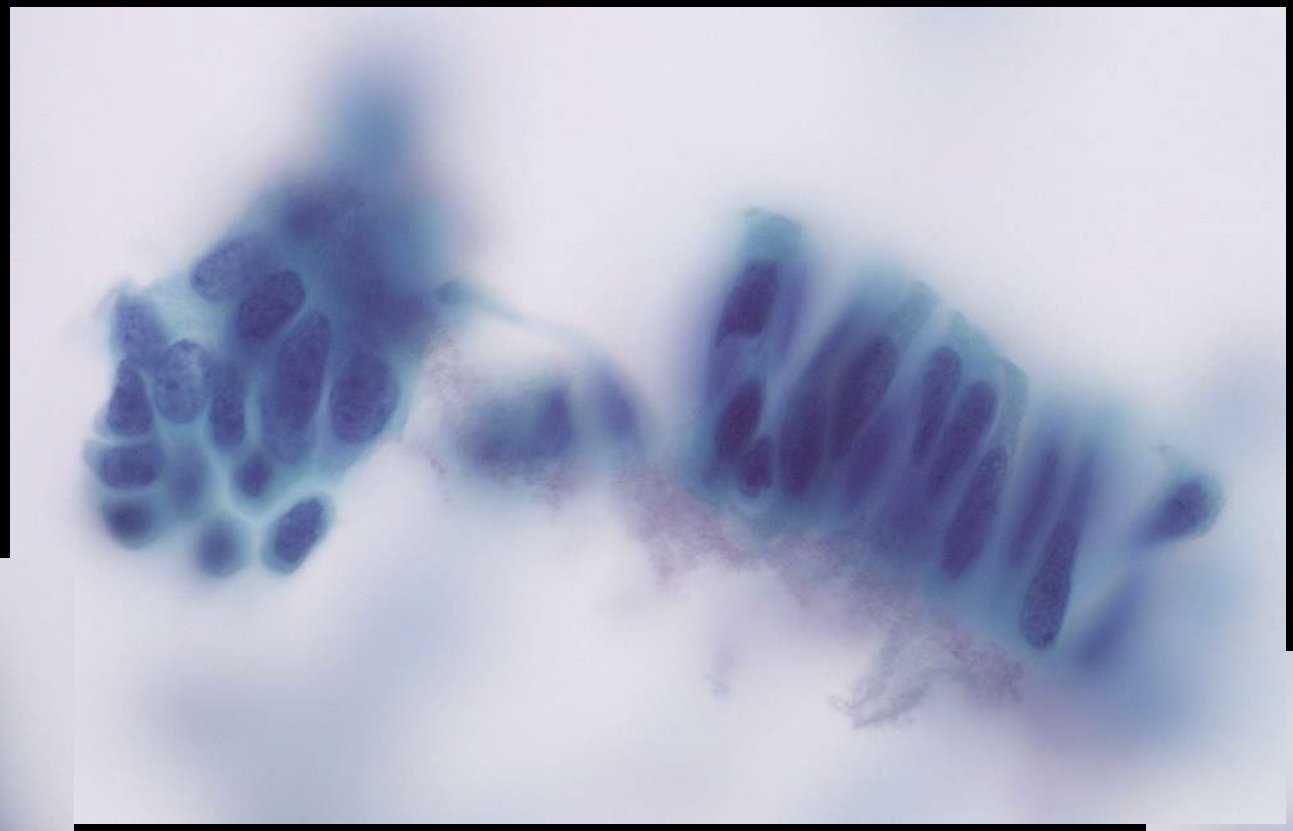


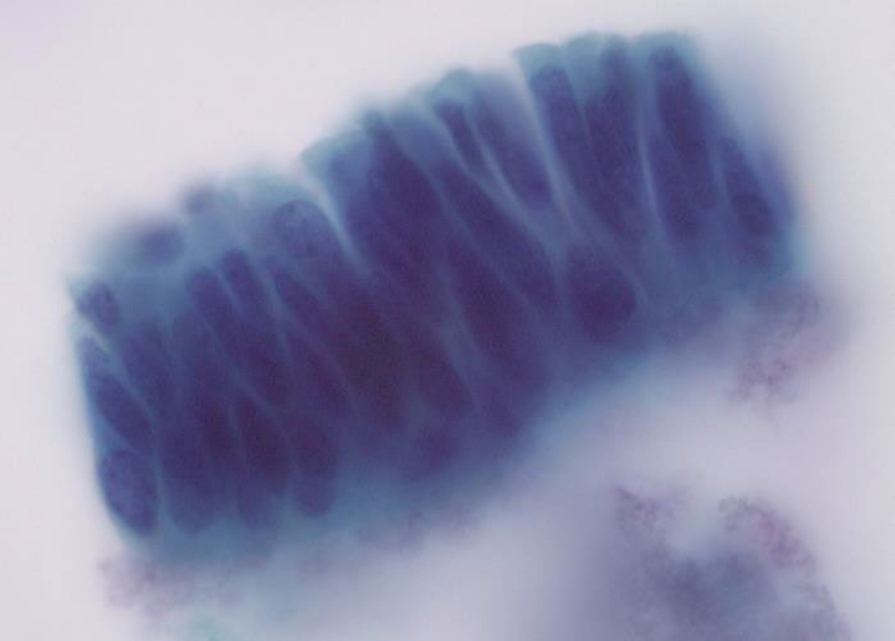
Adenocarcinoma In Situ

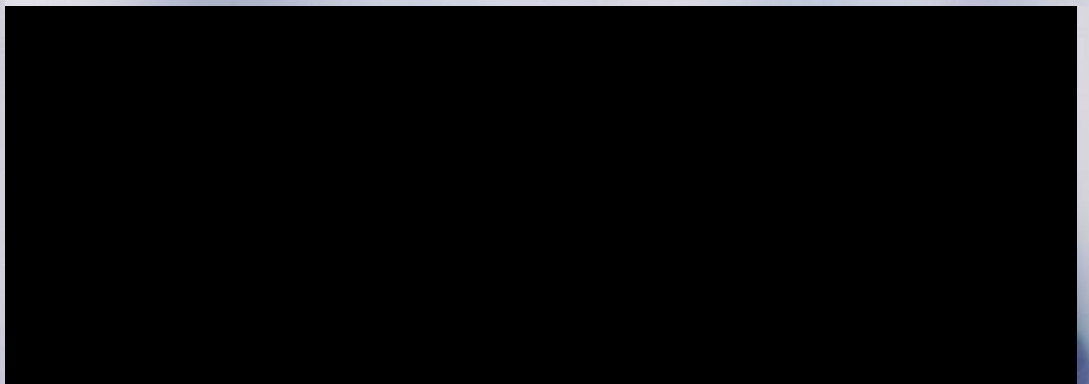


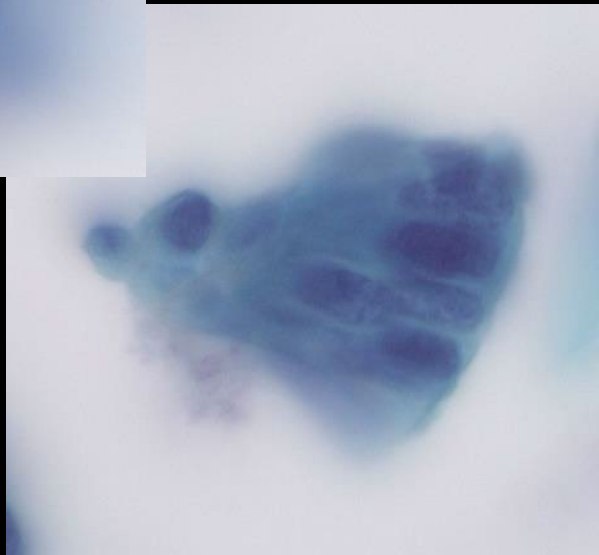
Bird Tails and Strips



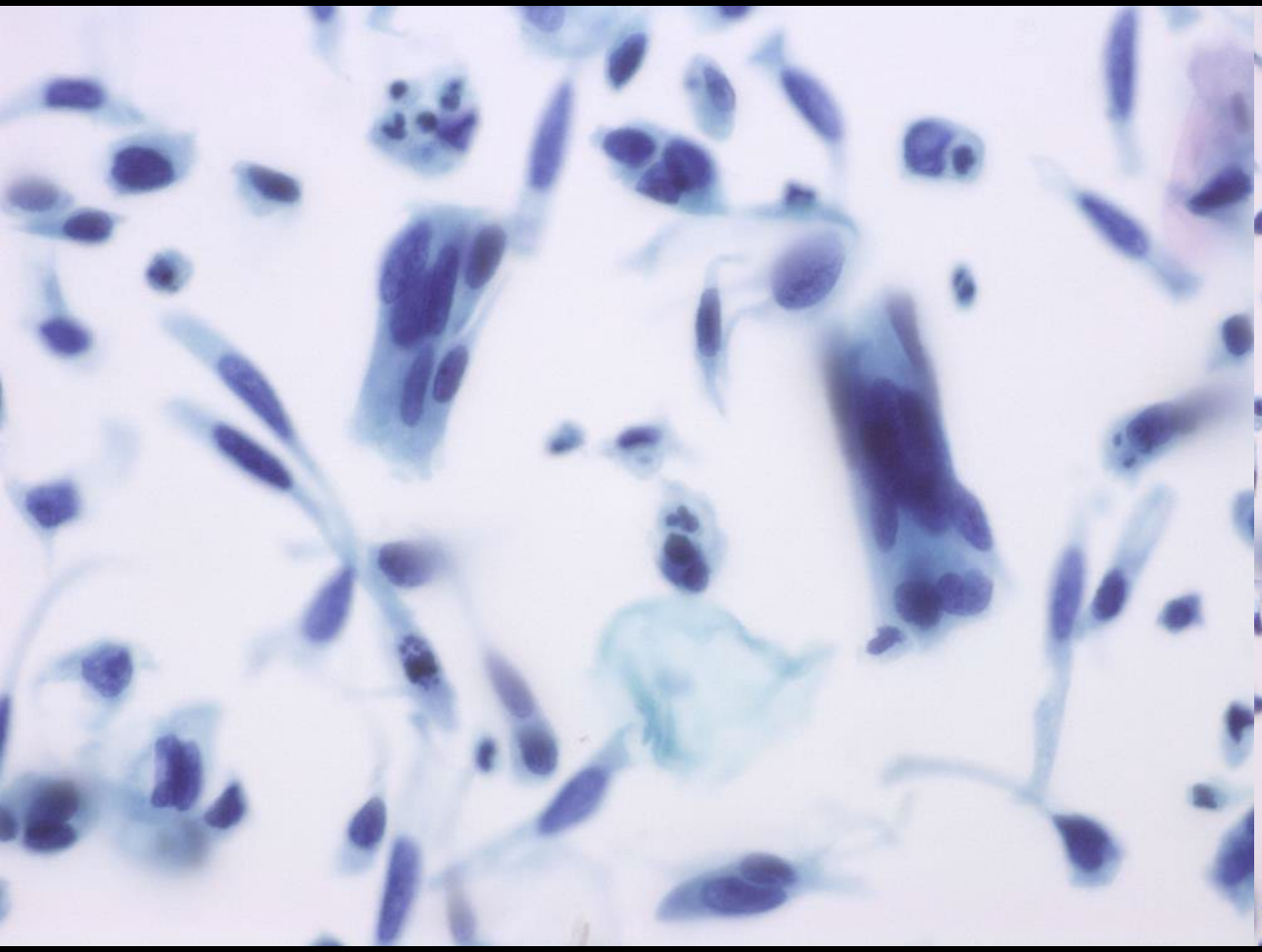


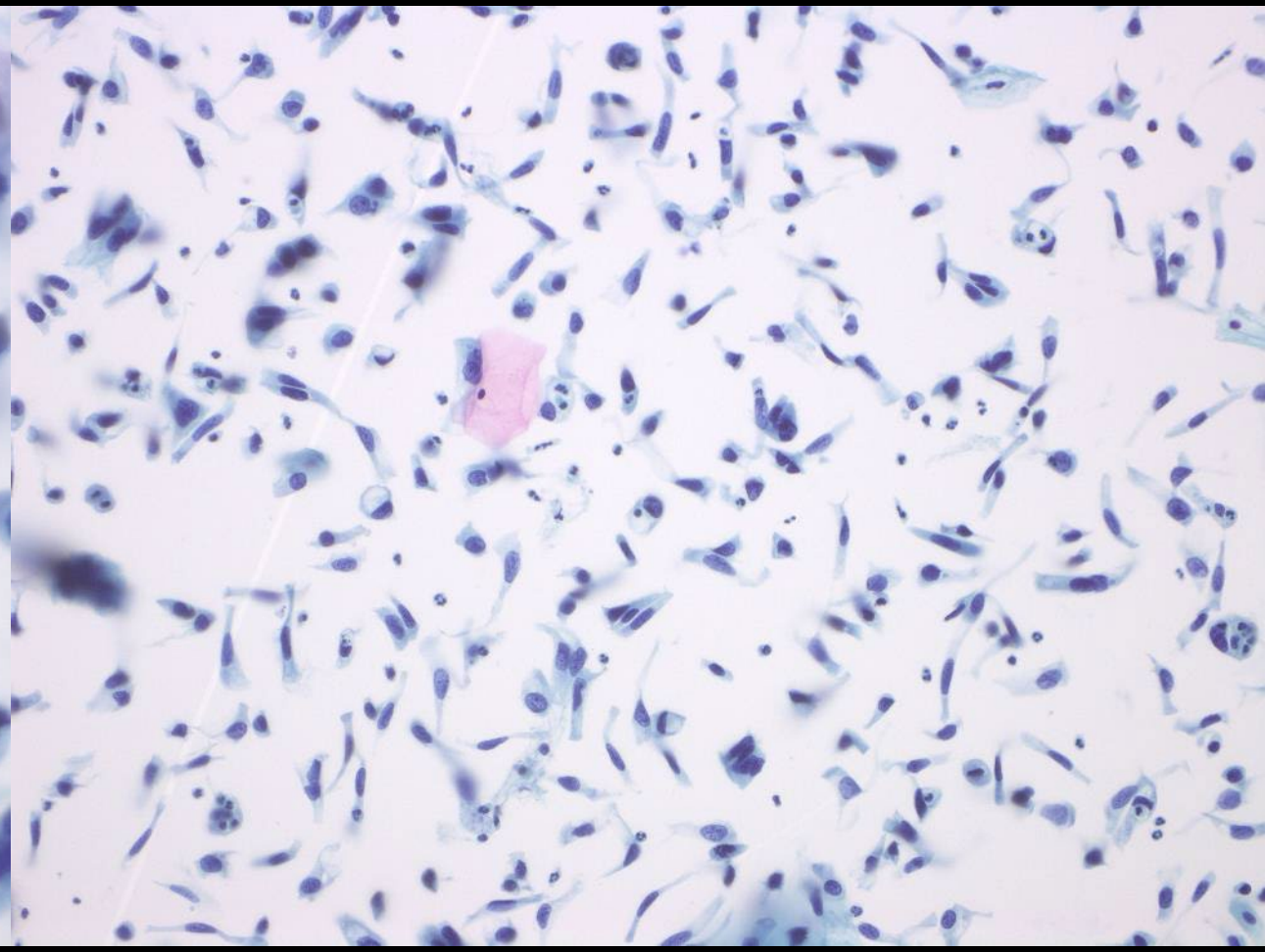




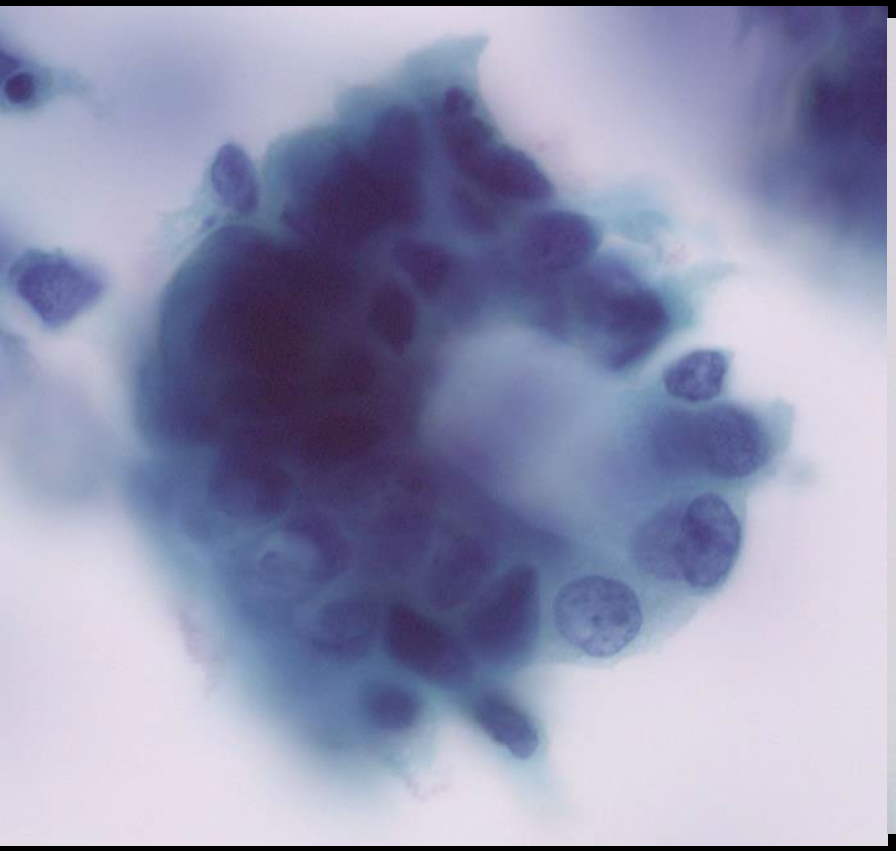


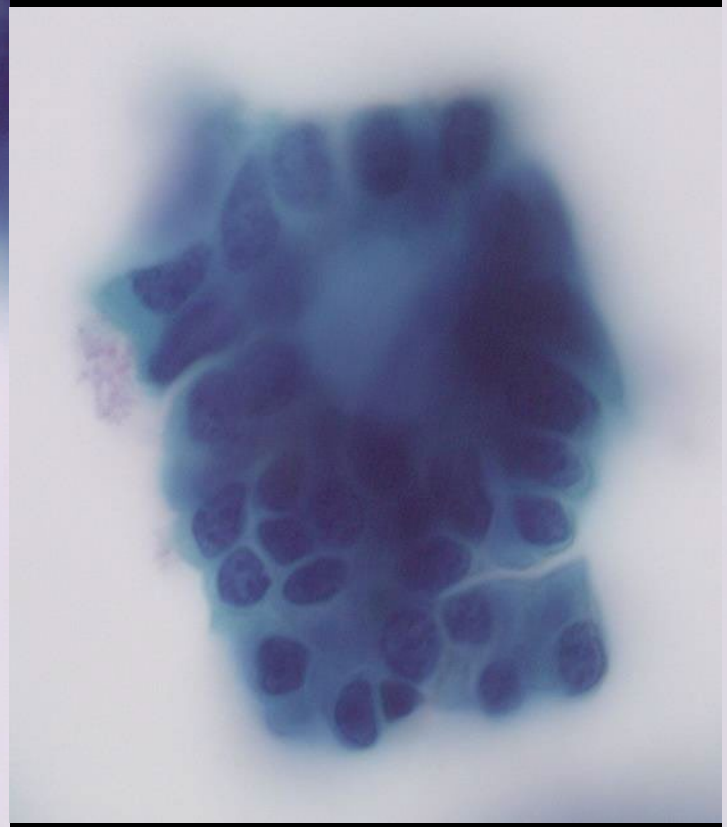
Individual Tumor Cells

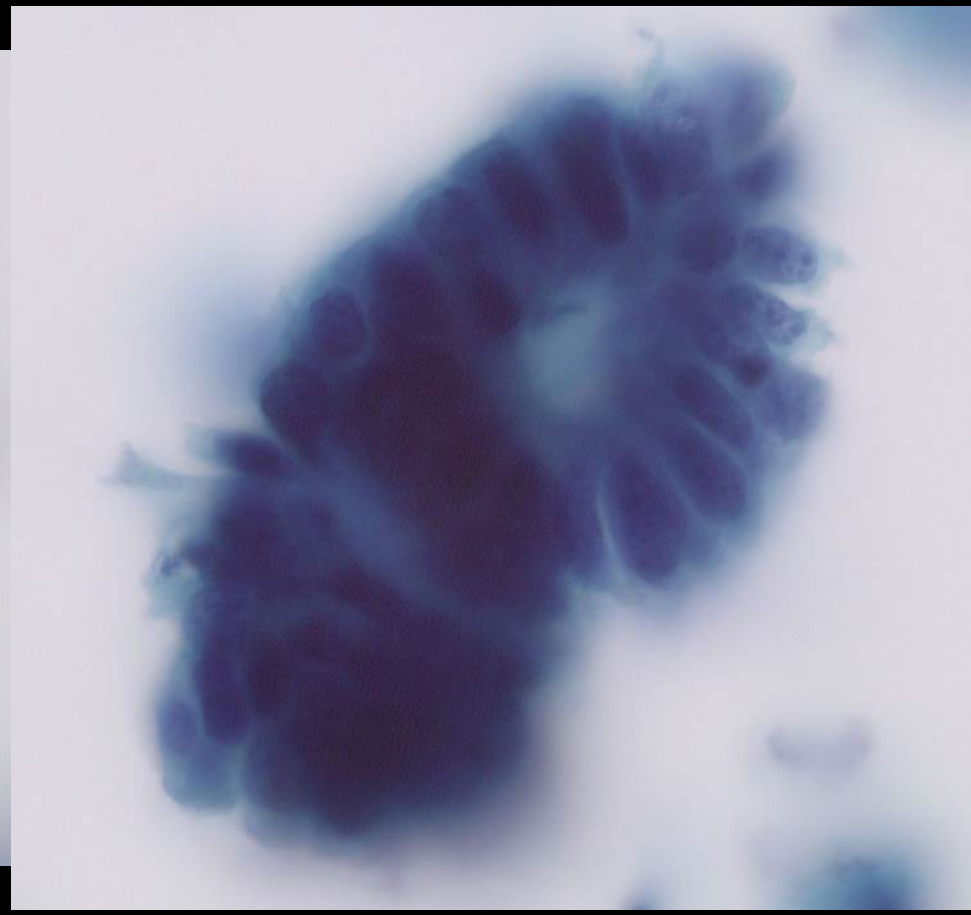




Rosettes







Atypical Glandular Cells (AGC)

HOUSTON Methodist®
LEADING MEDICINE

Atypical Glandular Cells (AGC)

- Atypical glandular cells
  - NOS (not otherwise specified)
  - Favor neoplastic
- Atypical endocervical cells
  - NOS (not otherwise specified)
  - Favor neoplastic
- Atypical endometrial cells

AGC in Liquid-Based Pap Tests

- AGC is more frequent in liquid-based Pap tests, but is still uncommon (mean 0.2% of all Paps)
- HPV testing has been proposed for triage because cervical lesions are usually HPV+, especially types 18 and 16
- However, most cancers found in follow-up for AGC are endometrial*

*Zhao *et al.* Gynecol Oncol 2009; 114: 383.

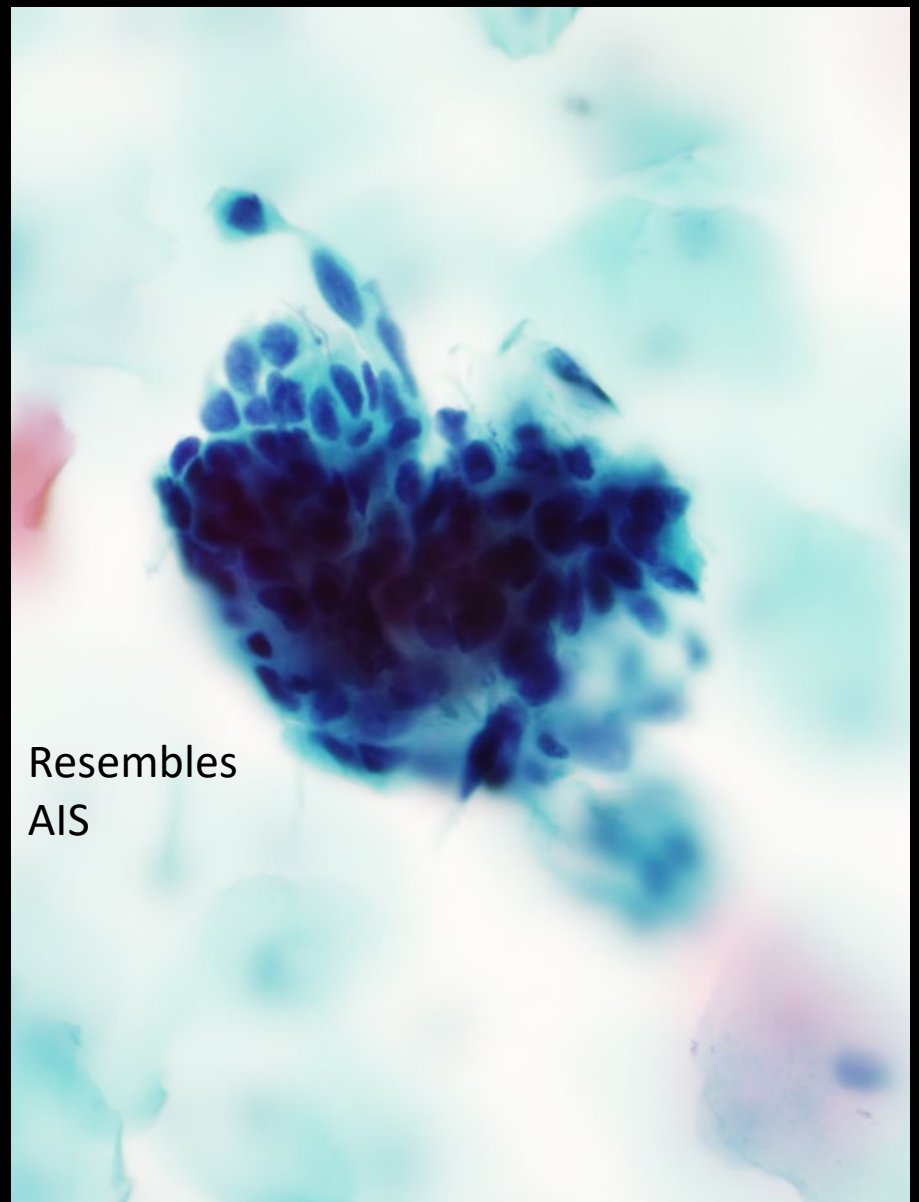
Atypical Endocervical Cells, NOS

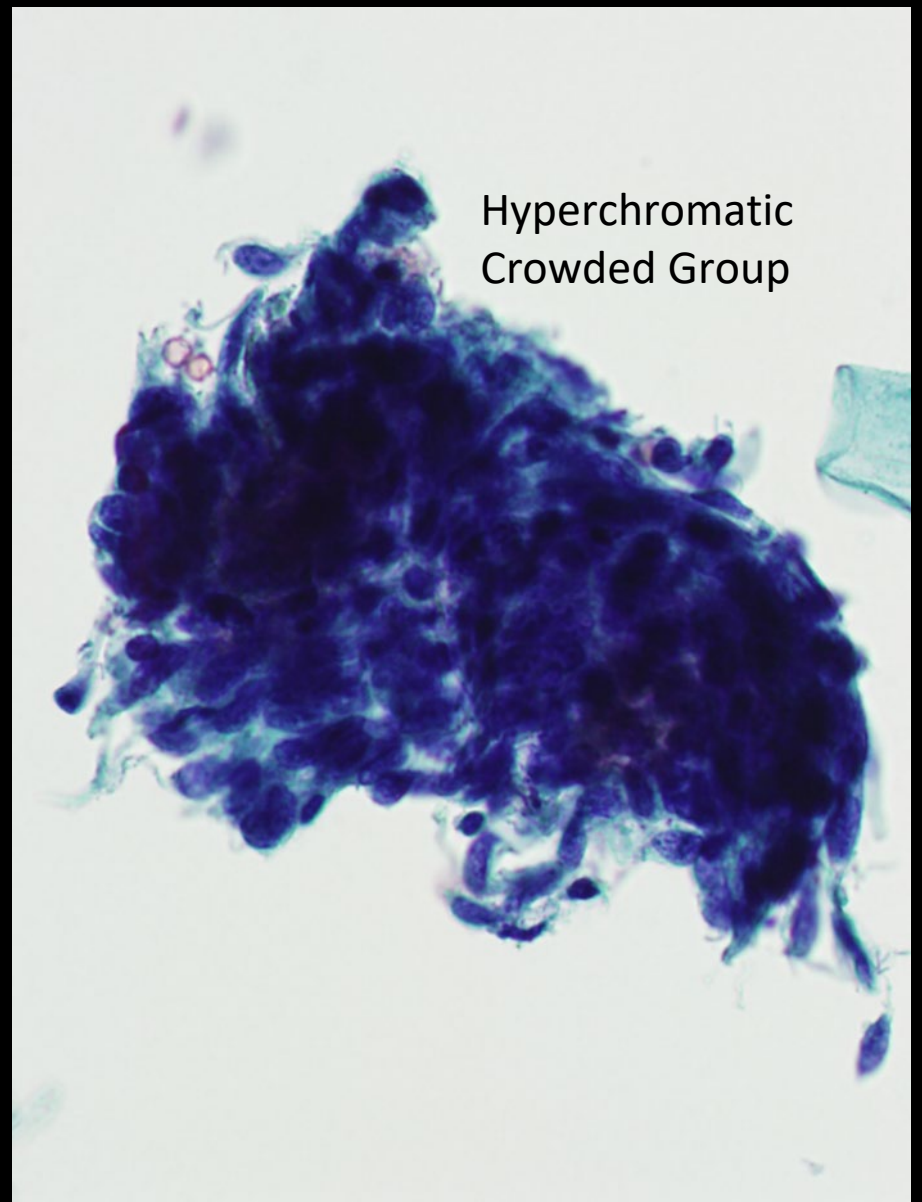
- Should be present:
  - Sheets and strips with some cell crowding/overlap and/or pseudostratification
  - Increased N:C ratios
  - Some variation in nuclear size and shape
- May or may not be present:
  - Nuclear enlargement (3-5x normal)
  - Mild hyperchromasia or chromatin irregularity
  - Occasional nucleoli
  - Rare mitoses
  - Distinct cell borders

Atypical Endocervical Cells, Favor Neoplastic

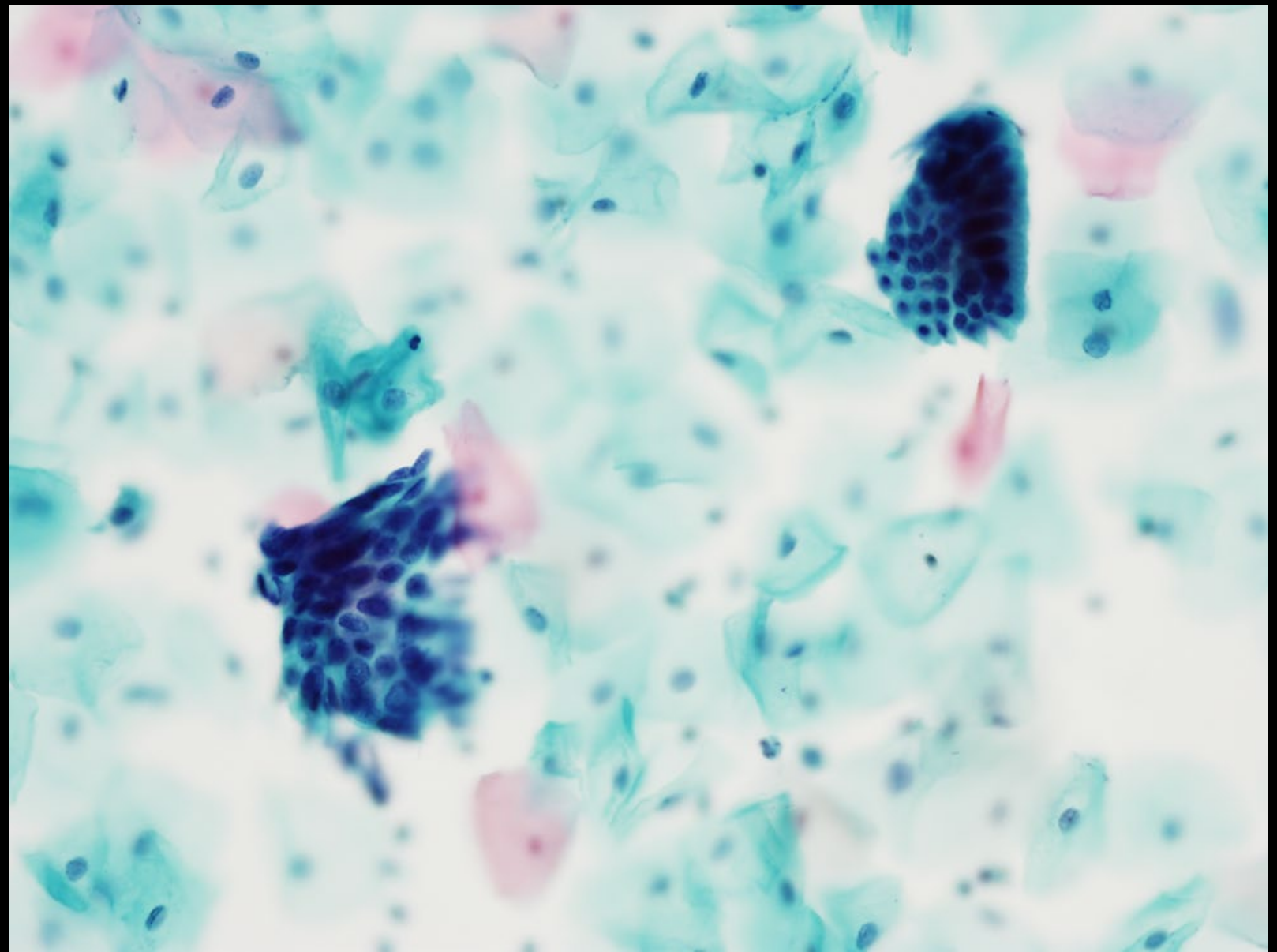
- Should be present:
  - Sheets and strips with nuclear crowding/overlap and/or pseudostratification
  - Enlarged hyperchromatic nuclei (often elongated)
  - Increased N:C ratios
- May or may not be present:
  - Rare cell groups with feathering or rosettes
  - Occasional mitoses or apoptotic debris
  - Ill-defined cell borders

Atypical Endocervical Cells





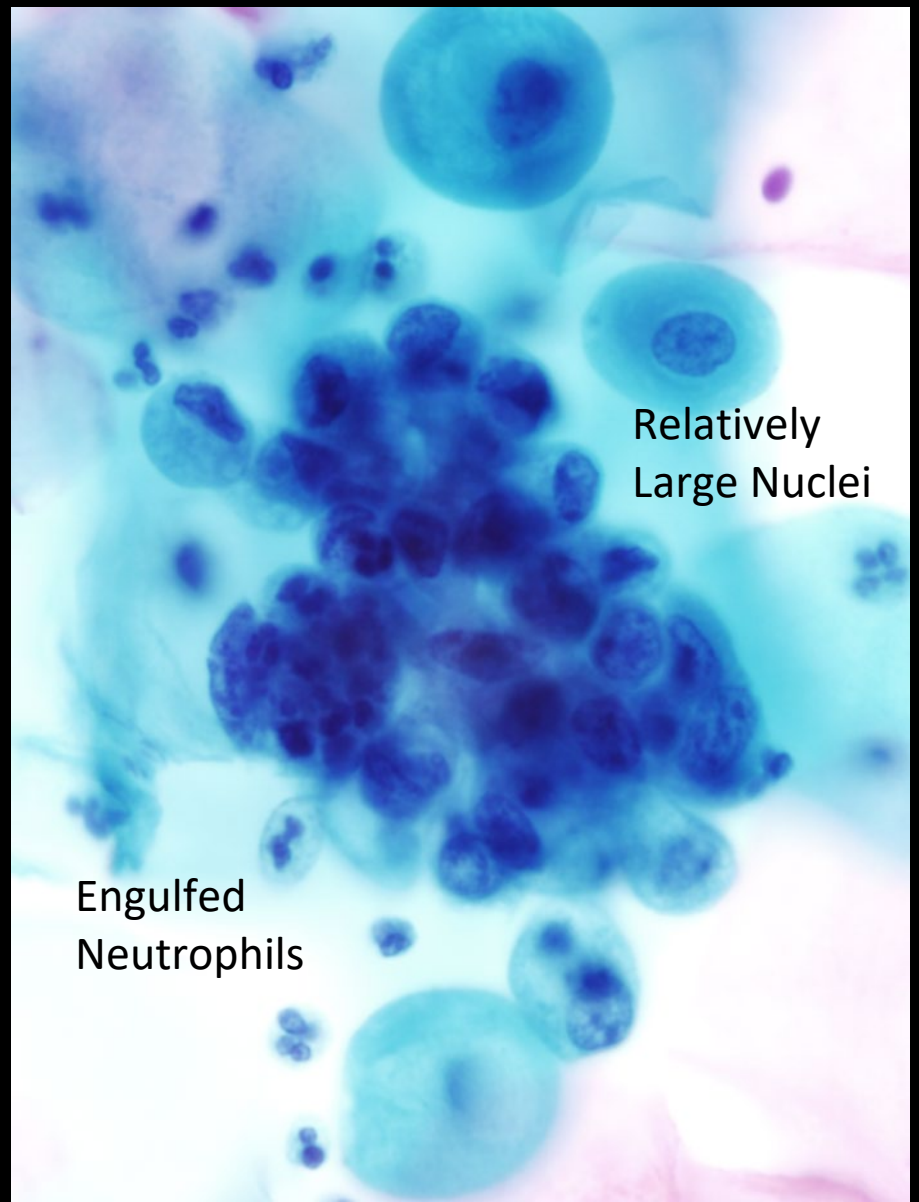
Contrast Atypical Versus Normal

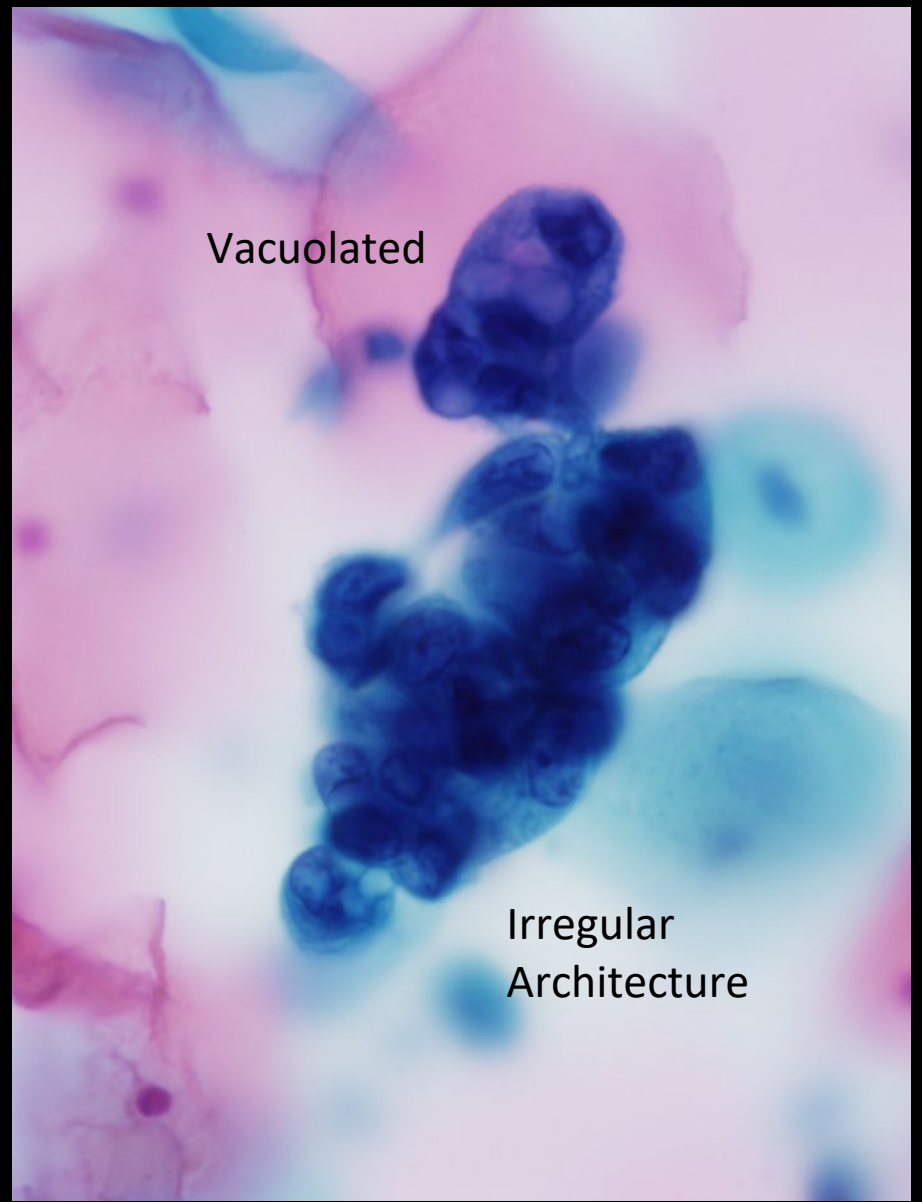


Atypical Endometrial Cells

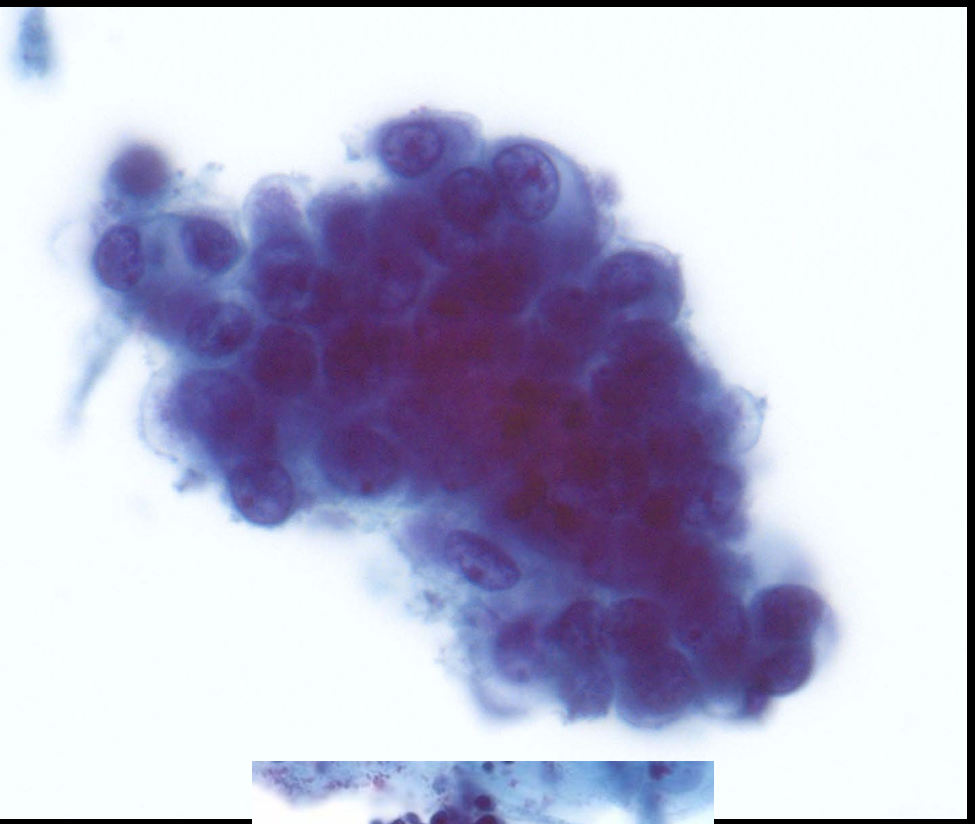
- No separate criteria for NOS vs. favor neoplastic
- Should be present:
  - Cells occur in small groups (5-10)
  - Nuclear enlargement (often slight)
  - Mild hyperchromasia
  - Chromatin heterogeneity
  - Ill-defined cell borders
- May or may not be present:
  - Small nucleoli
  - Vacuolated cytoplasm

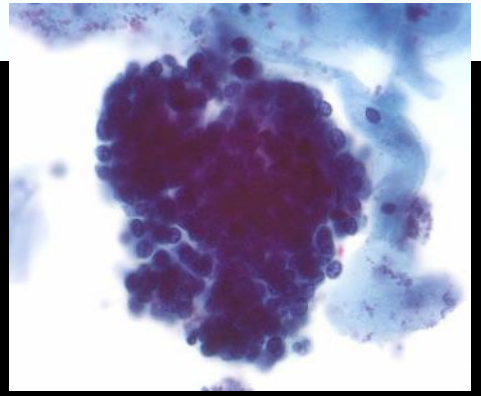
Atypical Endometrial Cells

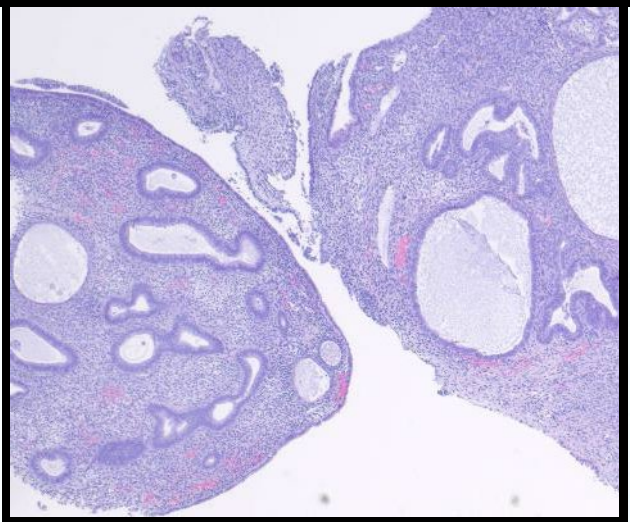


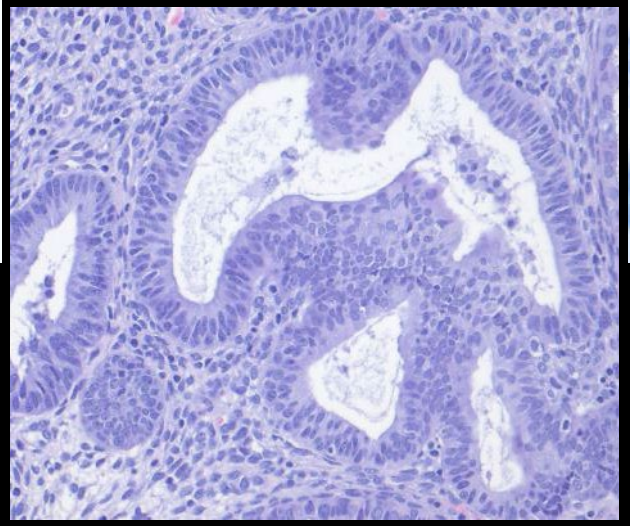


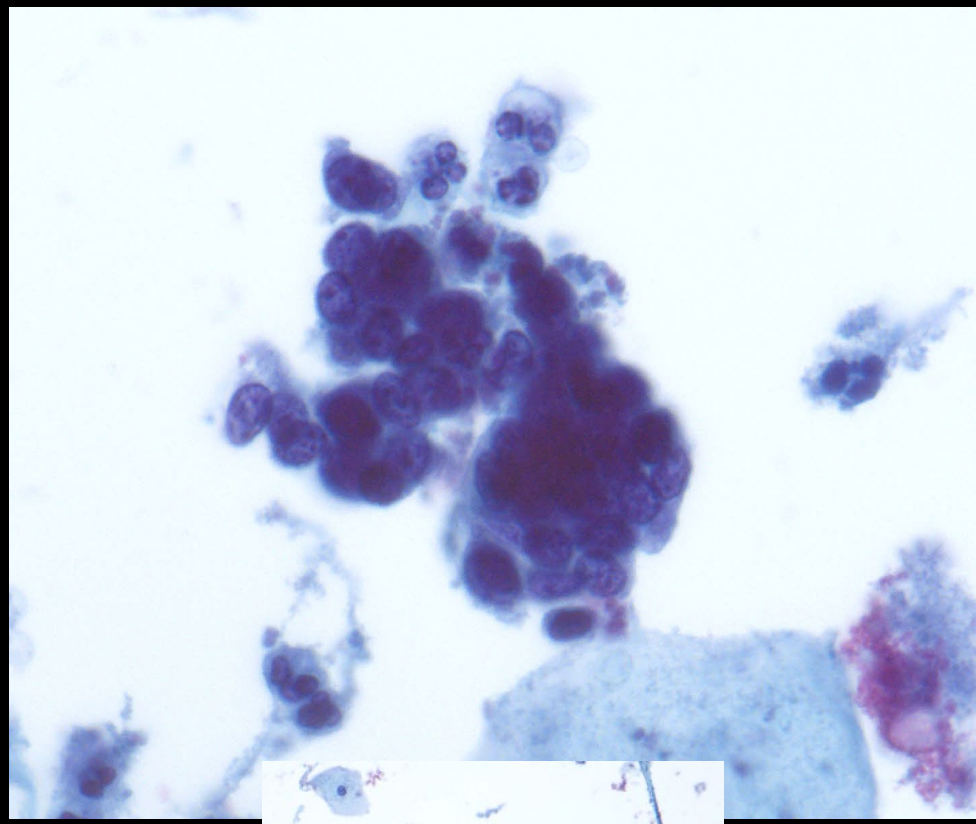
Endometrial Polyp

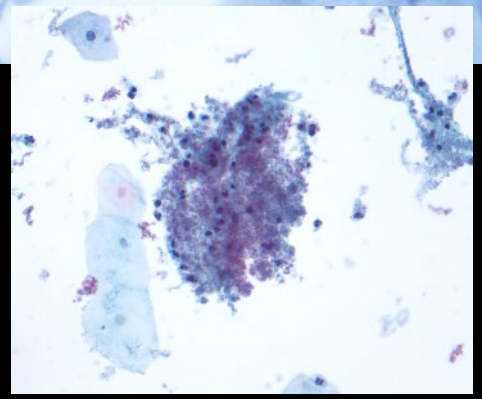








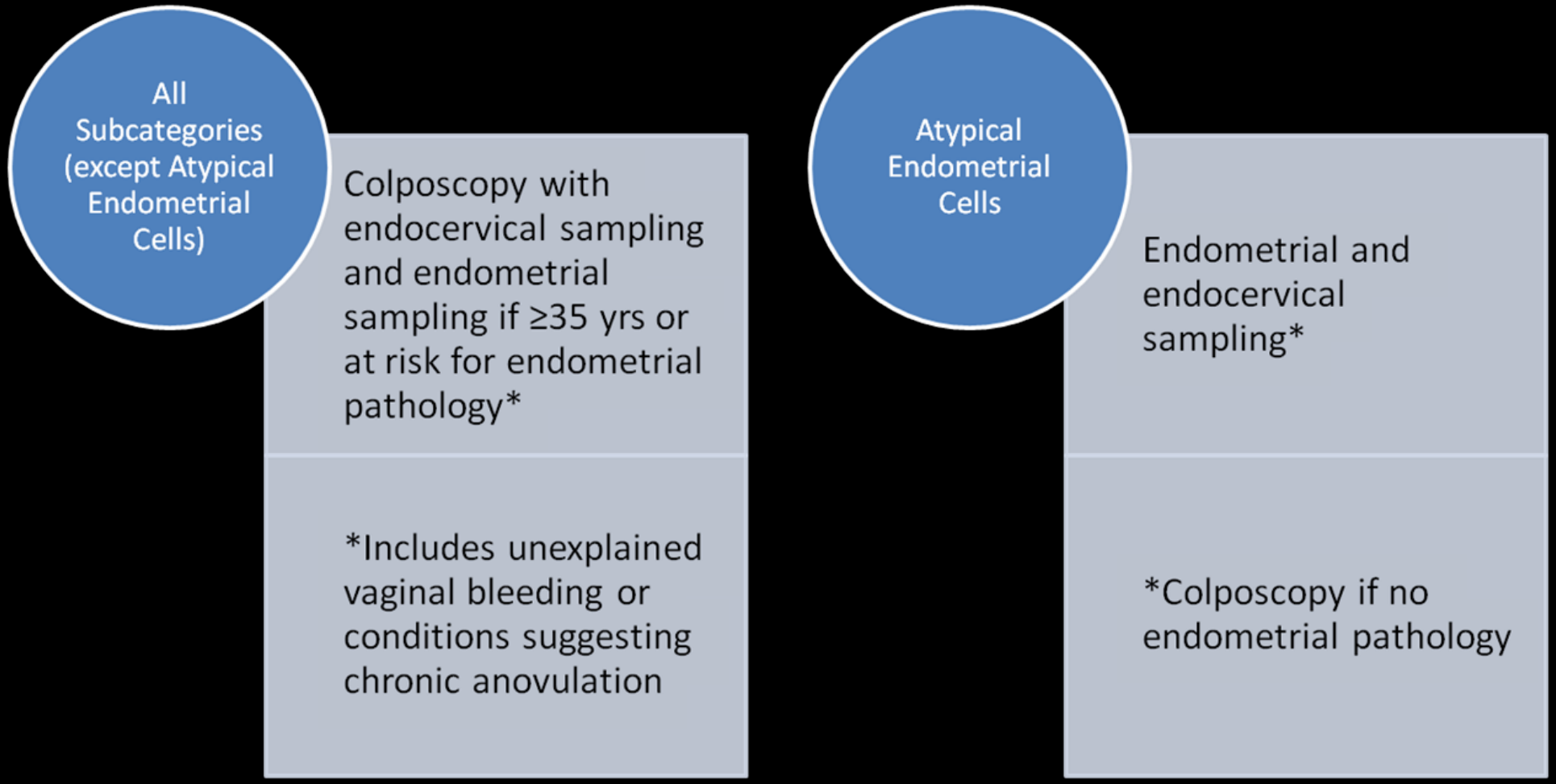




Do these distinctions really matter?

- For the most part, the ASCCP guidelines acknowledge that we as cytologists have a difficult time accurately sub-categorizing atypical glandular cells
  - The follow-up guidelines extensively overlap
  - There are a few significant differences to keep in mind, however

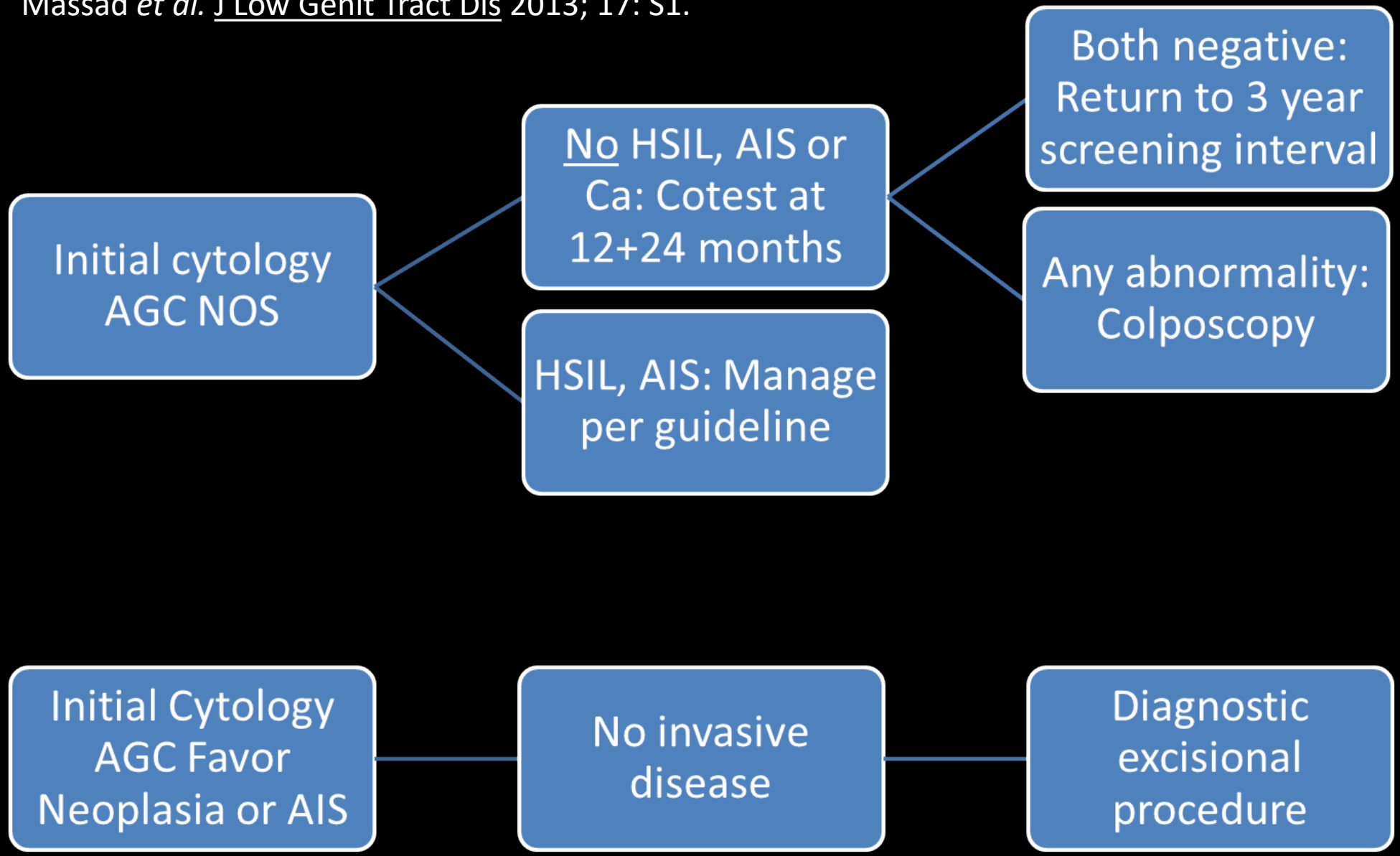
ASCCP Algorithm for AGC



Massad *et al.* J Low Genit Tract Dis 2013; 17: S1.

ASCCP Follow-up Guidelines

Massad *et al.* J Low Genit Tract Dis 2013; 17: S1.



NOS Versus Favor Neoplastic or AIS

- If you use AGC favor neoplastic or AIS, the patient will always get at least a LEEP according to ASCCP guidelines
- AGC NOS allows for more discretion on the part of gynecologists to avoid LEEP if the initial biopsy is negative, LSIL, or HSIL
- LEEP has long been thought to increase the risk of pregnancy loss, but now this is being challenged on the basis of socioeconomic status adjustment

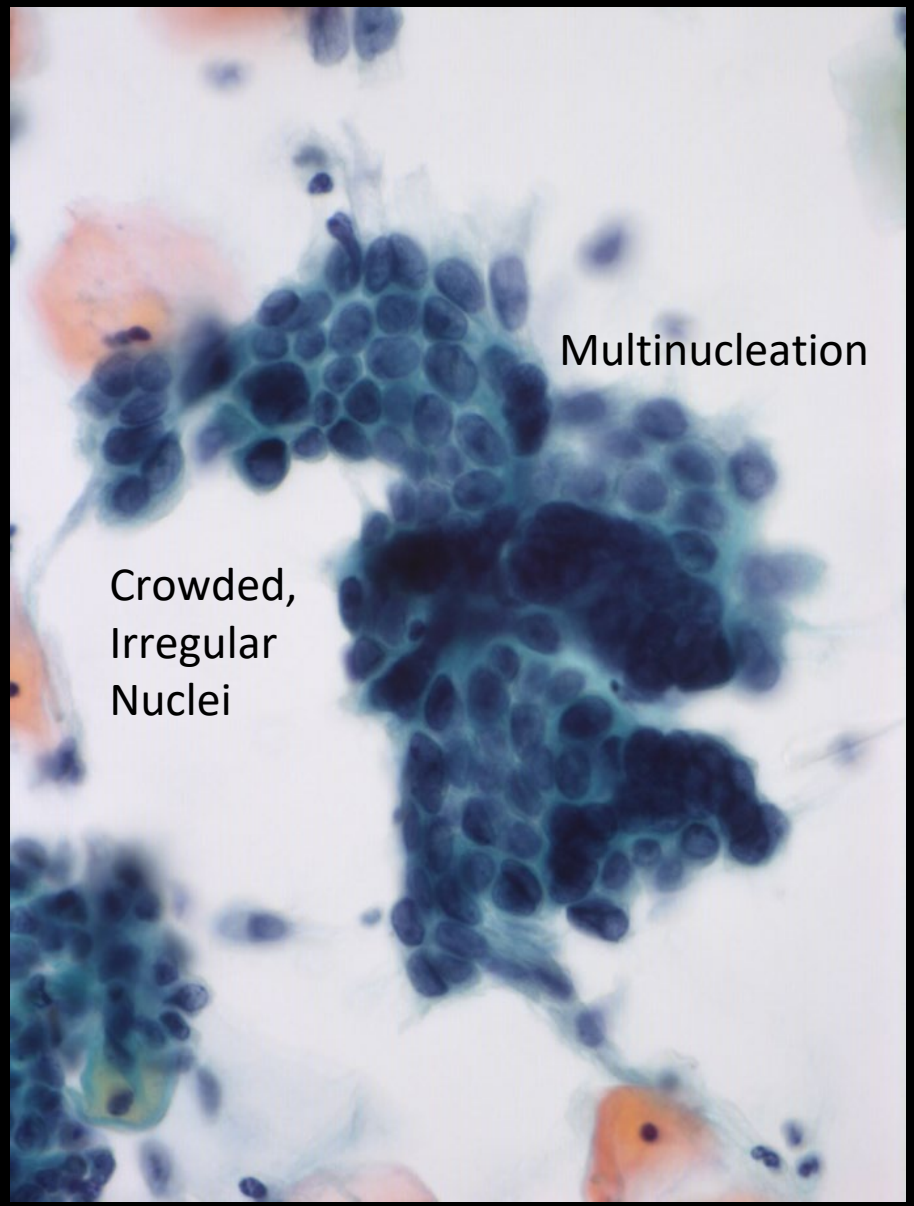
Squamous Intraepithelial Lesions

- Correct categorization of squamous dysplasia can help to keep AGC rates down without losing sensitivity
- HSIL in a gland does not have prominently elongated nuclei or AIS-like architecture
- Lesions that look endocervical but not very AIS-like may be better categorized as ASC-H instead

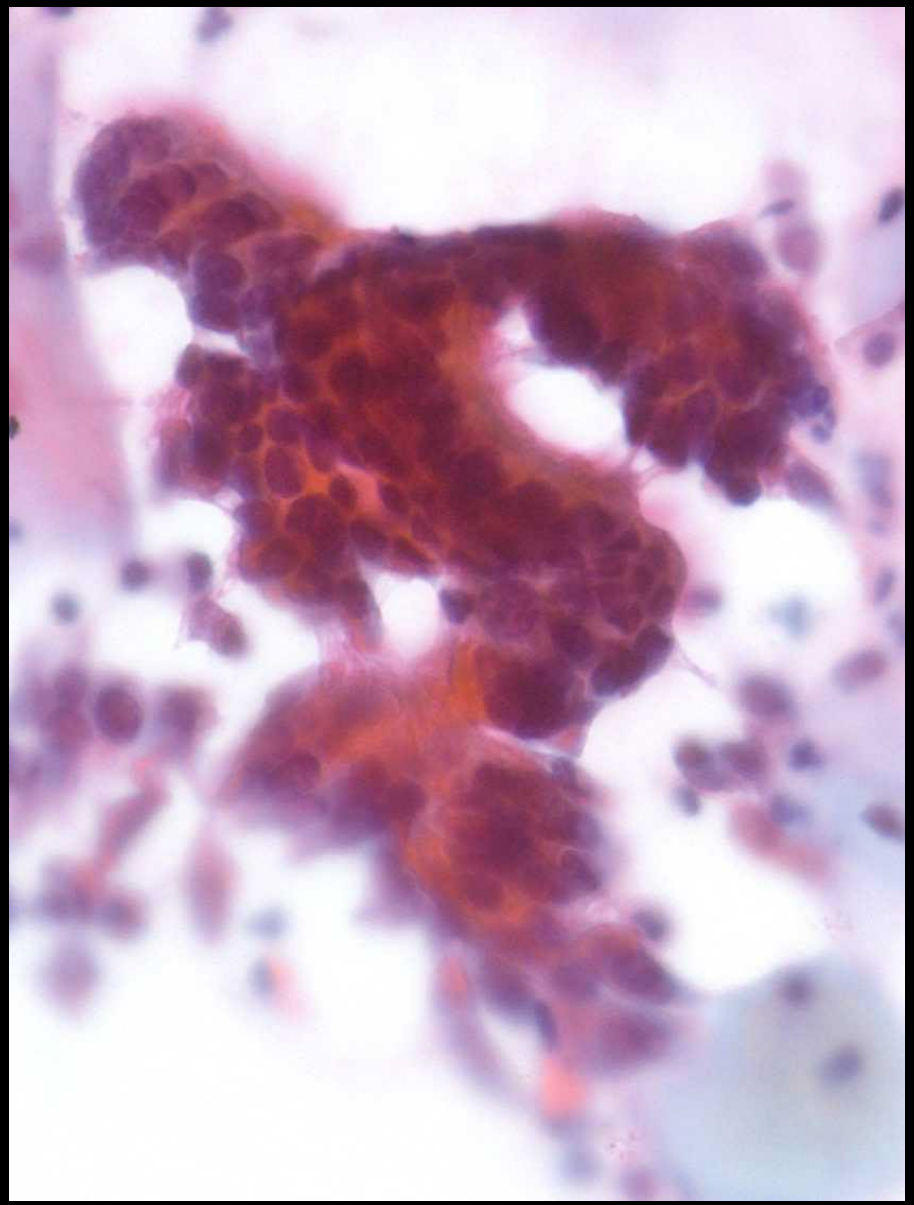
Many AGC cases will be benign

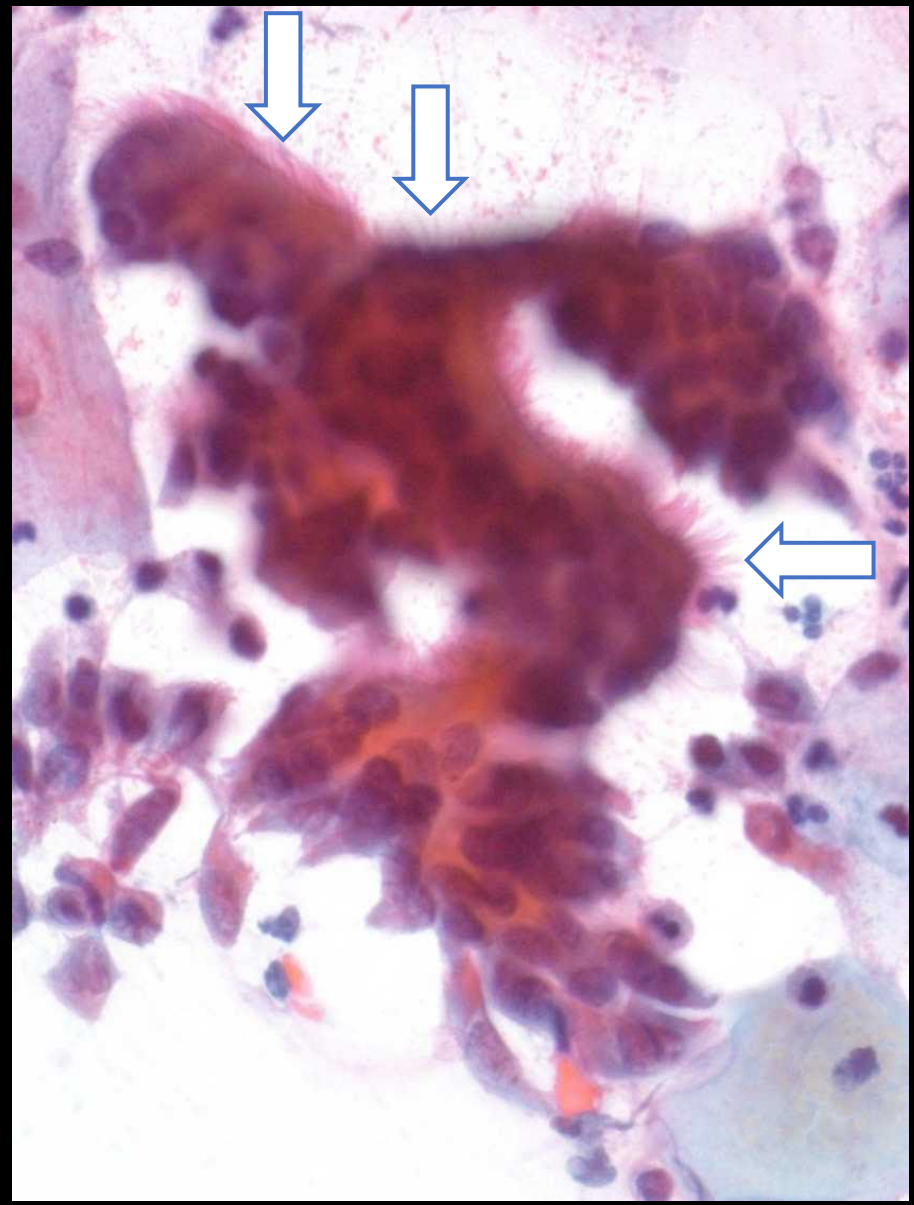
- There are cases that show atypia deserving of an interpretation of AGC that will be benign on biopsy follow-up
- Tubal metaplasia, microglandular hyperplasia, and endocervical polyps can show AGC features, especially if complicated by inflammation or repair
- IUD effects are another well-known mimic
- Menstrual endometrium is an under-appreciated problem

Tubal Metaplasia

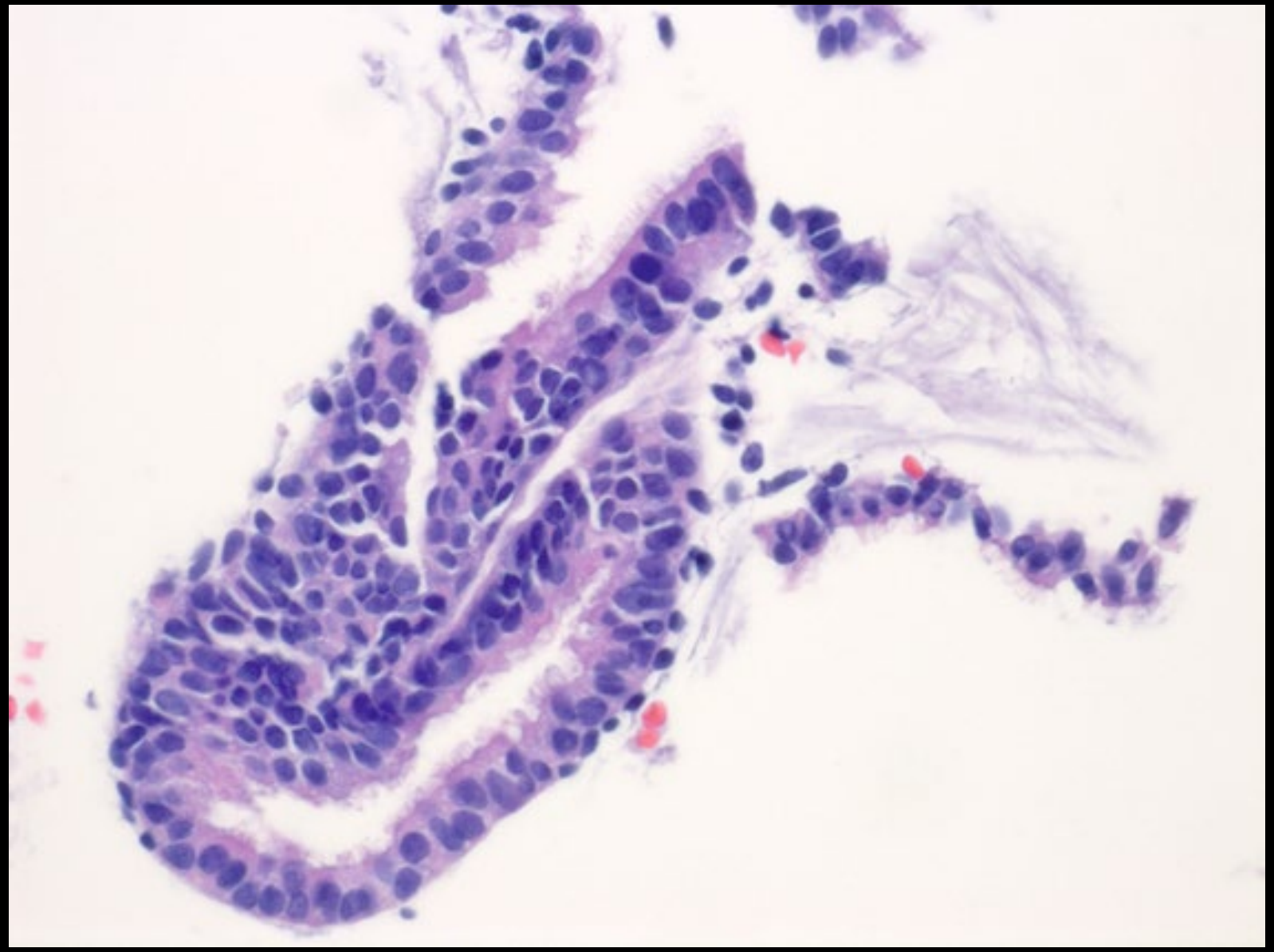


Look for Cilia in Tubal Metaplasia

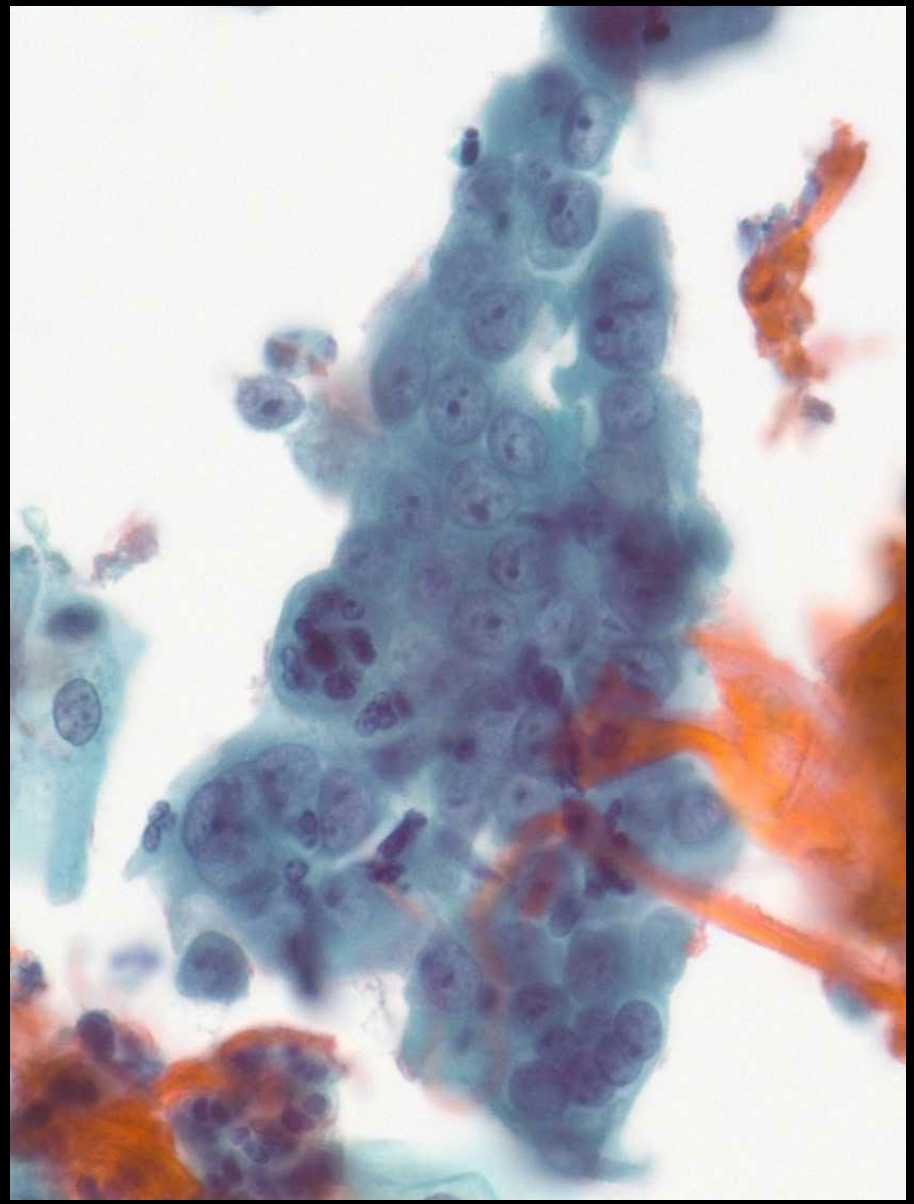


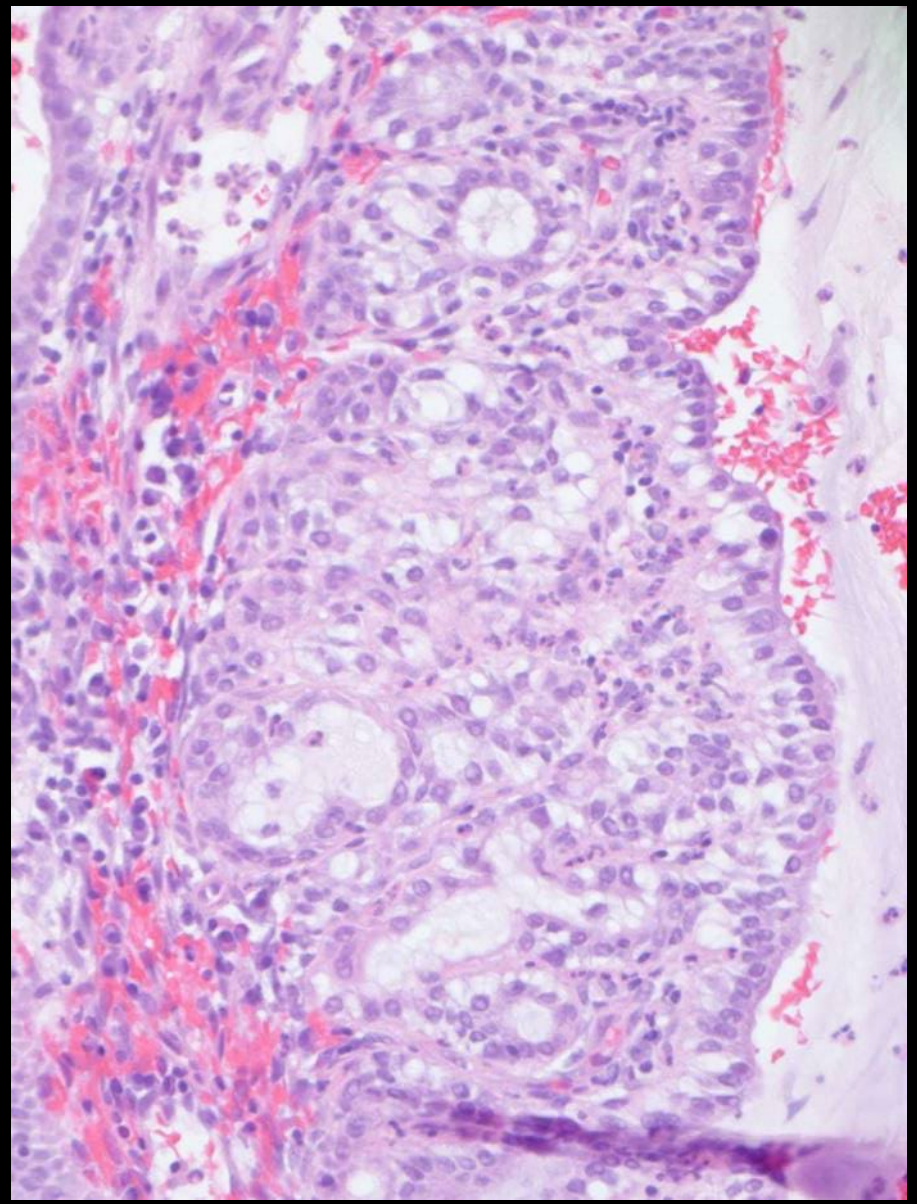


Tubal Metaplasia Curettage Histology

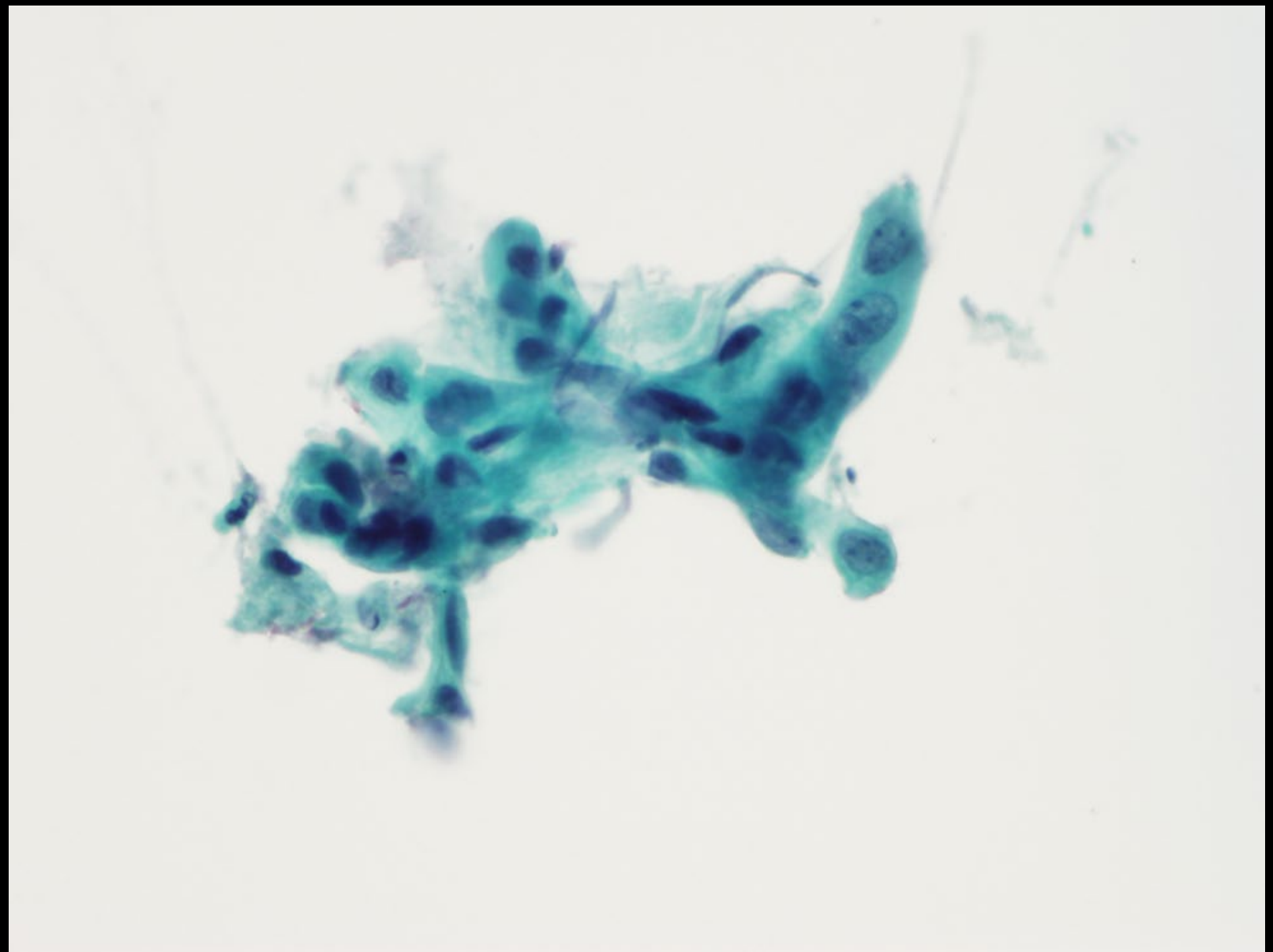


Microglandular Hyperplasia

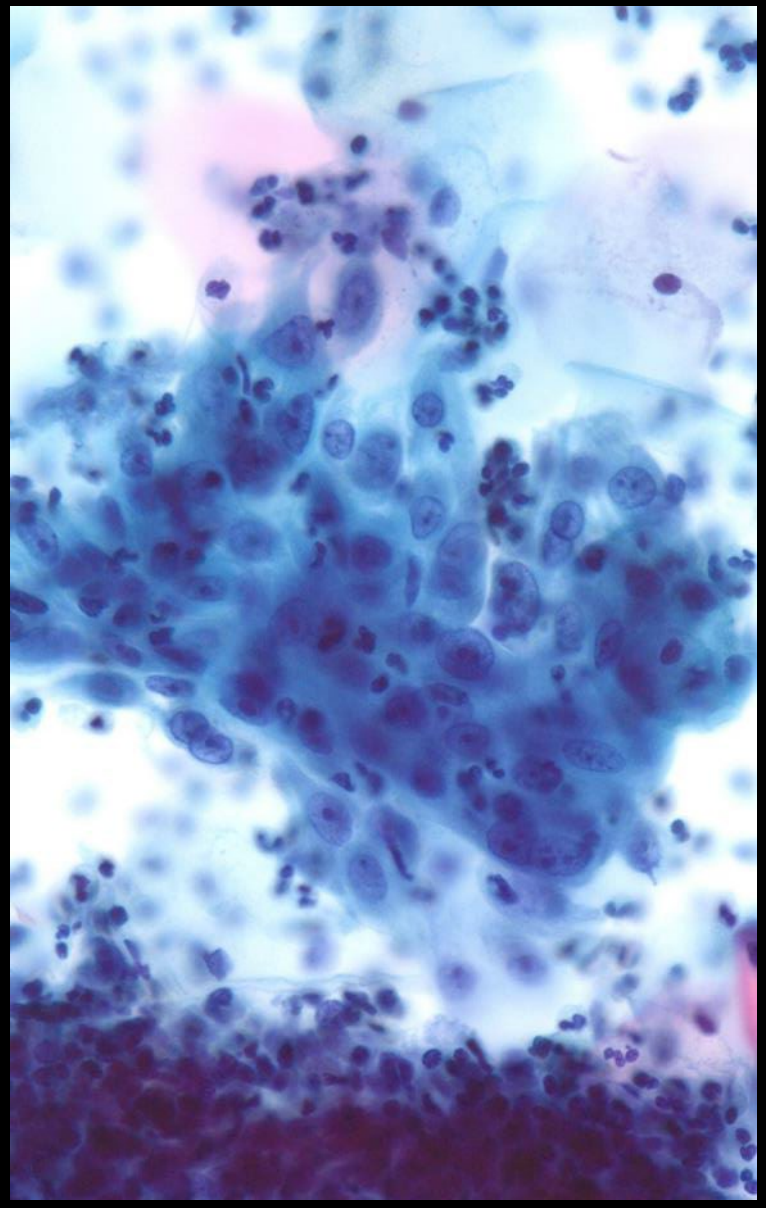


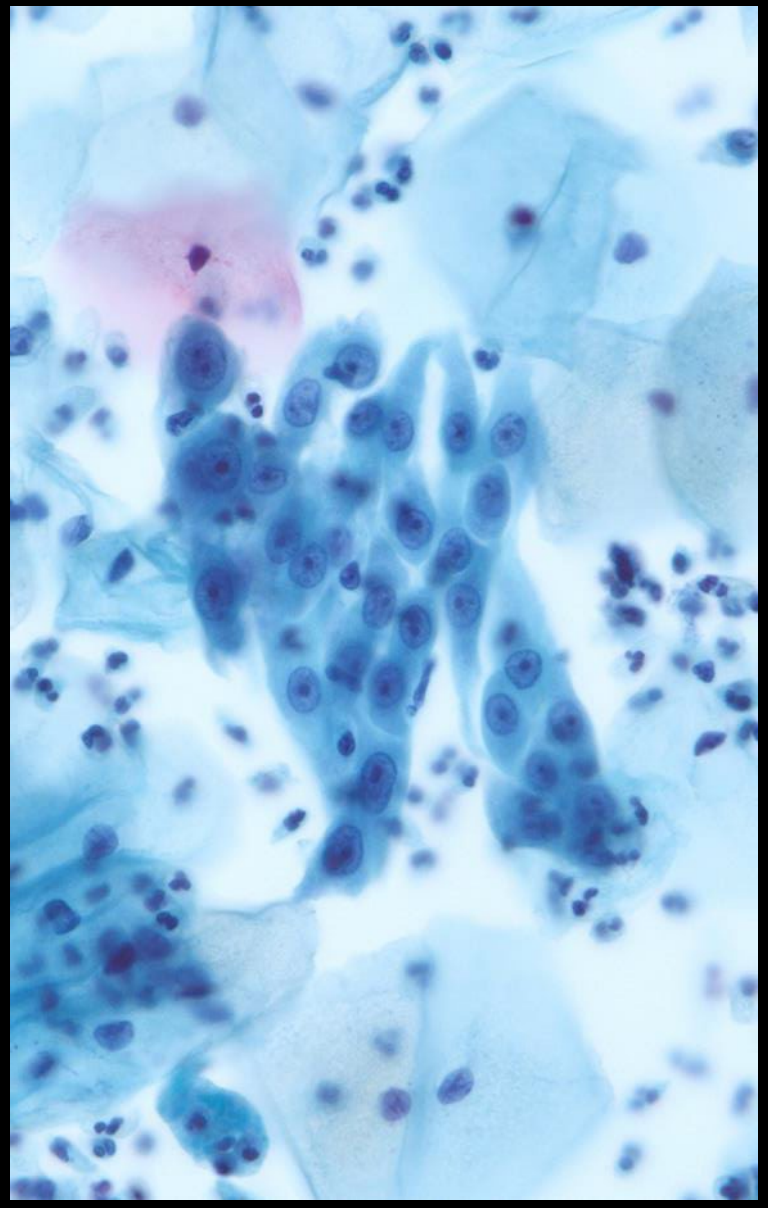


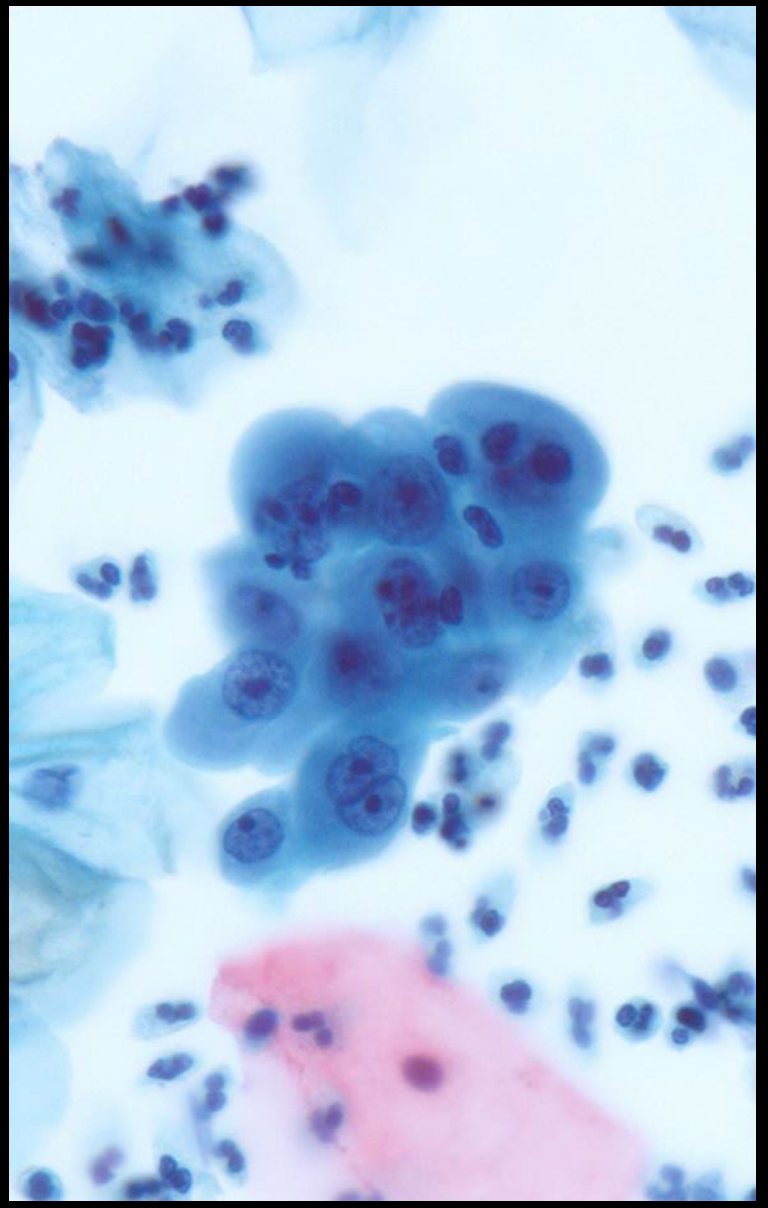
Microglandular Hyperplasia Marked Atypia



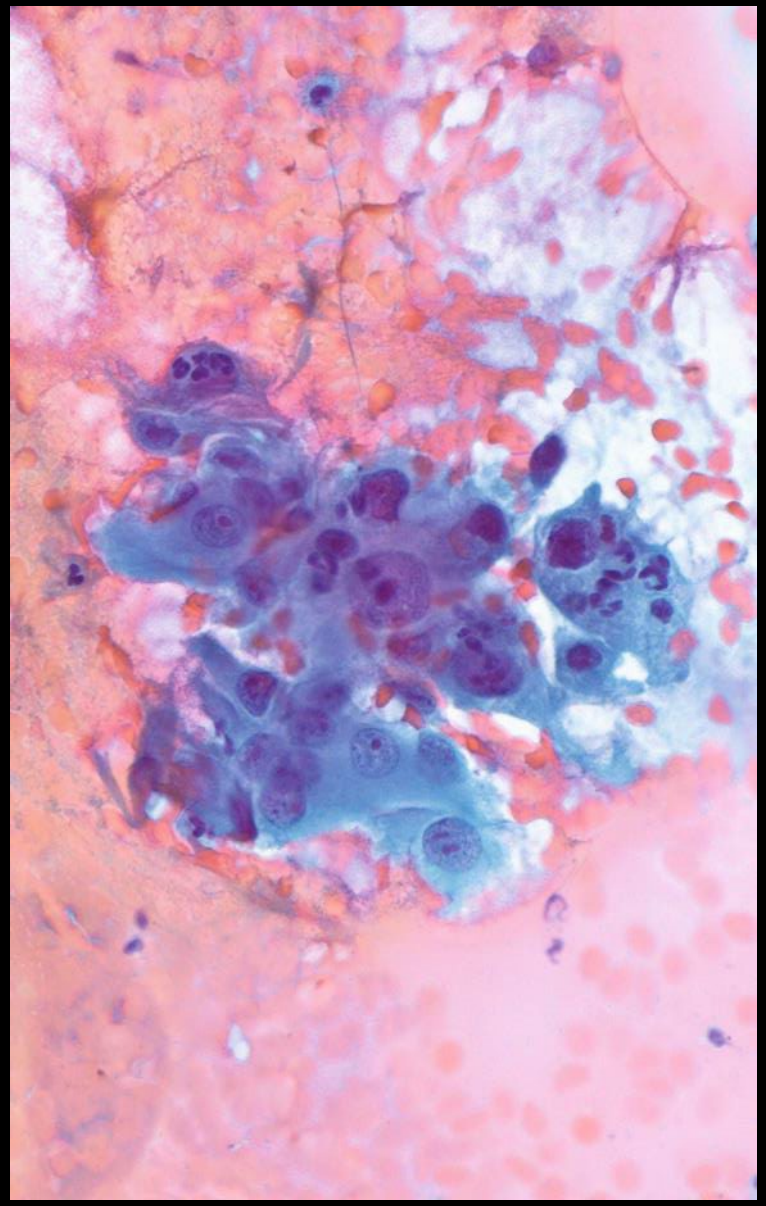
Atypical Repair

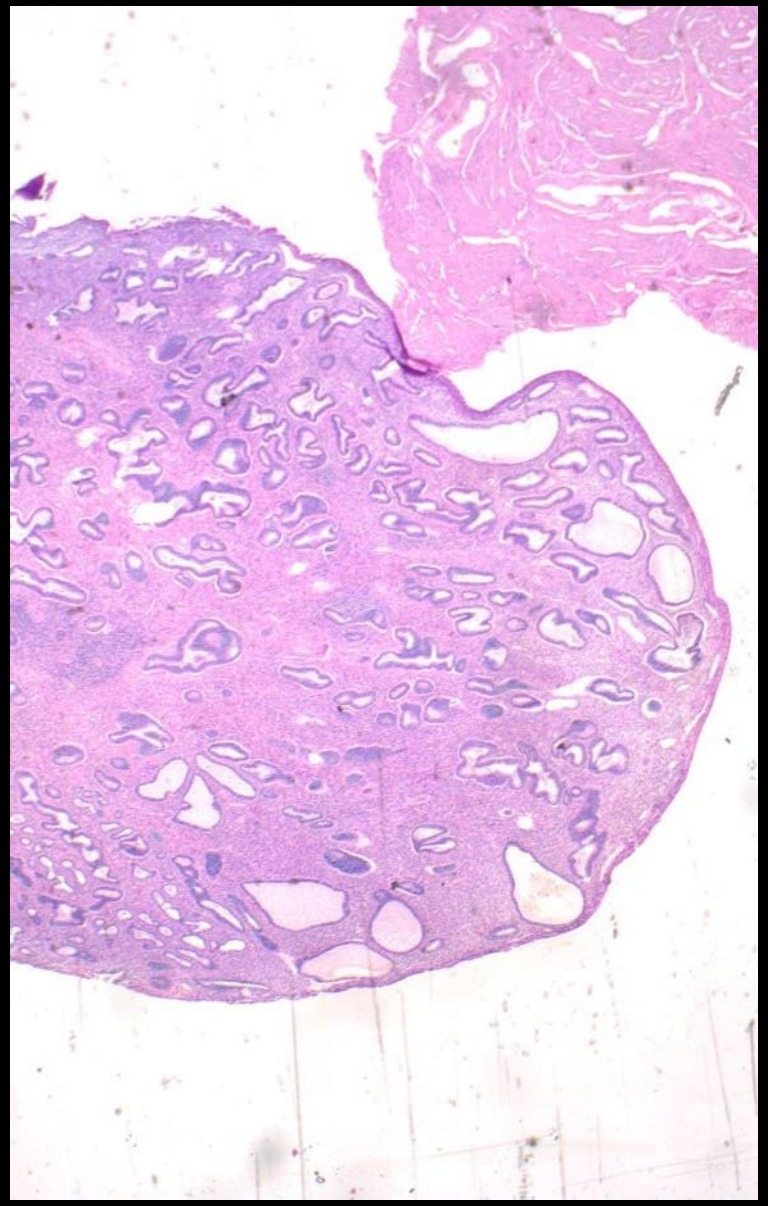


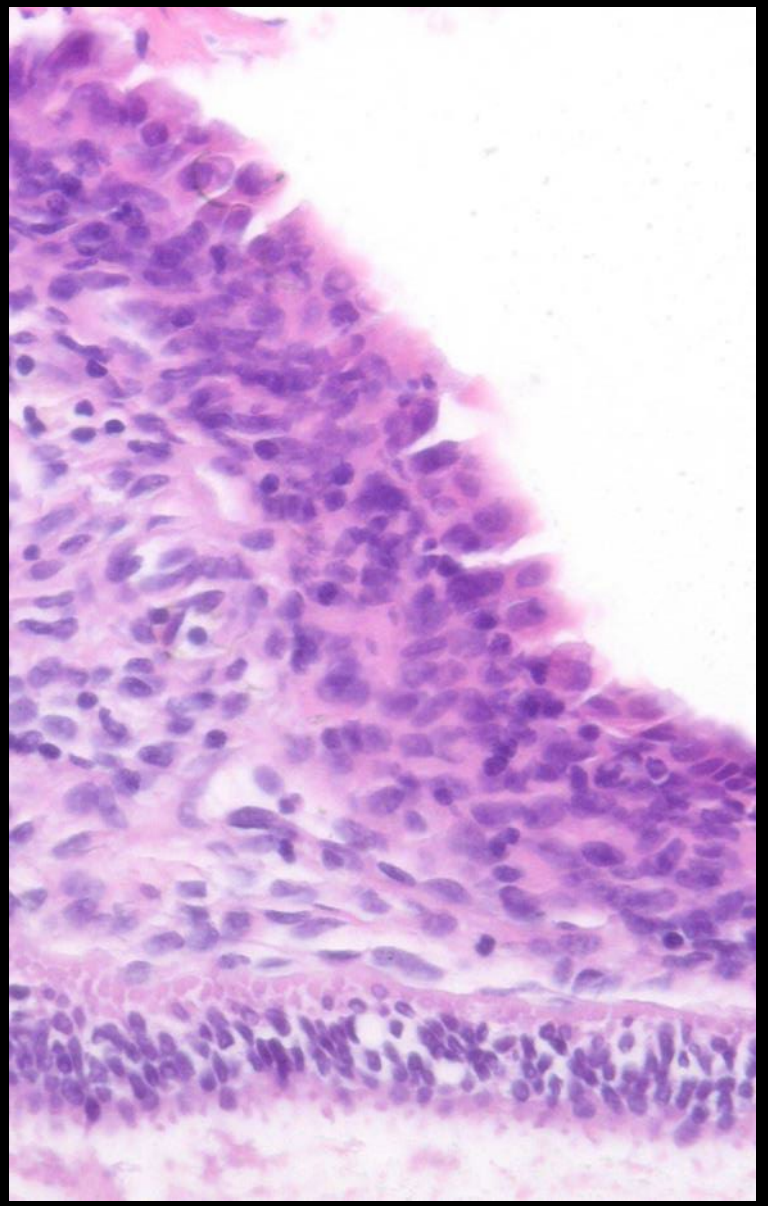




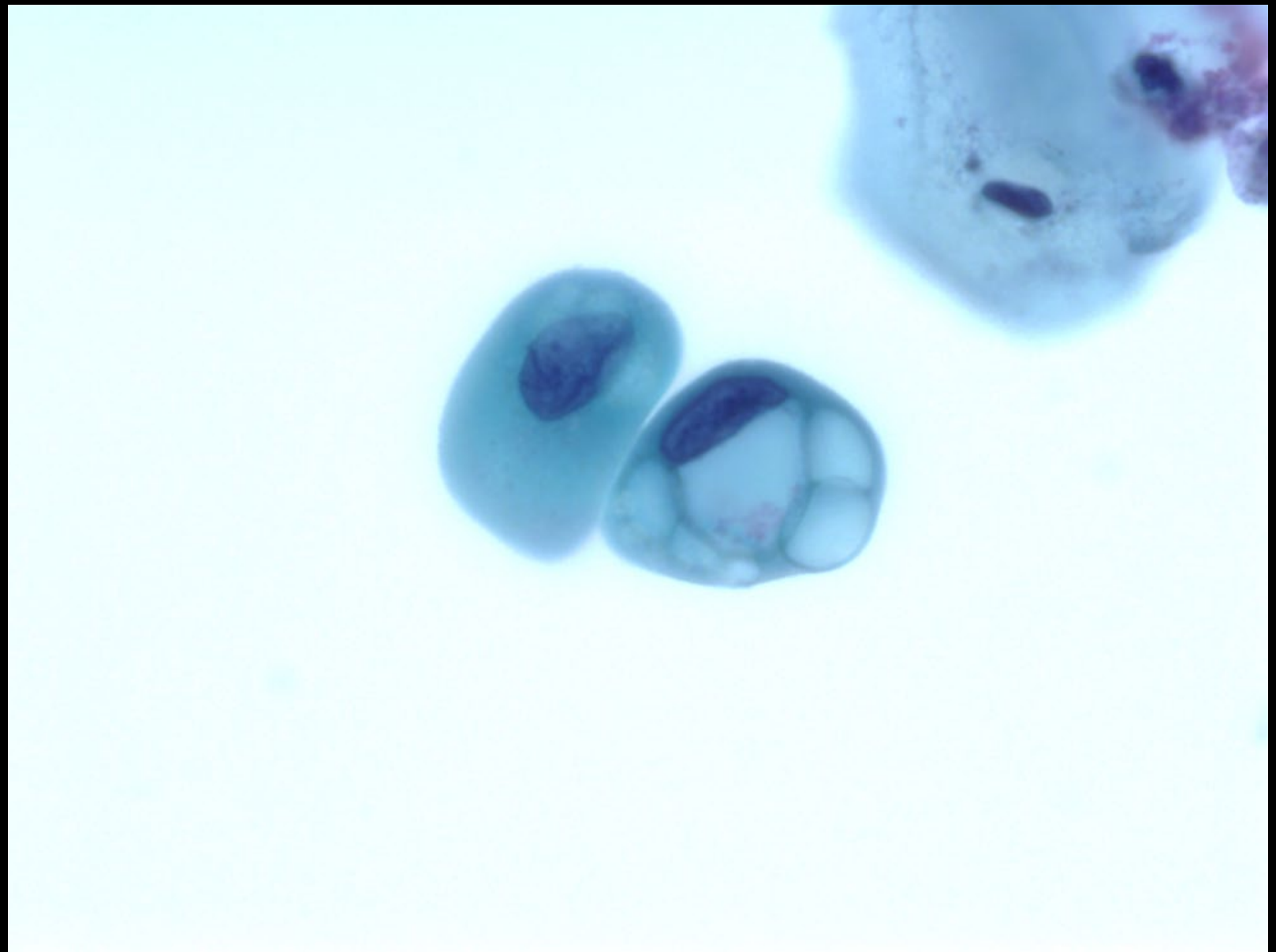
Polyp-Associated Repair



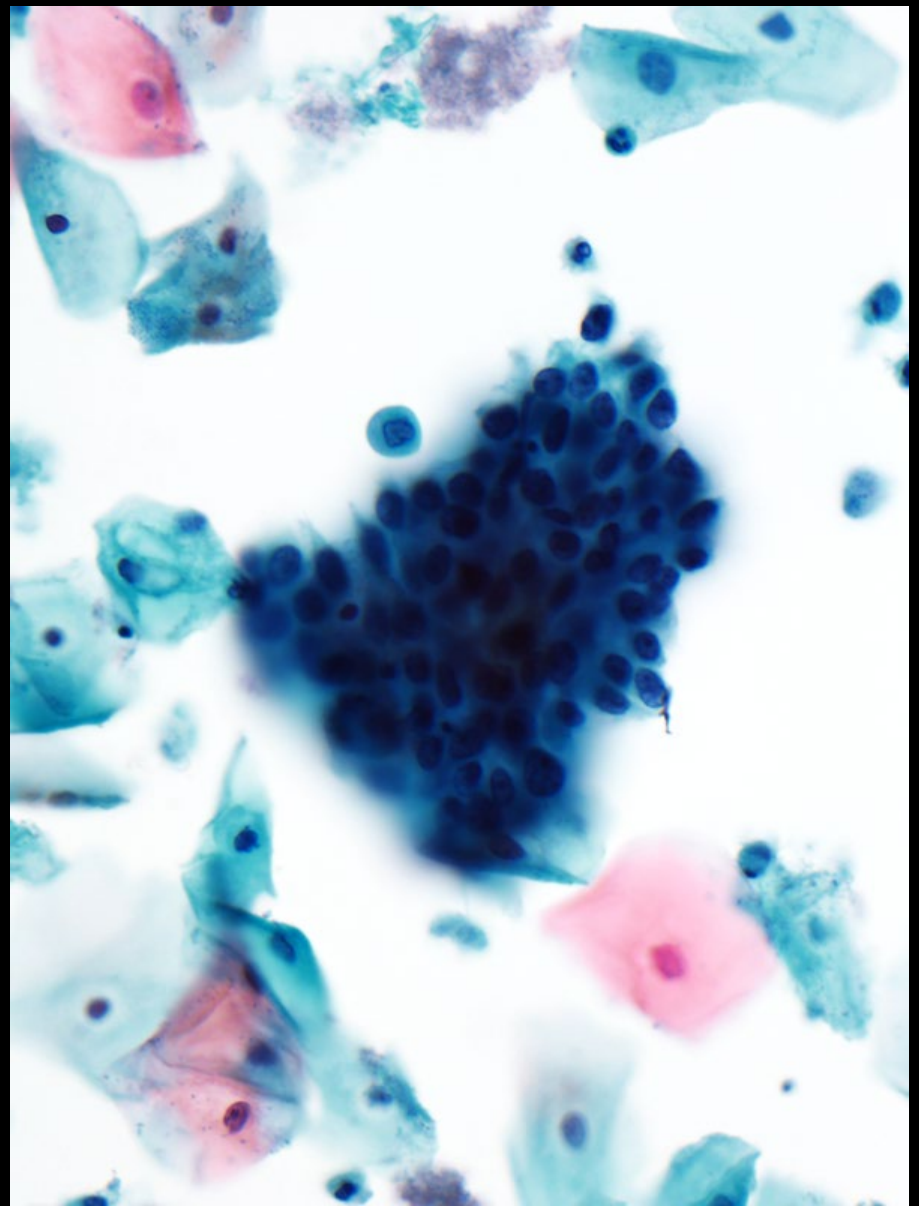


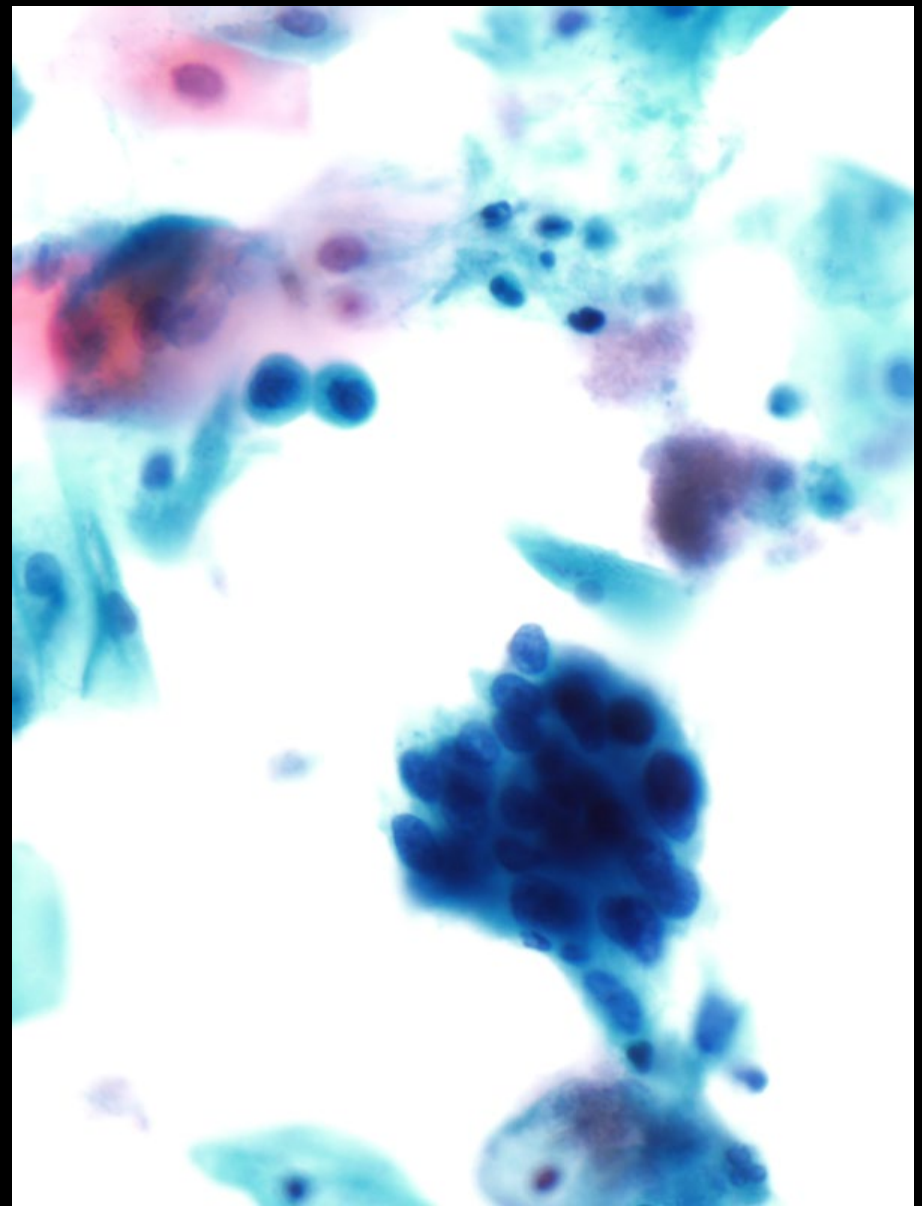


Vacuolated IUD Cell

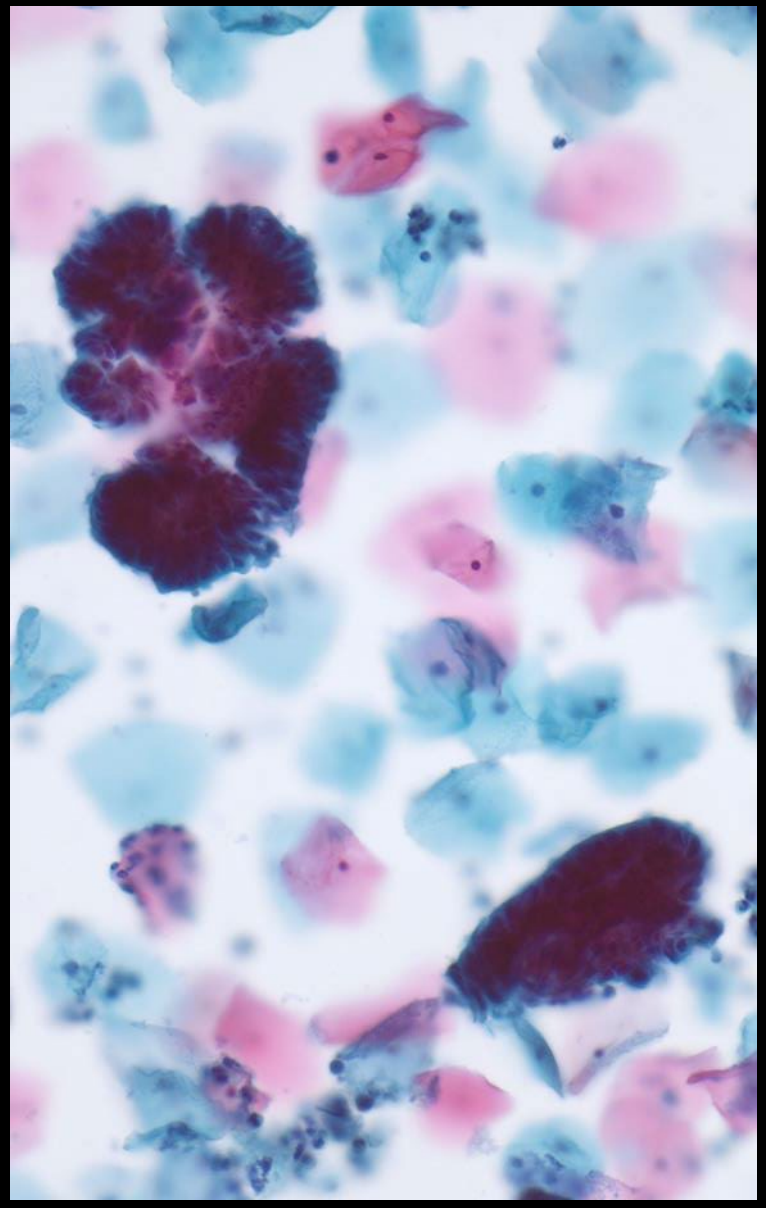


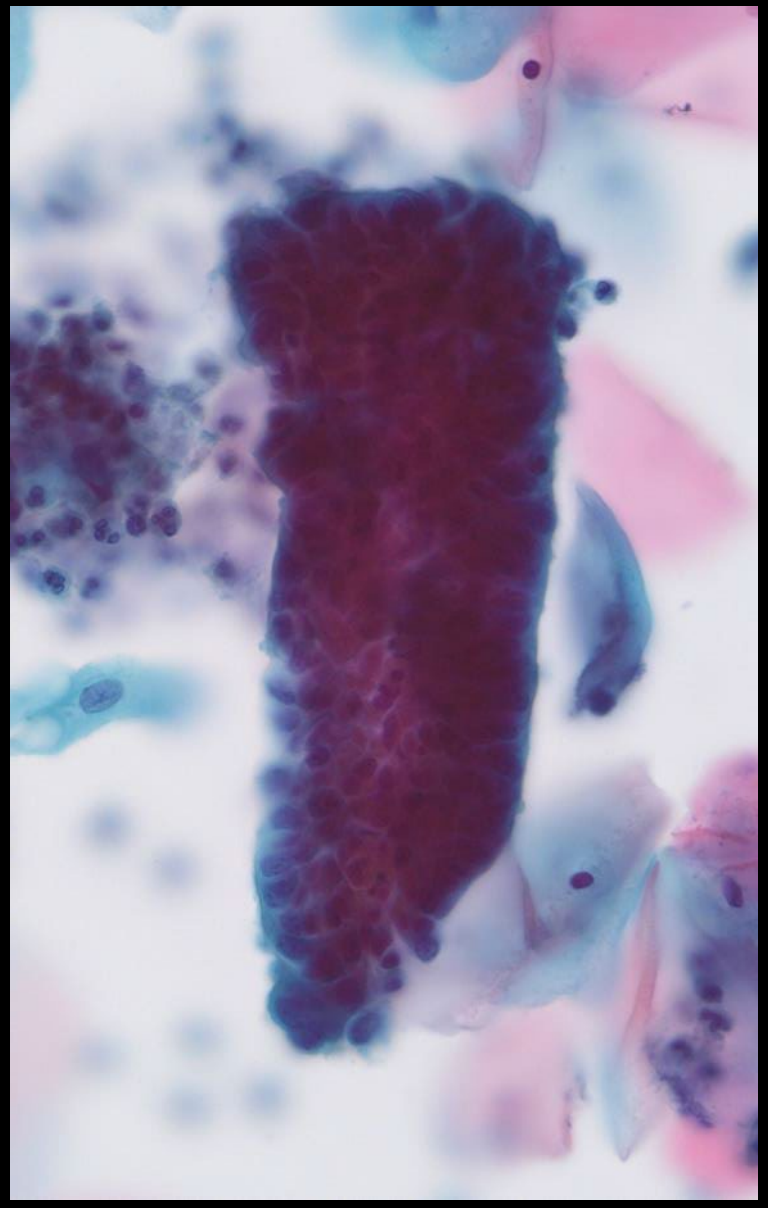
Menstrual Endometrium



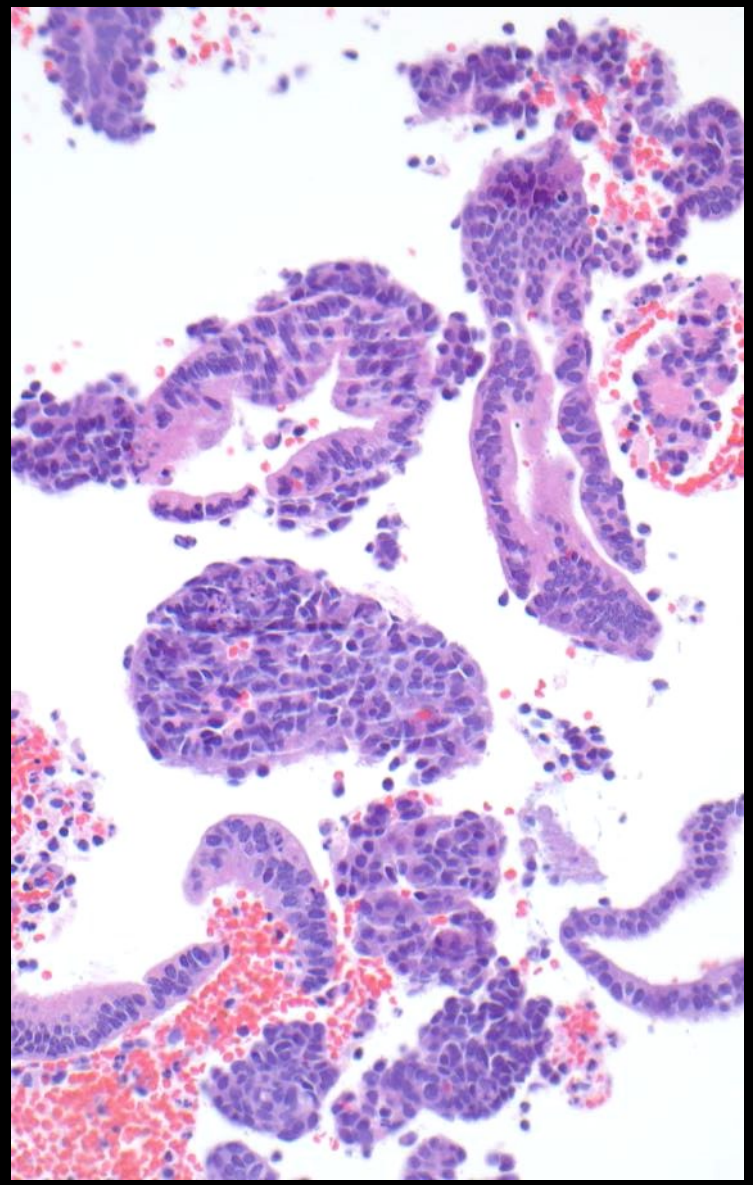


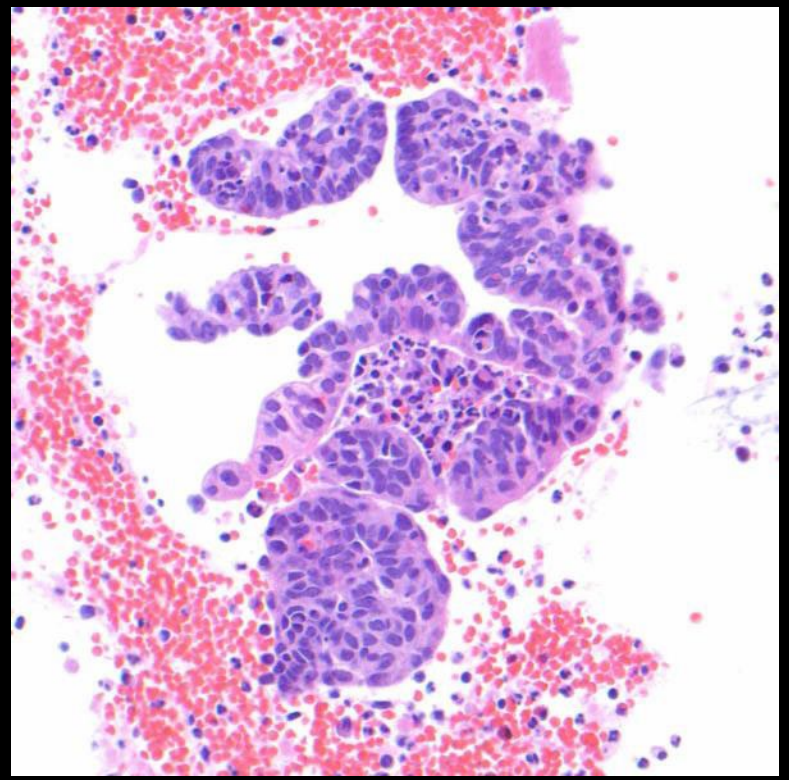
Menstrual Endometrium Geometric Clusters

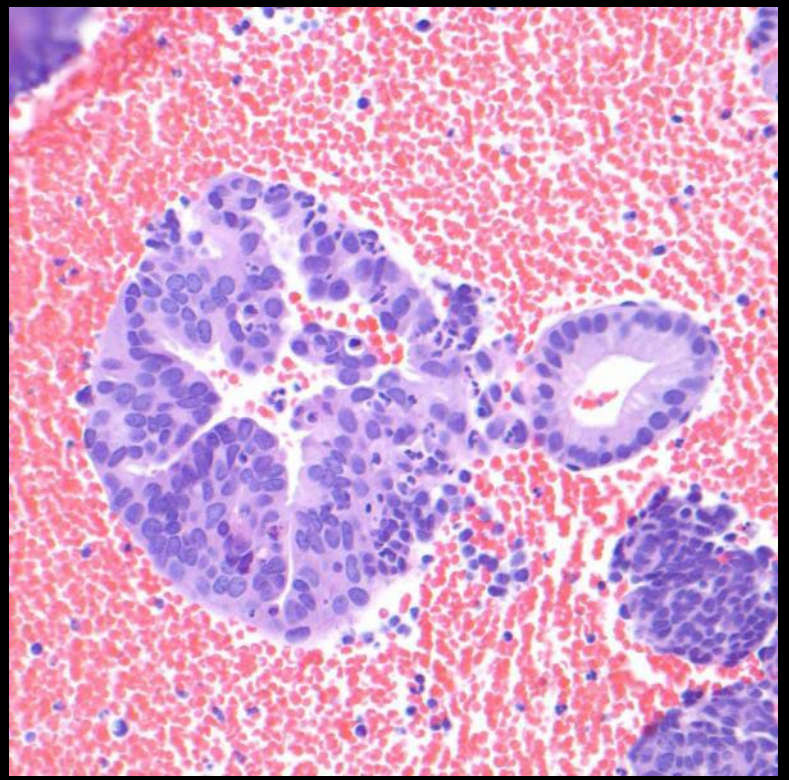




Menstrual Endometrium Biopsy







Menstrual Endometrium

- Menstrual endometrium is “fresh” and looks different from the typical rounded up degenerated groups
- Menstrual endometrium may mimic AIS or even small cell carcinoma
- Pap tests during menstruation should be avoided, but rescheduling is difficult so sometimes it happens
- The LMP is often not given or is about one month earlier

Summary Tips for AGC

- If it’s cervical but doesn’t look like AIS or squamous dysplasia, it’s probably benign/reactive
- Whenever considering AGC, also think about squamous dysplasia
- Look for features of tubal metaplasia besides cilia and terminal bars as these are frequently absent
- Remember endometrial carcinoma in older women
- Don’t be too aggressive about using “favor neoplastic”
- HPV is of limited value for triage

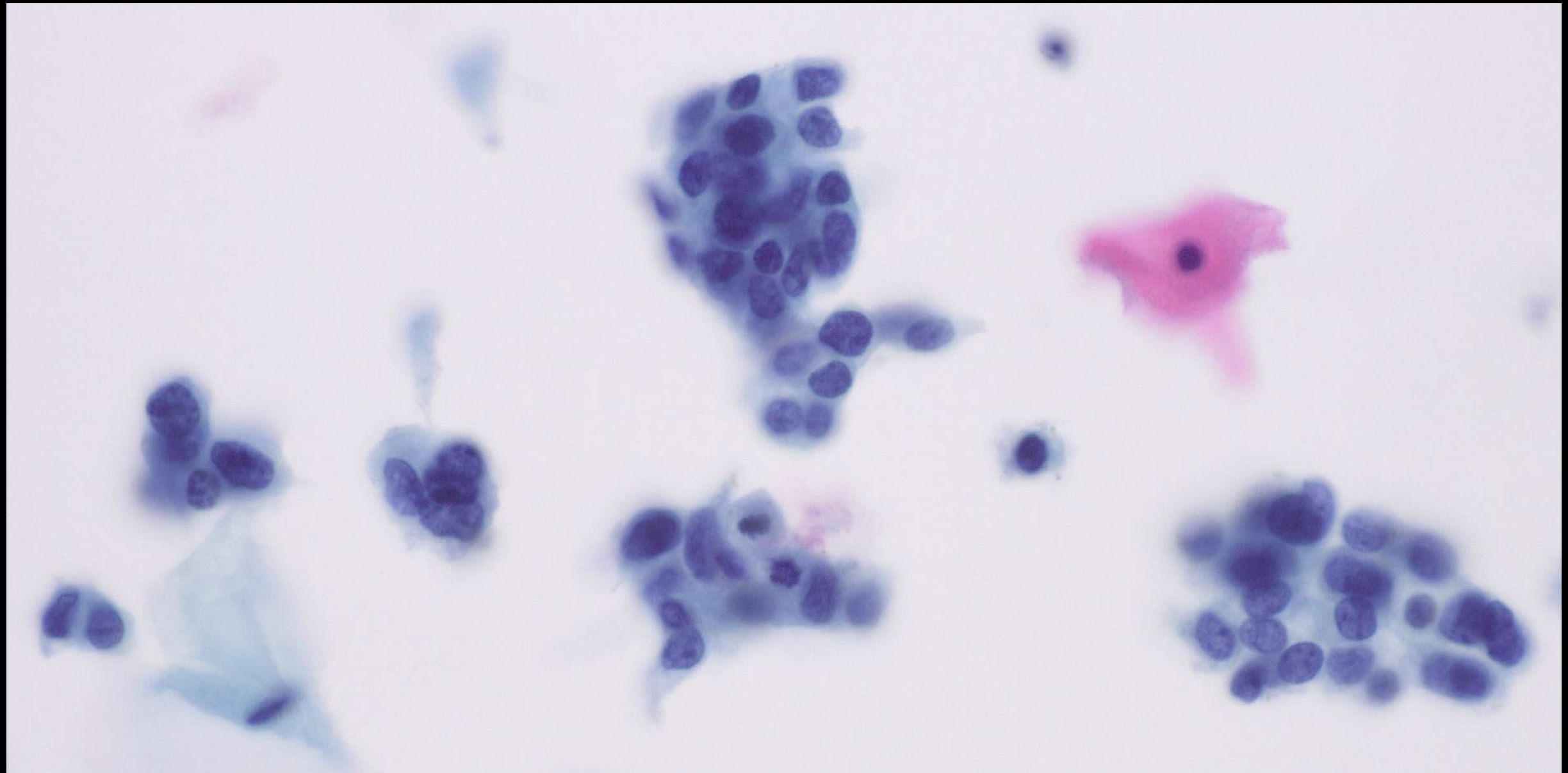
Small Cell Carcinoma

HOUSTON Methodist
LEADING MEDICINE

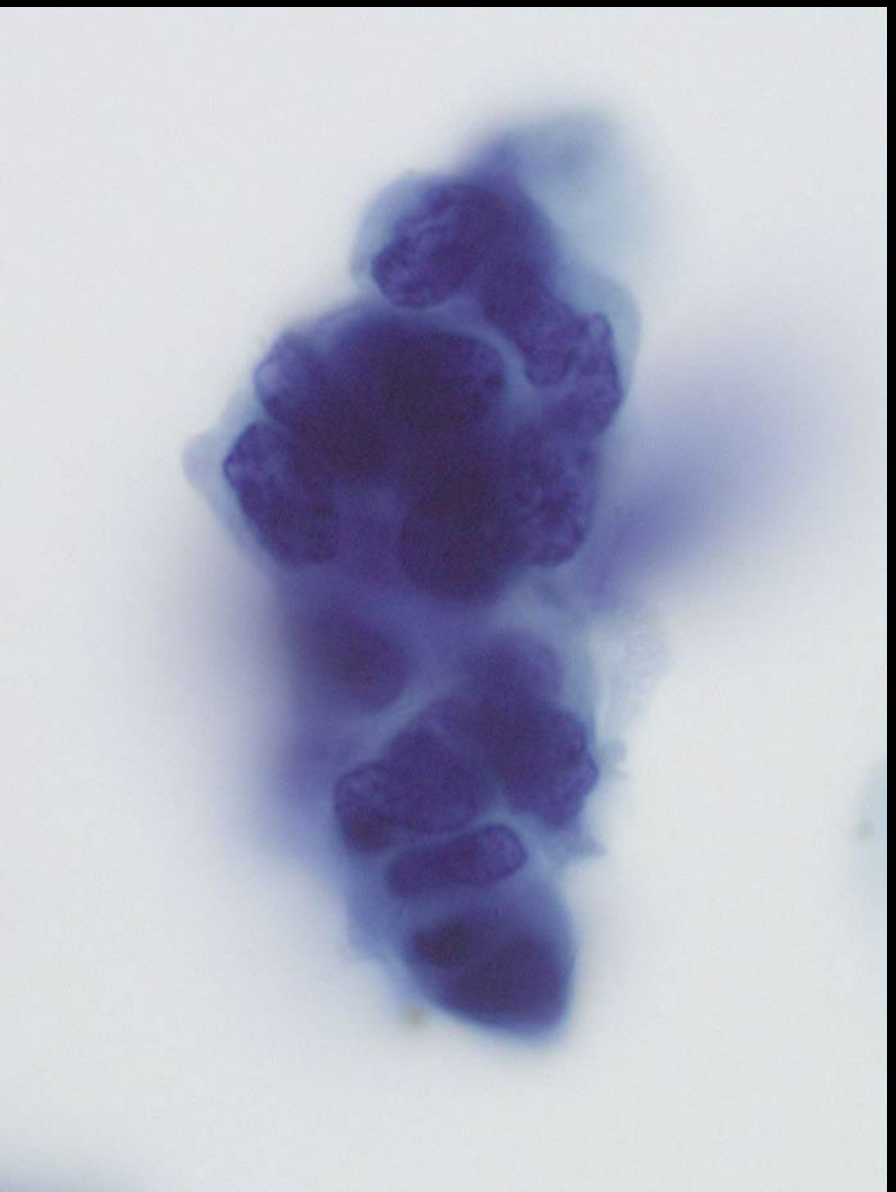
Small Cell Carcinoma

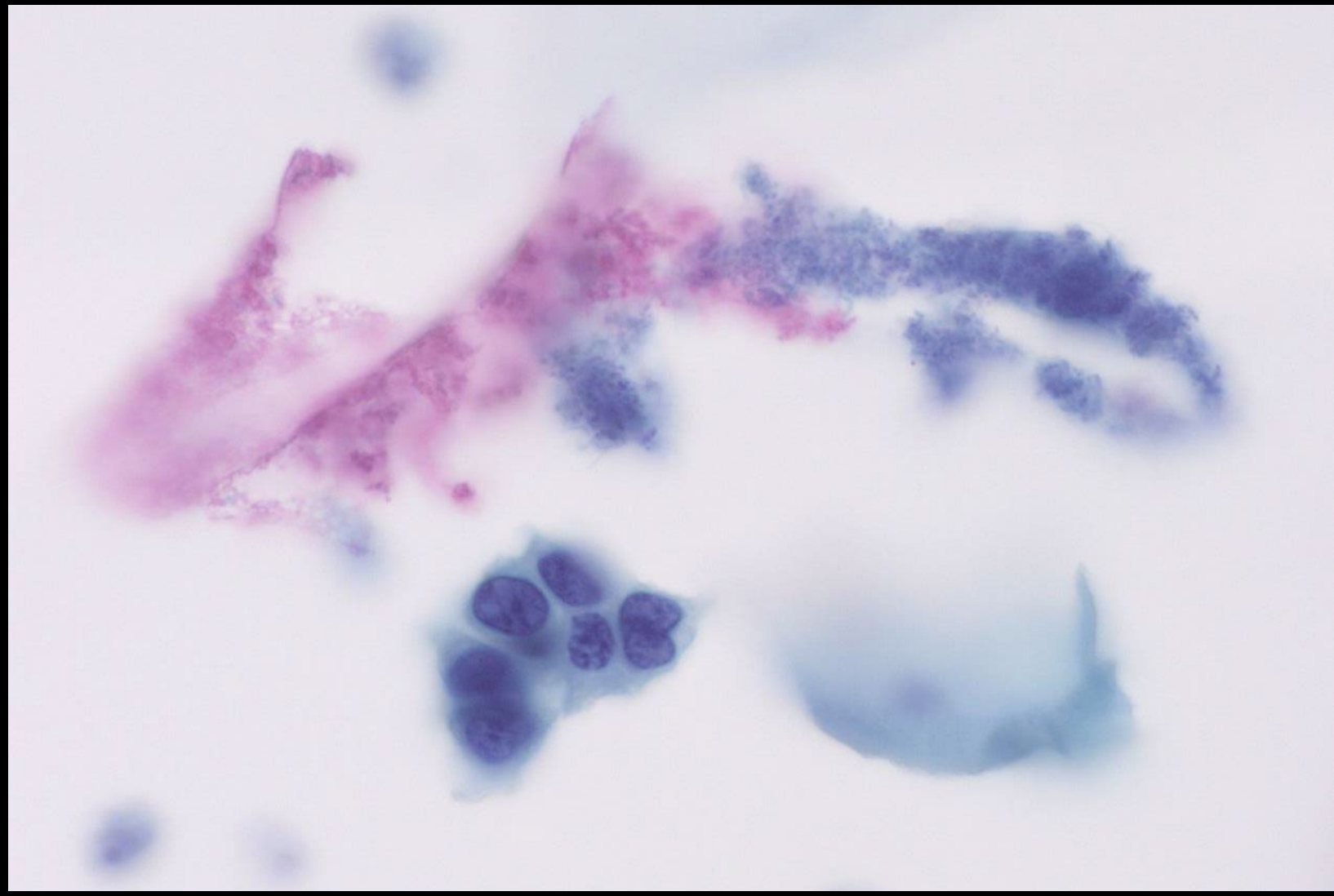
- Small cell carcinoma is rare as a cervical primary
- It is associated with HPV (types 18 and 16)
- May have a previous history of HPV+ or SIL
- Highly aggressive and usually fatal
- May be difficult to distinguish from metastasis
  - Younger age favors cervical primary
  - HPV testing of the tumor may be helpful

Small Cell Carcinoma



Small Cell Carcinoma





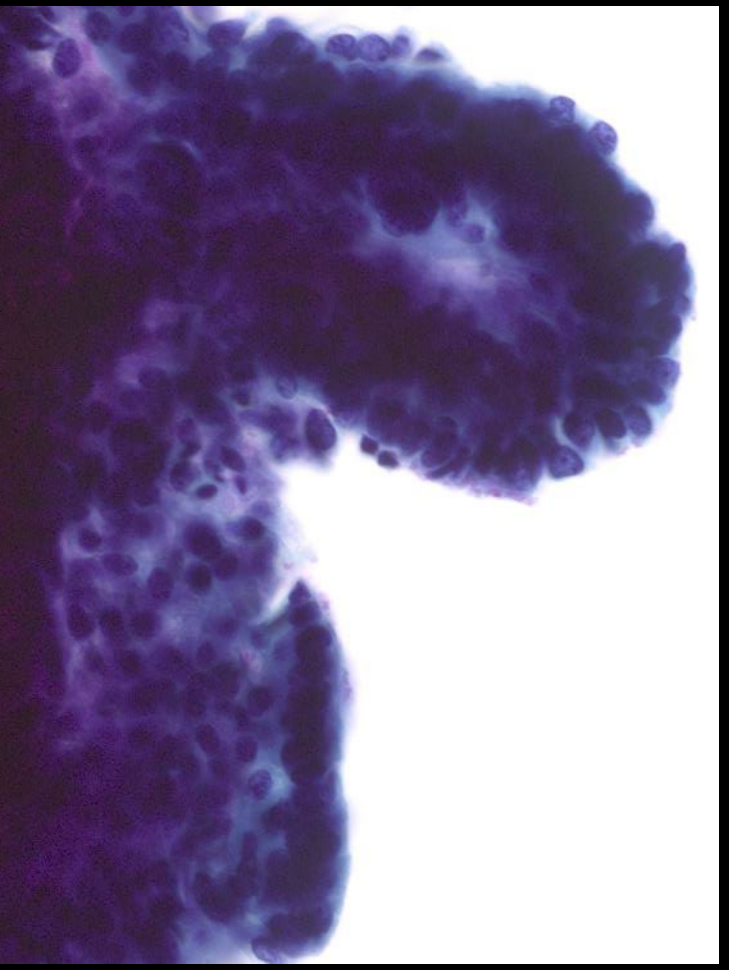
Extrauterine Malignancies

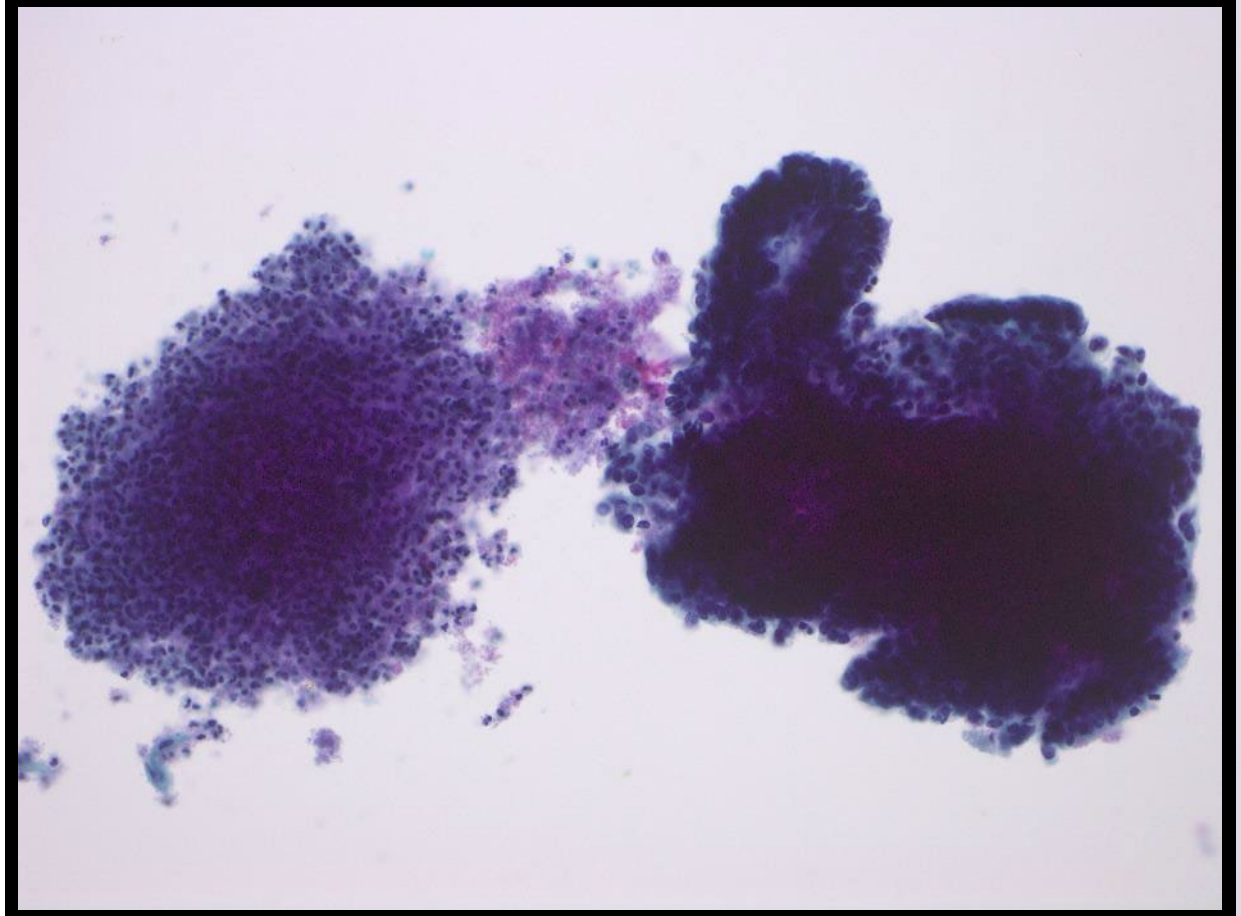
HOUSTON Methodist
LEADING MEDICINE

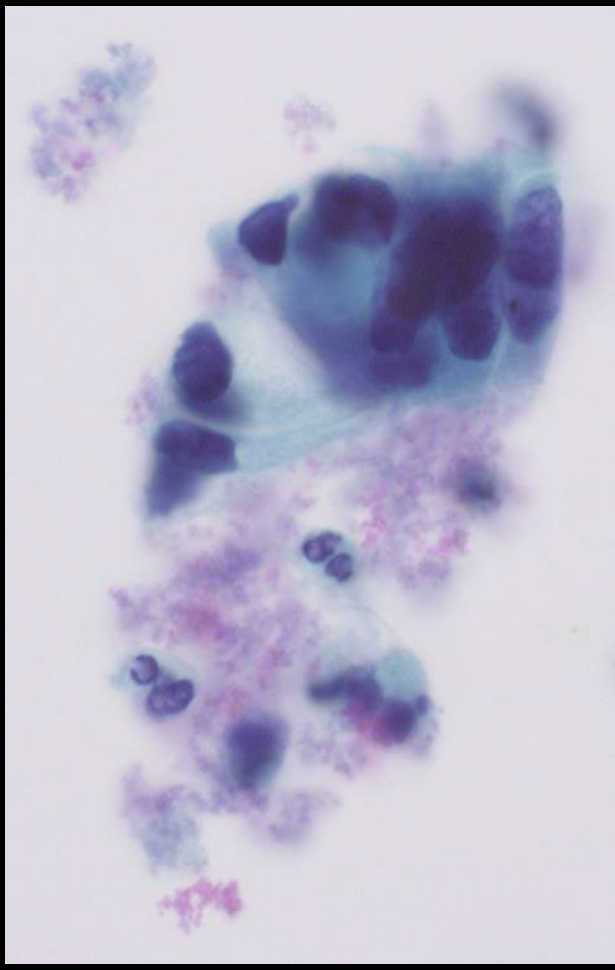
Extra-Uterine Malignancies

- Malignancies from adjacent structures may invade directly into the vagina or cervix and appear in Pap tests
  - Rectum, bladder, and vulva most common
- Metastasis from distant sites may also rarely occur
  - Lobular breast carcinoma may be especially problematic
- These malignancies usually have an obvious prior history
- Cell blocks and immunohistochemistry may be helpful

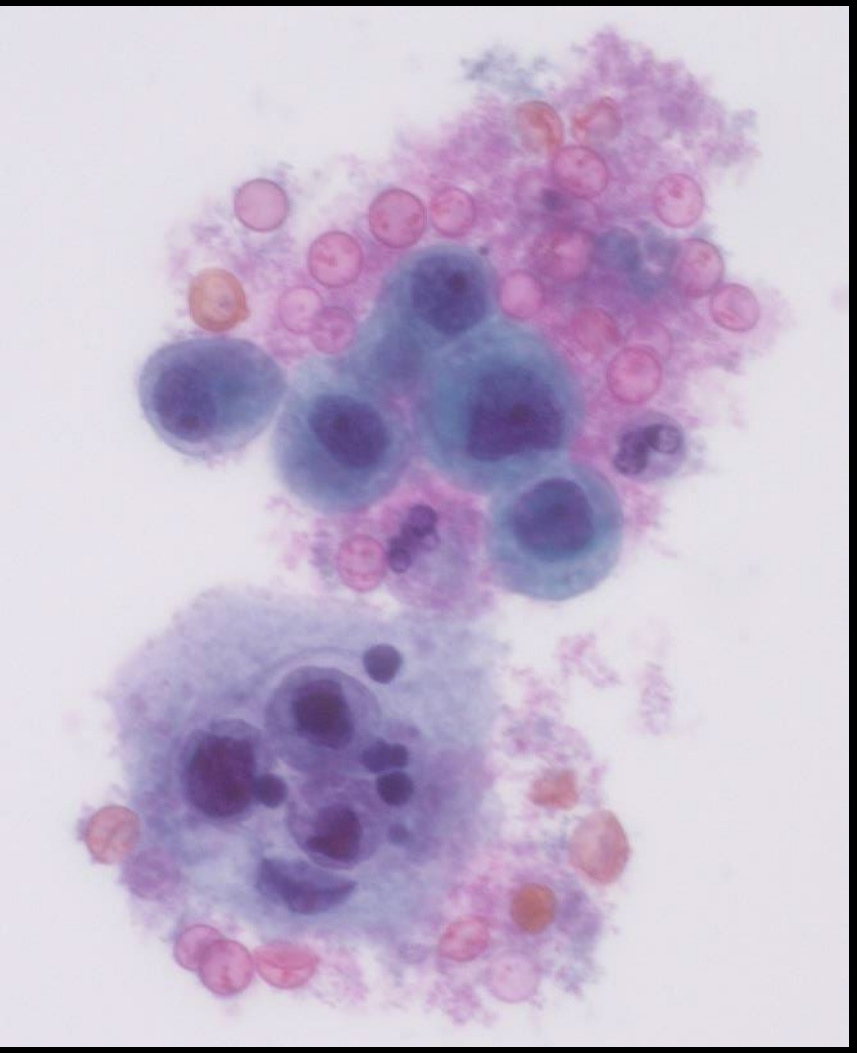
Rectal Adenocarcinoma

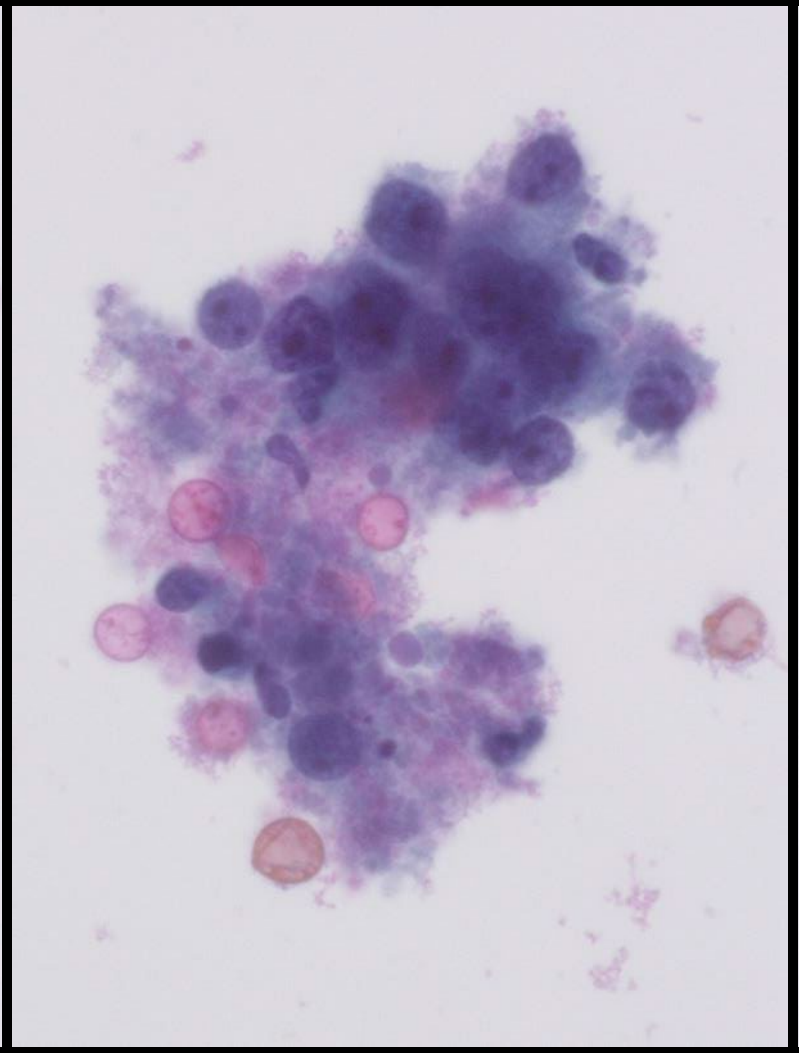


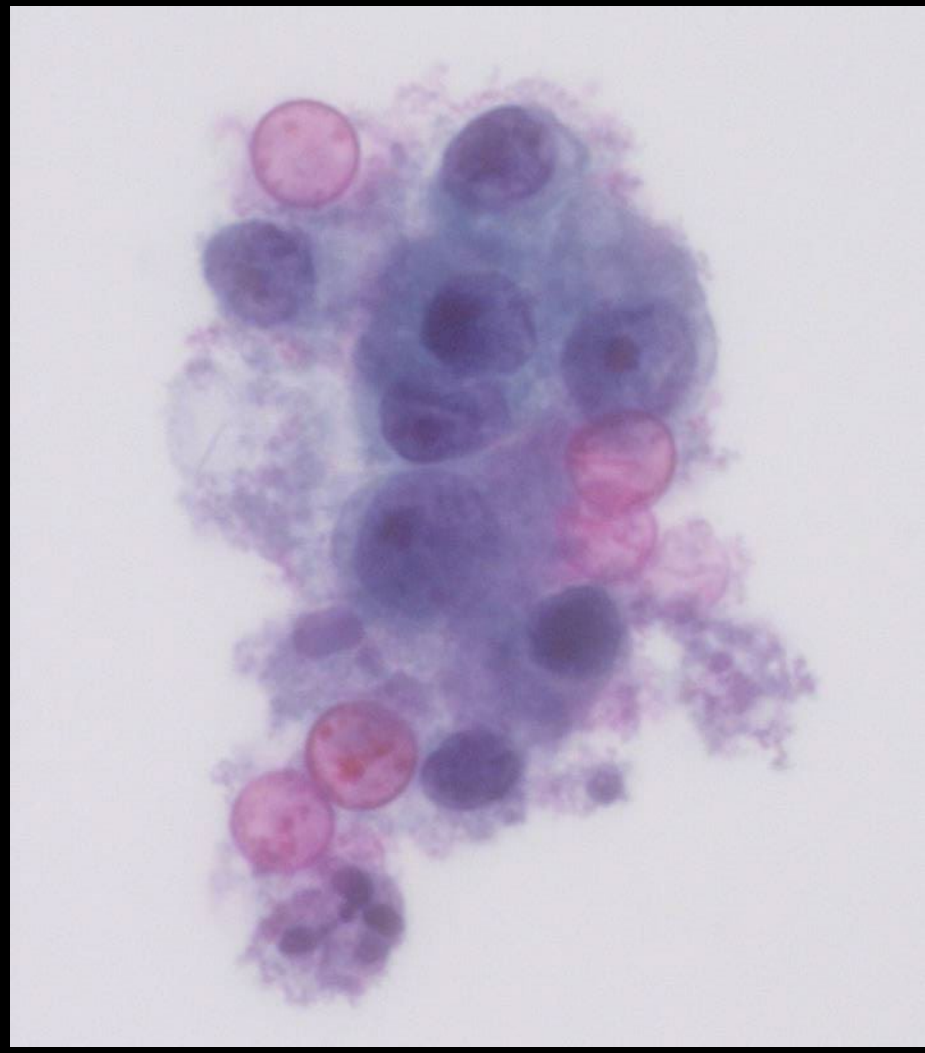




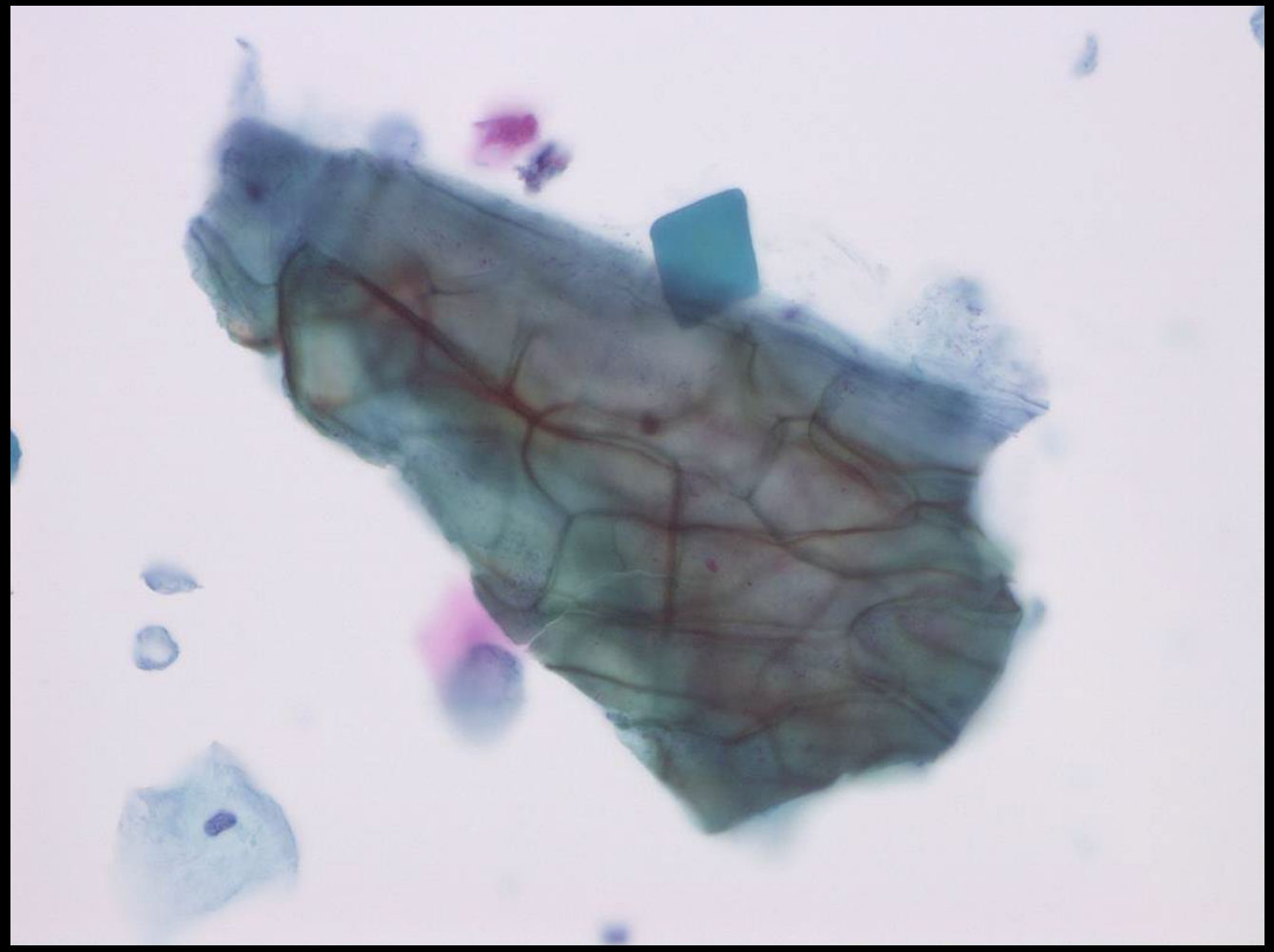
Rectal Adenocarcinoma (Signet Ring Type)

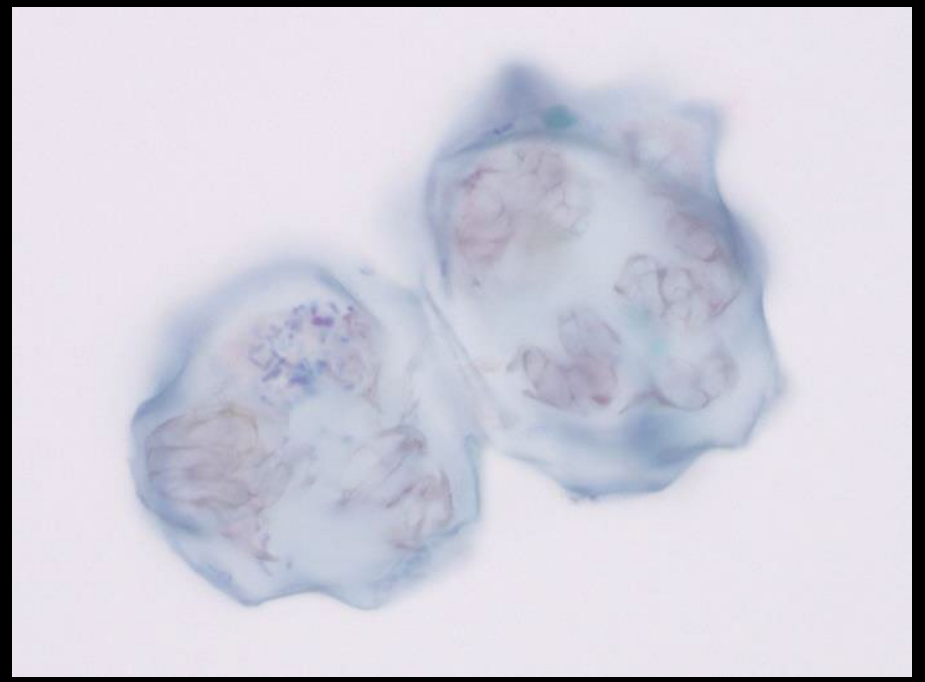


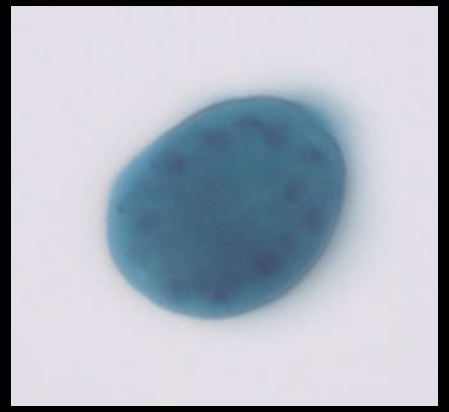




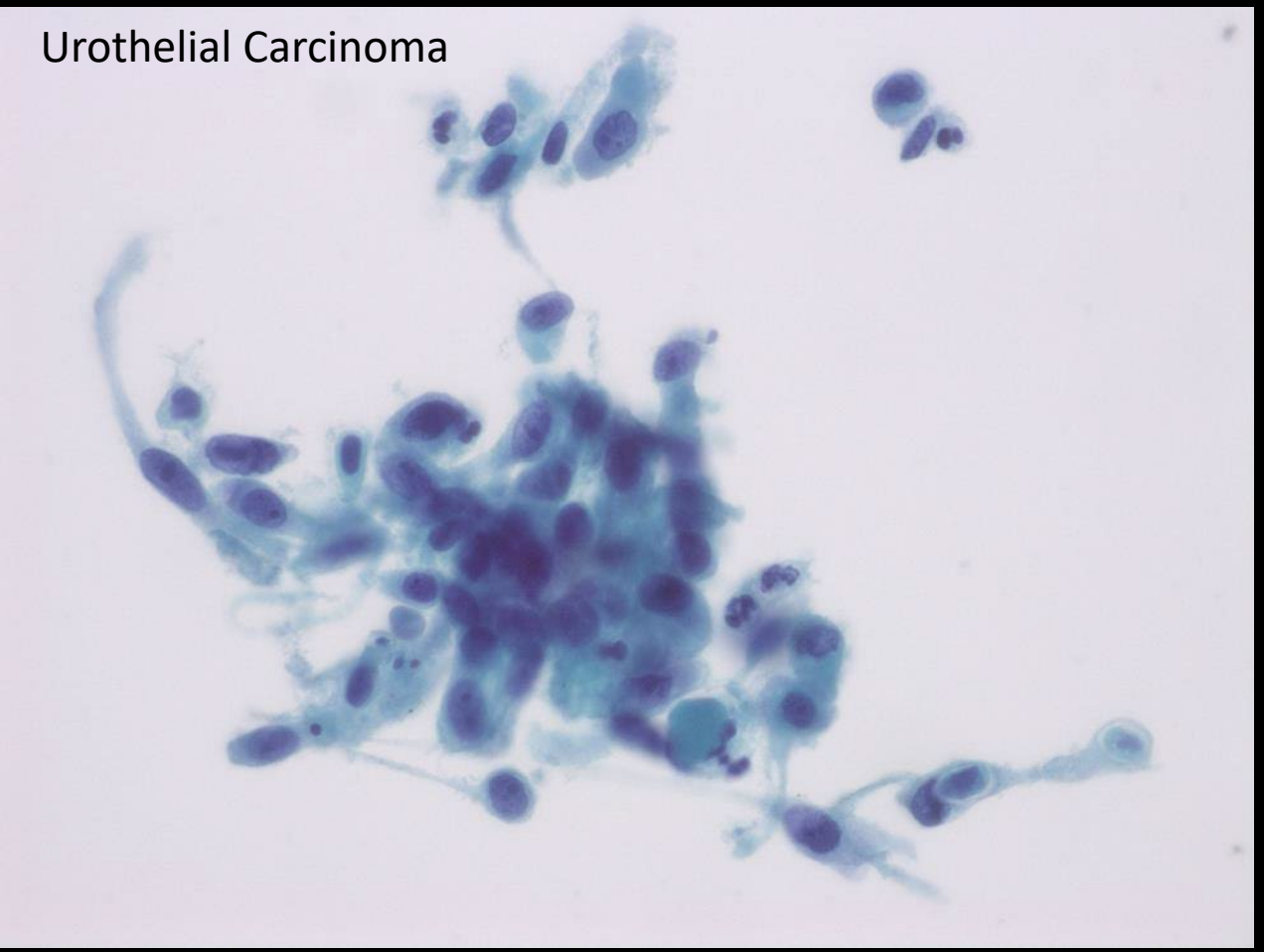
Vegetable Matter Due to Fistula Post-Irradiation

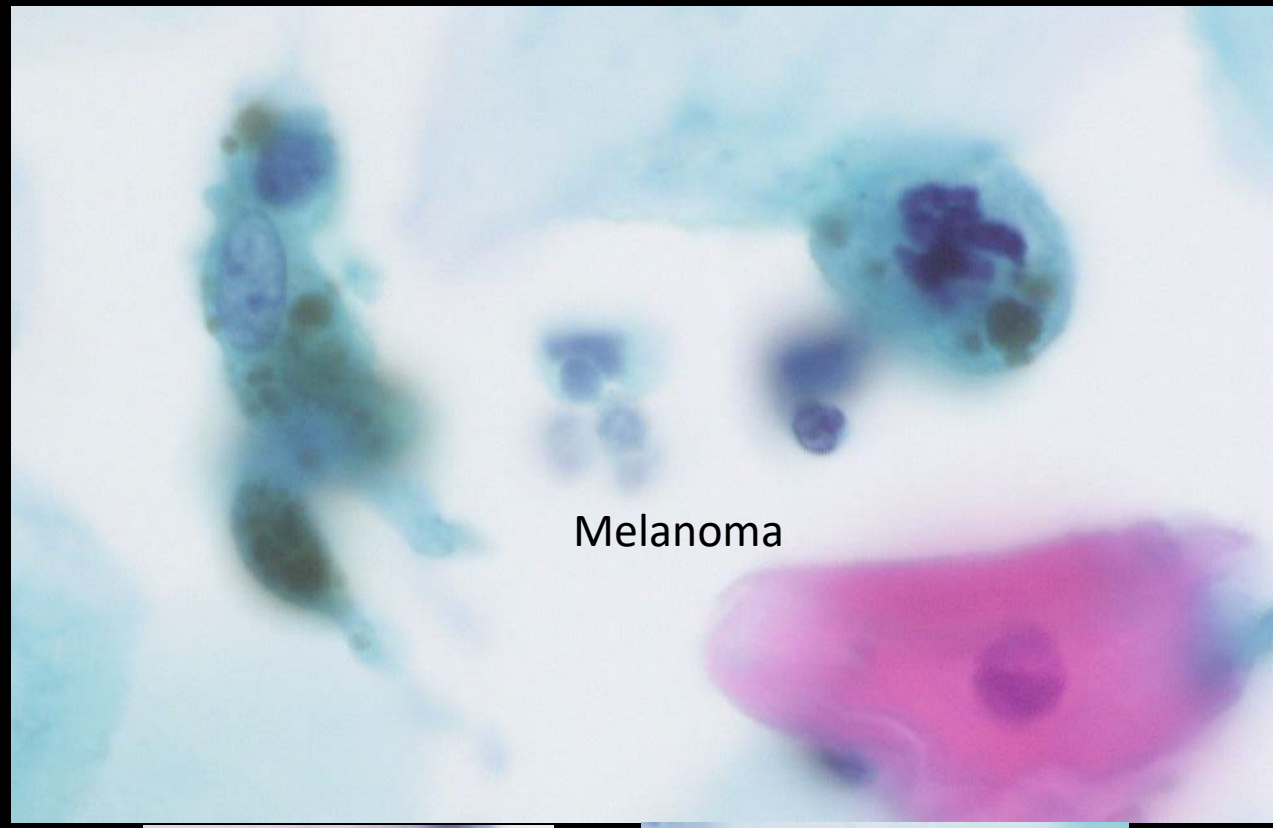


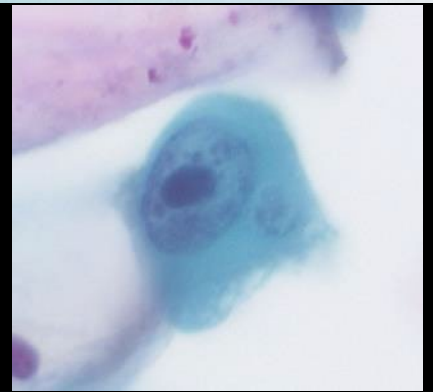


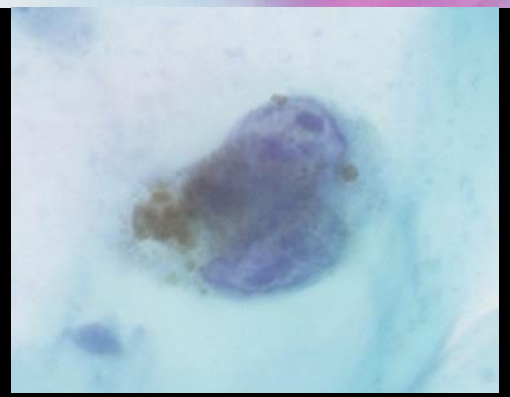


Other Extra-Uterine Malignancies





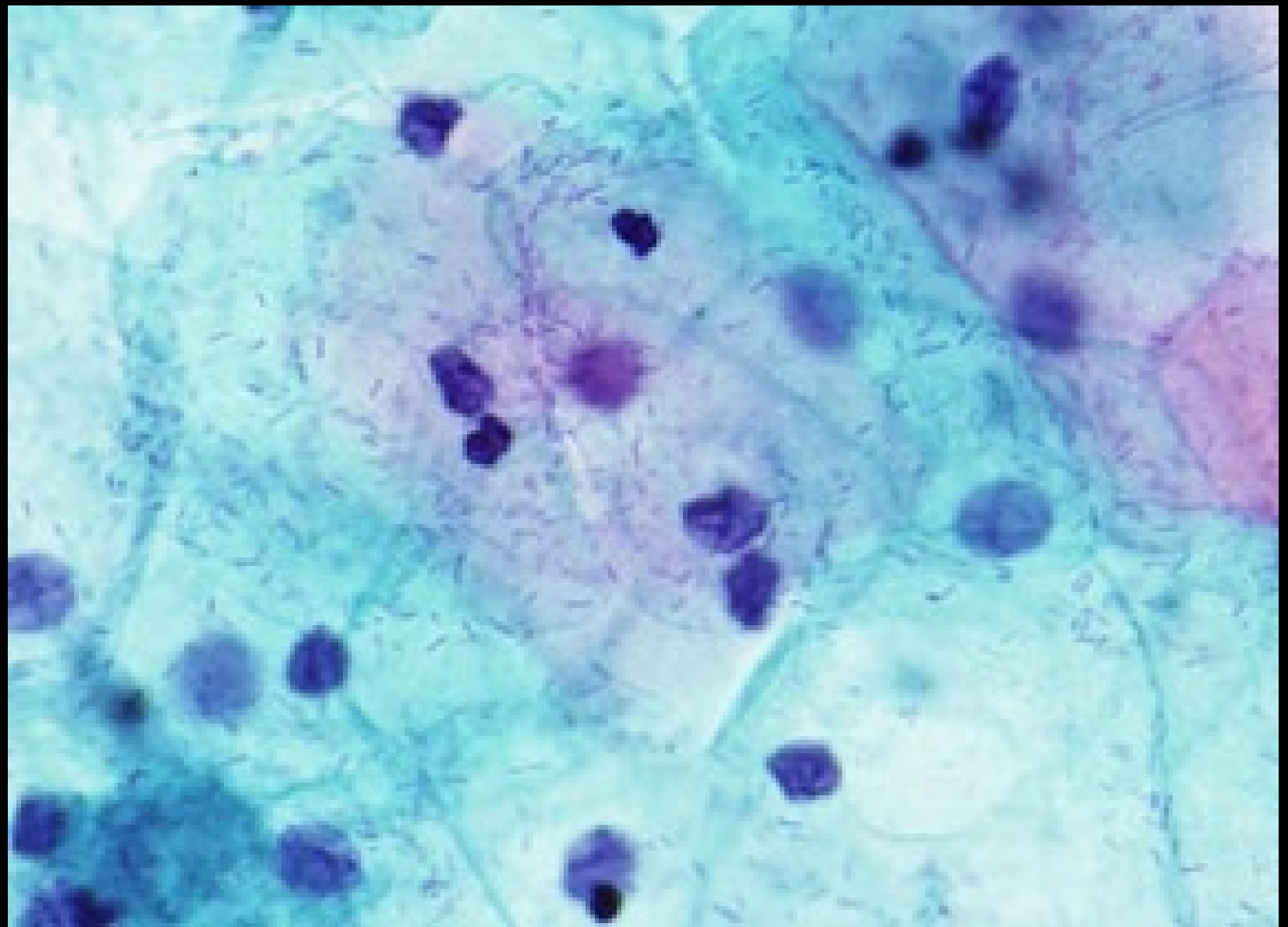




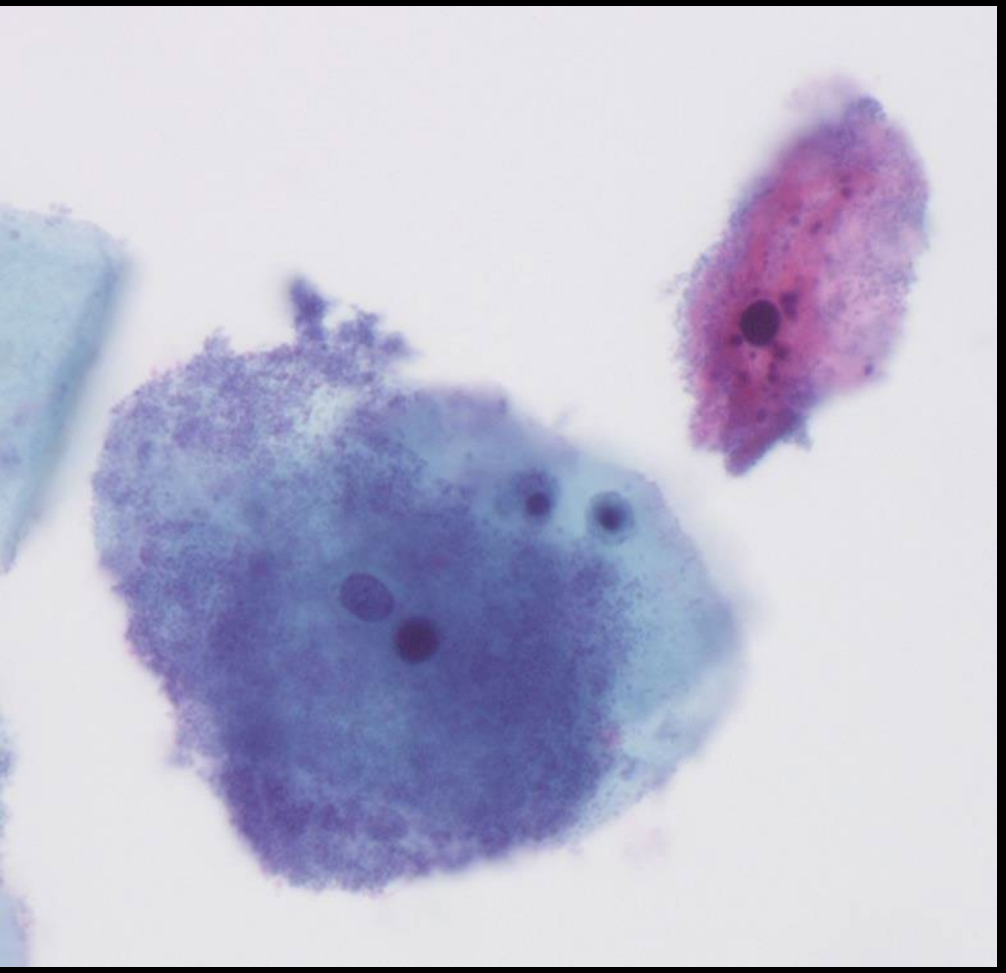
Organisms

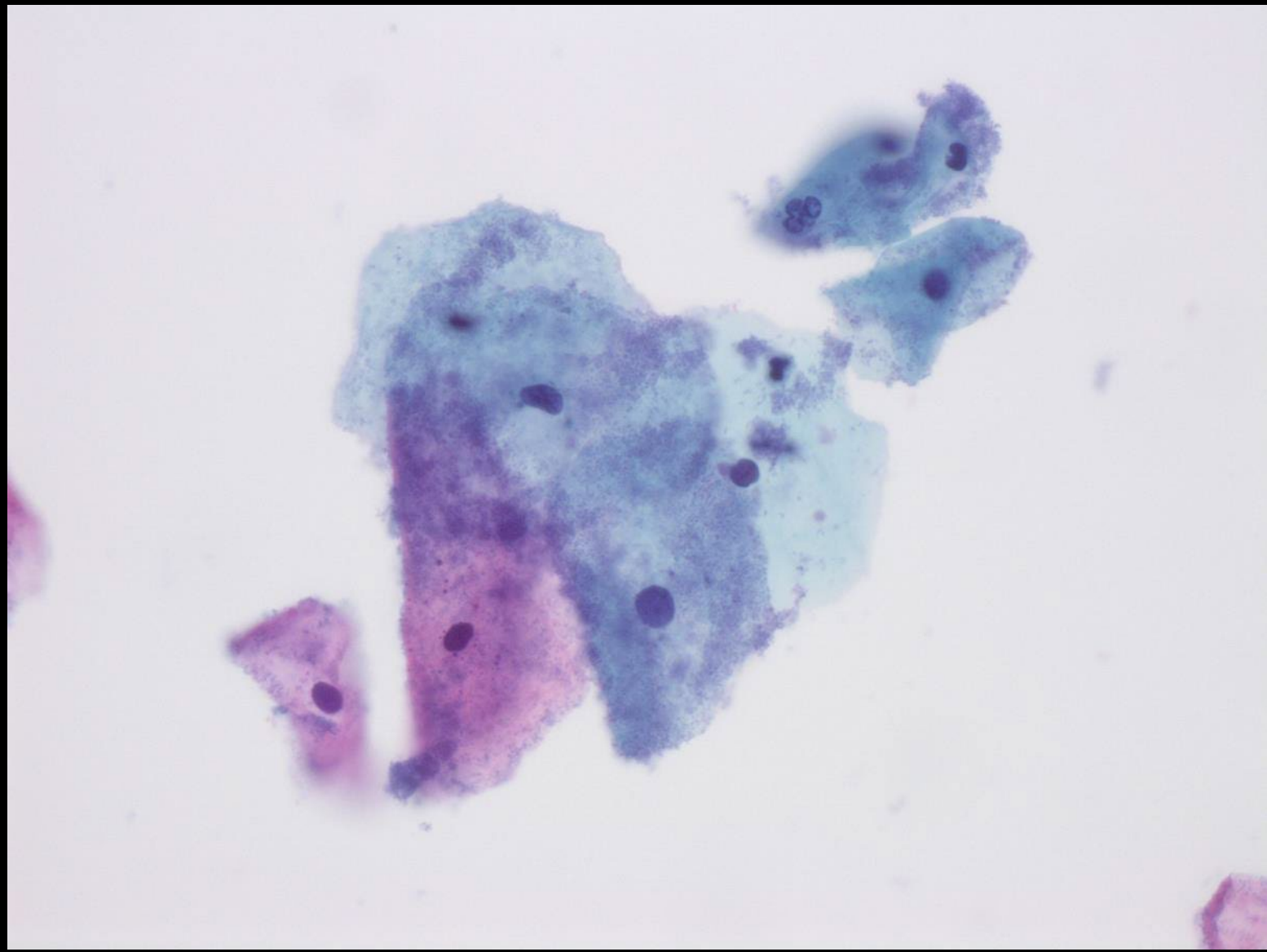
HOUSTON Methodist
LEADING MEDICINE

Normal - Lactobacillus (Döderlein Bacillus)

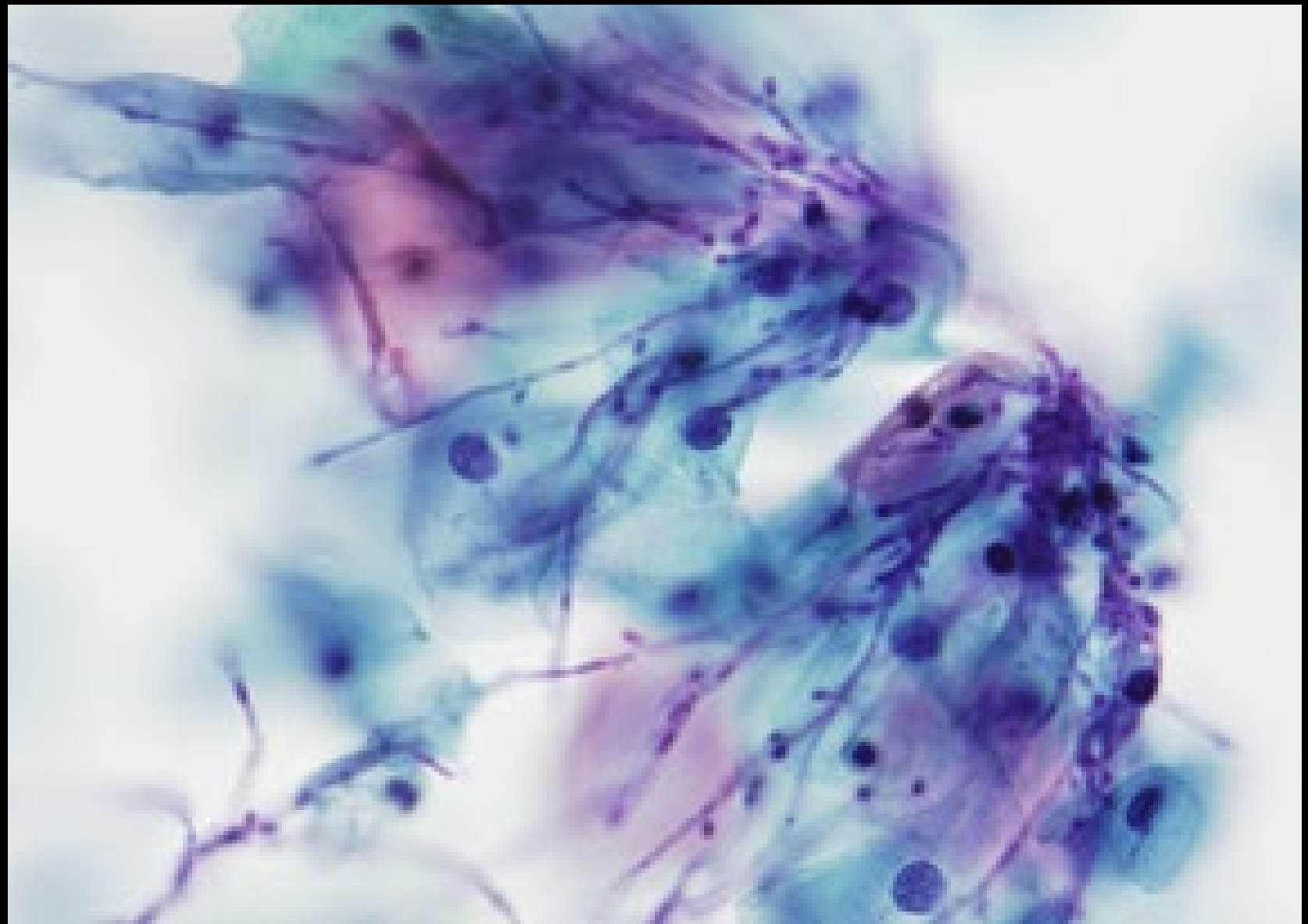


Bacterial Vaginosis - Gardnerella

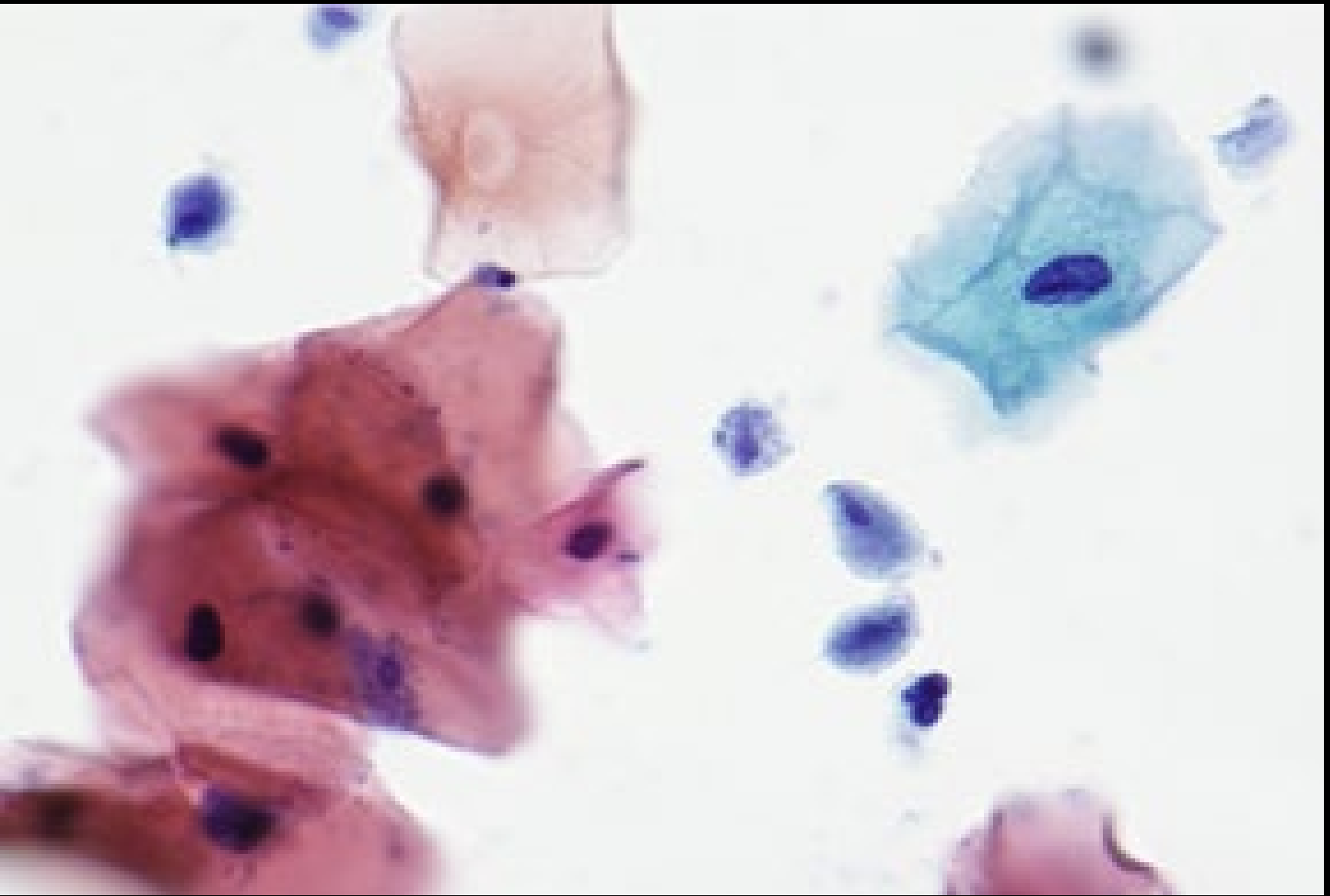


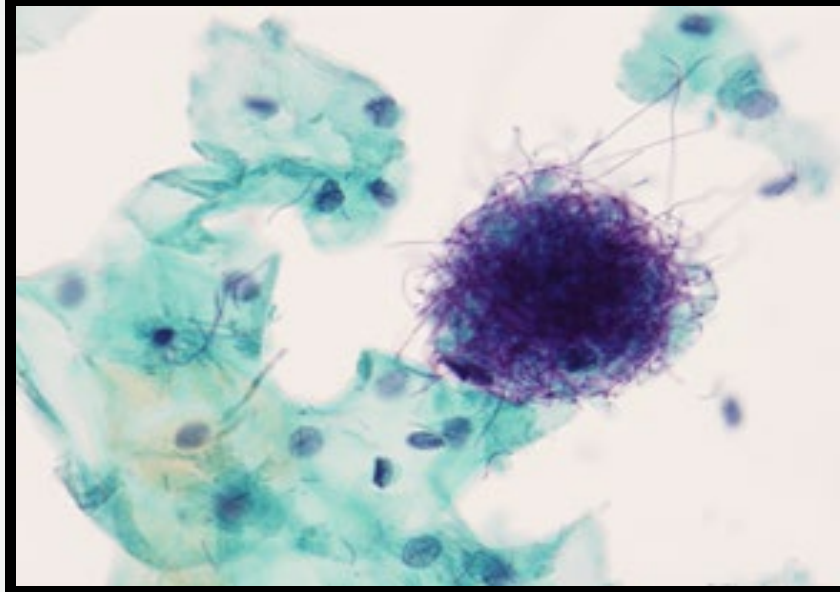


Candida

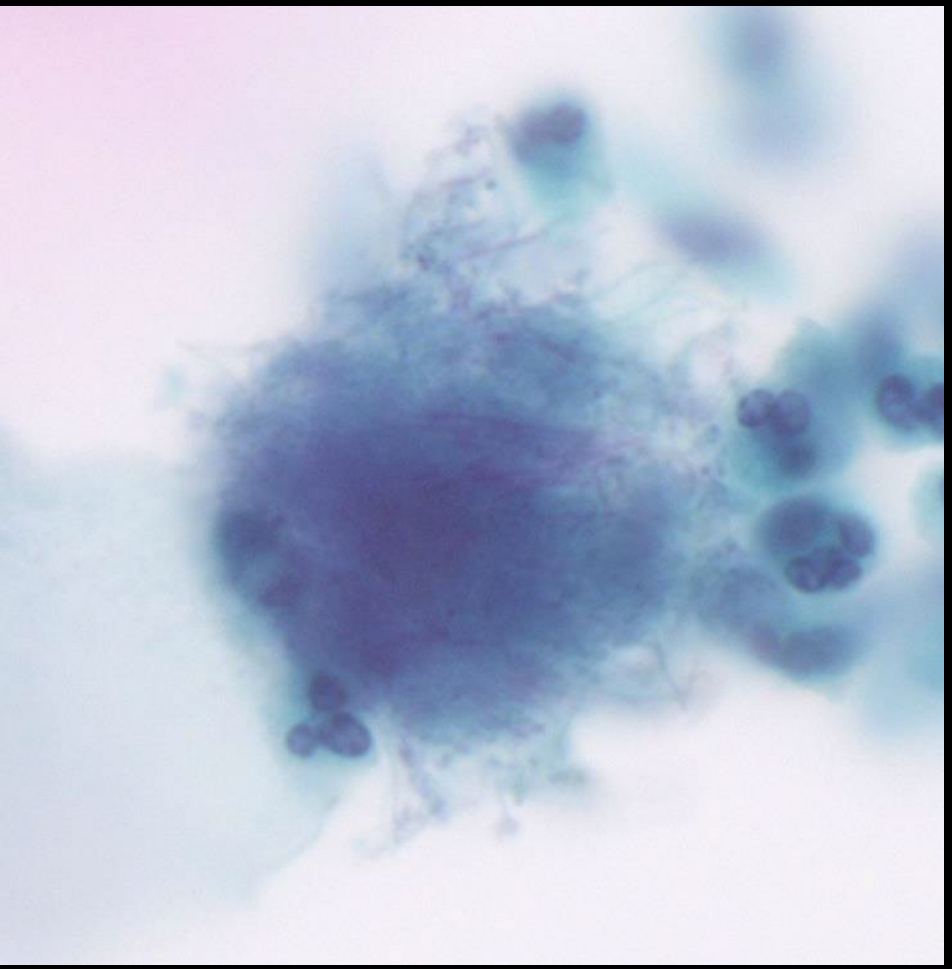


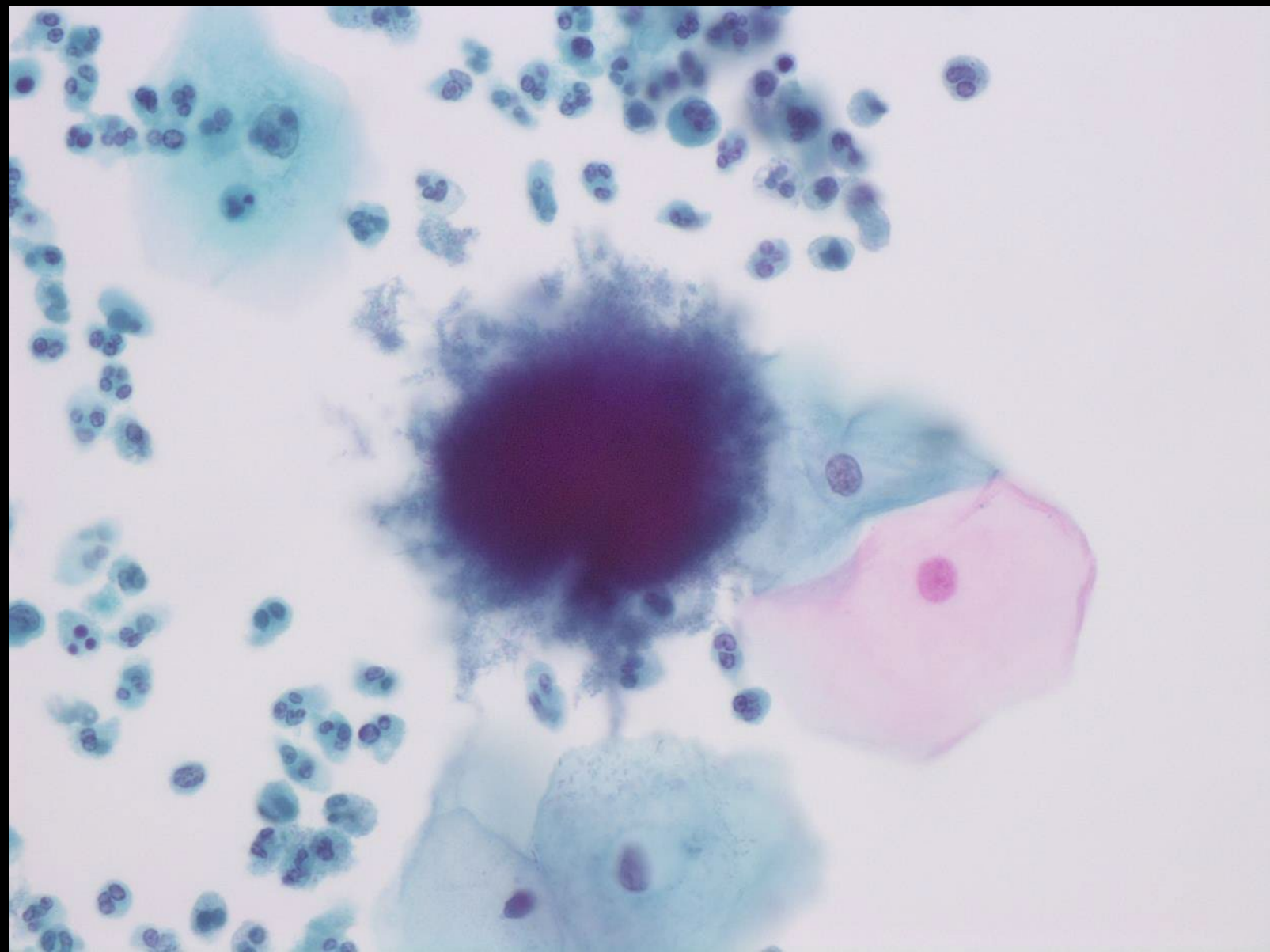
Trichomonas and Leptothrix





Actinomyces





Herpes