



# HKIAP 2023 Scientific Congress Spring Scientific Meeting

## UTERINE PATHOLOGY

PHILIP IP

CLINICAL PROFESSOR OF PATHOLOGY

SCHOOL OF CLINICAL MEDICINE

HKU



# UTERINE PATHOLOGY

1. PRACTICAL ISSUES OF ENDOMETRIAL PROLIFERATIVE LESIONS IN SMALL BIOPSIES
2. ENDOMETRIAL CANCER REPORTING BEYOND 2020 WHO CLASSIFICATION
3. SLIDE SEMINAR: APPROACH TO DIAGNOSIS OF UTERINE MESENCHYMAL NEOPLASMS



# Learning Objectives: Practical issues of Endometrial Proliferative lesions in small biopsies

- ▶ Improve proficiency in the assessment of endometrial cytologic atypia.
- ▶ Recognise the different forms of endometrial metaplasias, their significance, and their association with premalignant lesions or carcinomas.
- ▶ Learn the importance of obtaining a drug history in everyday signouts of small endometrial biopsies.



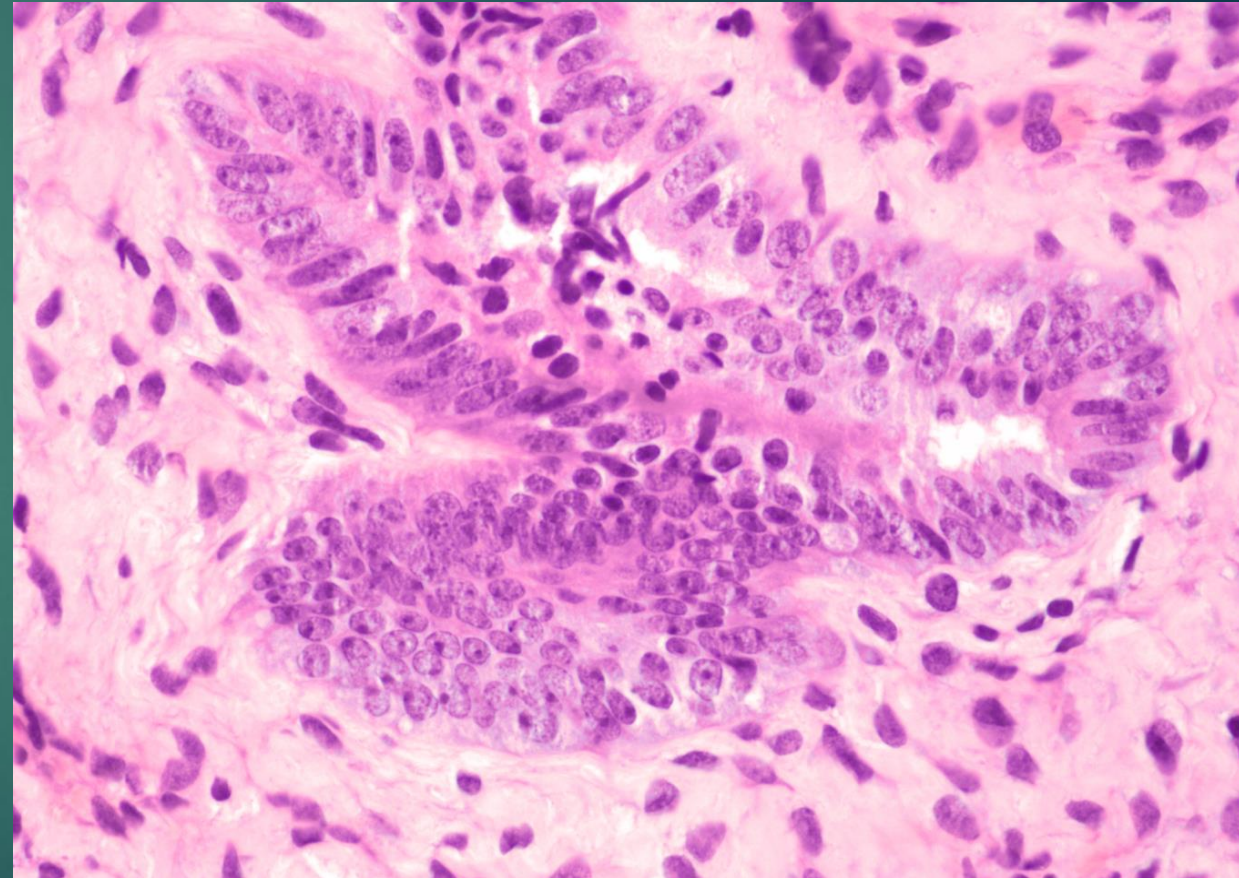
# Endometrial Hyperplasia: WHO 2020

- ▶ **Hyperplasia without atypia**
- ▶ **Atypical hyperplasia**
  
- ▶ Atypia refers only to cellular atypia.



# Atypical Hyperplasia: Morphology

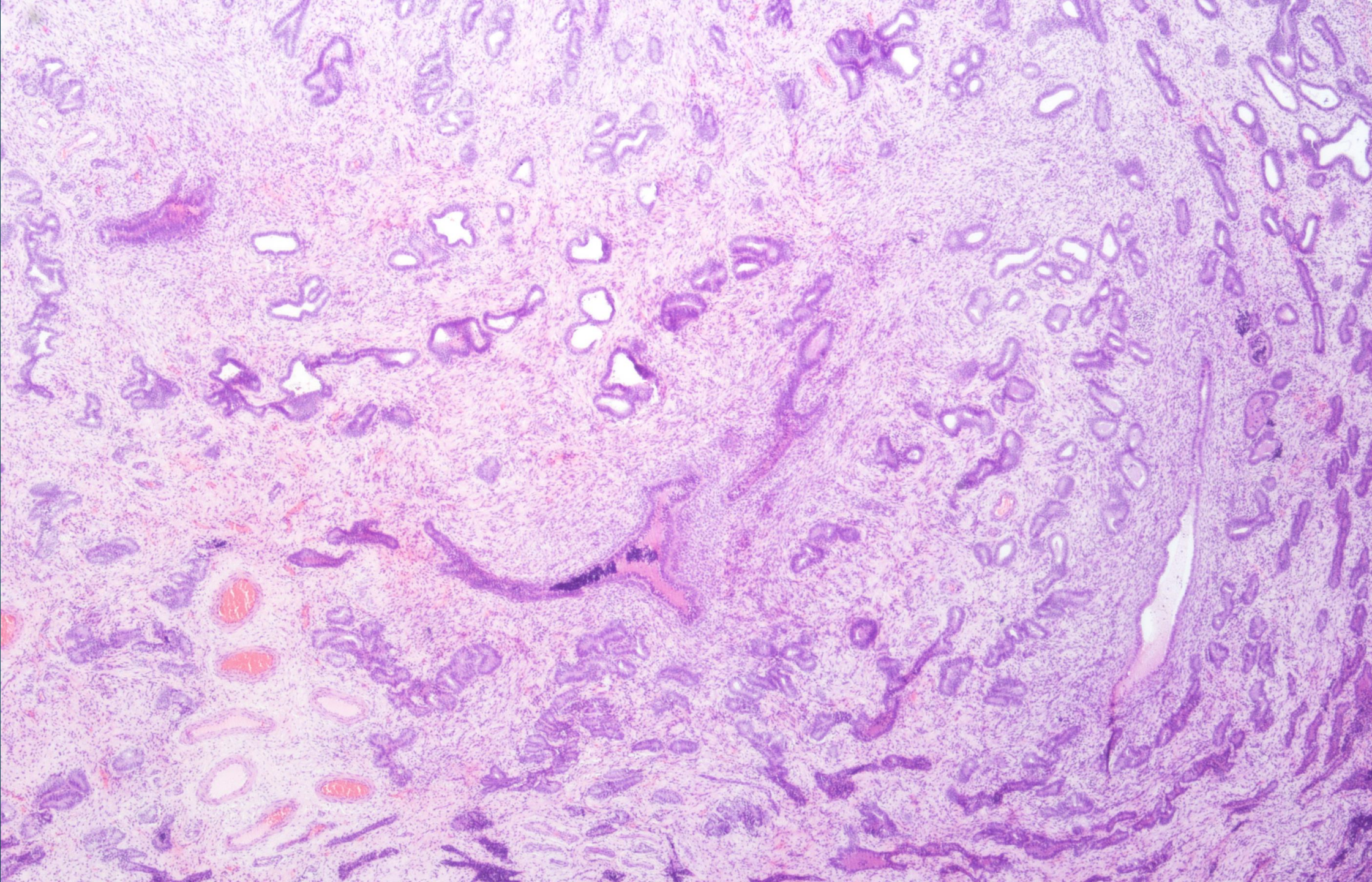
- ▶ **Atypia** refers only to **cellular atypia**.
- ▶ Loss of nuclear polarity
- ▶ Round, rather than oblong nuclei
- ▶ Nuclear enlargement and pleomorphism
- ▶ Altered chromatin (coarse or vesicular)
- ▶ Prominent nucleolus





# Difficulties in Assessment of Cytologic atypia

- ▶ **Difficulty of assessment may arise in the following scenarios:**
- ▶ Focal (or multifocal) atypical hyperplasia
- ▶ Superimposed secretory change
- ▶ Co-existing metaplasia
- ▶ Prior hormonal treatment





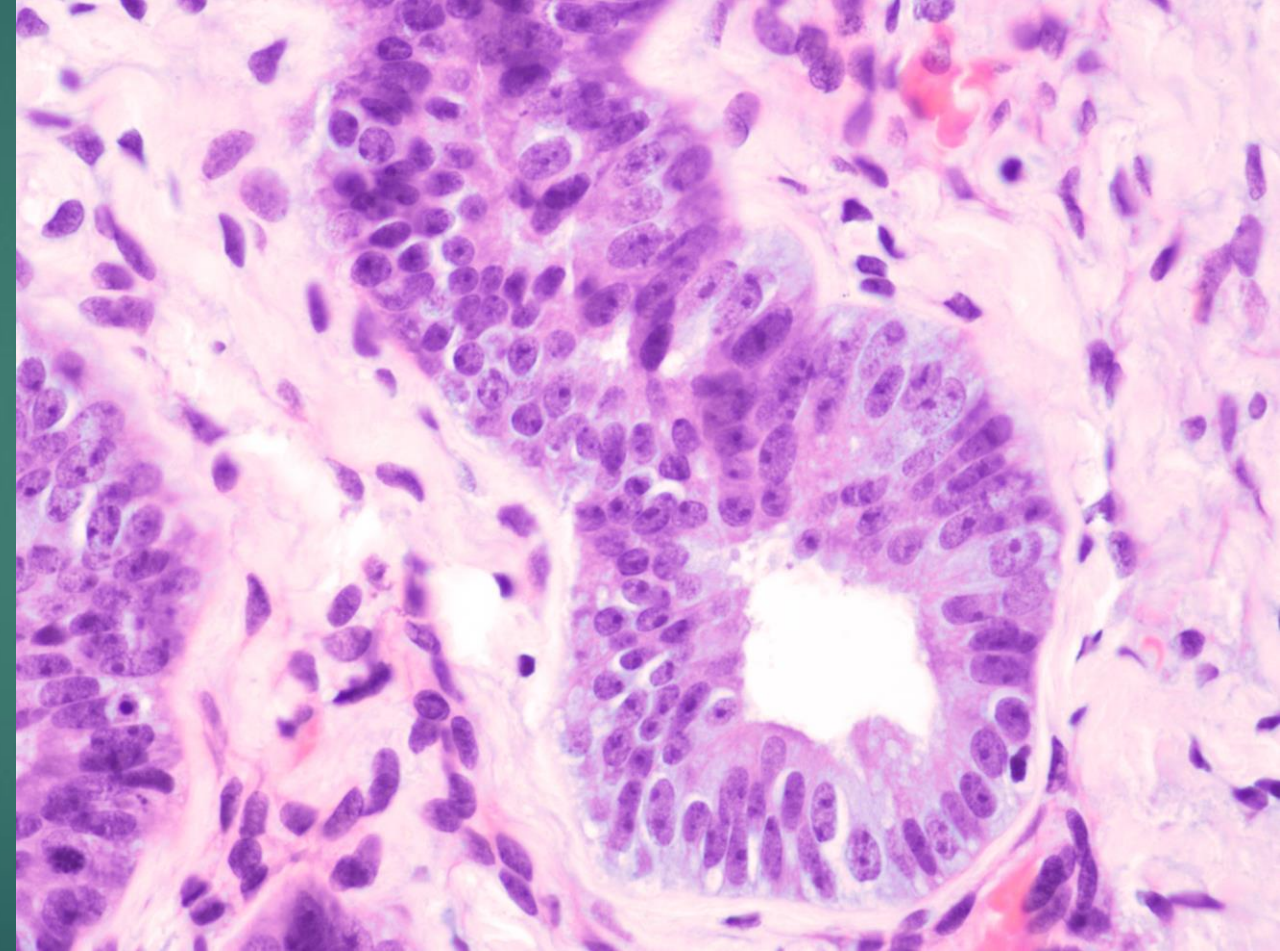
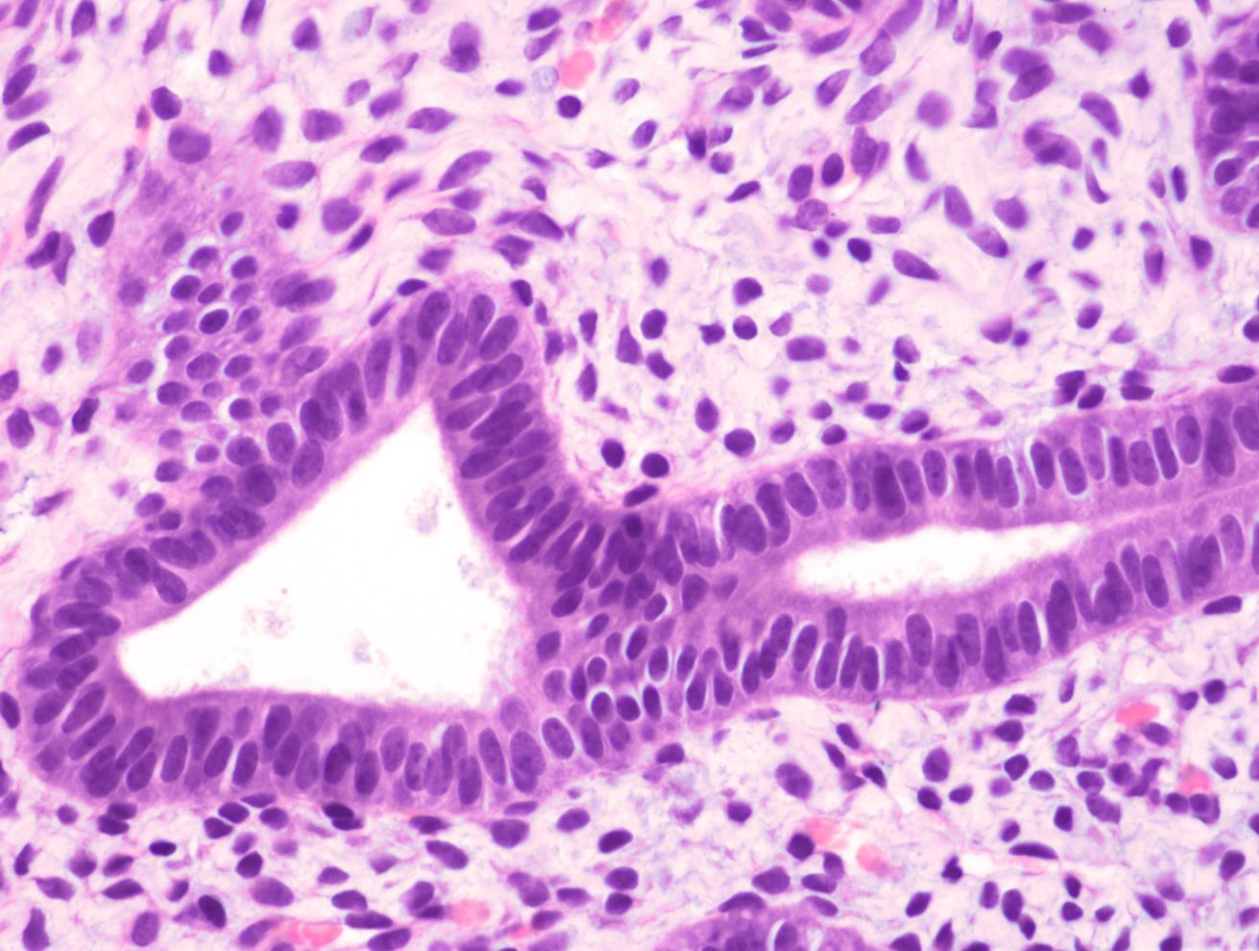
# Focal Atypical Hyperplasia

- ▶ 'Focal' refers to the hyperplastic focus restricted to part of the endometrium (defined by ChatGPT).
- ▶ Endometrial intraepithelial neoplasia (EIN), although used synonymously with atypical hyperplasia now, but the original definition is useful for diagnosis of focal atypical hyperplasia.
- ▶ Gland to stroma ratio of >1:1
- ▶ Epithelial cells that differ cytologically from those of the background glands
- ▶  $\geq 1$  mm





# Focal Atypical Hyperplasia



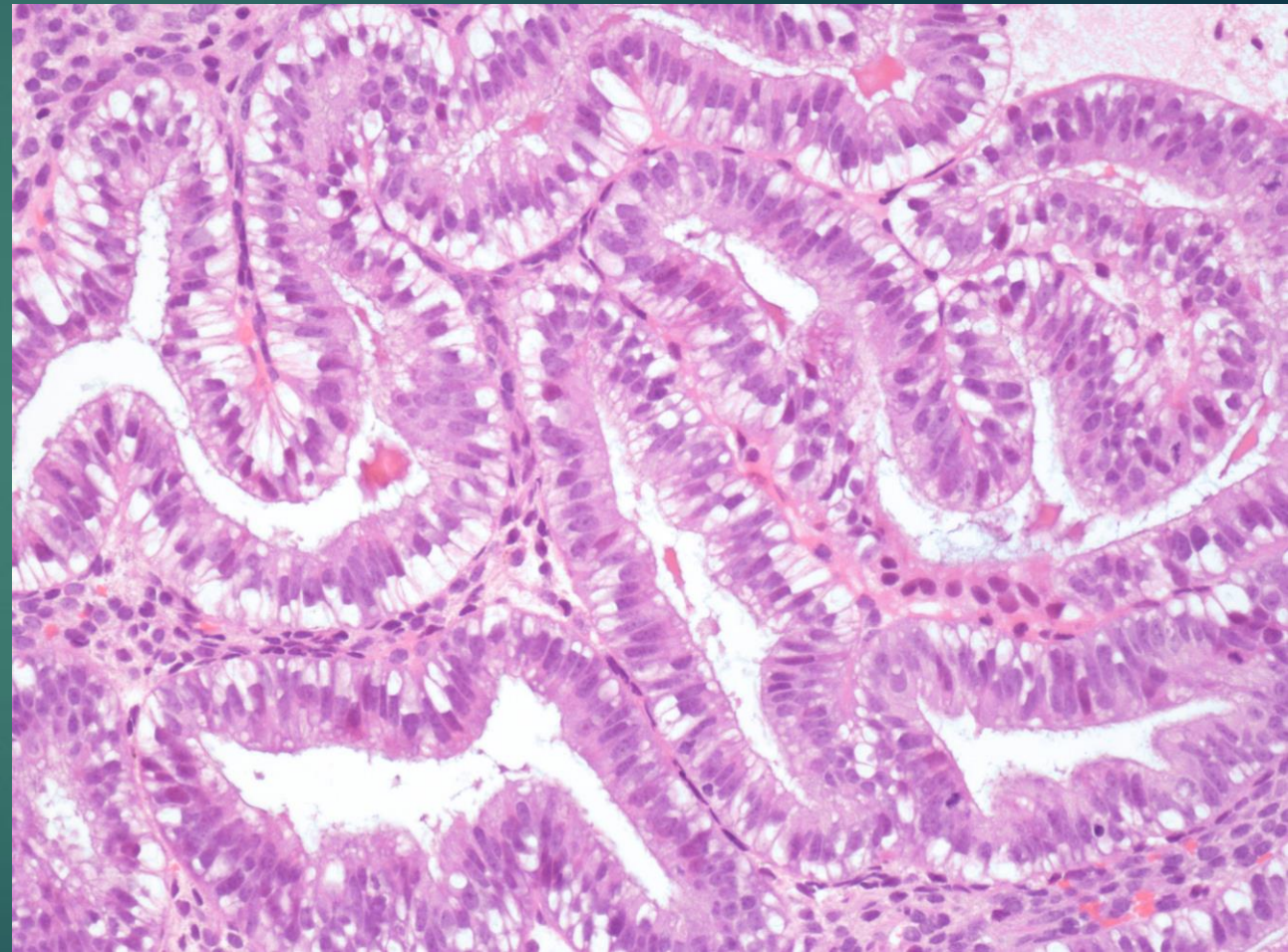
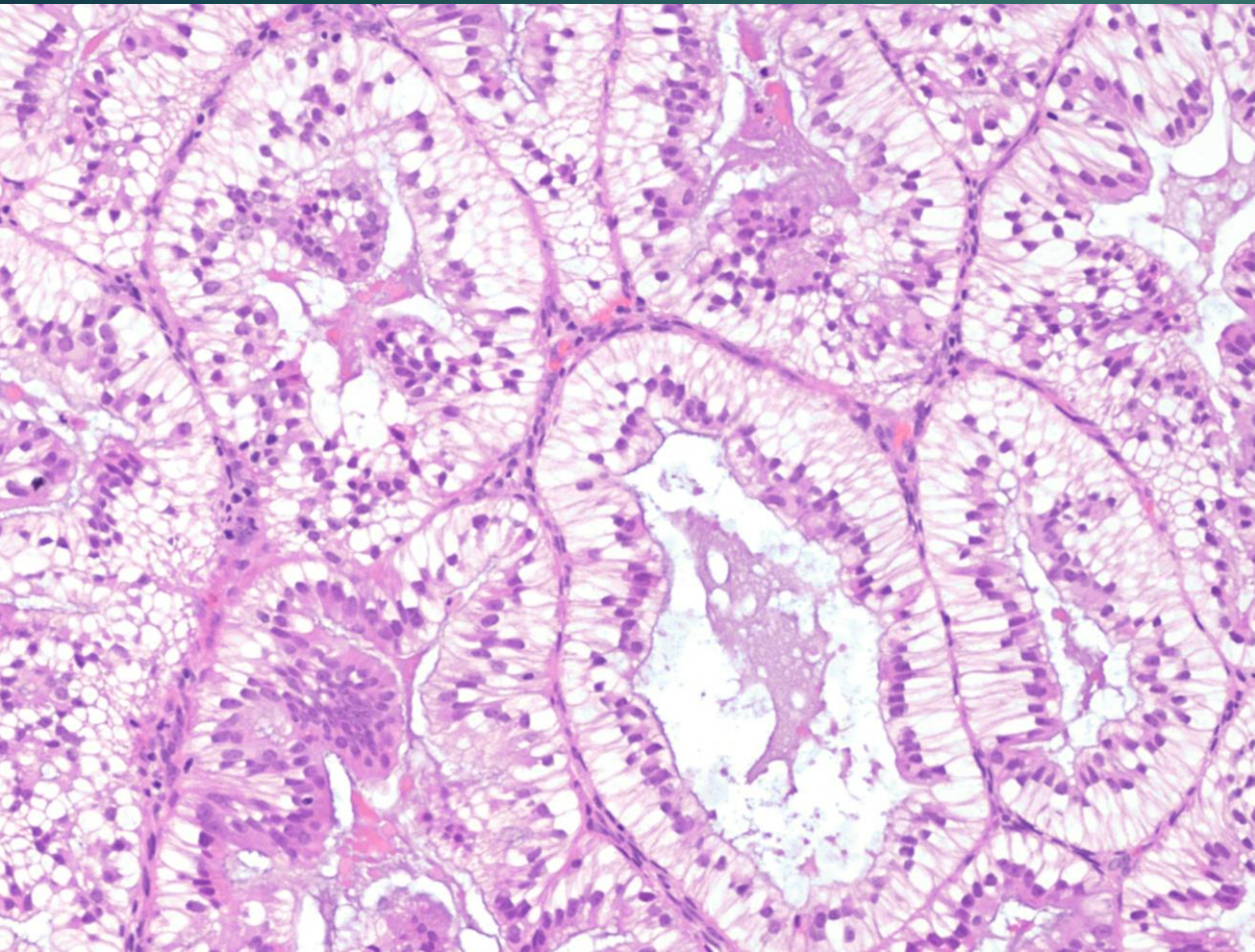


# Hyperplasia with Secretory change

- ▶ Secretory change in crowded glands may be due to spontaneous ovulation after several anovulatory cycles, or due to exogenous hormones. Knowledge of clinical and drug history is essential.
- ▶ Microscopically, 'compared with normal secretory endometrium, hyperplasia shows greater degree of gland crowding, irregularly shaped glands with budding, branching, staghorn-shapes, and more haphazardly disposed'.

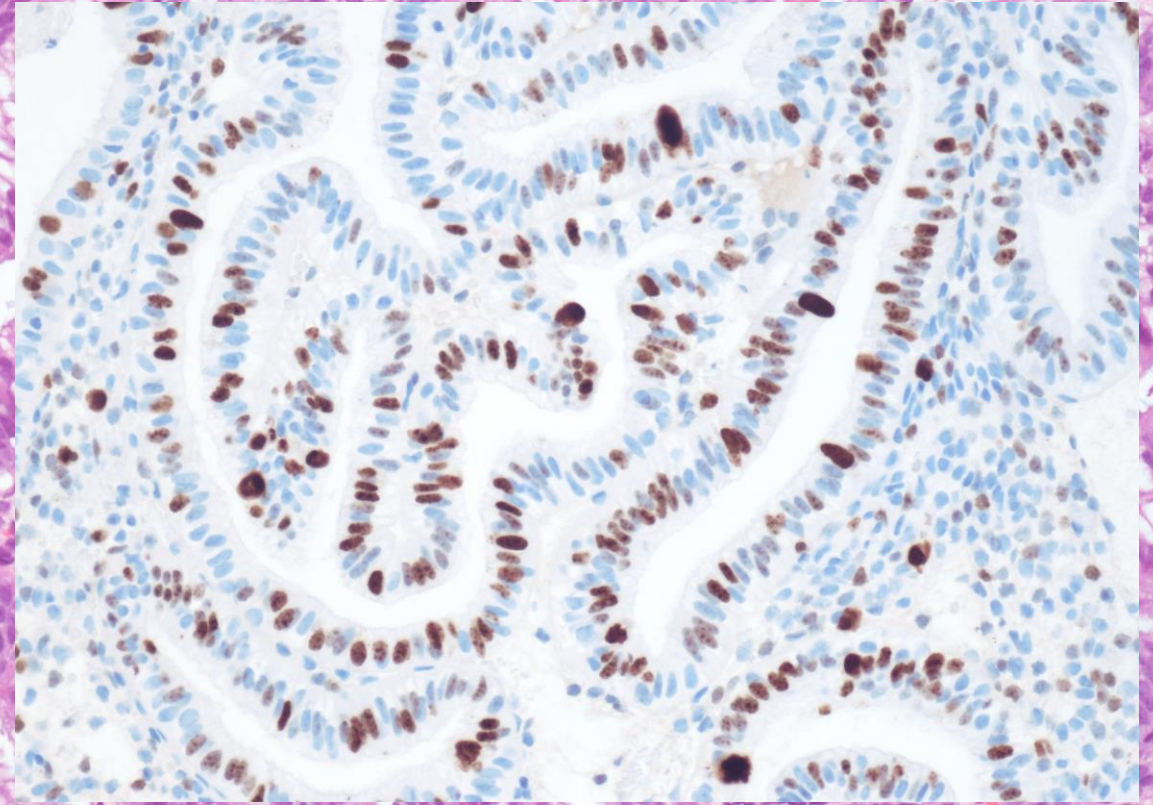
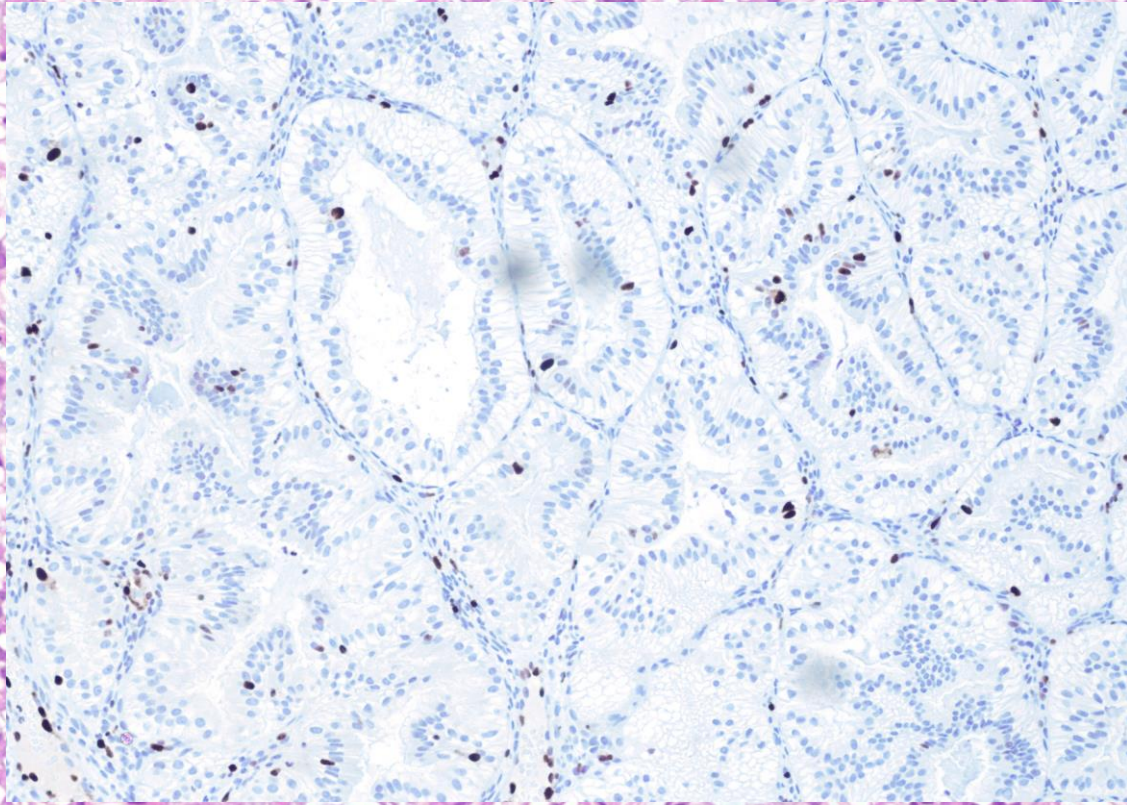


# Secretory Endometrium vs. Hyperplasia





# Secretory Endometrium vs. Hyperplasia





# Hyperplasia with Secretory change

- ▶ MIB1 proliferative index (Ki-67):
- ▶ ~2.6% in normal secretory endometrium
- ▶ 17% in nonatypical hyperplasia
- ▶ 36% in atypical hyperplasia
- ▶ 60% in endometrial Ca

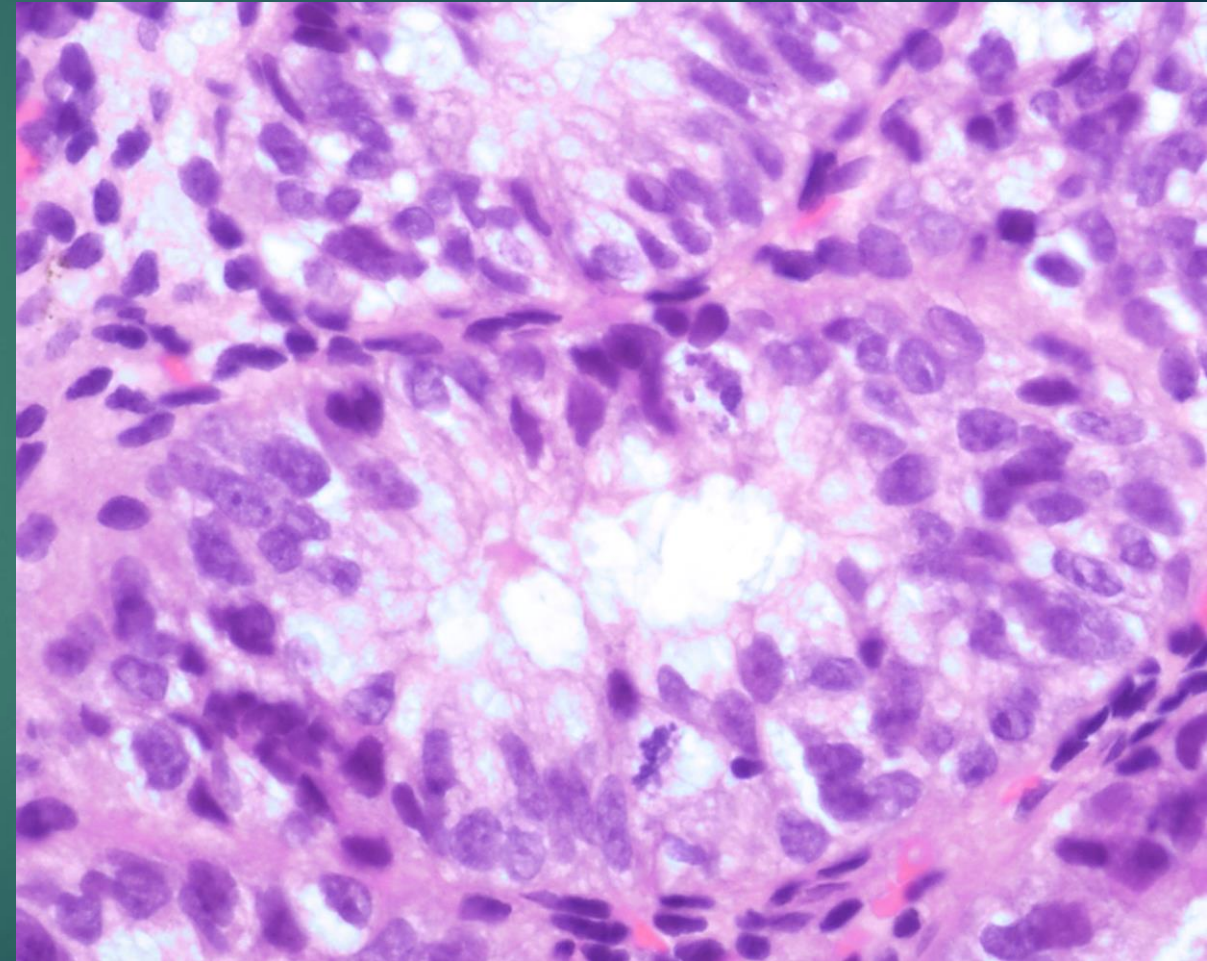
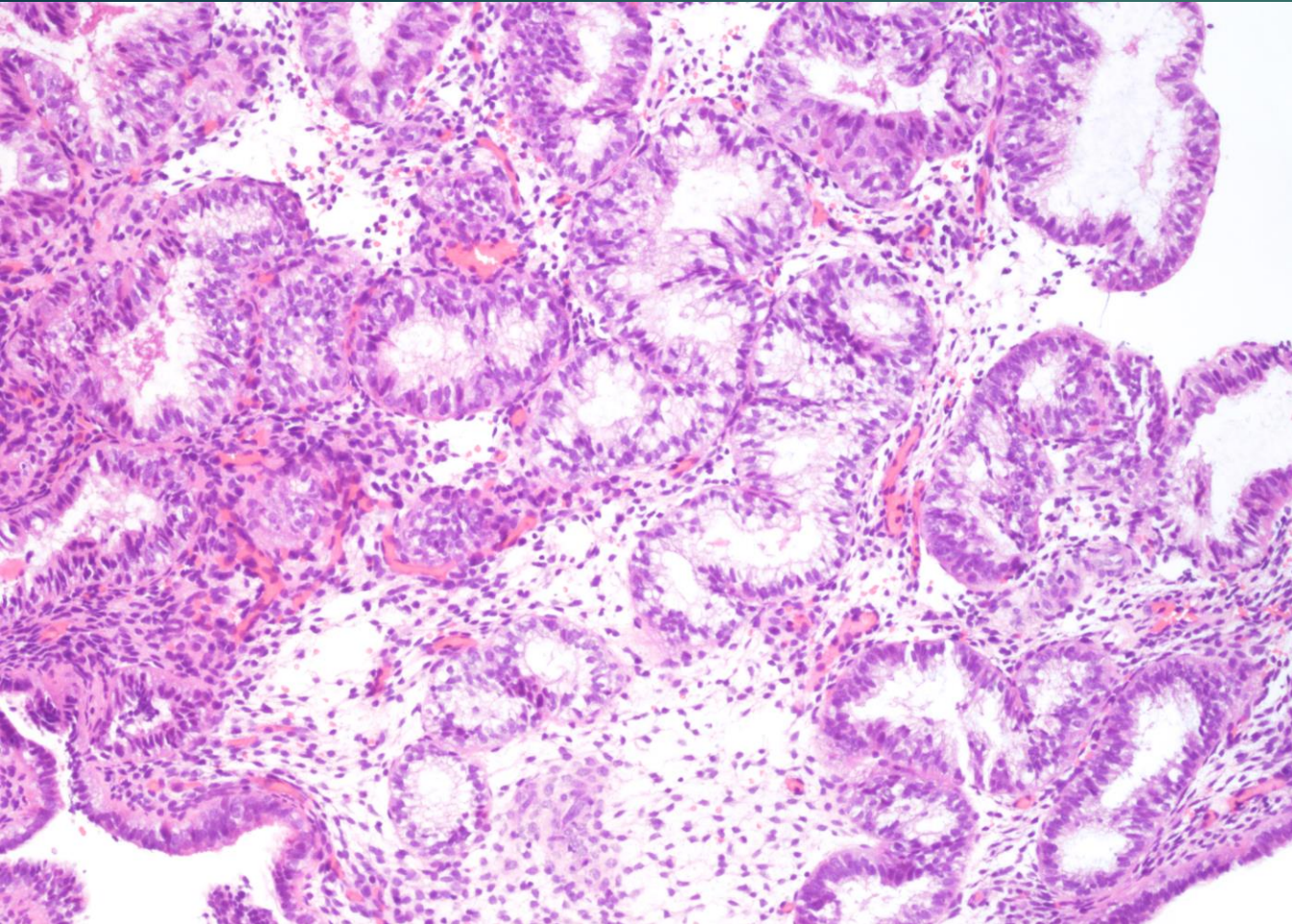
Truskinovsky AM. et al. Int J Gynecol Pathol. 2014

Jeffus SK. et al. Int J Gynecol Pathol. 2014

Gurda GT. et al. Int J Gynecol Pathol. 2014



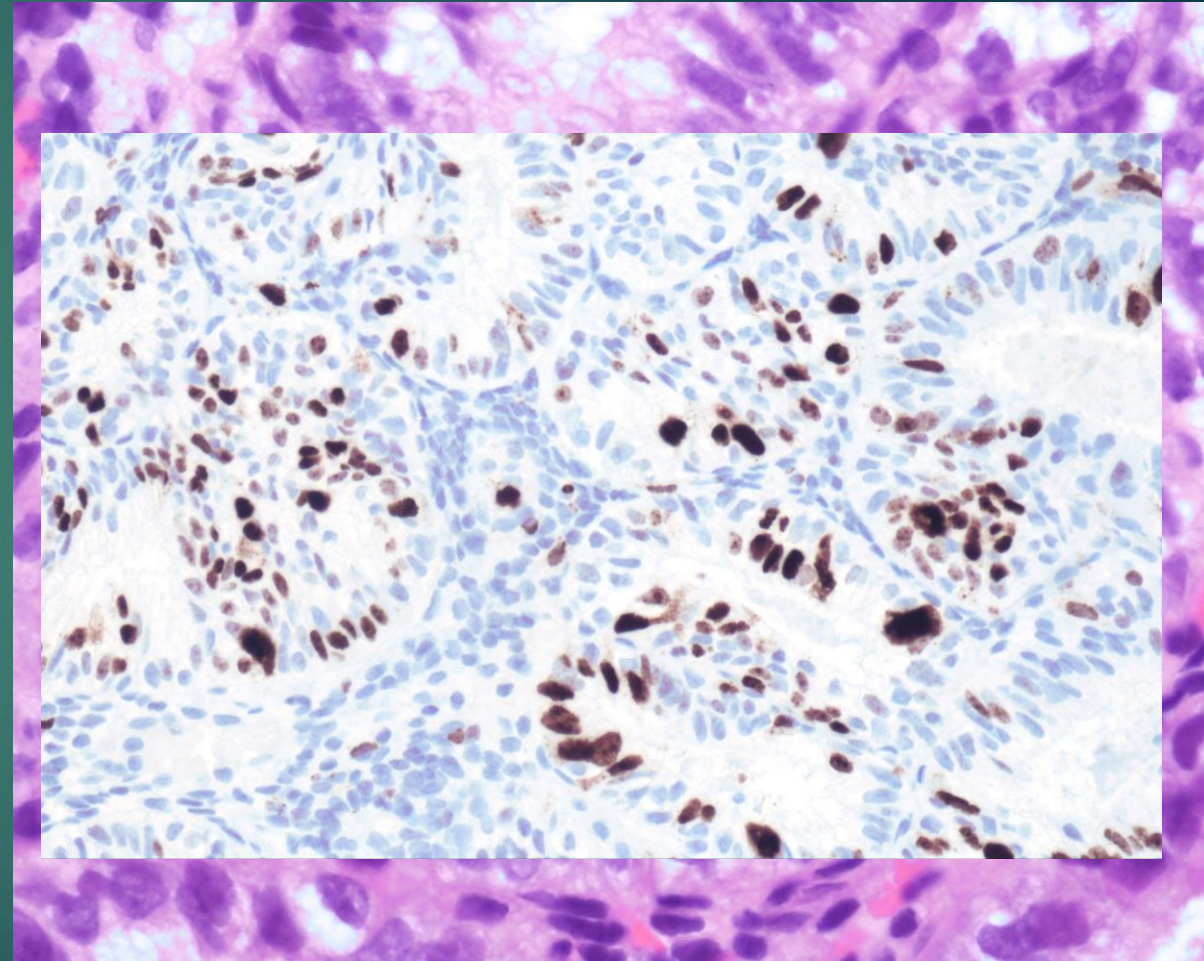
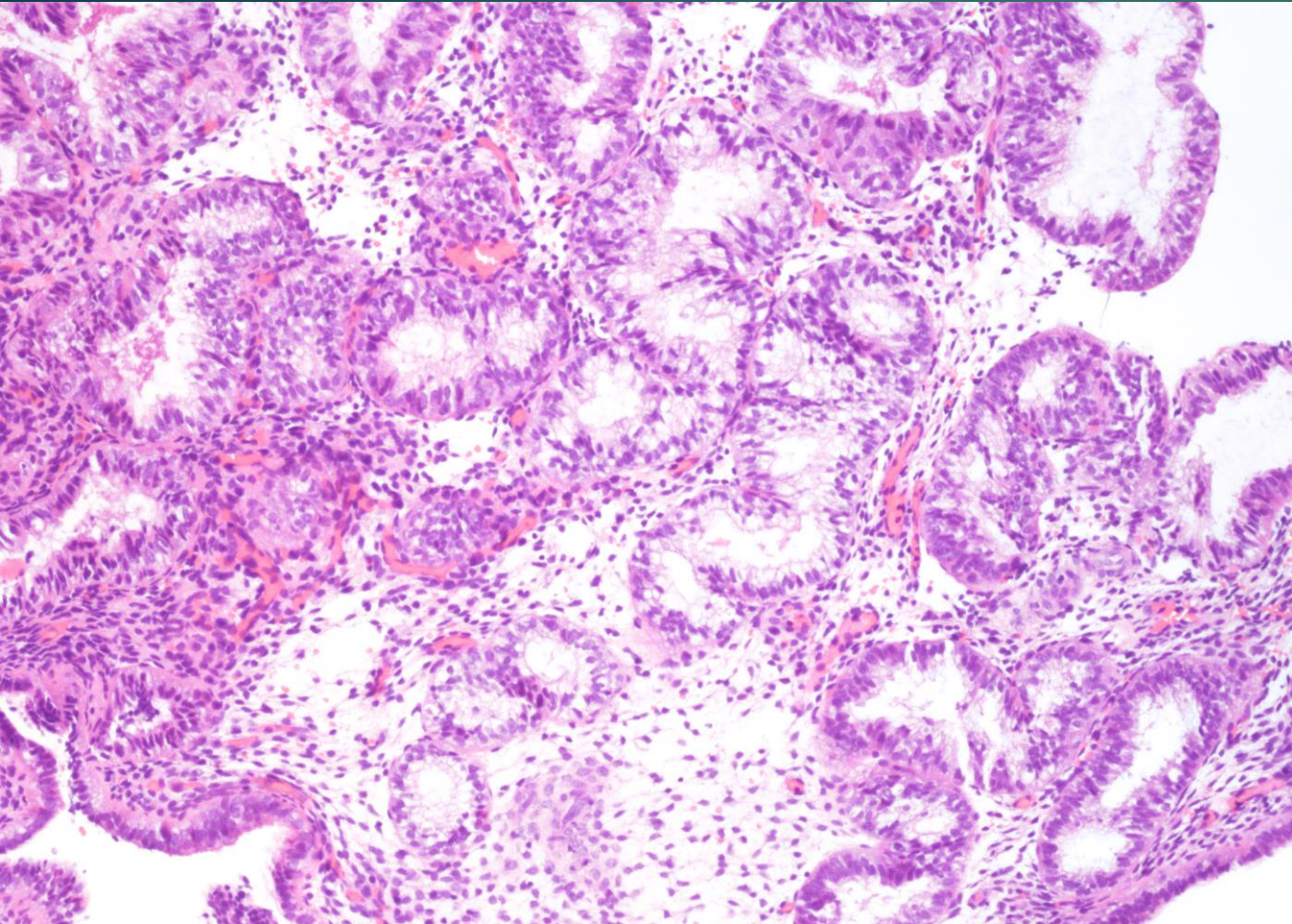
# Hyperplasia with Secretory change



- In small samples, careful evaluation of presence of nuclear atypia and mitotic figures.



# Hyperplasia with Secretory change

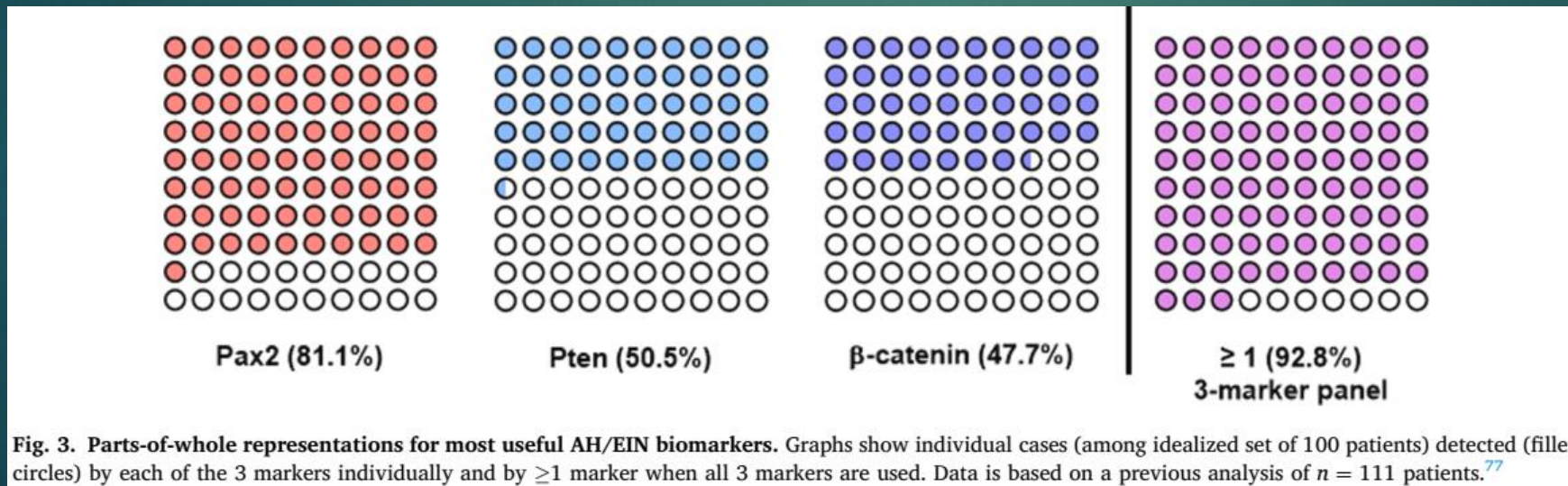


- In small samples, careful evaluation of presence of nuclear atypia and mitotic figures.



# Biomarkers for confirming Atypical Hyperplasia

- ▶ PAX2 loss: Sensitivity >80%, all or nothing staining.
- ▶ PTEN: 50% loss in AH
- ▶ Abnormal (nuclear)  $\beta$ -catenin ~50% of EC







# Endometrial Metaplasia

- ▶ Morphologic alteration from one cell type to another, changes may involve cytoplasm, nuclear, and/or architectural.
- ▶ Secondary to hormonal levels, repair, stromal breakdown, chronic inflammation, or polyp infarction.
- ▶ May be seen in benign and malignant conditions.

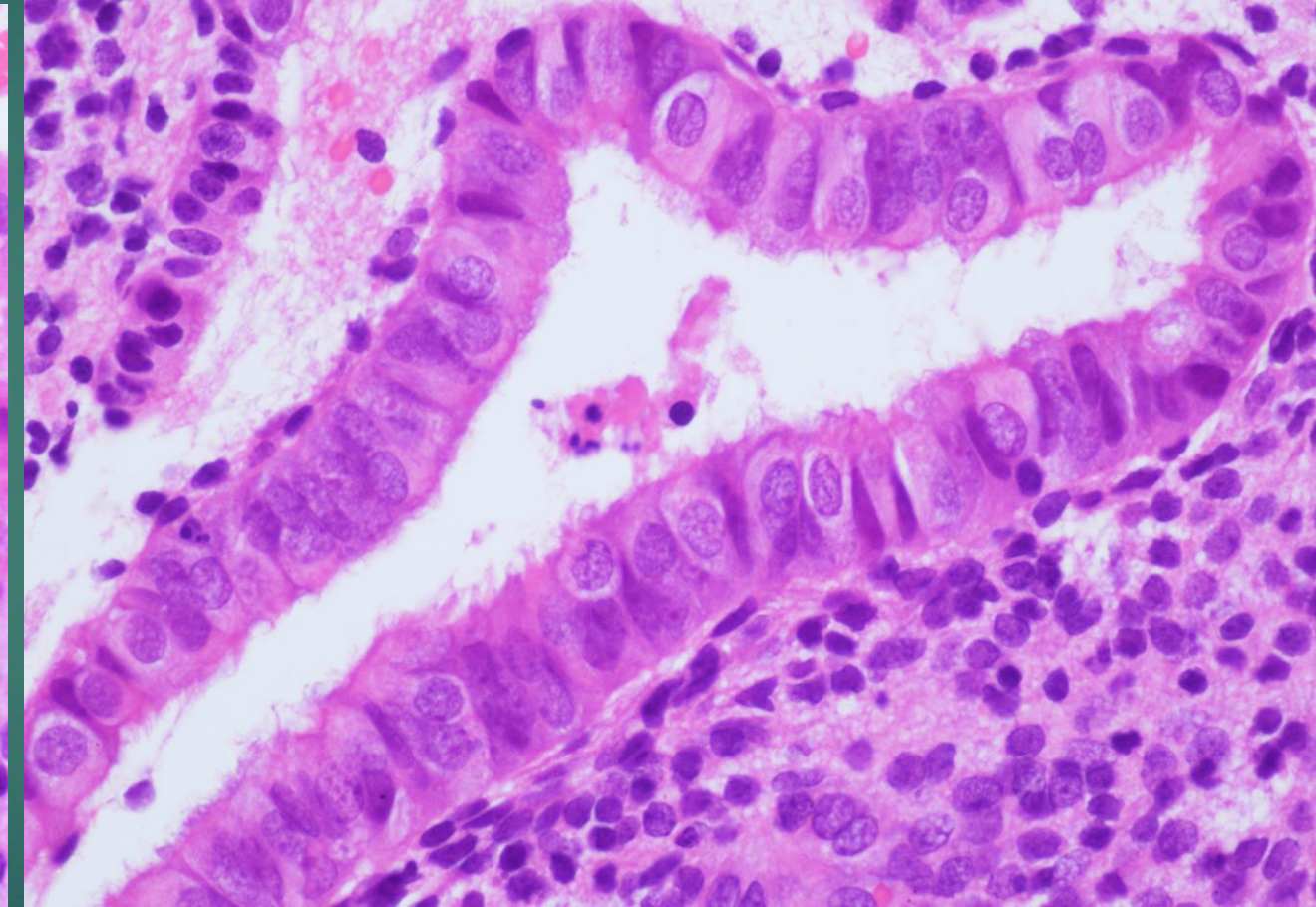
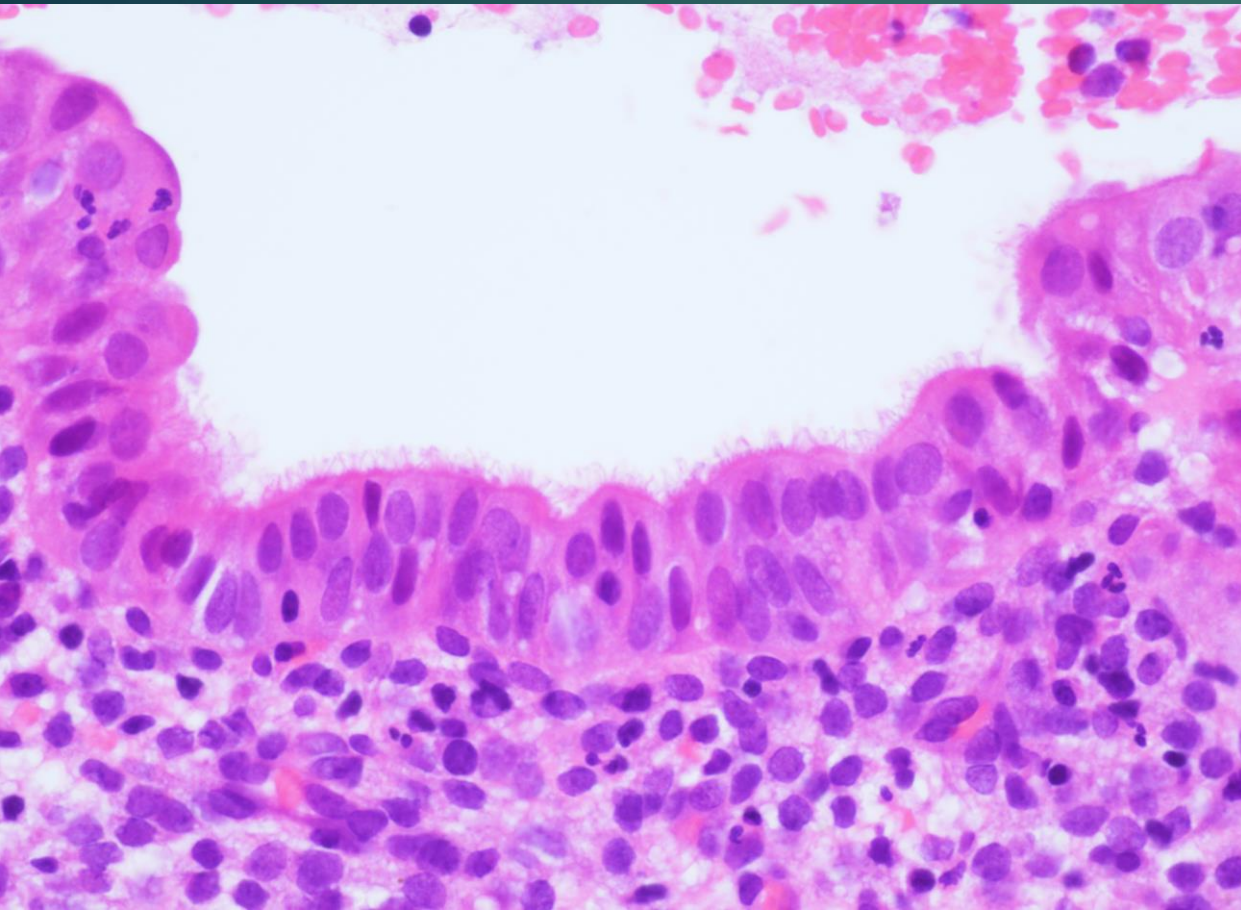


# Endometrial Metaplasia

- ▶ Ciliated/tubal
- ▶ Hobnail
- ▶ Morular
- ▶ Squamous
- ▶ Mucinous
- ▶ Papillary proliferation
- ▶ Syncytial papillary
- ▶ Clear cell

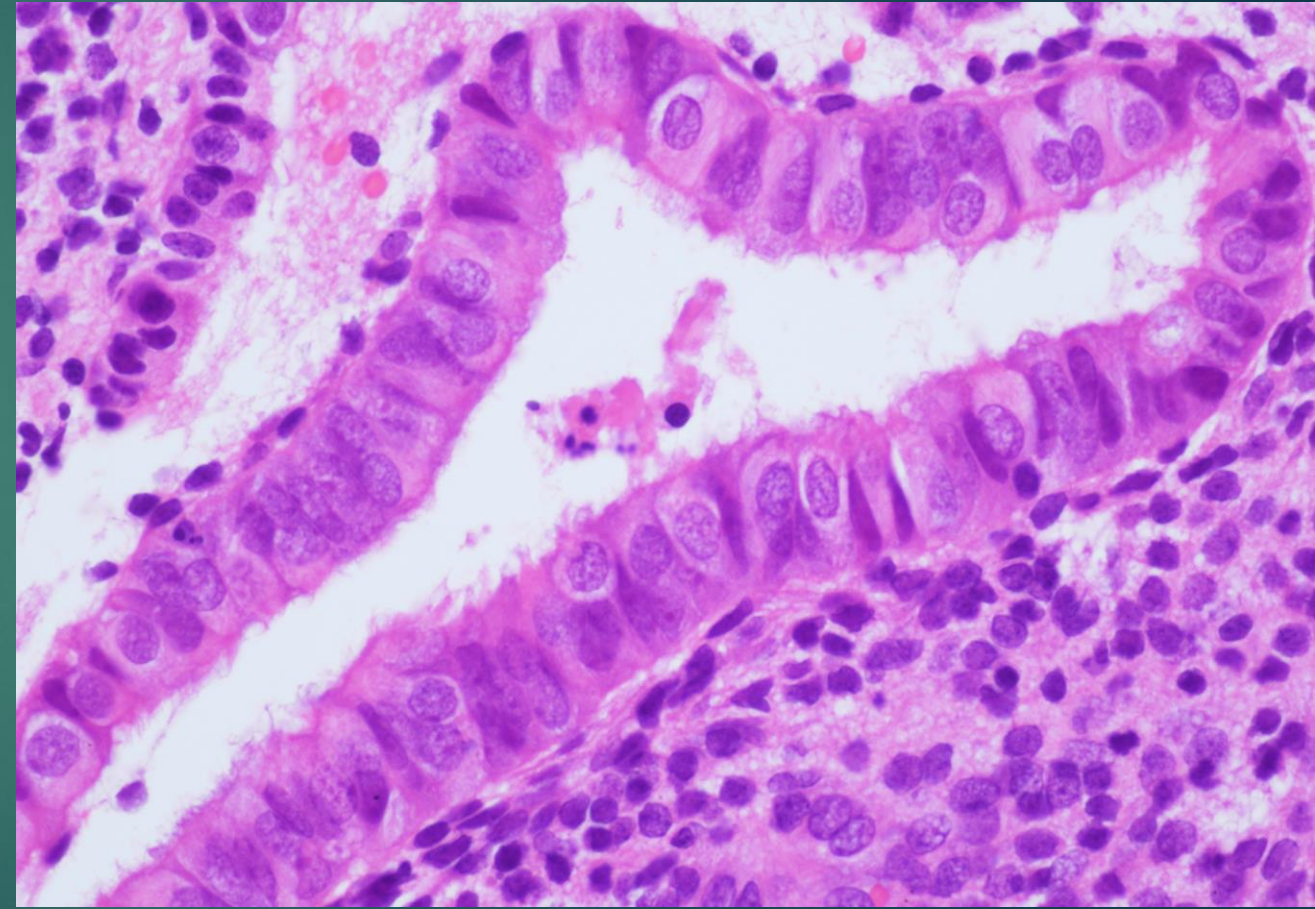
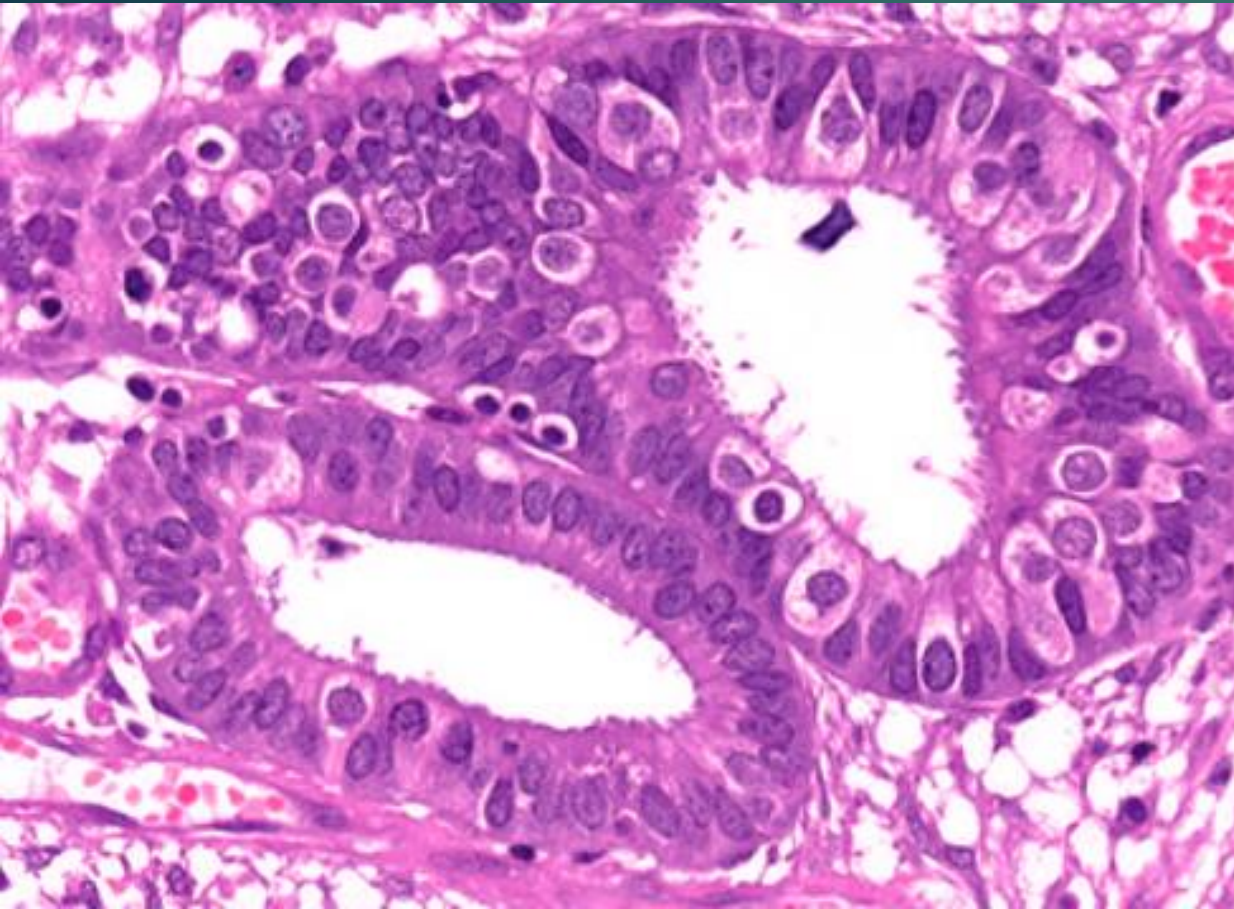


# Ciliated cell / Tubal Metaplasia





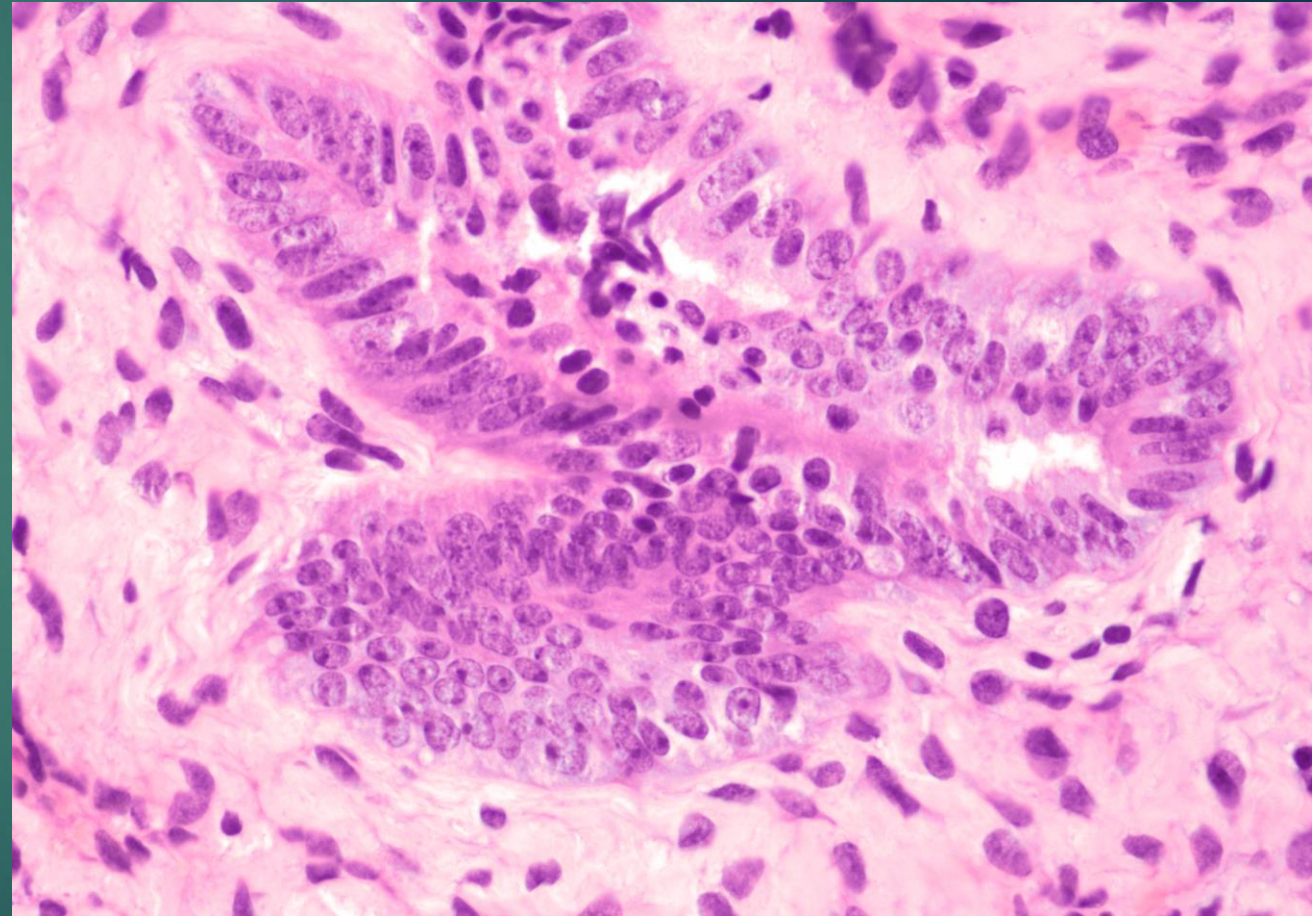
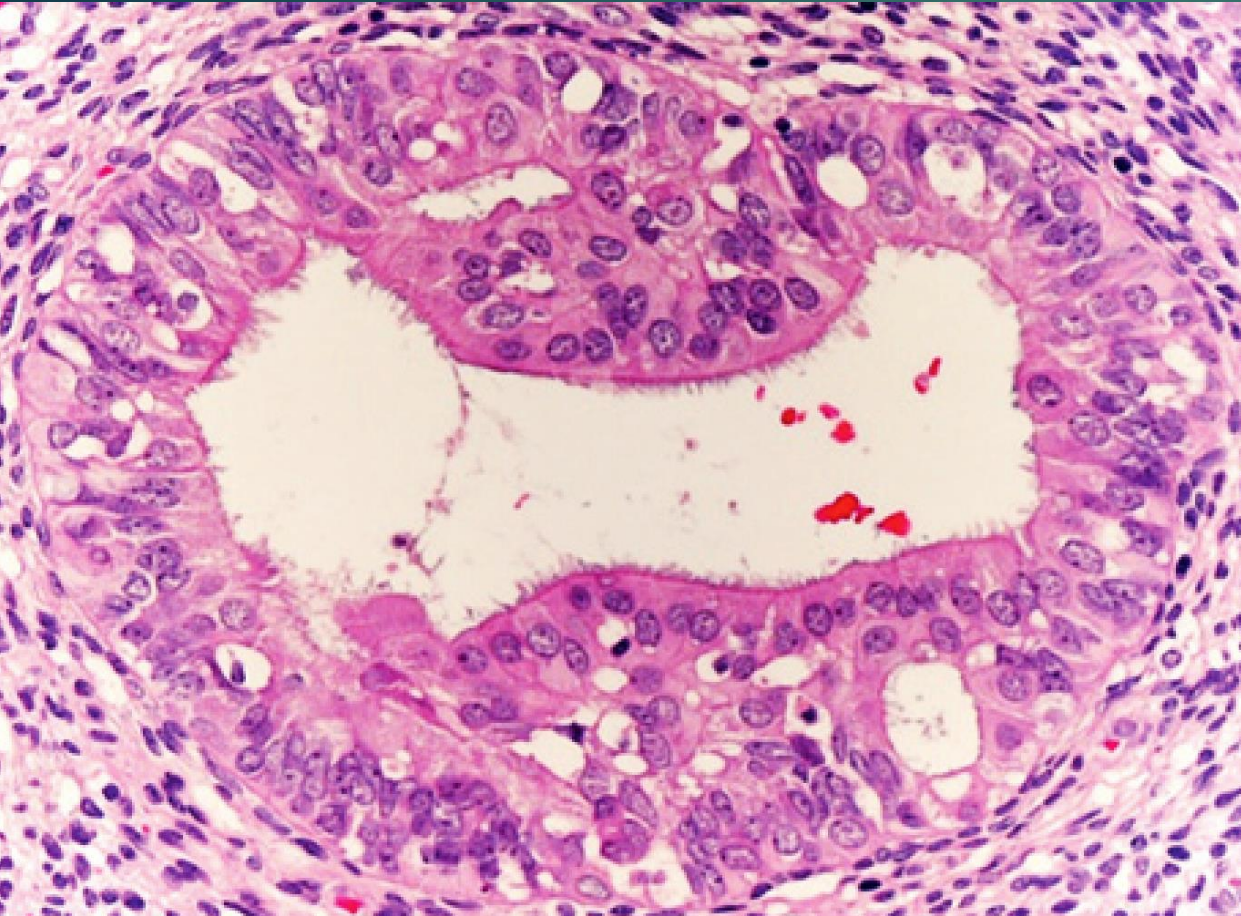
# Ciliated cell / Tubal Metaplasia



Ip PPC, Djordjevic B. WHO Classification of Female Genital tumours, 5<sup>th</sup> ed. p. 269-270  
Simon RA et al. Mod Pathol. 2011  
Nicolae A. et al. J Clin Pathol. 2011



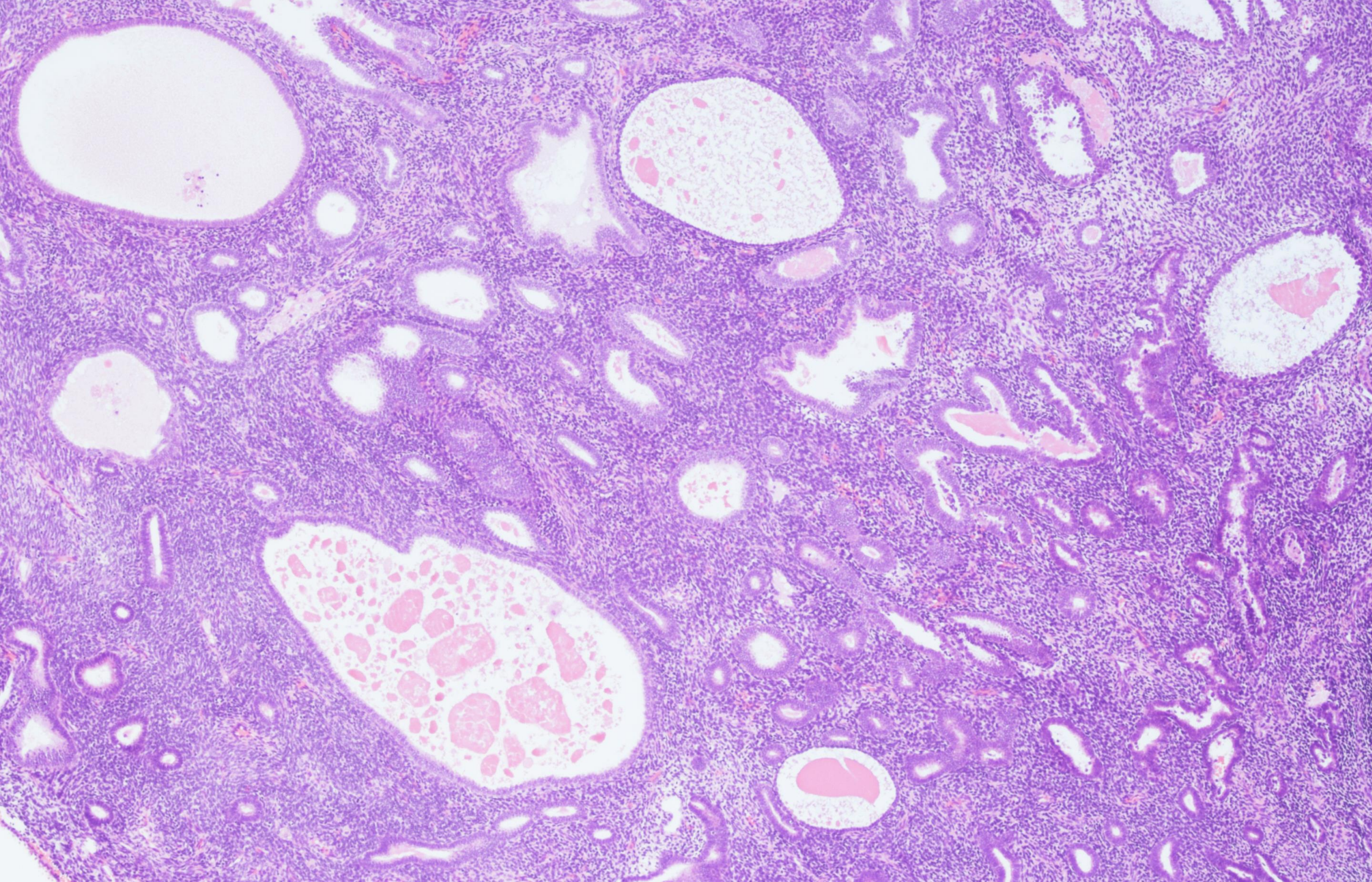
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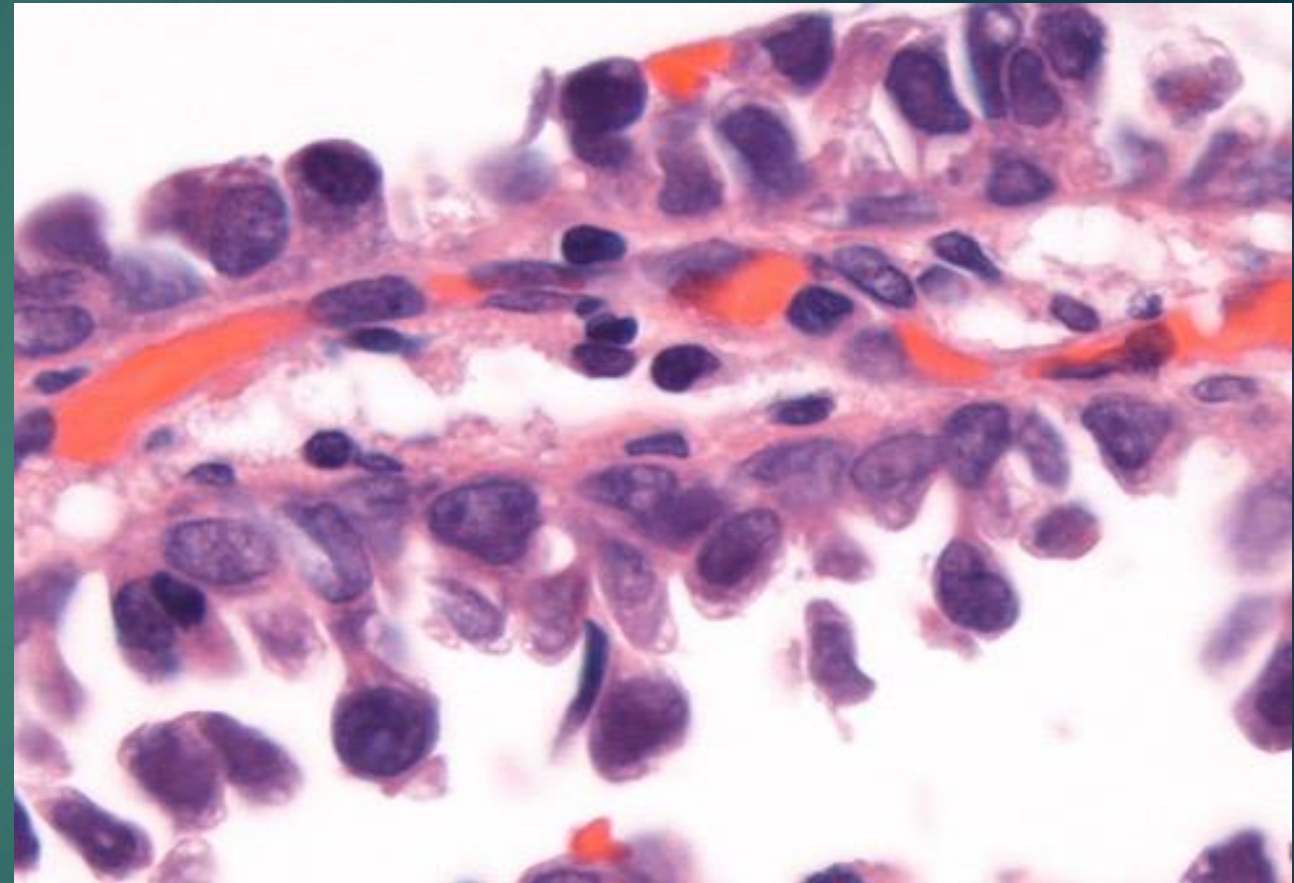
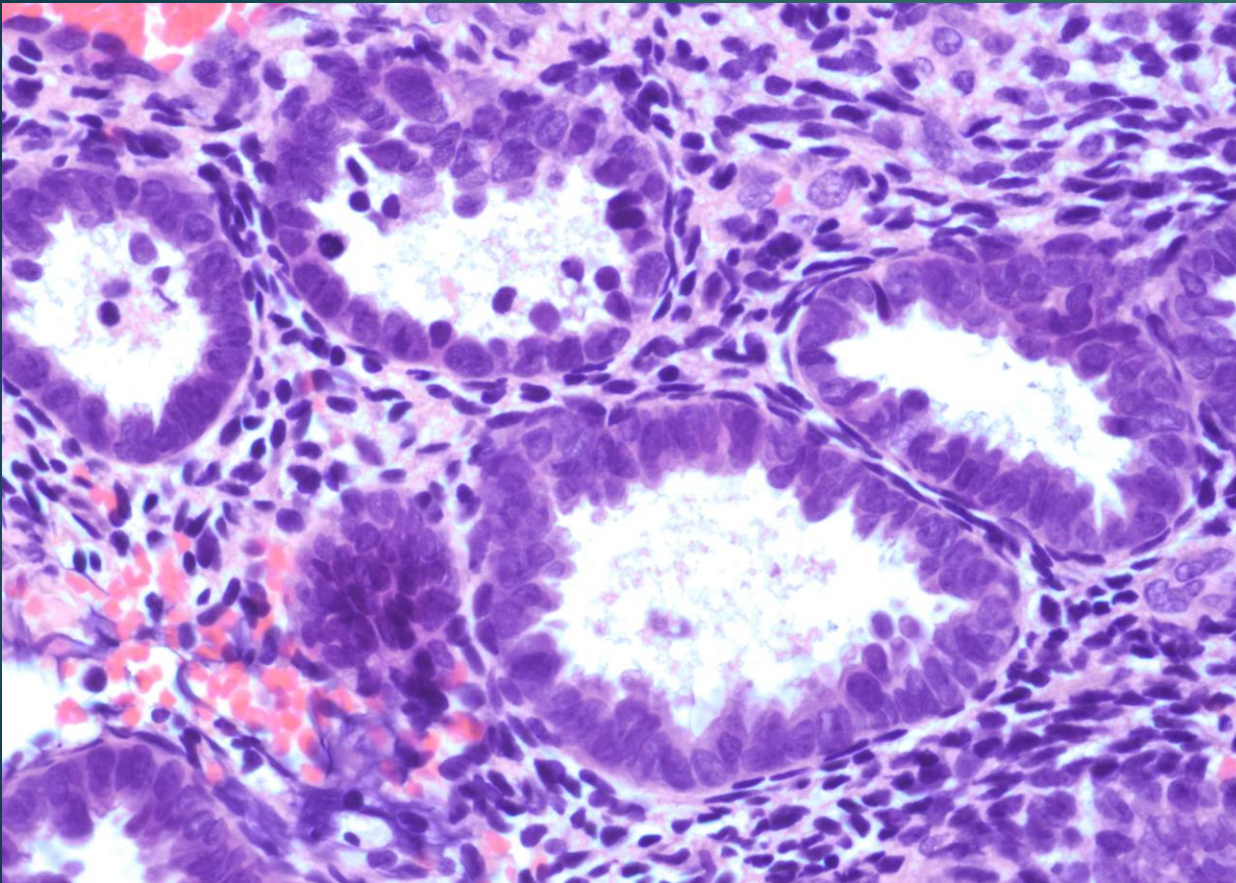
Simon RA et al. Mod Pathol. 2011

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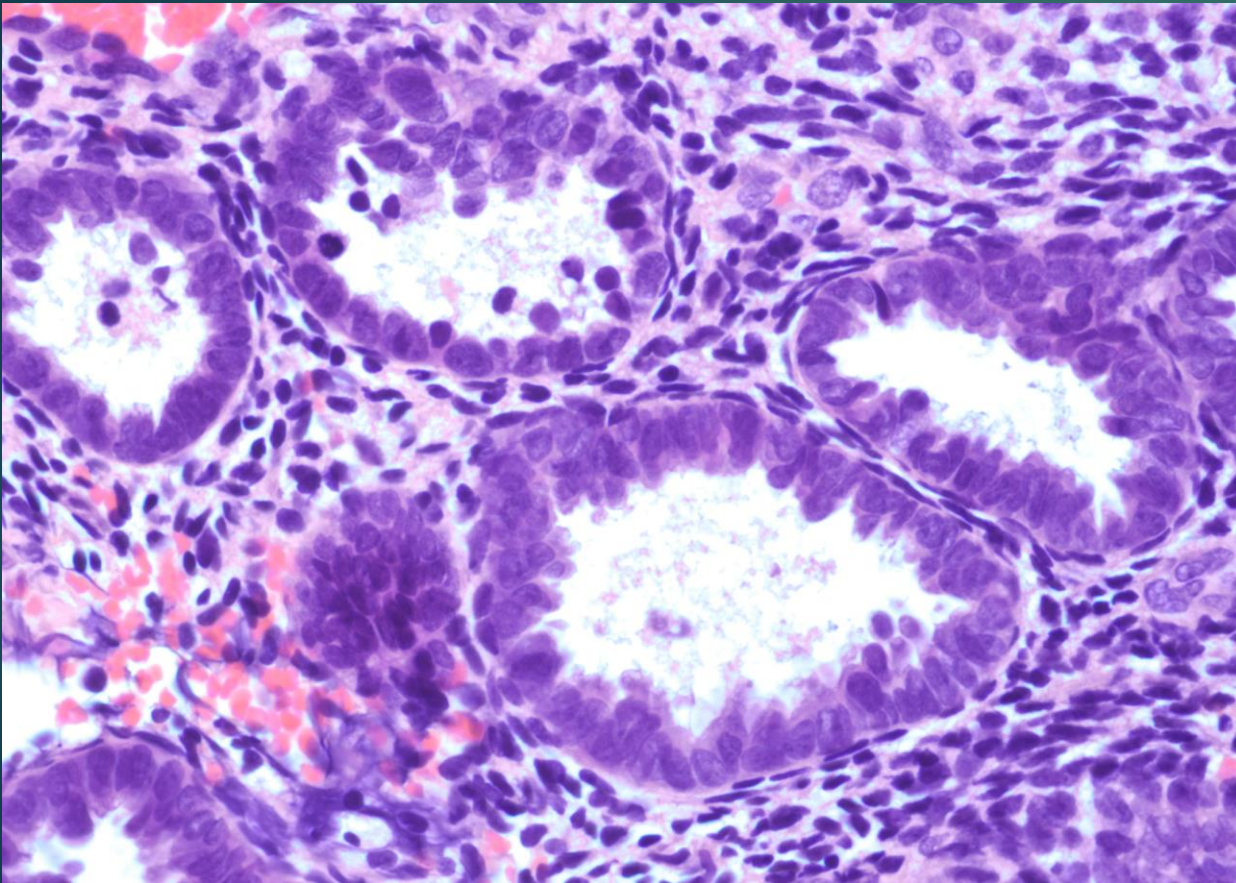
# Hobnail Metaplasia



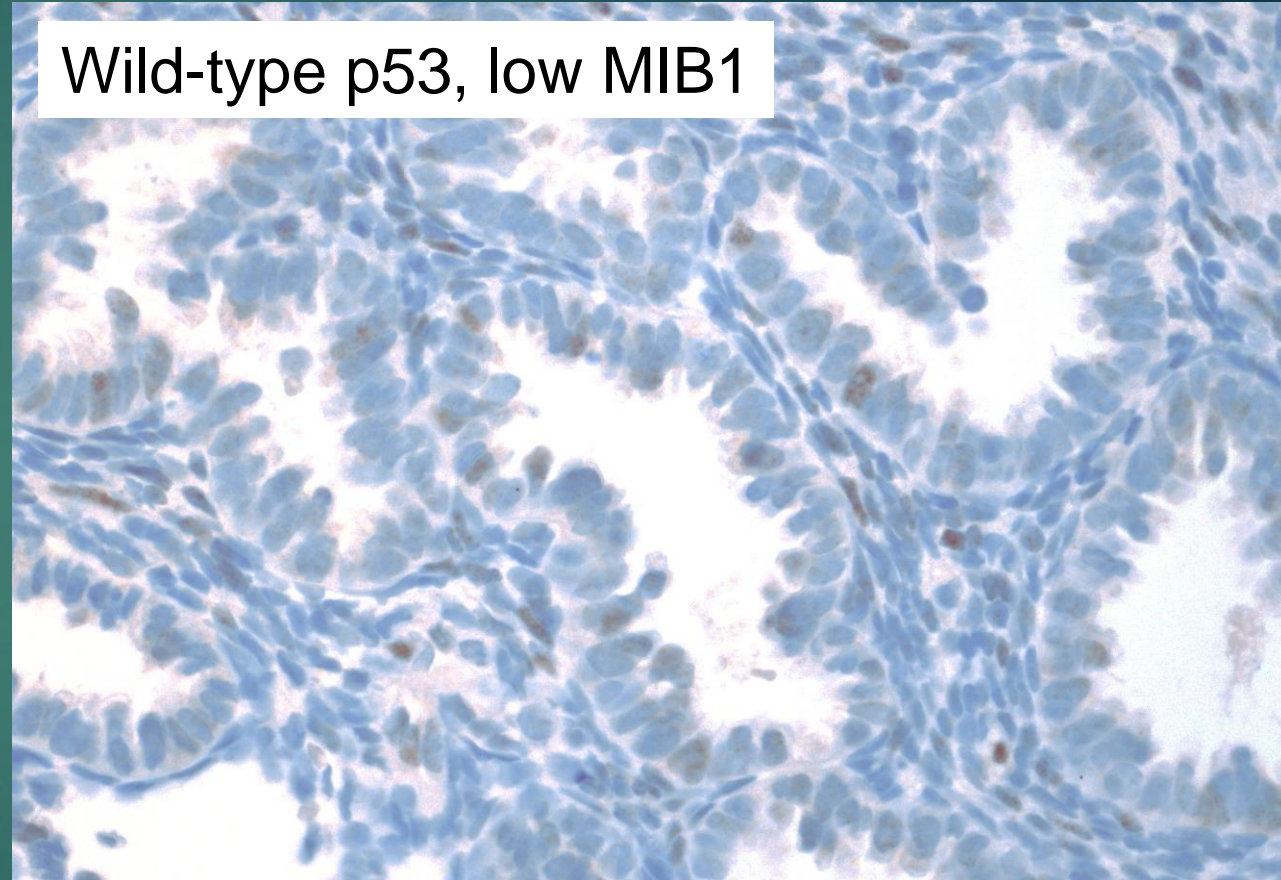
- Idiopathic, associated with a polyp, reactive change to endometrial curettage, hormonal, or radiation therapy.



# Hobnail Metaplasia



Wild-type p53, low MIB1

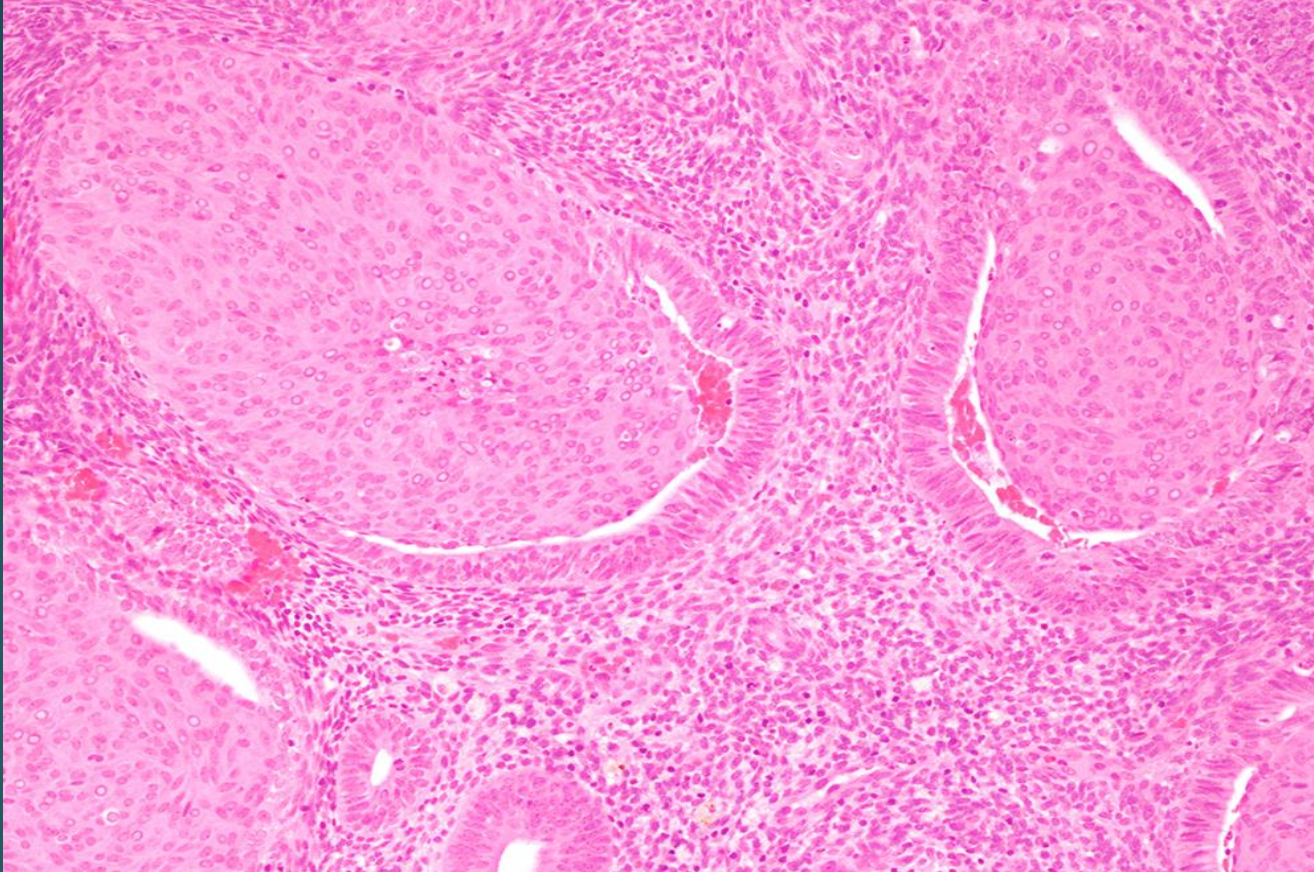


- Idiopathic, associated with a polyp, reactive change to endometrial curettage, hormonal, or radiation therapy.





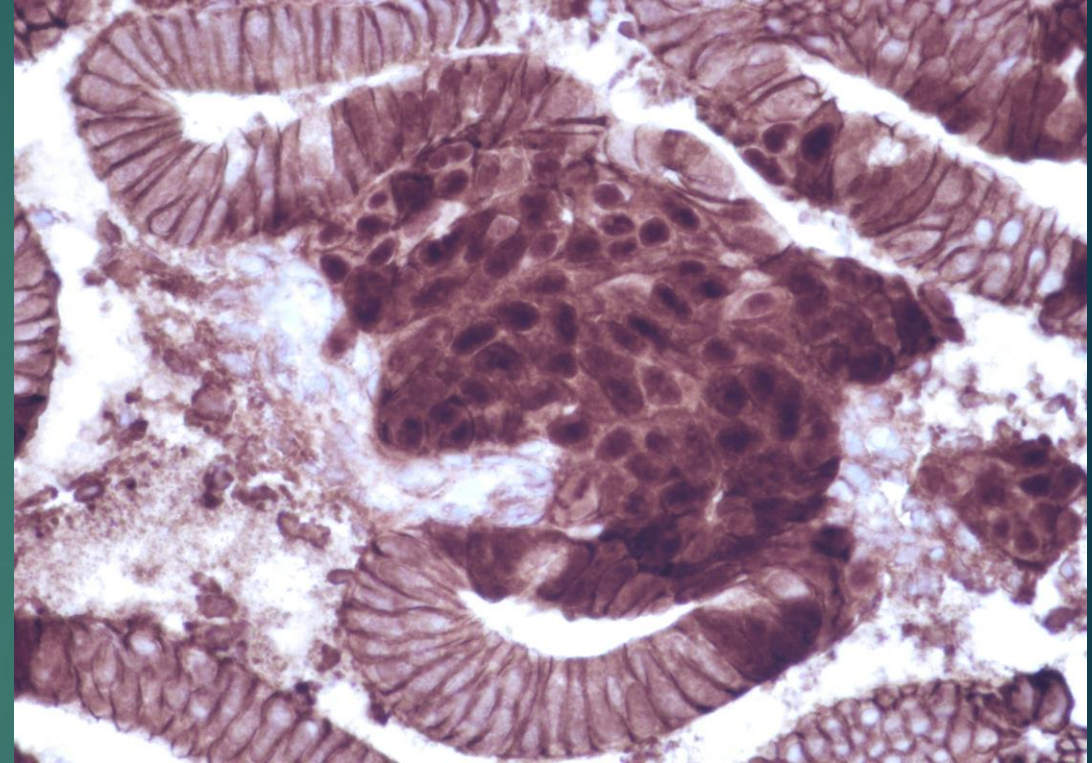
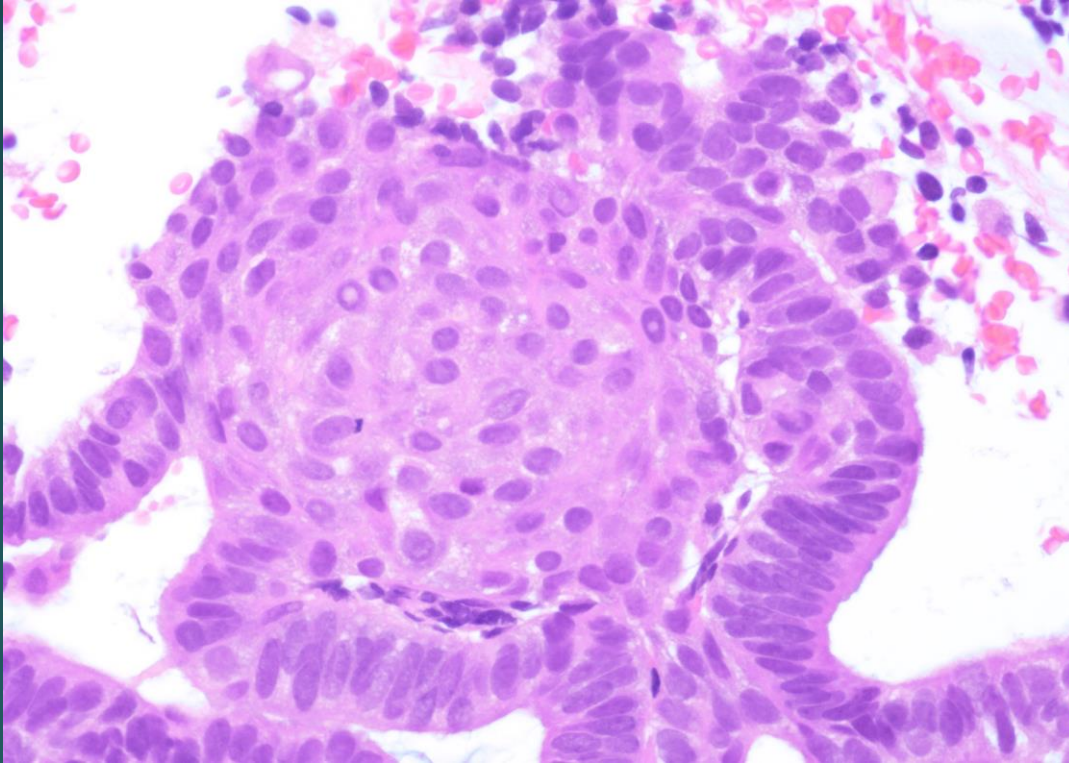
# Morular Metaplasia



- ▶ Intraglandular nests of cells assume appearance of 'mulberries'.
- ▶ Round to spindled cells with indistinct cell borders and lack abundant cytoplasm, intercellular bridges, or overt keratin.



# Morular Metaplasia



- ▶ Initially thought to be immature squamous metaplasia, and often **casually** referred to as 'squamous morules' because they often coexist.
- ▶ Express CDX2, CD10, SATB2, and nuclear  $\beta$ -catenin (due to *CTNNB1* mutations), but are negative for p63 or p40, ER/PR.



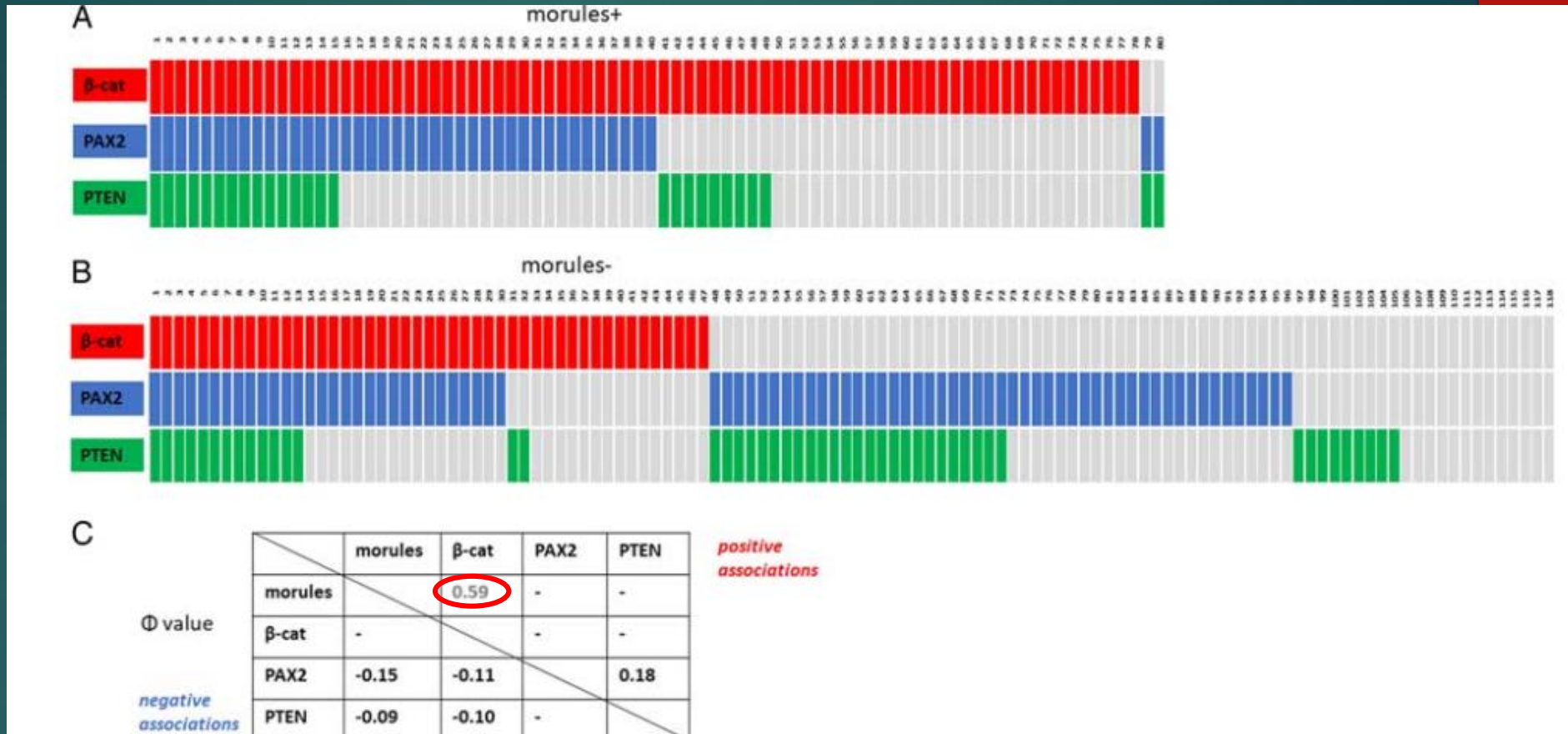
# Morules But Not Squamous Differentiation are a Reliable Indicator of *CTNNB1* ( $\beta$ -catenin) Mutations in Endometrial Carcinoma and Precancers

*Shuang Niu, MD, PhD,\*† Elena Lucas, MD,\*† Kyle Molberg, MD,\*† Amanda Strickland, MD,‡  
Yan Wang, MD,\* Kelley Carrick, MD,\*† Glorimar Rivera-Colon, MD,\*† Katja Gwin, MD,\*†  
Jeffrey A. SoRelle, MD,\*§ Diego H. Castrillon, MD, PhD,\*†||¶ Wenxin Zheng, MD,\*†||¶  
and Hao Chen, MD, PhD\*†*

- ▶ Endometrioid ca with (n=36) vs. without morules (n=36).
- ▶ Atypical hyperplasia with (n=80) vs. without morules (n=118).
- ▶ Immunohistochemistry and NGS (1425 genes).



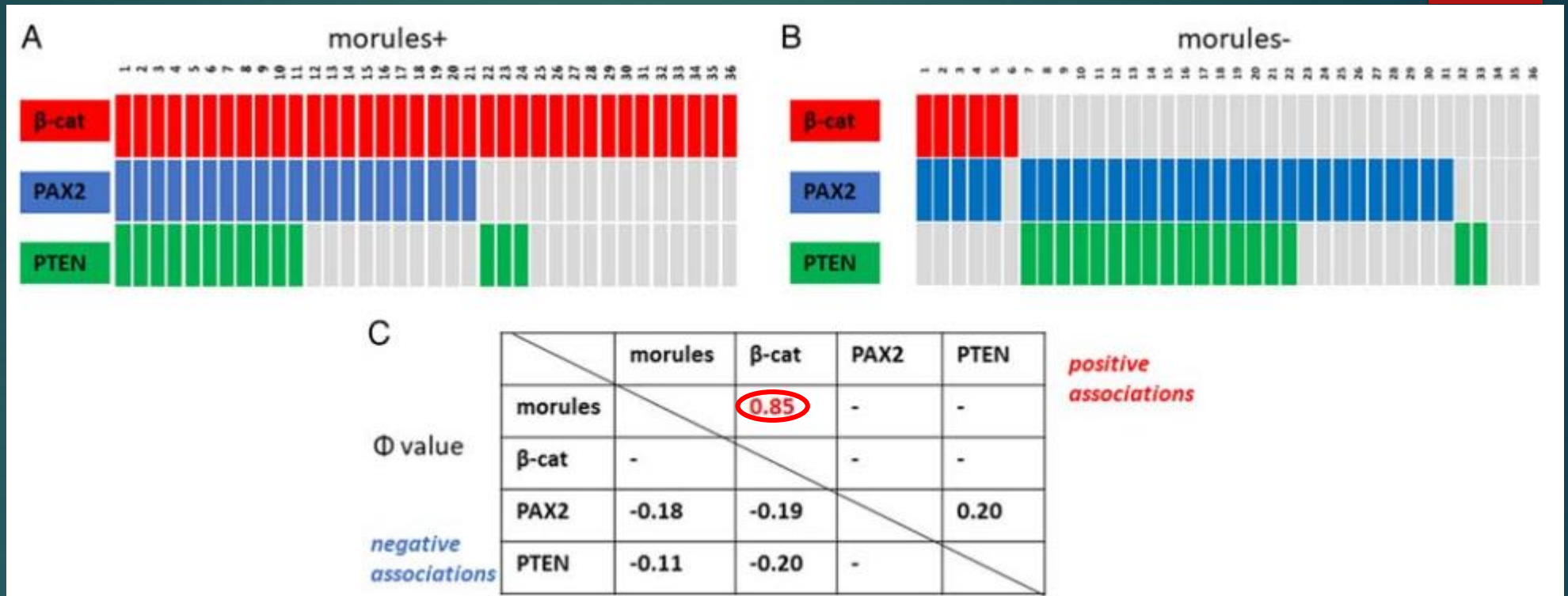
# Morular Metaplasia: Atypical Hyperplasia



- ▶ β-catenin nuclear staining present in 98% with morules and 40% without morules.
- ▶ Strong positive correlation between morules and glandular β-catenin nuclear staining ( $p < 0.0001$ ,  $\Phi$  0.59), but not with PAX2 or PTEN.



# Morular Metaplasia: Endometrioid Ca



- ▶  $\beta$ -catenin nuclear staining present in 100% with morules and 17% without morules.
- ▶ Strong positive correlation between morules and glandular  $\beta$ -catenin nuclear staining ( $p < 0.00001$ ,  $\Phi$  0.85), but not with PAX2 or PTEN.



# Morular Metaplasia: DNA alterations

| Case No. | Exon 3 Hotspots | Mutation    |
|----------|-----------------|-------------|
| 1        | S37             | p. Ser37Phe |
| 2        | T41             | p. Thr41Ile |
| 3        | S37             | p. Ser37phe |
| 4        | D32             | p. Asp32Tyr |
| 5        | S37             | p. Ser37Phe |
| 6        | S33             | p. Ser33Cys |
| 7        | T41             | p. Thr41Ile |
| 8        | S37             | p. Ser37Phe |
| 9        | T41             | p. Thr41Ile |
| 10       | S33             | p. Ser33Cys |
| 11       | S37             | p. Ser37Phe |
| 12       | D32             | p. Asp32Tyr |
| 13       | D32             | p. Asp32His |
| 14       | S33             | p. Ser33Tyr |
| 15       | G34             | p. Gly34Glu |
| 16       | S33             | p. Ser33Tyr |
| 17       | S37             | p. Ser37Phe |
| 18       | S37             | p. Ser37Cys |
| 19       | S33             | p. Ser33Phe |
| 20       | S37             | p. Ser37Ala |

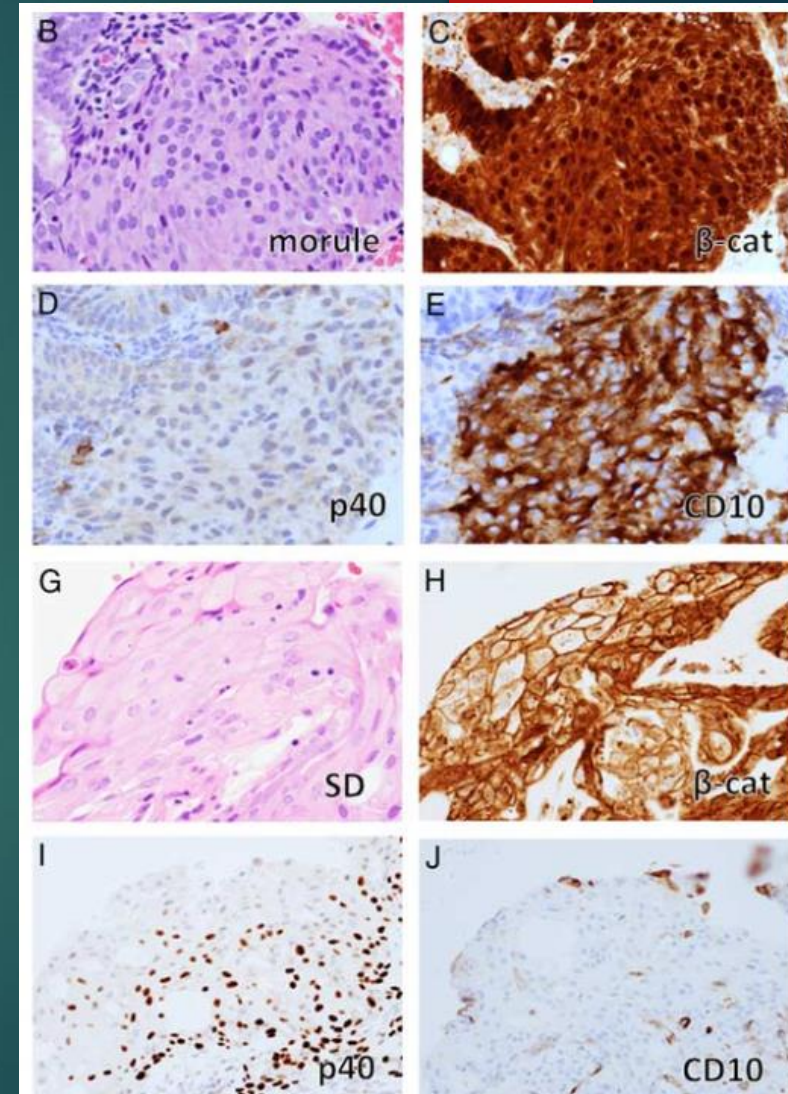
|                  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | Total cases | %  |      |
|------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|-------------|----|------|
| <i>CTNNB1</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 20 | 100% |
| <i>PTEN</i>      | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 9  | 45%  |
| <i>PIK3CA</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 7  | 35%  |
| <i>PIK3R1</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 2  | 10%  |
| <i>NF1</i>       | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 2  | 10%  |
| <i>AKT1</i>      | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 2  | 10%  |
| <i>NOTCH2</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>ARID1A</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>ARID5B</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>FOXA2</i>     | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>JAK1</i>      | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>TET2</i>      | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>KRAS</i>      | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>DDIT3</i>     | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>ABCC3</i>     | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>SPTA1</i>     | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>MAP3K6</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>MAX</i>       | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>ZC3H7B</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>SNAPC3</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>SPIB</i>      | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>GPR34p</i>    | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |
| <i>TNFRSF11A</i> | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■  | ■           | 1  | 5%   |

- ▶ 100% atypical hyperplasia with morular metaplasia had *CTNNB1* alterations involved exon 3 hotspots, causing defective proteosomal degradation and nuclear accumulation.



# Morular Metaplasia: Significance

- ▶ Presence of *CTNNB1* alterations (and  $\beta$ -catenin nuclear staining) in morular metaplasia is a reliable indicator of underlying atypical hyperplasia and/or endometrioid Ca.
- ▶ Concurred with historical observations.



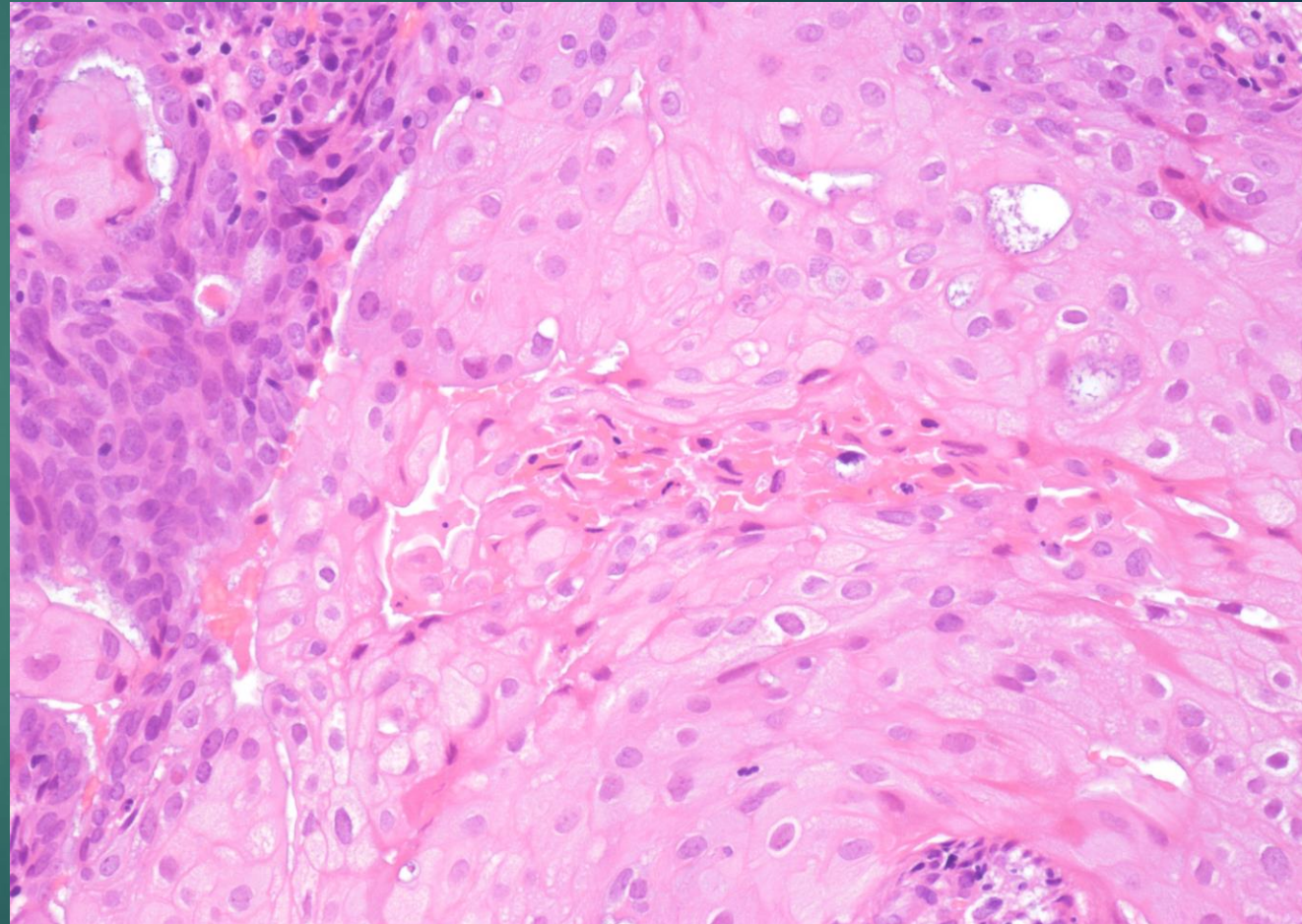
Niu S. et al. Am J Surg Pathol. 2022  
Lin MC. et al. Mod Pathol. 2009  
Chiarelli S. et al. Clin Cancer Res. 2006

Brachtel EF. et al. Am J Surg Pathol. 2005  
Saegusa M. et al. J Pathol. 2001



# Squamous Metaplasia

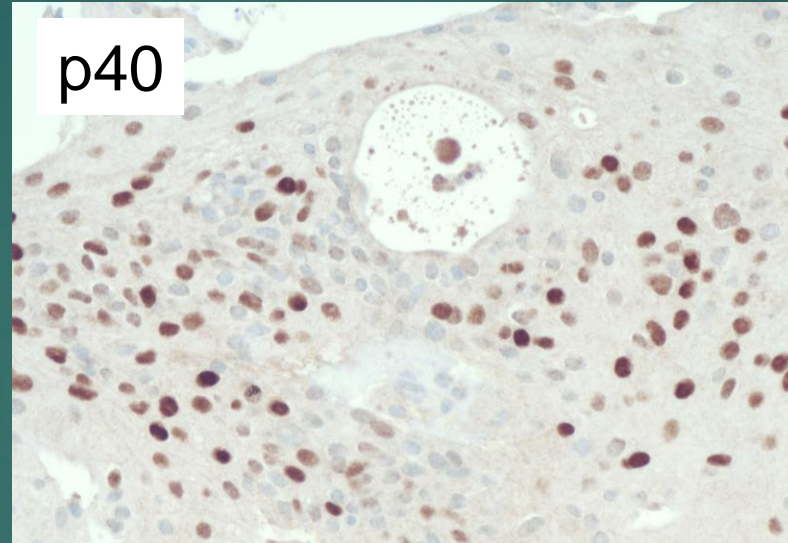
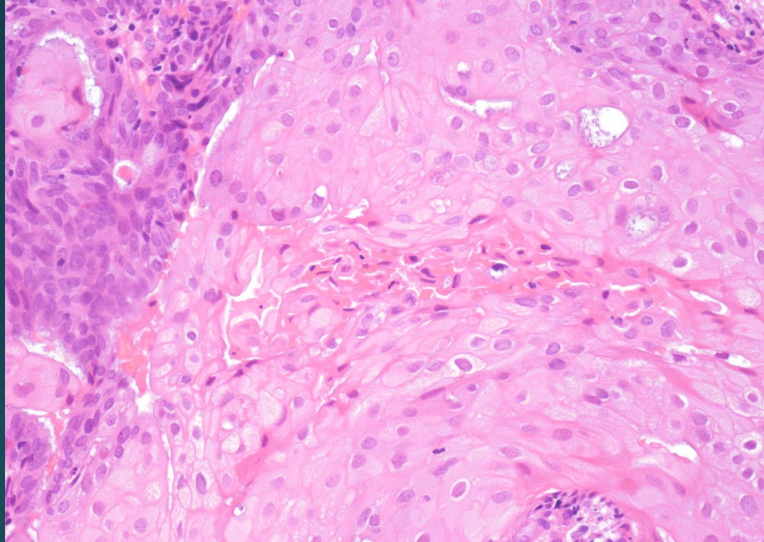
- ▶ Replacement of surface or superficial glands by mature squamous cells with overt keratinization and/or glycogenation.
- ▶ Secondary to nonneoplastic conditions such as chronic endometritis, pyometra, presence of an intrauterine device, and uterine prolapse.







# Squamous Metaplasia



- ▶ Expresses p63, p40 but negative for the 'morular' markers.
- ▶ In the absence of secondary causes, atypical hyperplasia or endometrioid carcinoma with squamous differentiation should be considered.
- ▶ An extreme example is 'ichthyosis uteri', suggested to be premalignant by some.



# Endometrial Primary Squamous cell Carcinoma

- ▶ WHO Classification 2020: 'Other endometrial carcinomas'.
- ▶ By definition, Fluhmann criteria in 1928 still holds true:
- ▶ No coexisting endometrioid ca with squamous differentiation.
- ▶ No connection between endometrial and cervical squamous epithelium.
- ▶ Simultaneous cervical squamous cell ca absent.



# Molecular Analysis of HPV-independent Primary Endometrial Squamous Cell Carcinoma Reveals *TP53* and *CDKN2A* Comutations

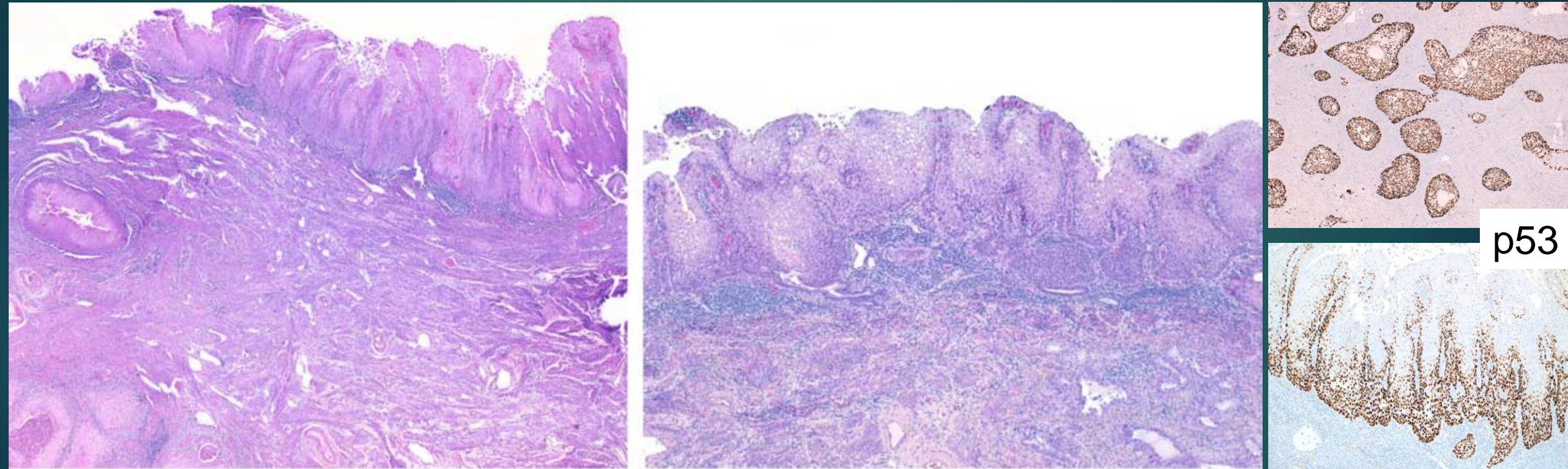
*A Clinicopathologic Analysis With Re-evaluation of Diagnostic Criteria*

*Mark R. Hopkins, MD,\* Doreen N. Palsgrove, MD,† Brigitte M. Ronnett, MD,\*  
Russell Vang, MD,\* Jeffrey Lin, MD,‡ and Tricia A. Murdock, MD\**

- ▶ 5 pure squamous cell carcinoma of endometrium.
- ▶ 3 with ichthyosis uteri.
- ▶ Mean age 79.4 y (range 66-92).
- ▶ Stage II (n = 2), stage III (n = 2), and stage IV (n = 1).
- ▶ Four patients died within 20 months.



# HPV-independent Squamous cell Carcinoma of Endometrium



- ▶ 5/5 had aberrant p53 expression, negative ER/PR, negative p16.
- ▶ Negative for high and low-risk HPV RNA by in-situ hybridization.
- ▶ WES: 4/5 had *TP53* and *CDKN2A* alterations.



# Differential diagnoses of Squamous Metaplasia

- ▶ Atypical hyperplasia / endometrioid ca with squamous differentiation.
- ▶ Cervical HPV-associated squamous cell carcinoma involving endometrium.
- ▶ Squamous metaplasia associated with benign conditions.
- ▶ Primary endometrial squamous cell carcinoma (diagnosis by exclusion) .

Hopkins MR. et al. Am J Surg Pathol. 2022  
Giordana G. et al. Pathol Oncol Res. 2013  
Goodrich S. et al. Diagn Cytopathol. 2013  
Horn L-C. et al. Ann Diagn Pathol. 2006  
Kataoka A. et al. Gynecol Oncol. 1997  
Goodman A. et al. Gynecol Oncol. 1996

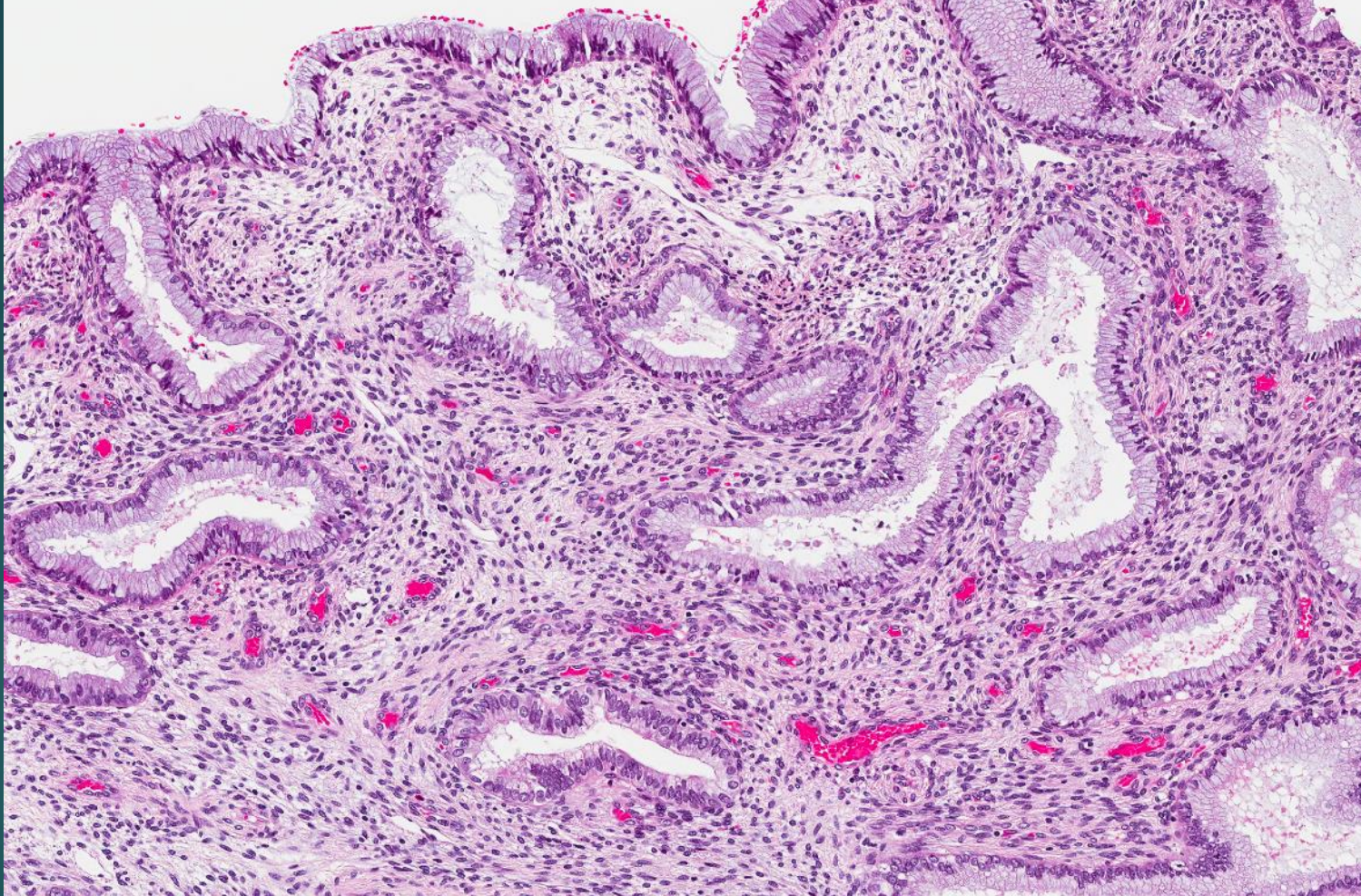


# Mucinous Metaplasia

- ▶ Two types:
- ▶ **Usual:** Columnar cells with mucin-rich cytoplasm, resembling endocervical epithelium. Basally located nuclei, focal intraglandular tufting allowed.
- ▶ **Gastric/gastrointestinal:** Abundance of mucinous cytoplasm, prominent and well-defined cell membranes, goblet cells, expression of gastrointestinal markers.



# Mucinous Metaplasia: Usual-type



- Resembles endocervical epithelium and commonly associated with endometrial polyp.
- Presence of small arterioles, endometrial stroma, paucity of plasma cells.



# Mucinous Proliferations in small biopsies

- ▶ Spectrum of mucinous lesions in endometrium:
- ▶ **Mucinous metaplasia**
- ▶ **'Atypical mucinous glandular proliferations'**
- ▶ **Endometrioid carcinoma (with mucinous differentiation)**
  
- ▶ Diagnosis in small biopsies is difficult because of the bland cytology, and architectural complexity is variable.

Fujiwara M and Longacre TA. Am J Surg Pathol. 2011  
Fadare O. et al. Pathology. 2018  
Sung JY. et al. Anticancer Res. 2018  
Vang R. et al. Int J Surg Pathol. 2003  
Nucci MR. et al. Mod Pathol. 1999



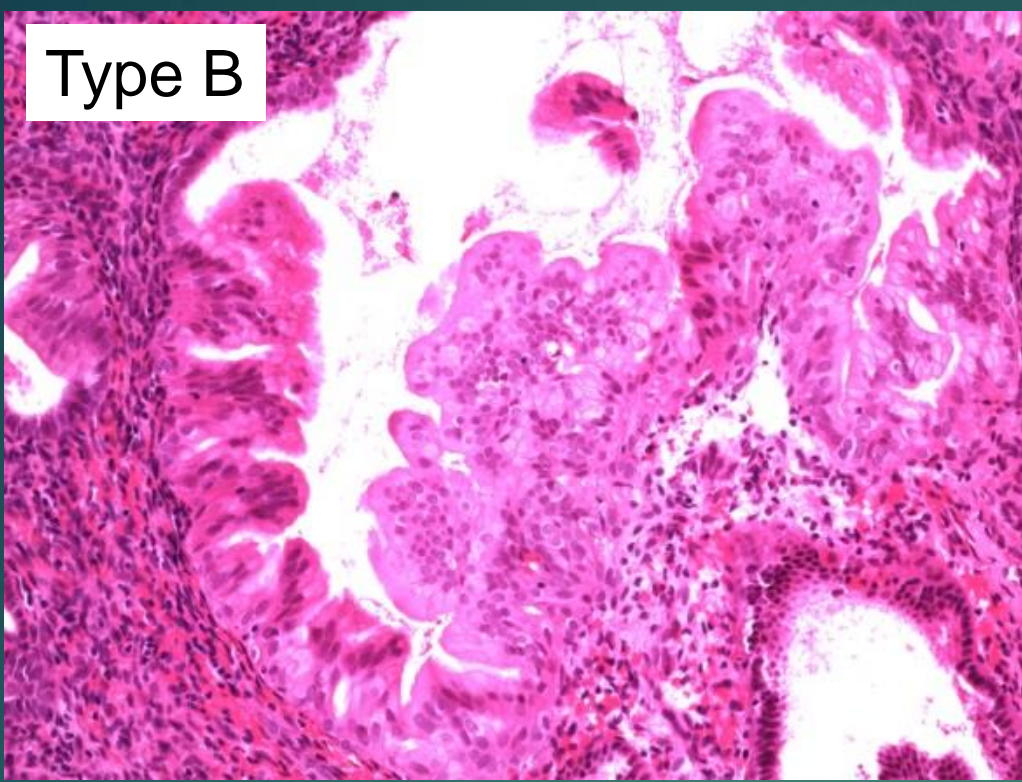


# Mucinous Proliferations in small biopsies

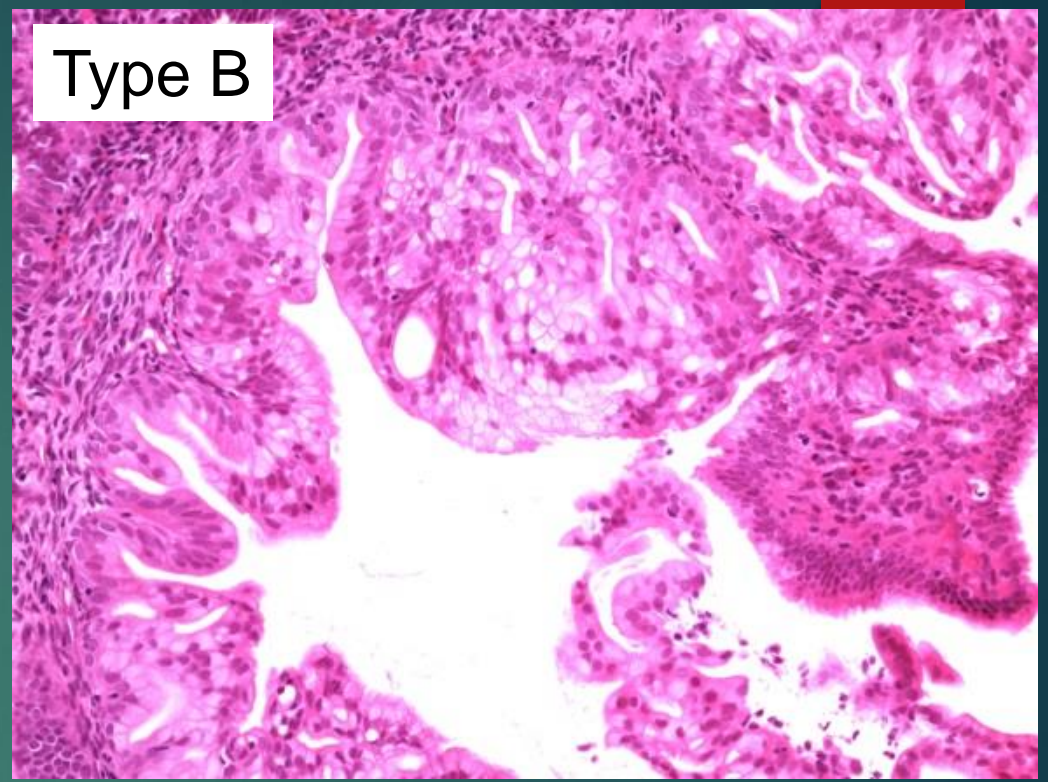
- ▶ Nucci and Young's criteria of mucinous proliferation
- ▶ Type A, singly, small tufts.
- ▶ Type B, pseudoglands with punch out spaces and no supporting stroma.
- ▶ Type C, architecturally complex with nuclear atypia.
- ▶ Types B and C are associated with subsequent carcinoma in 65% and 100% respectively, while type A had none.



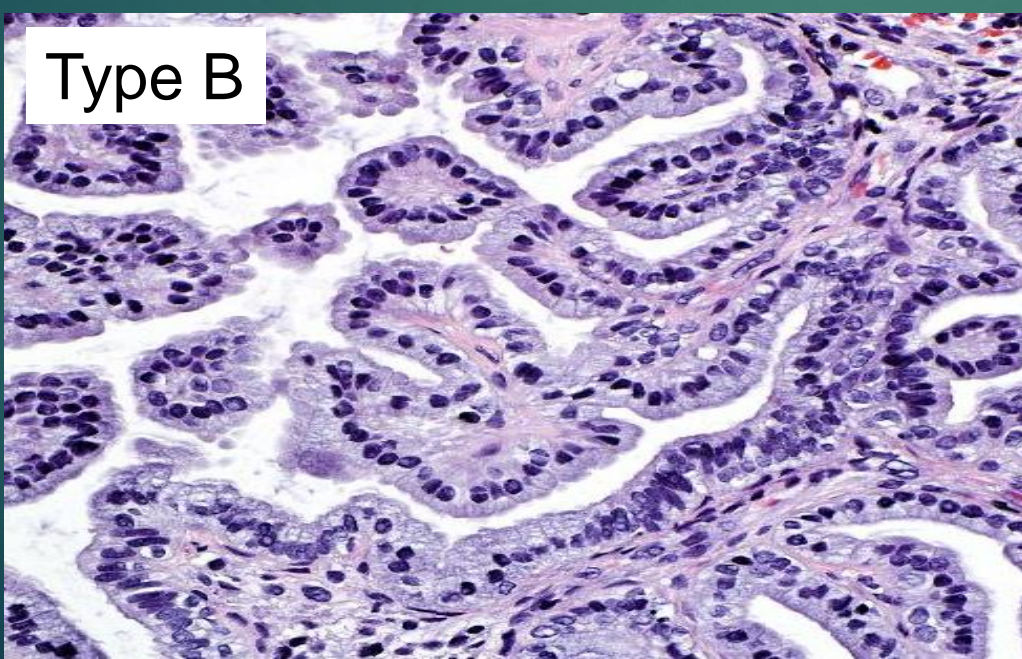
Type B



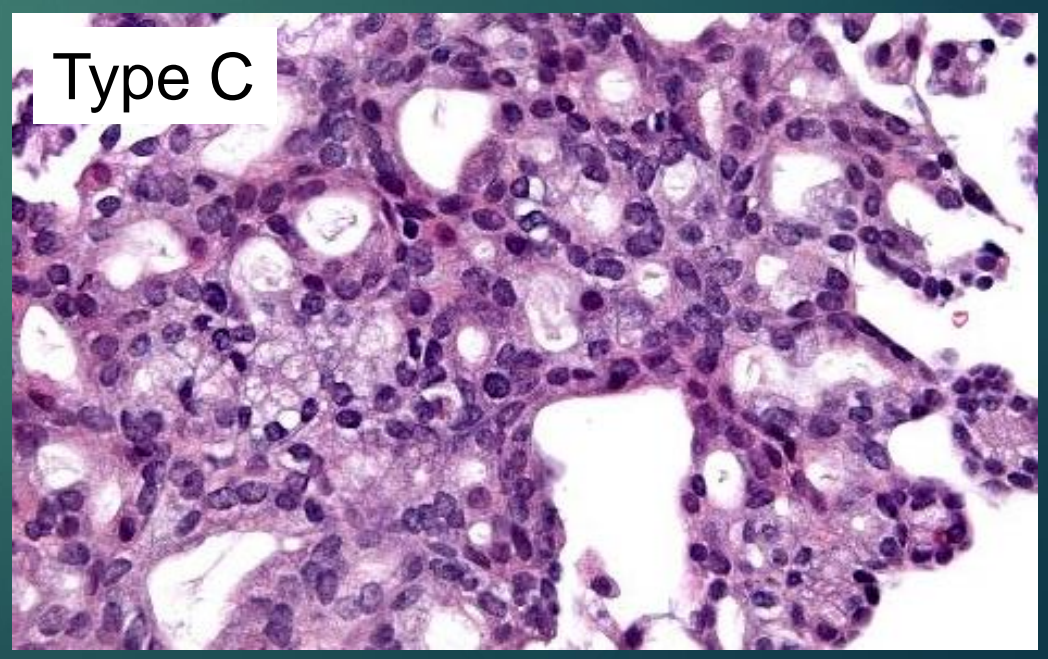
Type B



Type B



Type C





# 'Atypical Mucinous Glandular Proliferations' in small biopsies

**TABLE 1.** Follow-up After Diagnoses of AMGP in Biopsies or Curettages

| References                  | AMGP Cases (n) | Mean Age (Range) | AMGP: Carcinoma Ratio | Follow-up Biopsies/ Curettages Only                                      | Follow-up Hysterectomy Rate | Follow-up Diagnoses in Hysterectomy   |
|-----------------------------|----------------|------------------|-----------------------|--|-----------------------------|---|
| Alomari et al <sup>20</sup> | 33             | 63 y (44-86)     | 8:2                   | Unstated   | 42% (14/33)                 | 50%: atypical hyperplasia<br>14%: adenocarcinoma<br>36%: benign   |
| Rawish et al <sup>21</sup>  | 41             | 46 y (37-59)     | 7:3                   | 9/41 with follow-up samplings: no residual lesion after 1 or 2 samplings | 71% (29/41)                 | 45%: adenocarcinoma (32%*)<br>38%: AMGP (27%*)<br>17%: benign/no residual mucinous lesion (41%*)          |
| He et al <sup>22</sup>      | 15             | 59.4 y (31-83)   | NA†                   | NA   | NA†                         | 67%: adenocarcinoma<br>13%: atypical hyperplasia<br>13%: AMGP in an endometrial polyp.<br>7%: lost to f/u |

\*Parenthesized percentages also include patients who did not undergo a hysterectomy but who had benign follow-up.

†Study definitionally only included AMGP cases with follow-up repeat samplings or hysterectomies; follow-up results for in He et al<sup>22</sup> includes hysterectomies and repeat samplings.

AMGP indicates atypical mucinous glandular proliferation.



# 'Atypical Mucinous Glandular Proliferations' in small biopsies

- ▶ Historically, various terminologies were used to describe these 'borderline' mucinous lesions of endometrium.
- ▶ In WHO 2014, 'atypical mucinous glandular proliferation' was adopted to distinguish it from metaplasia and carcinoma. However, only moderate interobserver agreement among Gyn pathologists was noted.
- ▶ In WHO 2020, mucinous carcinoma is assimilated into endometrioid ca with mucinous differentiation.



# 'Atypical Mucinous Proliferations'

▶ Historically, these lesions were considered as mucinous hyperplasia.

▶ In WHO 2010, these lesions were distinguished into mucinous hyperplasia and mucinous carcinoma.

▶ In WHO 2020, these lesions were distinguished into mucinous hyperplasia and mucinous carcinoma.

So, what should we call confluent or complex mucinous proliferations with minimal atypia?

1. Atypical hyperplasia
2. Atypical hyperplasia with mucinous differentiation
3. Atypical mucinous hyperplasia

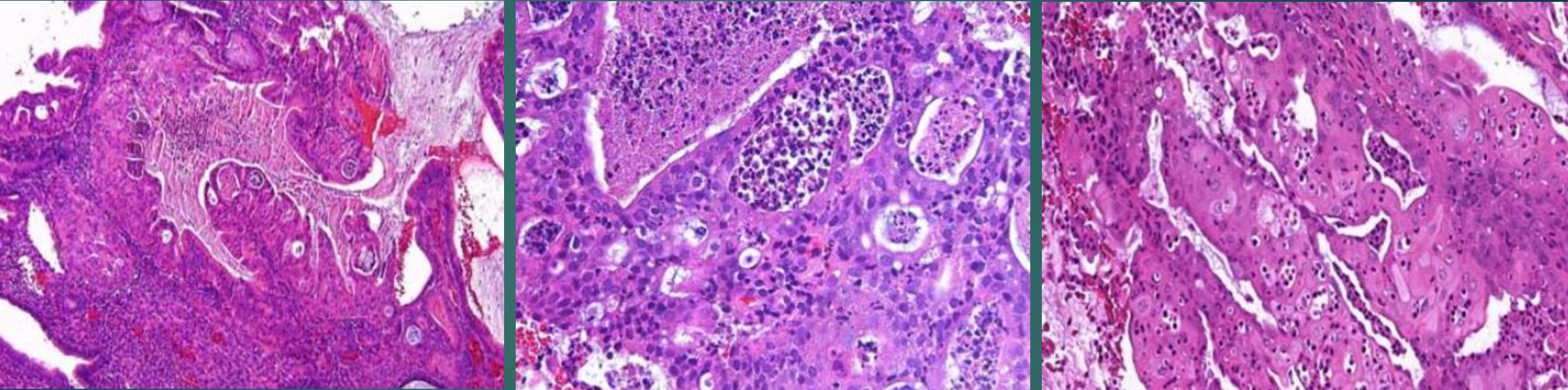


# ‘Atypical Mucinous Glandular Proliferations’ in small biopsies

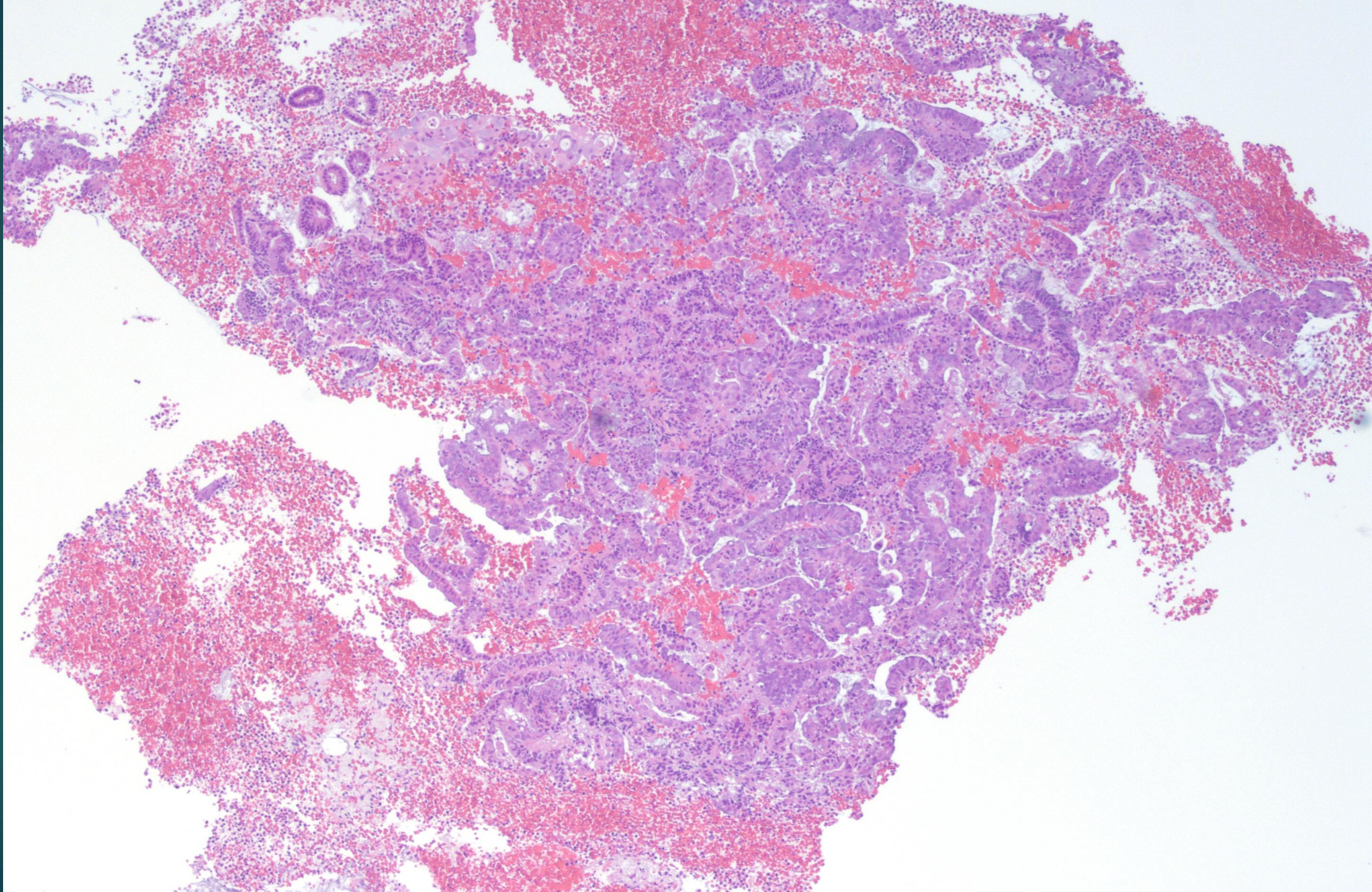
- ▶ Regardless of terminology, architecturally complex mucinous proliferation always warrants further investigations. Effective communication to clinician is important.
- ▶ *KRAS* mutations are found in >2/3 of atypical mucinous glandular proliferations and may be useful for distinguishing from mucinous metaplasia.



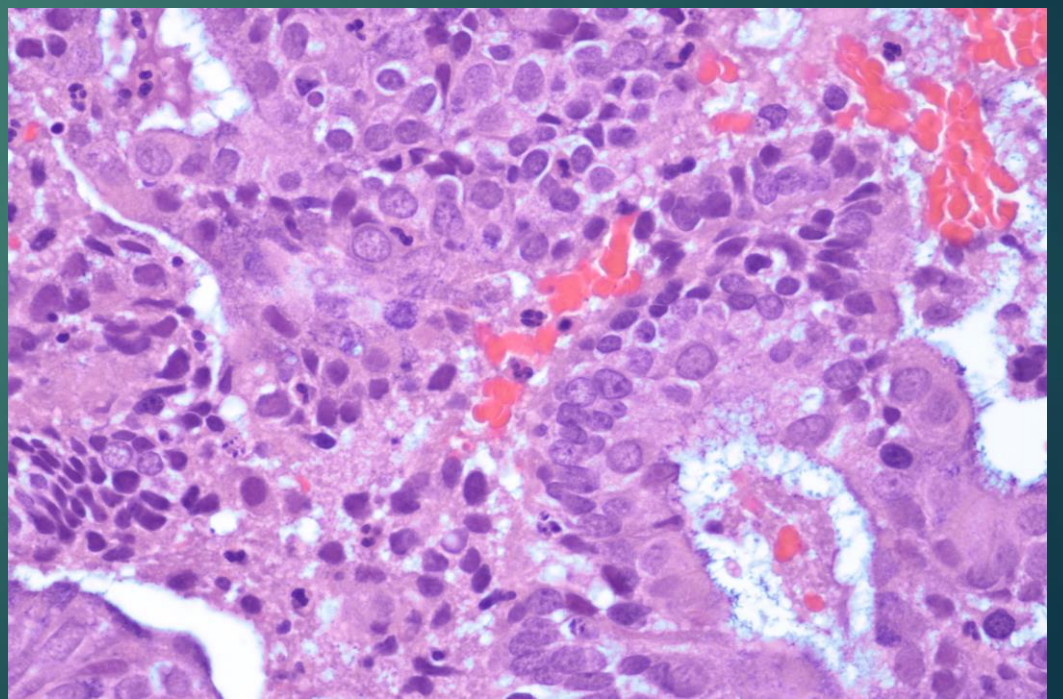
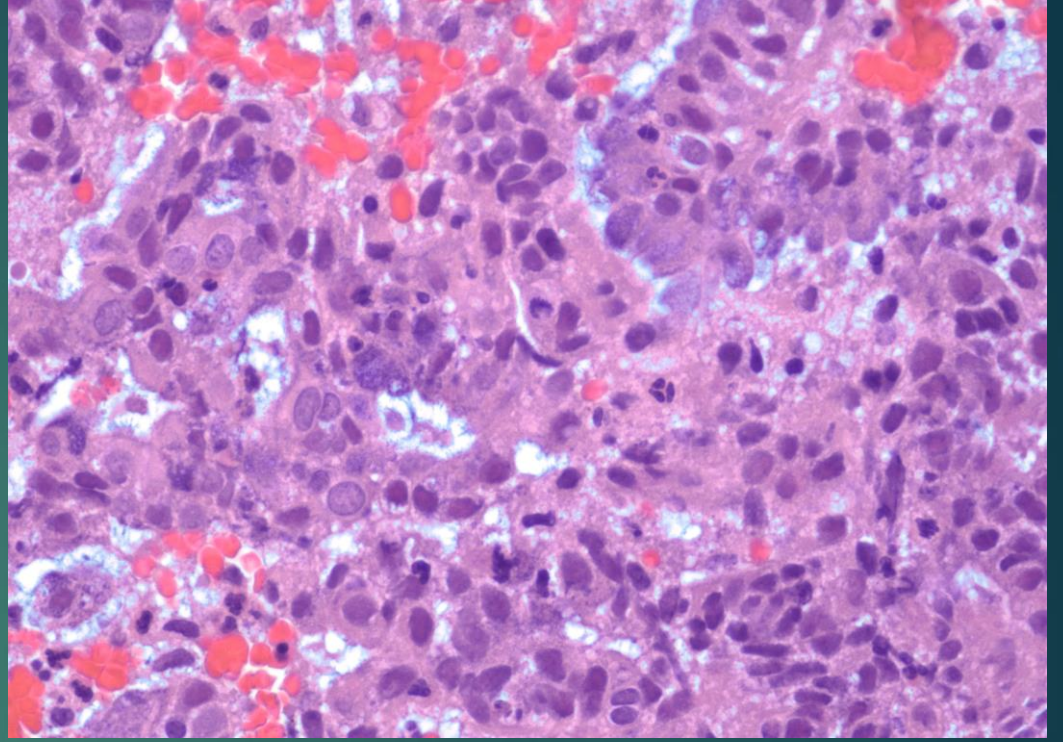
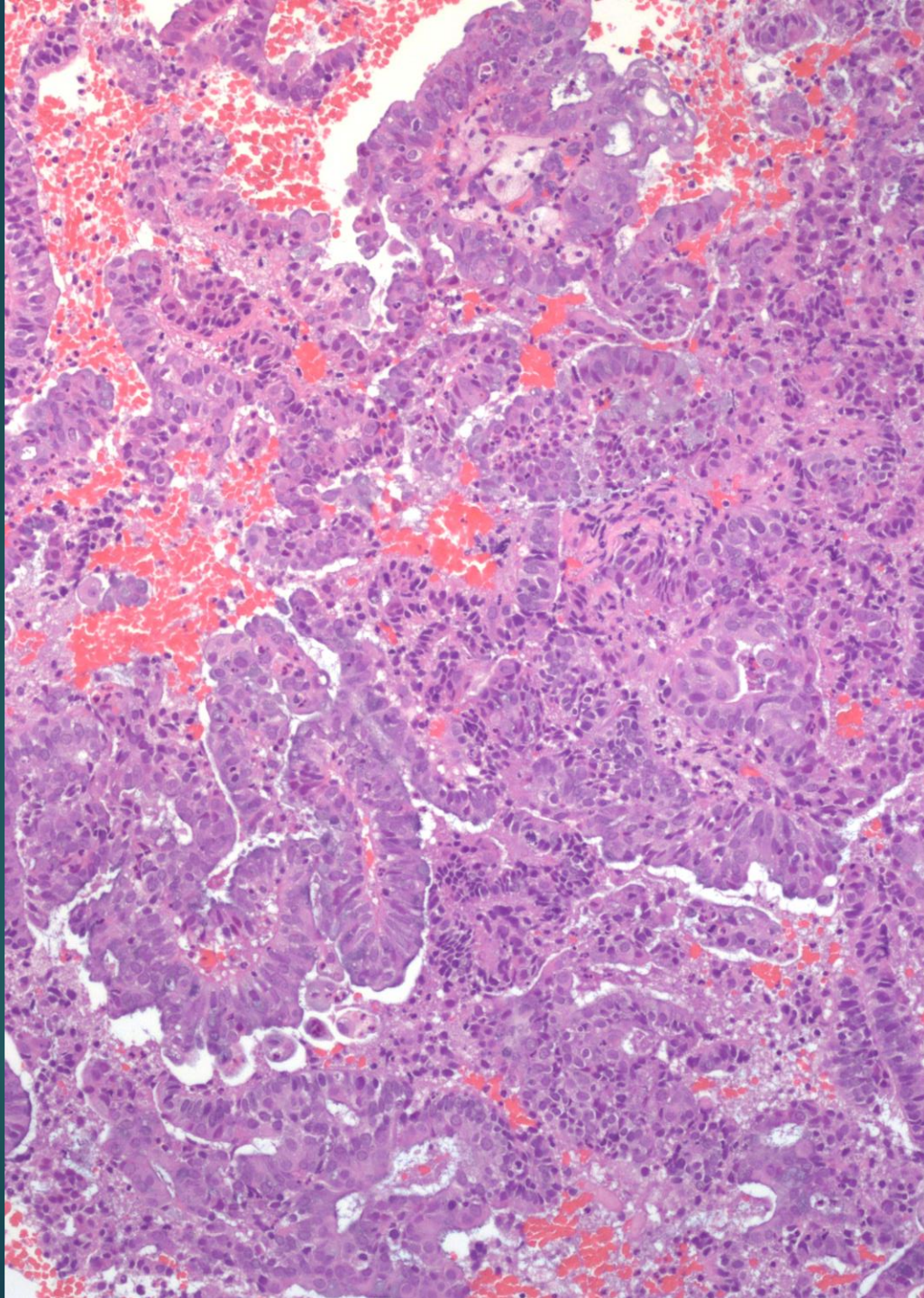
# Endometrial Ca with Microglandular Features in small biopsies



- ▶ The surface of an otherwise typical endometrioid ca may show microglandular features. Jacques et al. referred to these as 'surface epithelial changes'.









# Endometrial Ca with Microglandular Features in small biopsies

- ▶ Microglandular hyperplasia of cervix:
  - Premenopausal
  - Continuity with normal endocervical glands
  - CD34+, CD10- stromal cells.
  - Lack *KRAS* mutations.

Hong W. et al. Hum Pathol. 2015  
Stewart CJ. et al. Int J Gynecol Pathol. 2015  
Chekmareva M. et al. Int J Gynecol Pathol. 2008  
McCluggage WG et al. Histopathology. 2000  
Young RH and Scully RE. Am J Surg Pathol. 1992



# Utility of p63 and PTEN staining in distinguishing cervical microglandular hyperplasia from endometrial endometrioid carcinoma with microglandular/mucinous features

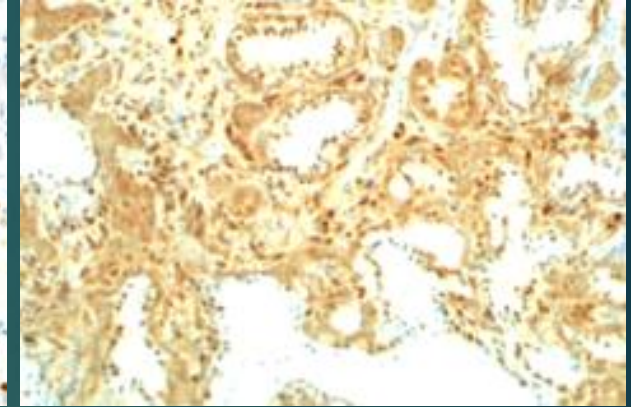
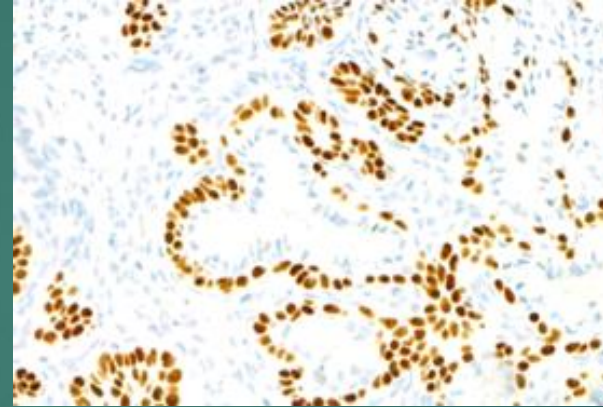
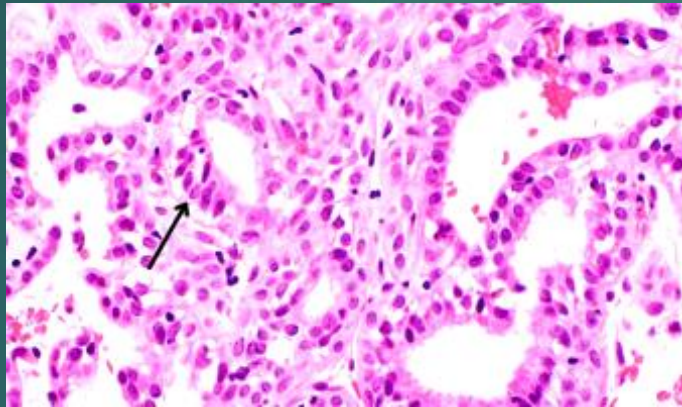
Batoul A. Aoun<sup>1</sup> & Stephanie L. Skala<sup>1,2</sup> 

<sup>1</sup>Department of Pathology and <sup>2</sup>Rogel Cancer Center, University of Michigan, Ann Arbor, MI, USA

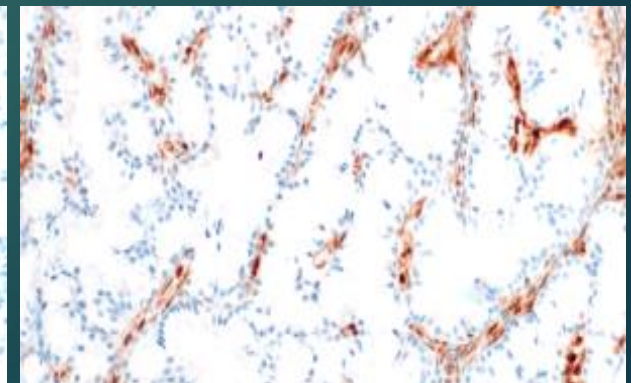
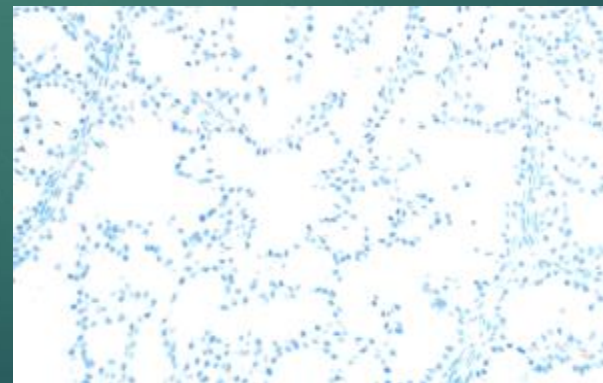
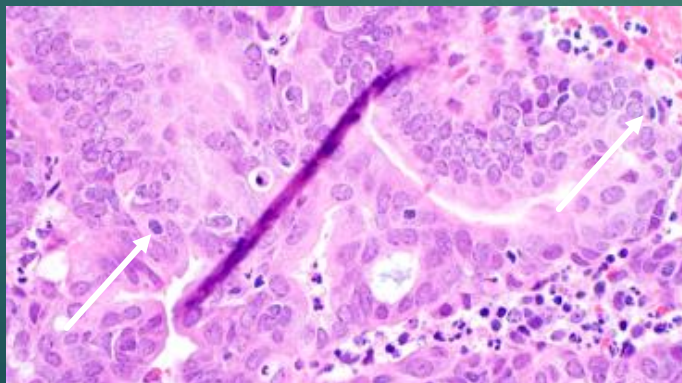
p63

PTEN

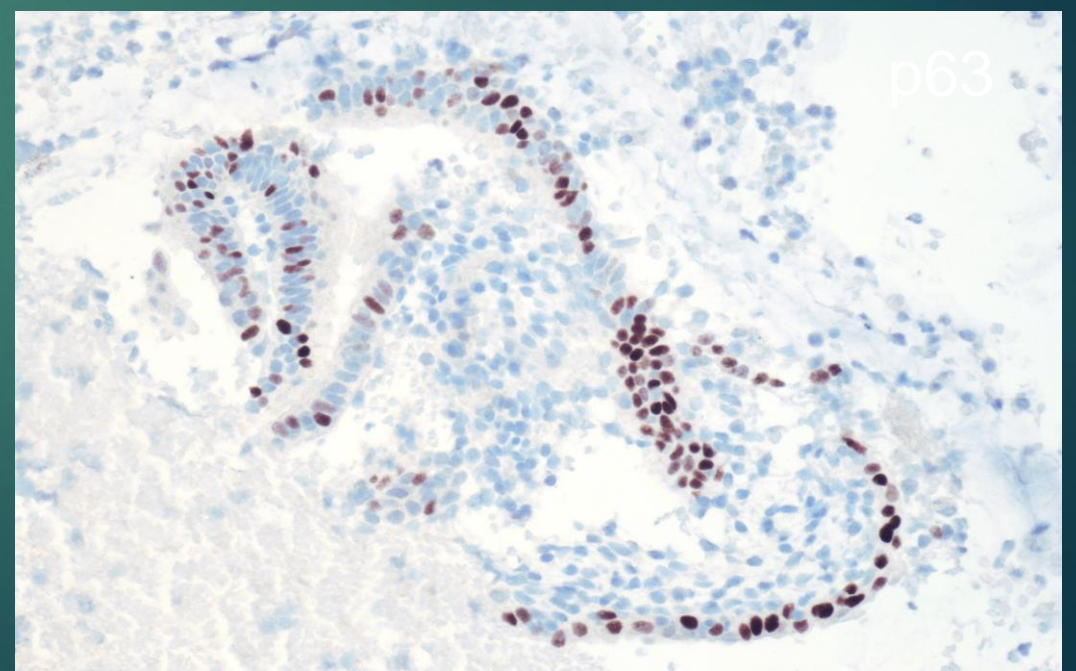
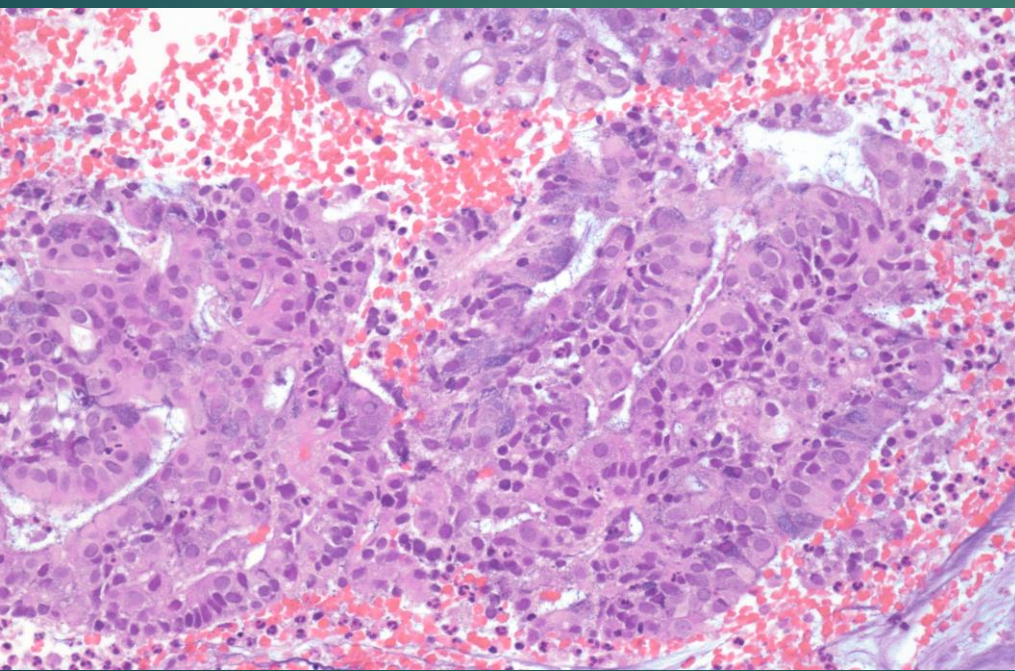
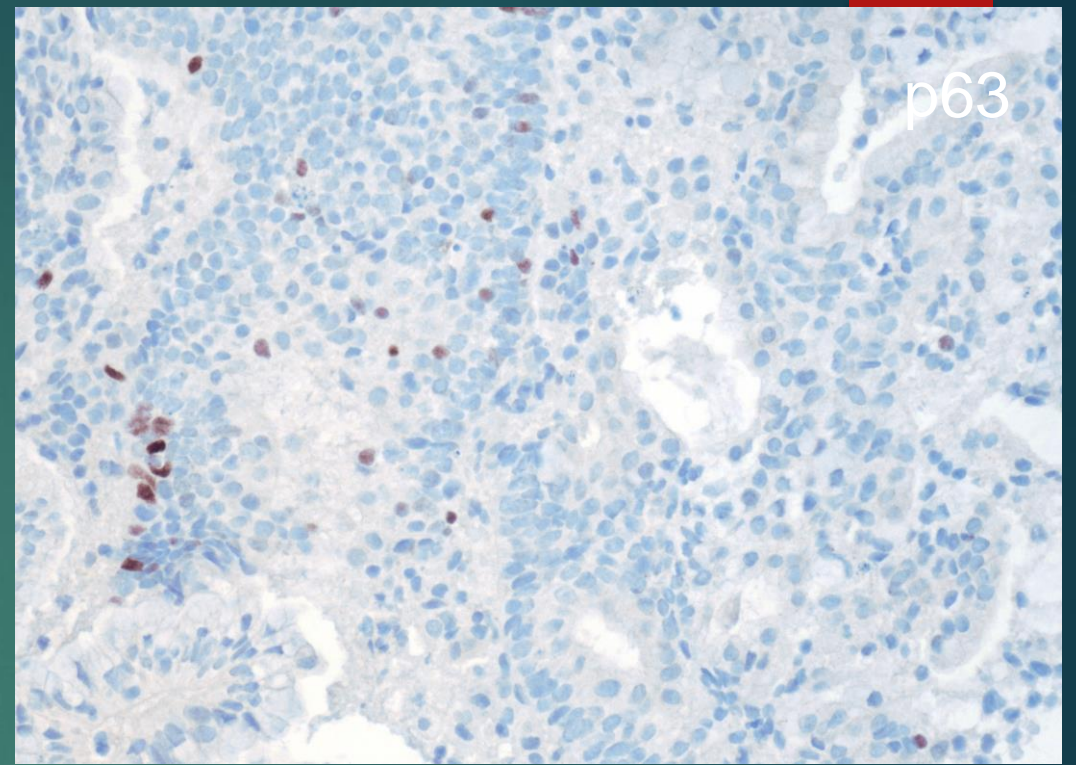
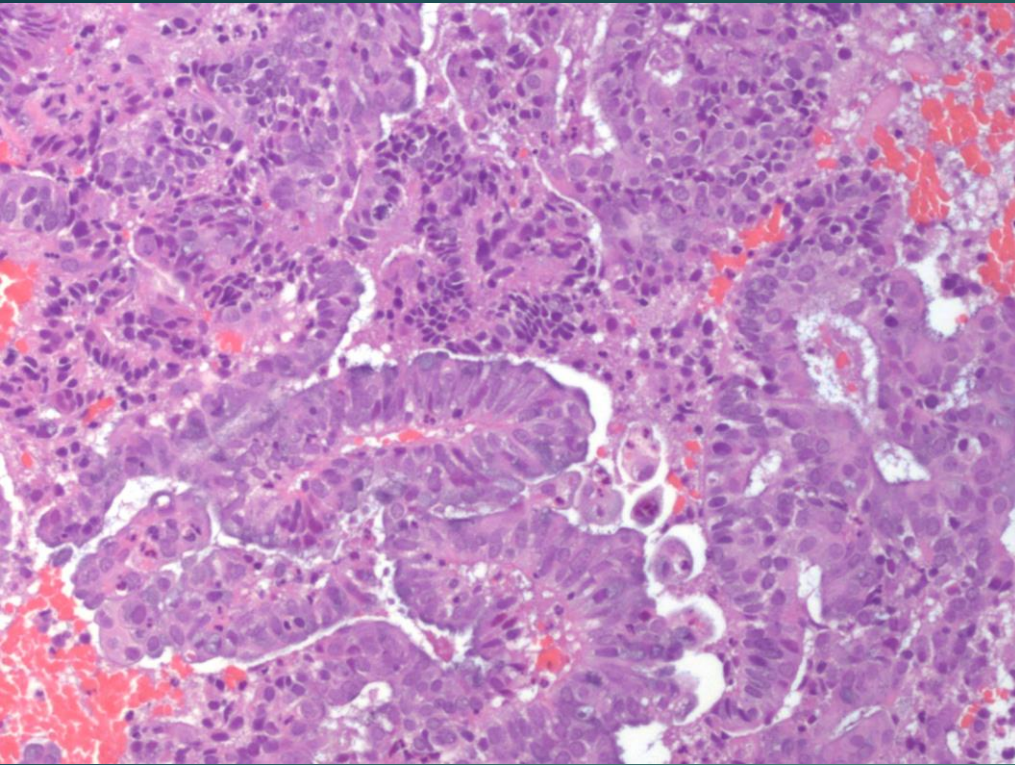
Microglandular hyperplasia

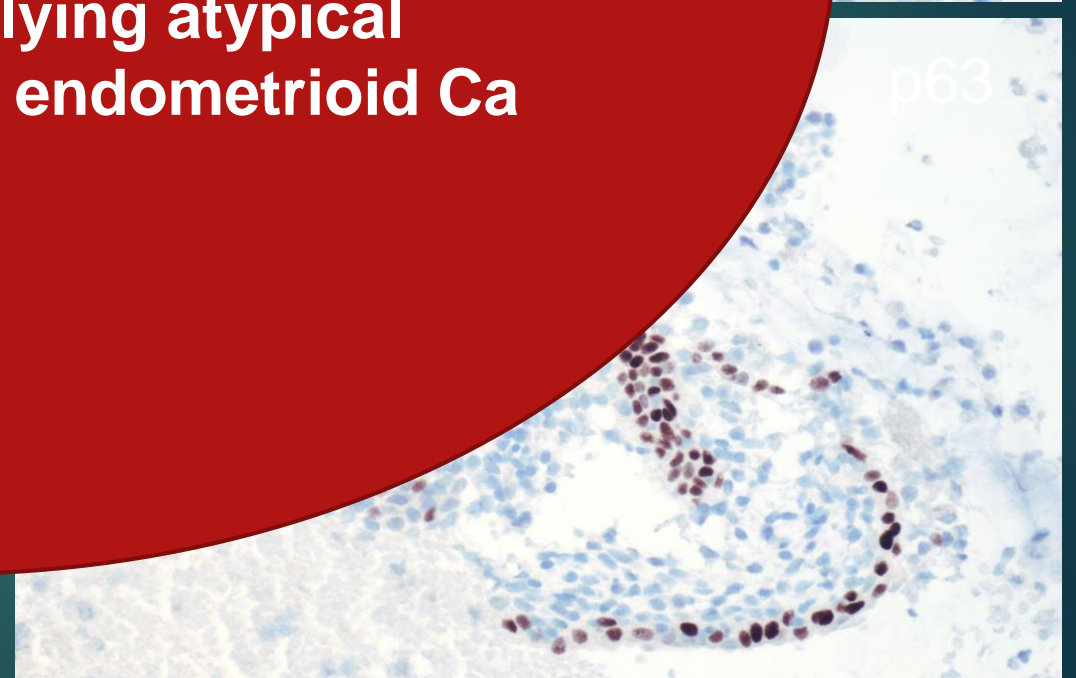
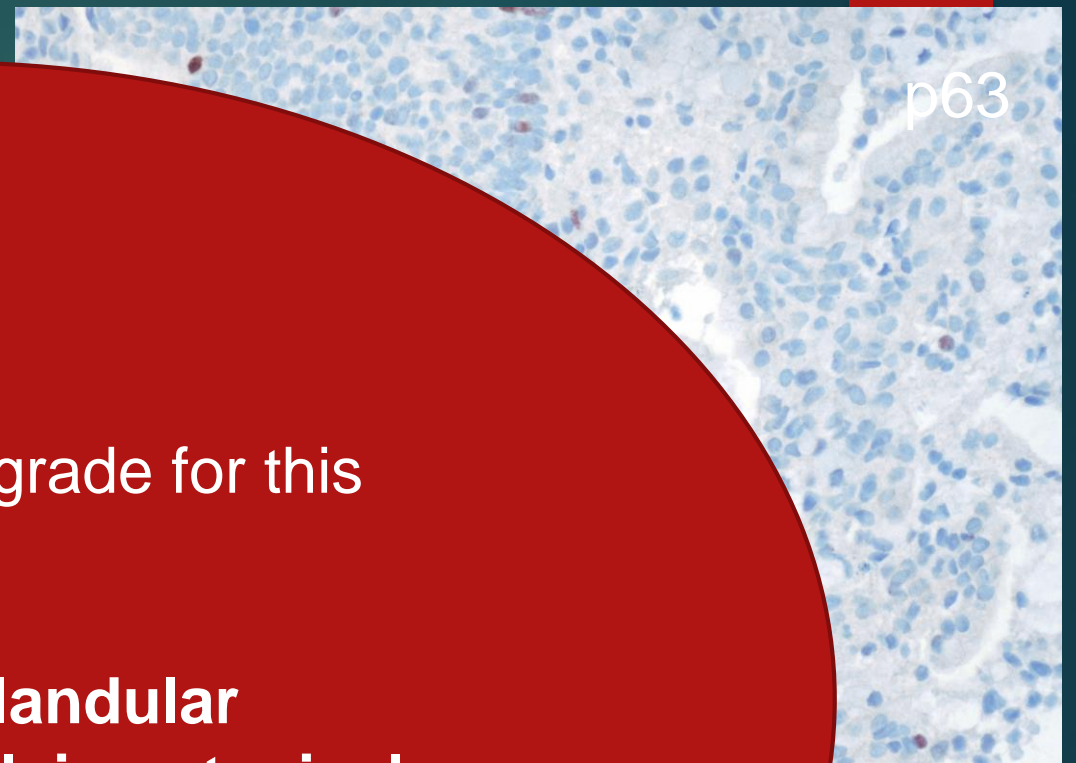
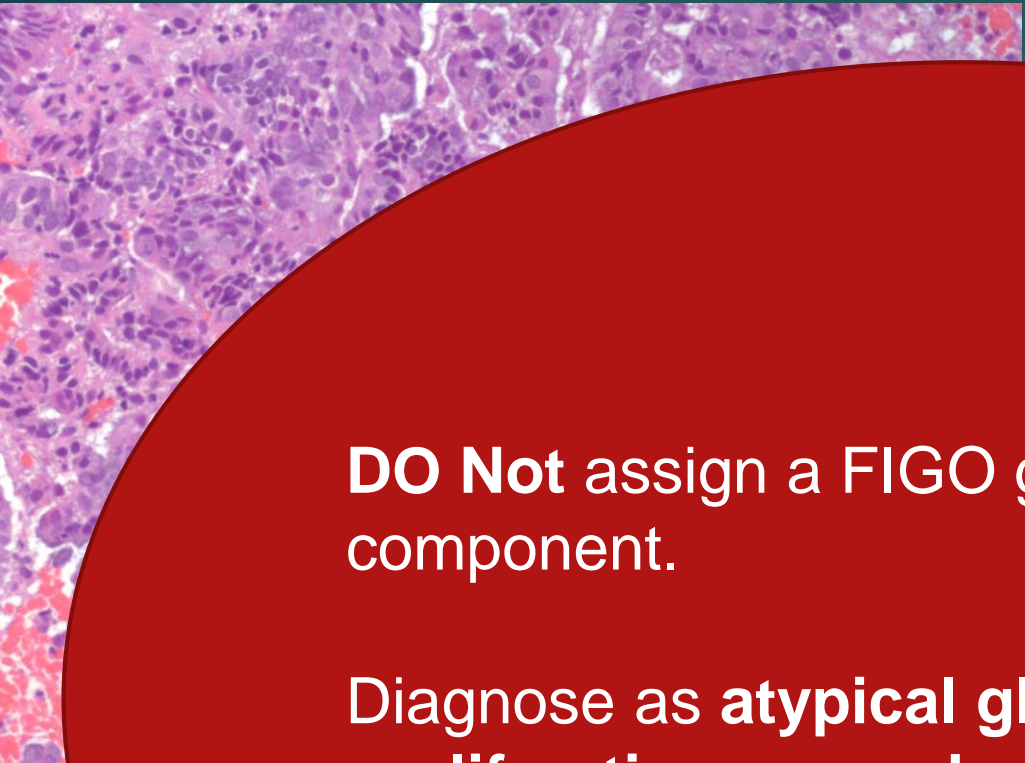


Surface microglandular features



► p63 + subcolumnar reserve cells in MGH.





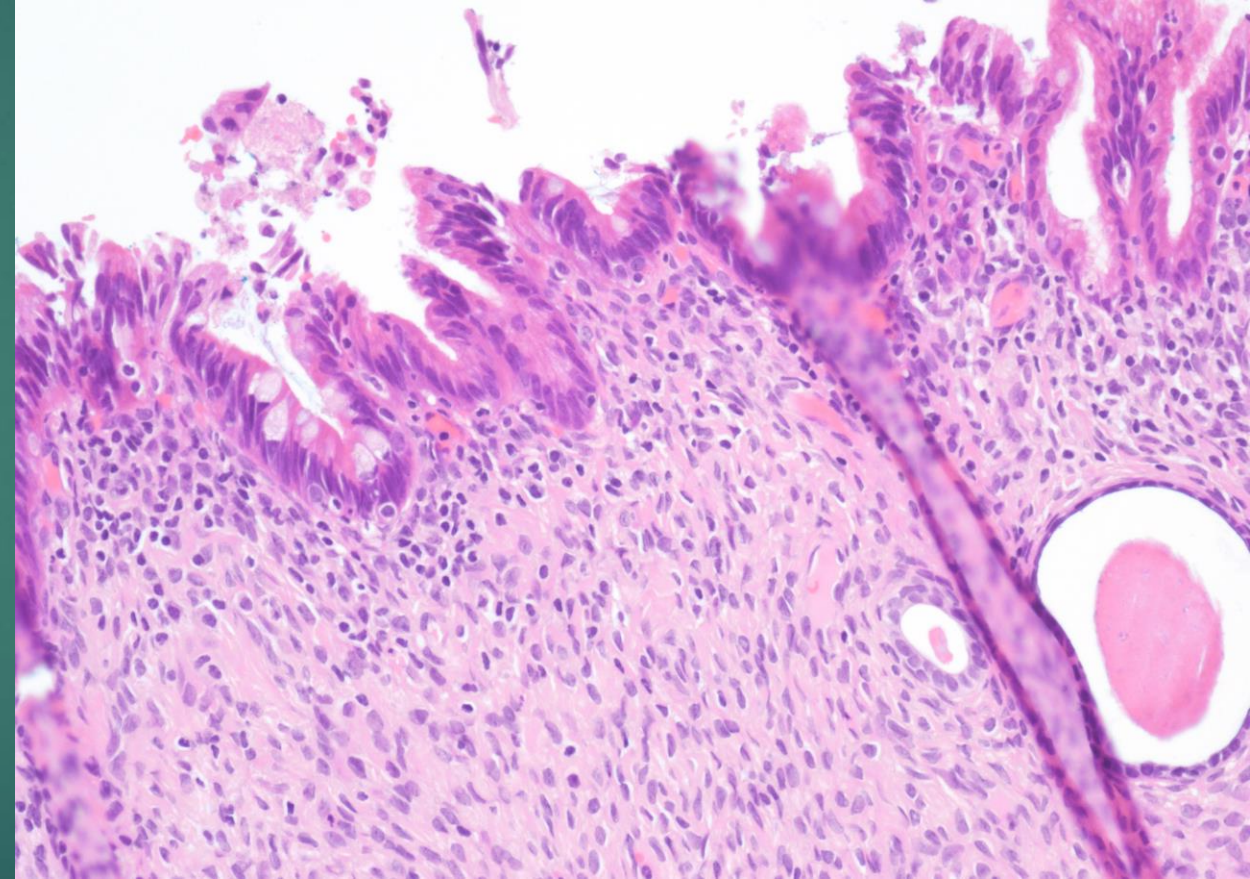
**DO Not** assign a FIGO grade for this component.

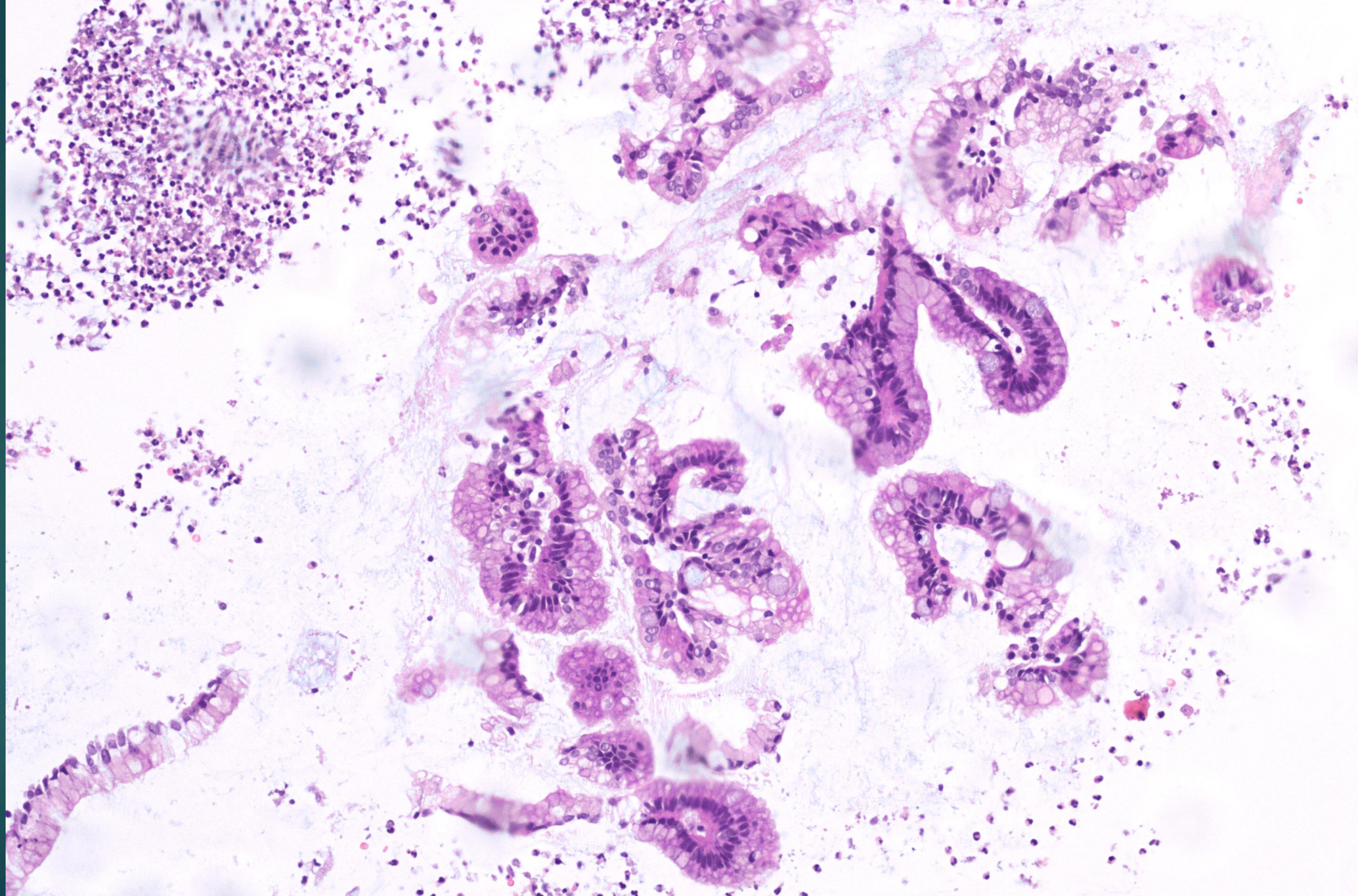
Diagnose as **atypical glandular proliferation, an underlying atypical hyperplasia/low-grade endometrioid Ca** has to be confirmed.



# Endometrial Gastrointestinal Mucinous lesions

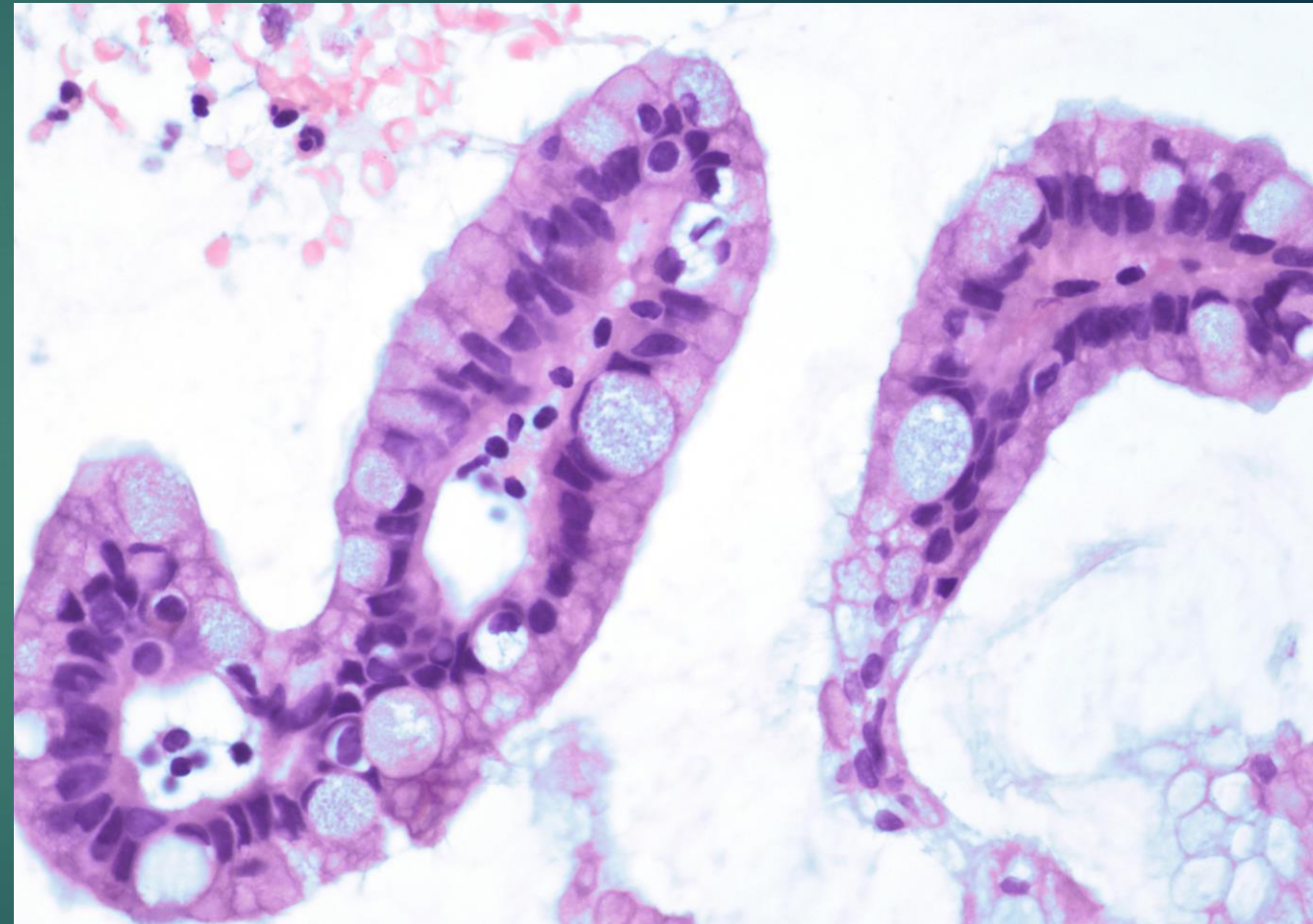
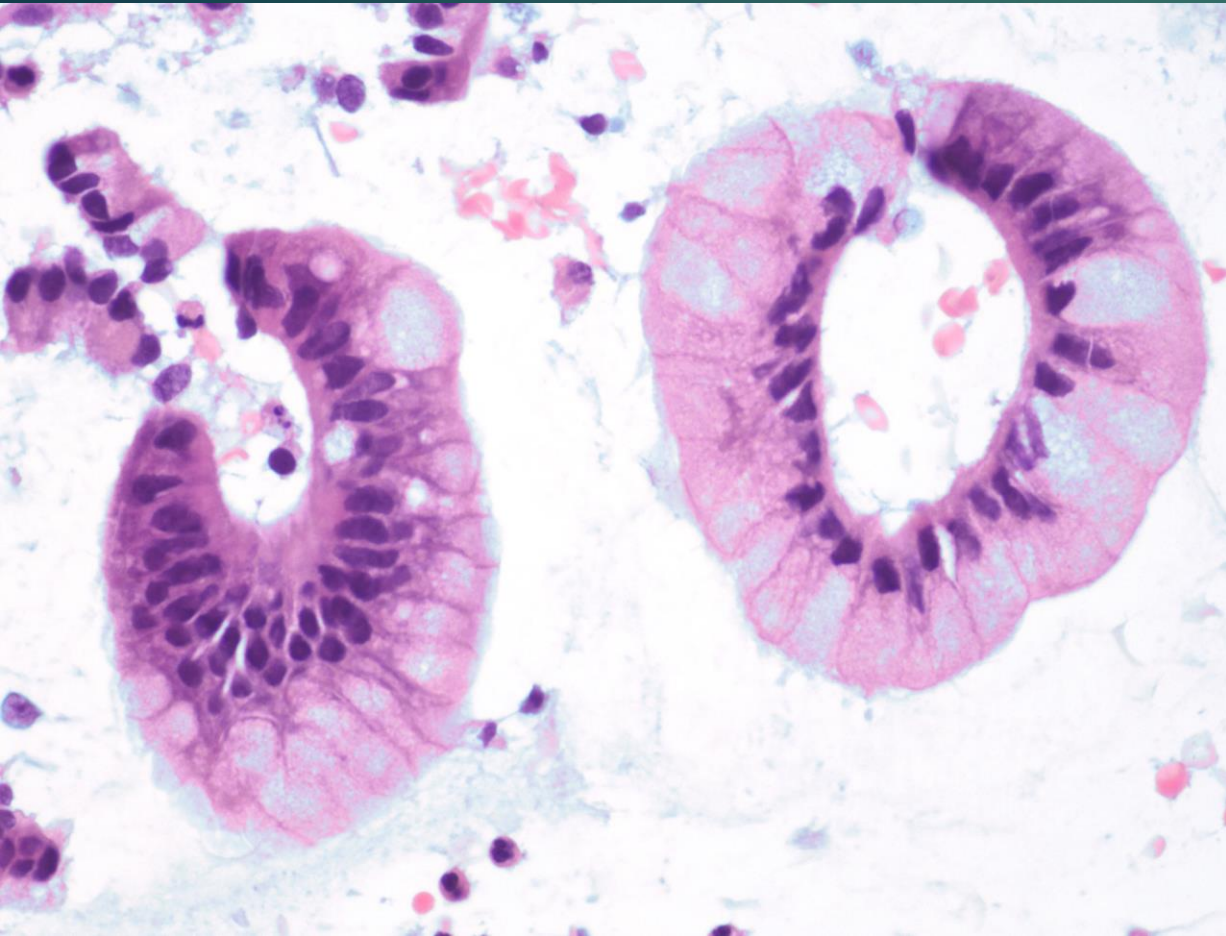
- ▶ Rare, poorly characterized lesions. Less common than in the cervix.
- ▶ Mucinous metaplasia (no atypia and no architectural complexity)
- ▶ Atypical mucinous glandular proliferation (atypia or architectural complexity)
- ▶ Mucinous carcinoma (both)







# 'Atypical Mucinous Glandular Proliferations' in small biopsies

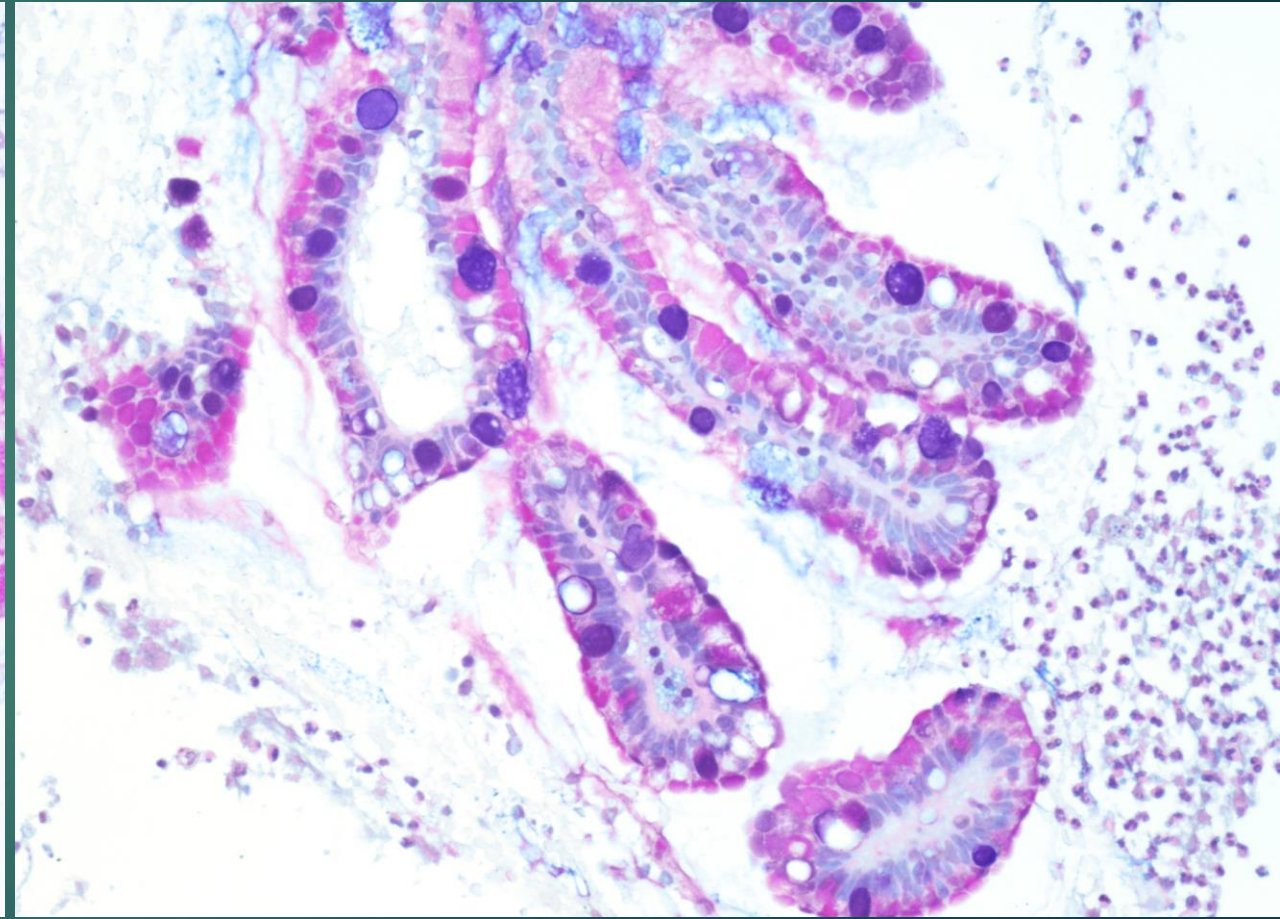
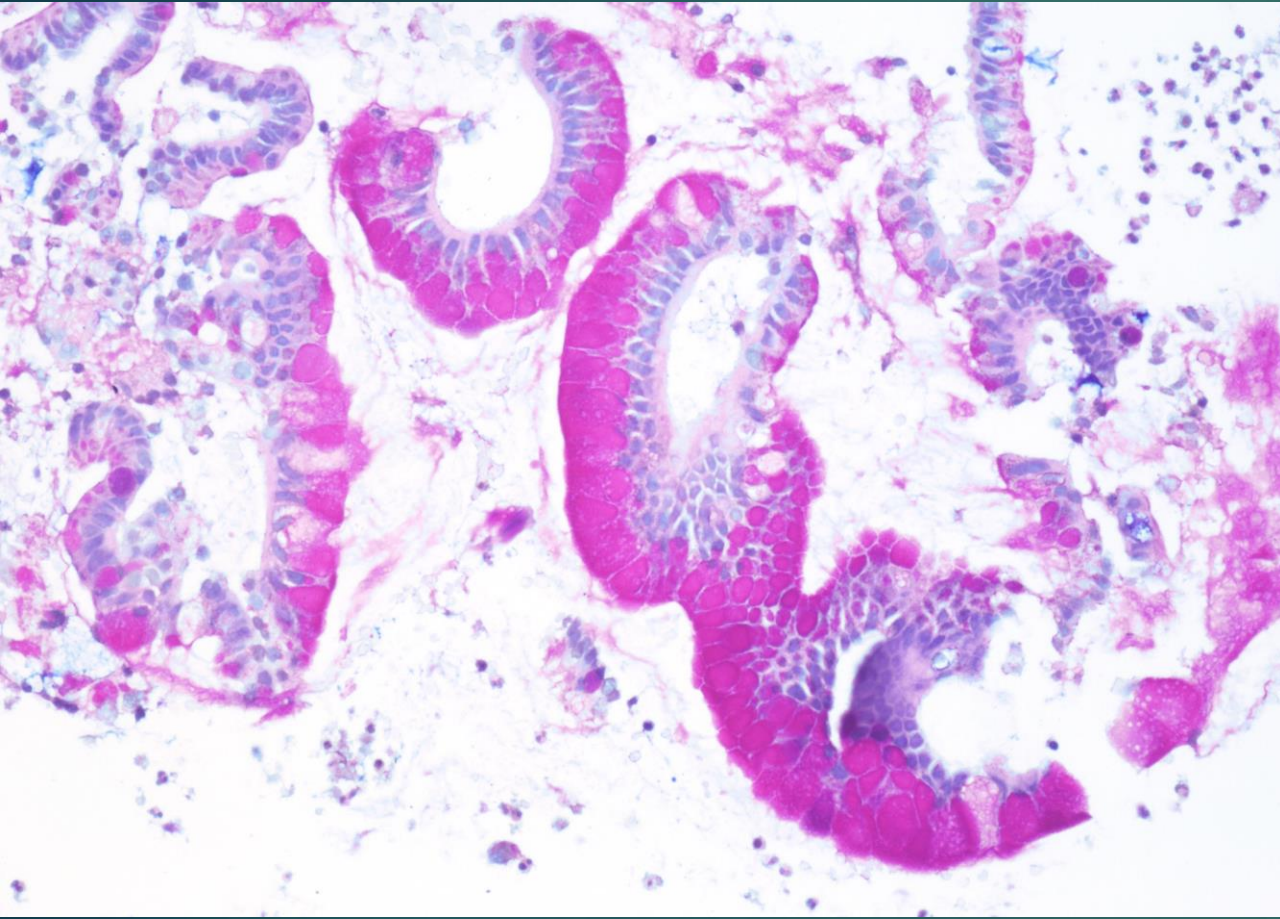


- Mucinous cells with voluminous, pale eosinophilic or clear cytoplasm, distinct cell borders +/- goblet cells.





# 'Atypical Mucinous Glandular Proliferations' in small biopsies



- Alcian blue/PAS: Neutral (gastric mucin) stains red/pink, acidic (intestinal mucin) stains lilac.



# Gastrointestinal Mucinous lesions: Immunohistochemistry

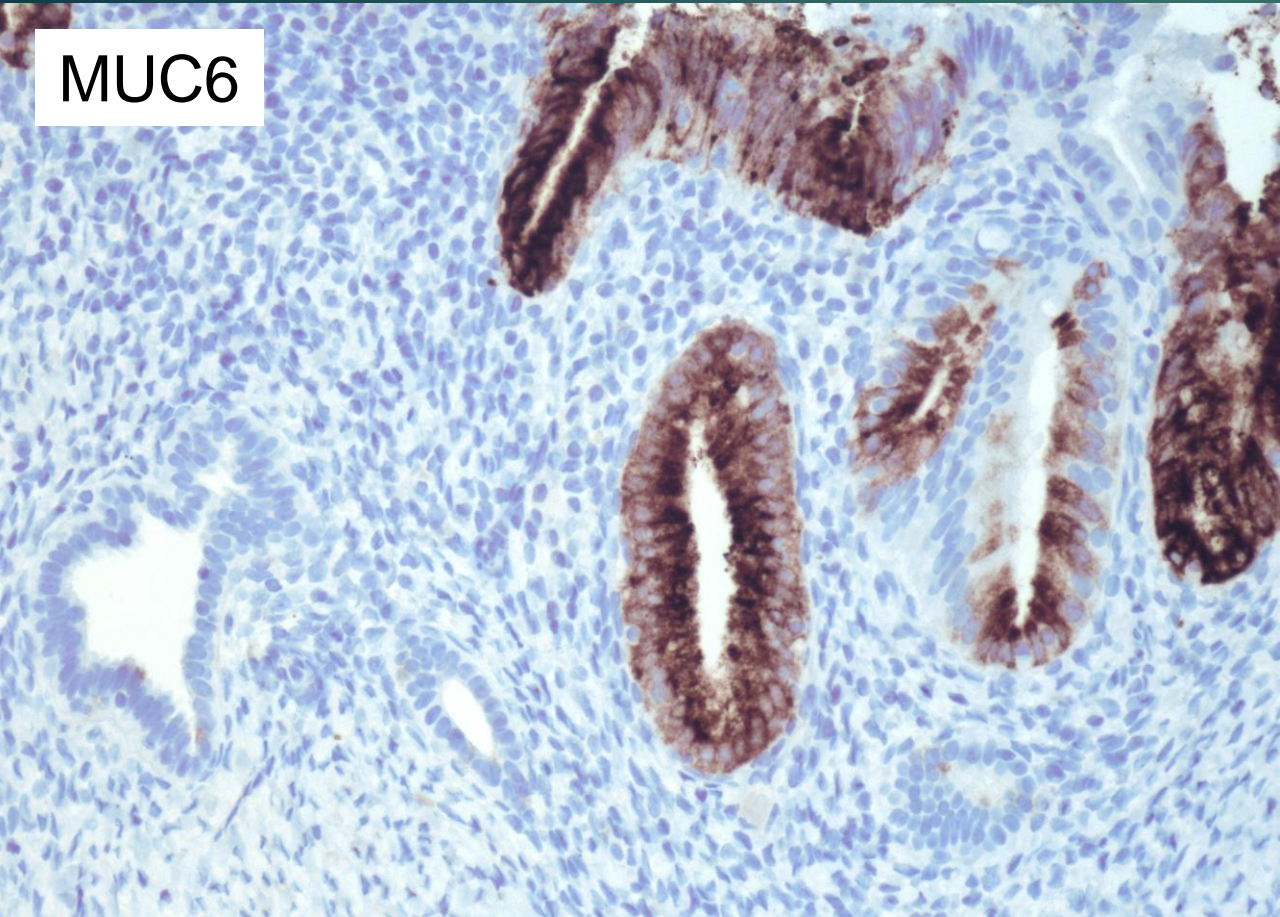
- ▶ Alcian blue / PAS
- ▶ CK7, CK20, CDX2, SATB2
- ▶ MUC6
- ▶ HIK1083

Kiyokawa T. et al. Am J Surg Pathol. 2022  
Kiyokawa T. et al. Int J Gynecol Pathol. 2021  
Stolnicu S. et al. Pol J Pathol. 2021  
Travaglino A. et al. Am J Surg Pathol. 2020  
Wong RW. et al. Am J Surg Pathol. 2020  
Hodgson A. et al. Histopathology. 2019  
Nicholae A. et al. Int J Gynecol Pathol. 2011  
Wells M. and Tiltman A. Histopathology. 1989

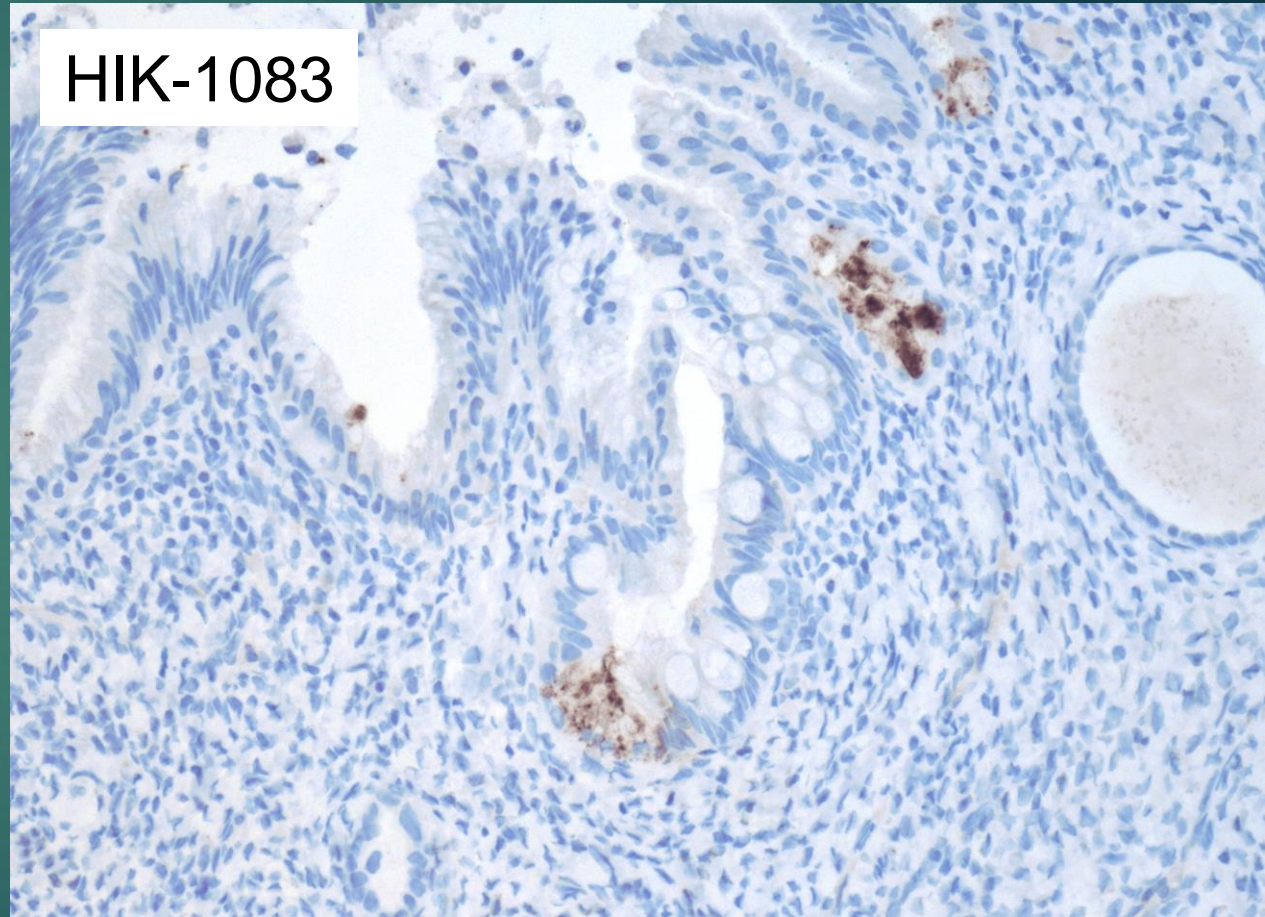


# Gastrointestinal Mucinous lesions: Immunohistochemistry

MUC6



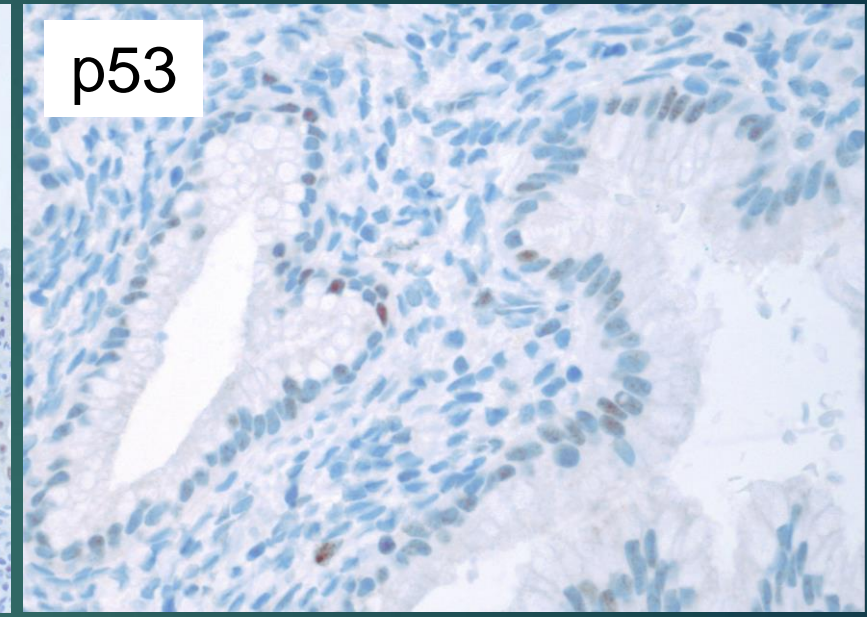
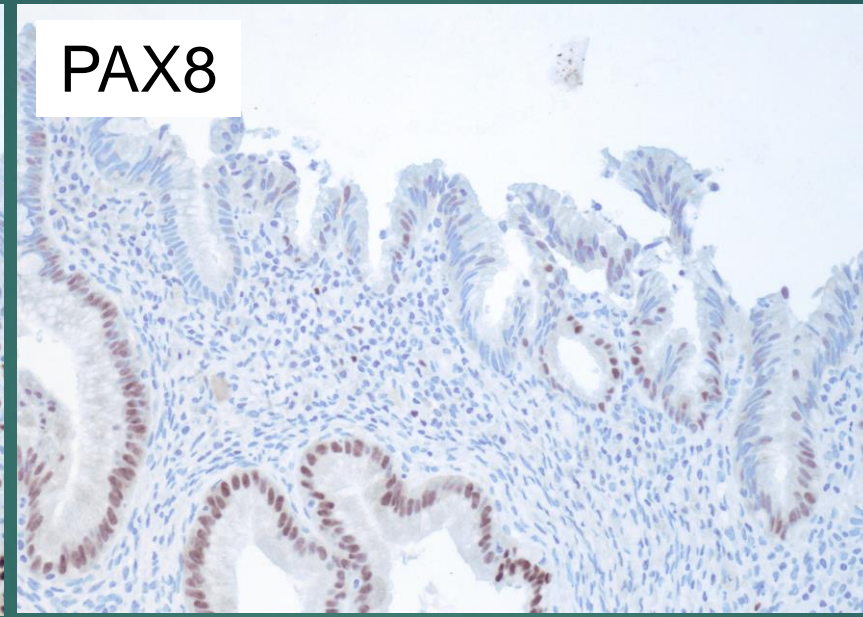
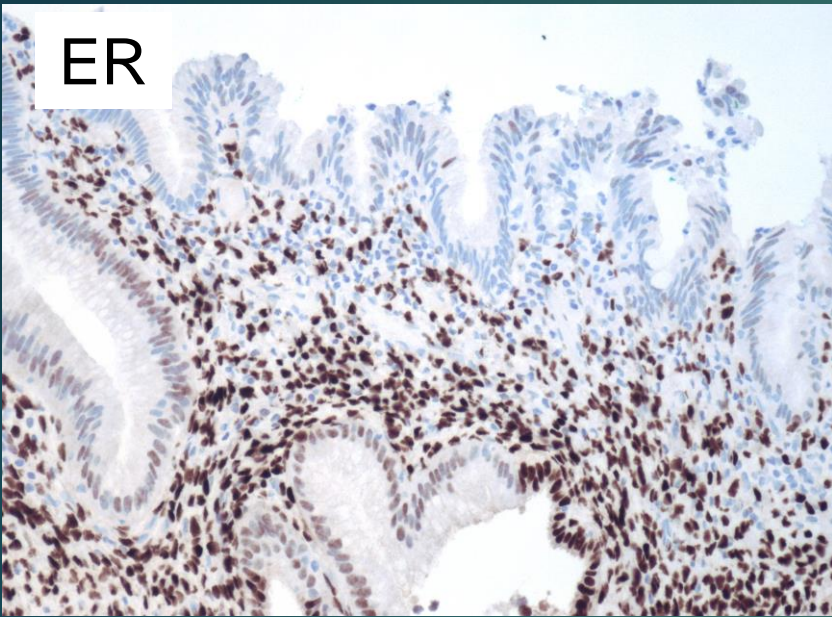
HIK-1083



- MUC6 (sensitive, not specific)
- HIK1083 (specific, focal staining, limited availability)



# Gastrointestinal Mucinous lesions: Immunohistochemistry



- Negative immunostains also helpful
- Loss/reduced ER, PAX8
- Wild-type p53 (in mucinous metaplasia)

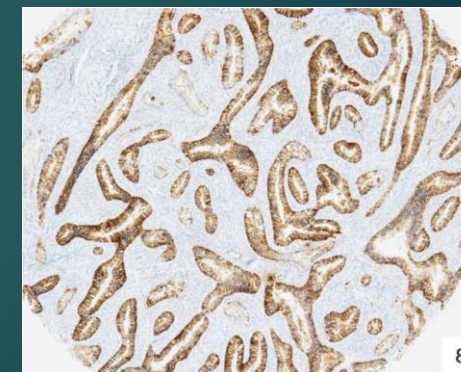


# Gastrointestinal Mucinous lesions: Immunohistochemistry

- **Claudin-18:** product of tight-junction complexes with 2 splice variants (stomach and lung). Expressed in stomach and pancreatobiliary neoplasms.
- **Trefoil factor 2 (TFF2):** mucin-associated peptide expressed in normal gastric mucosa.
- Evaluated in endocervical gastric lesions, may be applicable to endometrium.



| Total               | Claudin-18 (N = 175) | TFF2 (N = 175) | HIK1083 (N = 175) |
|---------------------|----------------------|----------------|-------------------|
| GAS                 | 15/23 (65.2)*        | 6/23 (26.1)*   | 9/23 (39.1)*      |
| Non-GAS             | 3/152 (2.0)*         | 4/152 (2.6)*   | 2/152 (1.3)*      |
| Usual               | 3/126 (2.4)          | 4/126 (3.2)    | 1/126 (0.8)       |
| SMC                 | 0/7 (0)              | 0/7 (0)        | 0/7 (0)           |
| Mucinous intestinal | 0/3 (0)              | 0/3 (0)        | 1/3 (33.3)        |
| Mucinous, NOS       | 0/1 (0)              | 0/1 (0)        | 0/1 (0)           |
| ECA, NOS            | 0/5 (0)              | 0/5 (0)        | 0/5 (0)           |
| Clear cell          | 0/7 (0)              | 0/7 (0)        | 0/7 (0)           |
| Endometrioid        | 0/3 (0)              | 0/3 (0)        | 0/3 (0)           |
| Sensitivity† (%)    | 65.2                 | 60.0           | 39.1              |
| Specificity‡ (%)    | 98.0                 | 97.3           | 98.7              |



Kiyokawa T. et al. Am J Surg Pathol. 2022  
 Kiyokawa T. et al. Int J Gynecol Pathol. 2021  
 Li WT. et al. Am J Surg Pathol. 2020  
 Asaka S. et al. Virchows Archiv. 2020

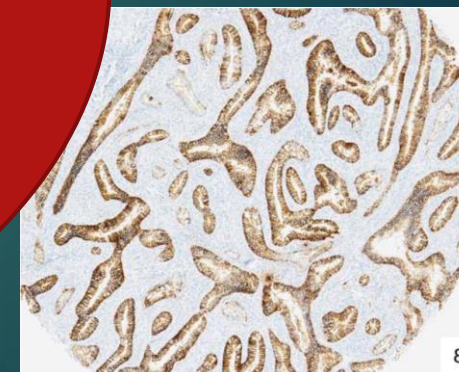


# Gastrointestinal Mucinous lesions: Immunohistochemistry

- **Claudin-18:** product of *CLDN18* gene has 2 splice variants (stomach and lung). Expressed in normal gastric mucosa and adenocarcinomas.
- **Trefoil factor 2 (TFF2):** product of *TFF2* gene is expressed in normal gastric mucosa.
- Evaluate the utility of TFF2 and Claudin-18 in the diagnosis of endometrial adenocarcinoma.

Claudin-18 and TFF2 showed similar specificity but improved sensitivity compared with HIK-1083 even in microarray samples.

Potential for use in small endometrial biopsies.



| Total               |         |      |         |
|---------------------|---------|------|---------|
| GAS                 |         |      |         |
| Non-GAS             |         |      |         |
| Usual SMC           |         |      |         |
| Mucinous intestinal |         |      |         |
| Mucinous, NOS       | 0/1 (0) |      |         |
| ECA, NOS            | 0/5 (0) |      |         |
| Clear cell          | 0/7 (0) |      |         |
| Endometrioid        | 0/3 (0) |      | 0/3 (0) |
| Sensitivity† (%)    | 65.2    | 60.0 | 39.1    |
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 Asaka S. et al. Virchows Archiv. 2020



**TABLE 3.** Reported Cases of Mucinous Carcinoma of the Gastrointestinal Type

| References                         | Age | Diagnosis  | Gastric vs. IM Morphology | FIGO Stage | Follow-up  |
|------------------------------------|-----|--|---------------------------|------------|--|
| Berger et al <sup>18</sup>         | 72  | Endometrial carcinoma, intestinal type, G1   | Intestinal                | IA         | NED  |
| Zheng et al <sup>95</sup>          | 71  | Mucinous adenocarcinoma with intestinal differentiation  | Intestinal                | IIIC       | AWD at 14 mo; recurrence in peritoneum                               |
| Nieuwenhuizen et al <sup>94</sup>  | NA  | Endometrial adenocarcinoma with goblet cell metaplasia, G2   | Intestinal                | NA         | NA   |
|                                    | NA  | Endometrial adenocarcinoma with goblet cell metaplasia, G2   | Intestinal                | NA         | NA   |
| Abiko et al <sup>99</sup>          | 56  | Minimal deviation mucinous adenocarcinoma (“adenoma malignum”)                                       | Gastric                   | IVB        | DOD at 28 mo; widespread metastases                                  |
| Buell-Gutbrod et al <sup>101</sup> | 55  | EEC with endocervical and intestinal type mucinous differentiation, G1                               | Intestinal                | IA         | NA   |
| Hino et al <sup>100</sup>          | 72  | Gastric-type mucinous adenocarcinoma (minimal deviation adenocarcinoma or adenoma malignum)          | Gastric                   | IIIC2      | DOD at 8 mo  |
| Rubio et al <sup>93</sup>          | 81  | Mucinous adenocarcinoma, gastrointestinal type   | Gastric and Intestinal    | IIIA       | NA   |
| Trippel et al <sup>102</sup>       | 62  | Mucinous adenocarcinoma with intestinal differentiation  | Intestinal                | IA         | DOD at 21 mo; recurrence in peritoneum                               |
| Mogor et al <sup>92</sup>          | 58  | Mucinous adenocarcinoma with intestinal differentiation, G2 (diagnosed in a vaginal cuff recurrence) | Intestinal                | IA         | NED at 87 mo   |
| McCarthy et al <sup>103</sup>      | 54  | EEC “with gastric-type differentiation,” G2  | Gastric                   | IA         | NED at 6 mo  |
|                                    | 65  | EEC “with gastric-type differentiation,” G1  | Gastric                   | IA         | NED at 4 mo  |
| Ardighieri et al <sup>96</sup>     | 49  | Mixed mucinous adenocarcinoma-intestinal type/EEC  | Intestinal                | IVB        | AWD at 6 mo  |
| Wong et al <sup>26</sup>           | 76  | Endometrial gastric (gastrointestinal)-type adenocarcinoma G1  | Gastric                   | IA         | DOD at 36 mo; recurrence in vagina, urinary bladder; bone metastases |
|                                    | 69  | Endometrial gastric (gastrointestinal)-type adenocarcinoma, G2                                       | Gastric                   | IB         | DOD at 7 mo  |
|                                    | 32  | Endometrial gastric (gastrointestinal)-type adenocarcinoma, G1                                       | Intestinal and Gastric    | IA         | NED at 7 mo  |
|                                    | 85  | Endometrial gastric (gastrointestinal)-type adenocarcinoma, G2                                       | Gastric                   | IIIA       | AWD at 9 mo with lung metastases                                     |
| Travaglino et al <sup>97</sup>     | 50  | Endometrial Gastric-type Carcinoma   | Gastric                   | NA         | NA   |
| Stolnicu et al <sup>98</sup>       | 64  | Endometrial adenocarcinoma with gastrointestinal differentiation, G2                                 | Intestinal and Gastric    | IA         |  |

Reference<sup>104</sup> is not included (uncertainty about mucinous carcinoma type).

AWD indicates alive with disease; DOD, dead of disease; EEC, endometrioid carcinoma of the endometrium; FIGO, International Federation of Gynecology and Obstetrics; G, FIGO grade; IM intestinal; NA, not available; NED, no evidence of disease.



**TABLE 3.** Reported Cases of Mucinous Carcinoma of the Gastrointestinal Type

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| Nieuwenhuizen et al <sup>94</sup> | NA  | Endometrial adenocarcinoma   |                           | NA         | NA                                       |
|                                   | NA  |  |                           |            | NA                                       |
| Abiko et al <sup>99</sup>         |     |  |                           |            | at 28 mo; metastases                     |
| Buell-Guth et al <sup>100</sup>   |     |  |                           |            |  |
| Hinojosa et al <sup>101</sup>     |     |  |                           |            |  |
| Rubinfeld et al <sup>102</sup>    |     |  |                           |            |  |
| Tanaka et al <sup>103</sup>       |     |  |                           |            |  |
| Morimoto et al <sup>104</sup>     |     |  |                           |            |  |
| McGee et al <sup>105</sup>        |     |  |                           |            |  |
| Ardigiani et al <sup>106</sup>    |     |  |                           |            |  |
| Wong et al <sup>107</sup>         |     |  |                           |            | recurrence secondary bladder; metastases |
|                                   |     |  |                           |            | DOD at 7 mo                              |
|                                   | 32  |  |                           |            | NED at 7 mo                              |
|                                   |     |  |                           |            |  |
|                                   | 85  | Endometrial gastric-type adenocarcinoma, G2                          | Gastric                   | IIIA       | AWD at 9 mo with lung metastases         |
| Travaglino et al <sup>97</sup>    | 50  | Endometrial Gastric-type Carcinoma                                   | Gastric                   | NA         | NA                                       |
| Stolnicu et al <sup>98</sup>      | 64  | Endometrial adenocarcinoma with gastrointestinal differentiation, G2 | Intestinal and Gastric    | IA         |  |

In WHO 2020: Endometrial mucinous carcinoma is assimilated into endometrioid carcinomas.

Endometrial gastric/gastrointestinal type mucinous carcinoma is categorized into 'other carcinomas'.

Reference<sup>104</sup> is not included (uncertainty about mucinous carcinoma type).  
 AWD indicates alive with disease; DOD, dead of disease; EEC, endometrioid carcinoma of the endometrium; FIGO, International Federation of Gynecology and Obstetrics; G, FIGO grade; IM intestinal; NA, not available; NED, no evidence of disease.





# Simple and Complex Hyperplastic Papillary Proliferations of the Endometrium

A Clinicopathologic Study of Nine Cases of Apparently Localized Papillary Lesions With Fibrovascular Stromal Cores and Epithelial Metaplasia

Michael B. Lehman, M.D., and William R. Hart, M.D.

- Historically been recognized (AFIP 1992, Sternberg's 2<sup>nd</sup> Ed) and emphasis has always been on its distinction from carcinoma.
- Papillae with fibrovascular stromal cores, variable branching complexity and extent. **No cytologic atypia.**
- Involve surface endometrium, subjacent glands.
- **Coexisting metaplasias.**

Lehman MB, Hart WR. Am J Surg Pathol. 2001  
Sternberg 2<sup>nd</sup> Ed, 1994

AFIP Atlas of Tumor Pathology 1992, Silverberg and Kurman, p. 204-5



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- ▶ 9 cases (4 simple, 5 complex)
- ▶ Simple: small foci or clusters.
- ▶ Complex: florid, many glands involved (resembles complex hyperplasia).



# Simple and Complex Hyperplastic Papillary Proliferations of the Endometrium

A Clinicopathologic Study of Nine Cases of Apparently Localized Papillary Lesions With Fibrovascular Stromal Cores and Epithelial Metaplasia

Michael B. Lehman, M.D., and William R. Hart, M.D.

- ▶ 9 cases (4 simple, 5 complex)
- ▶ **Simple: small foci or clusters.**
  - 2 had persistent lesions on follow-up.
- ▶ **Complex: florid, many glands involved (resembles complex hyperplasia).**
  - 2 had hyperplasias on follow-up.



# Papillary Proliferation of the Endometrium

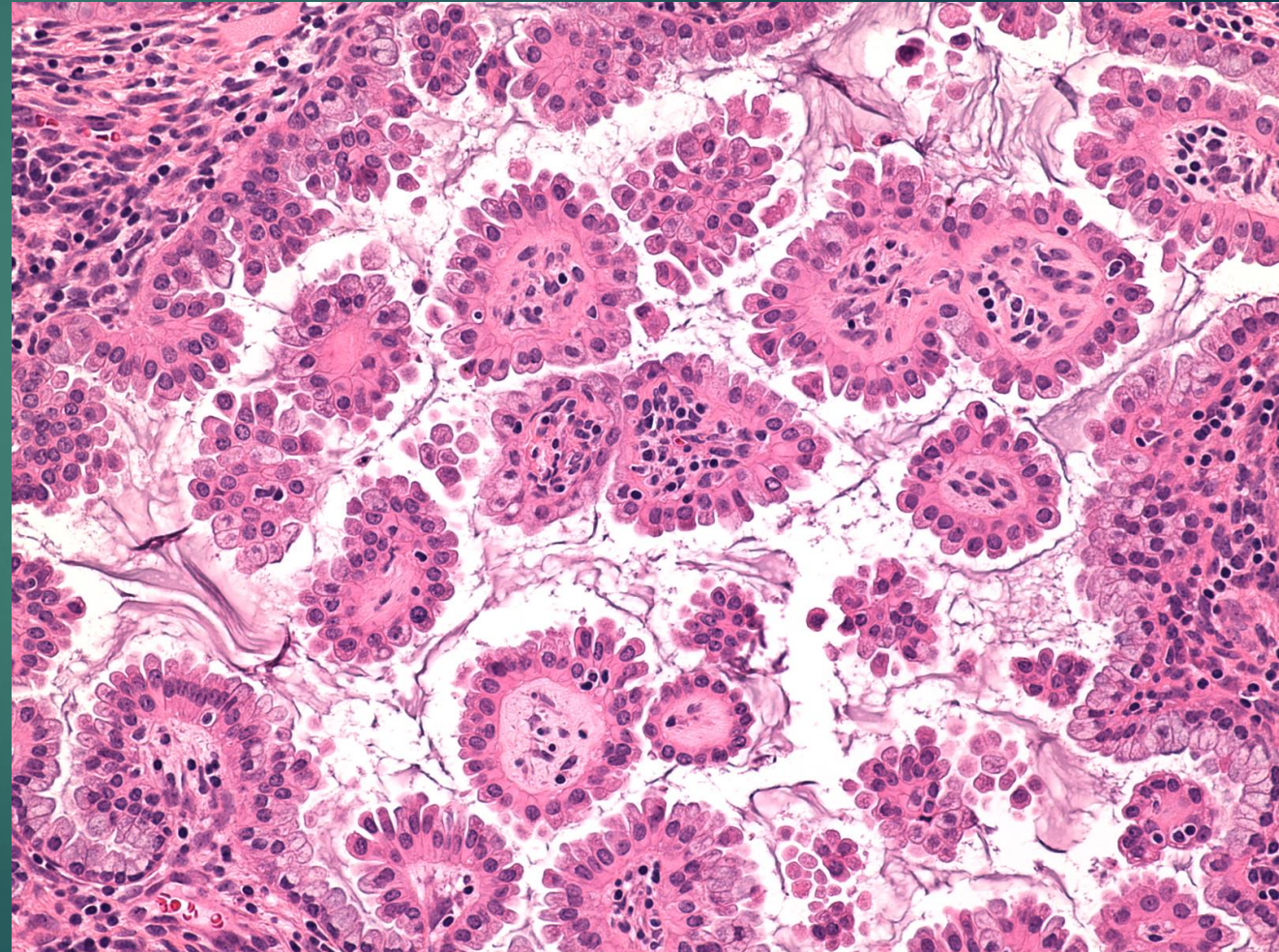
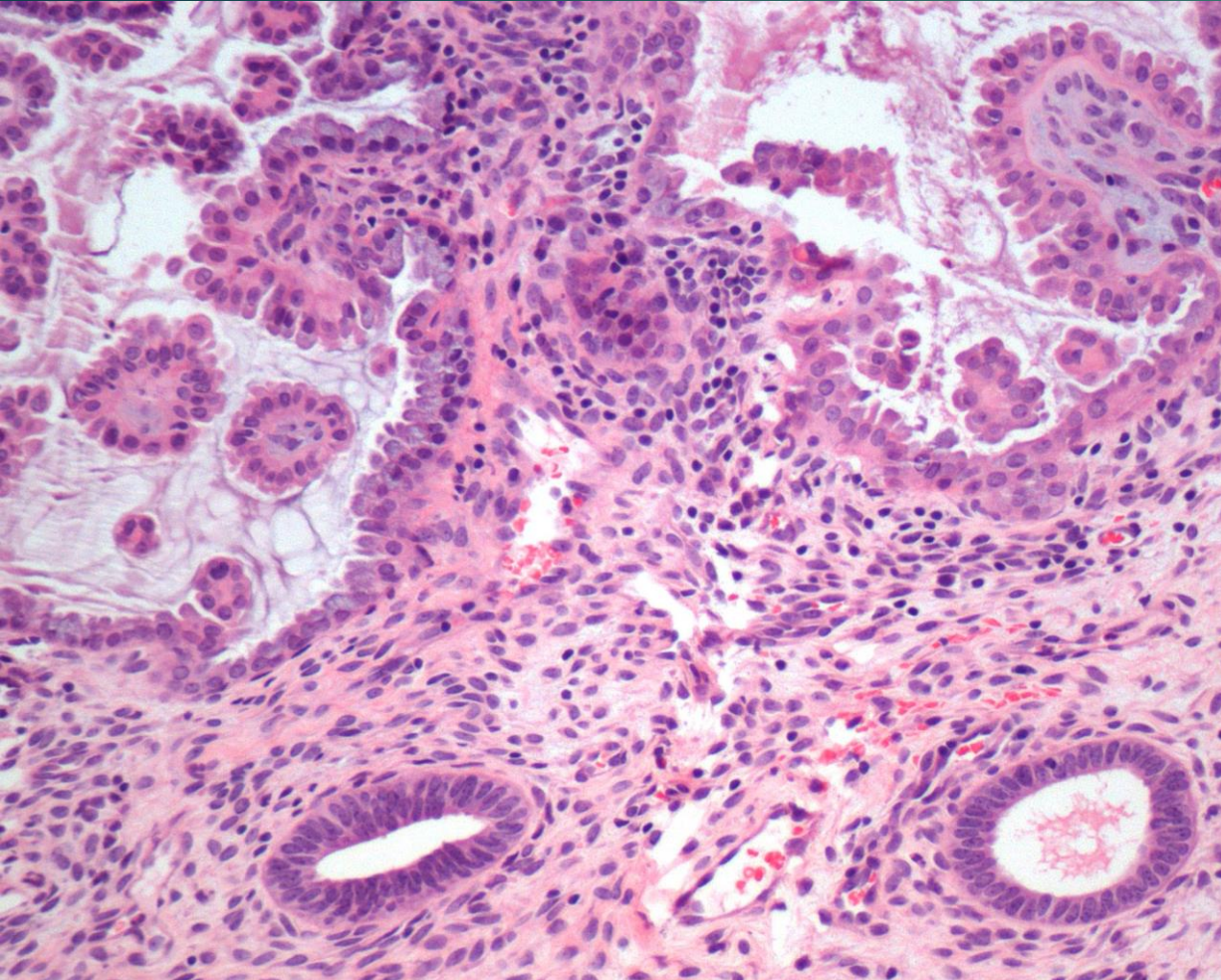
## *A Clinicopathologic Study of 59 Cases of Simple and Complex Papillae Without Cytologic Atypia*

*Philip P.C. Ip, MBChB, FRCPath,\* Julie A. Irving, MD,† W. Glenn McCluggage, MD, FRCPath,‡  
Philip B. Clement, MD,§ and Robert H. Young, MD, FRCPath||*

- ▶ **59 cases (abnormal bleeding, 61% postmenopausal, 27% had hormonal drugs)**
  
- ▶ **Simple papillae:**
  - Nonbranching stalks, occasional secondary branching
  - 1 to 2 foci
  
- ▶ **Complex papillae:**
  - short/long stalks, with secondary or complex branches
  - $\geq 3$  foci or  $>50\%$  involvement of a polyp by simple or complex papillae

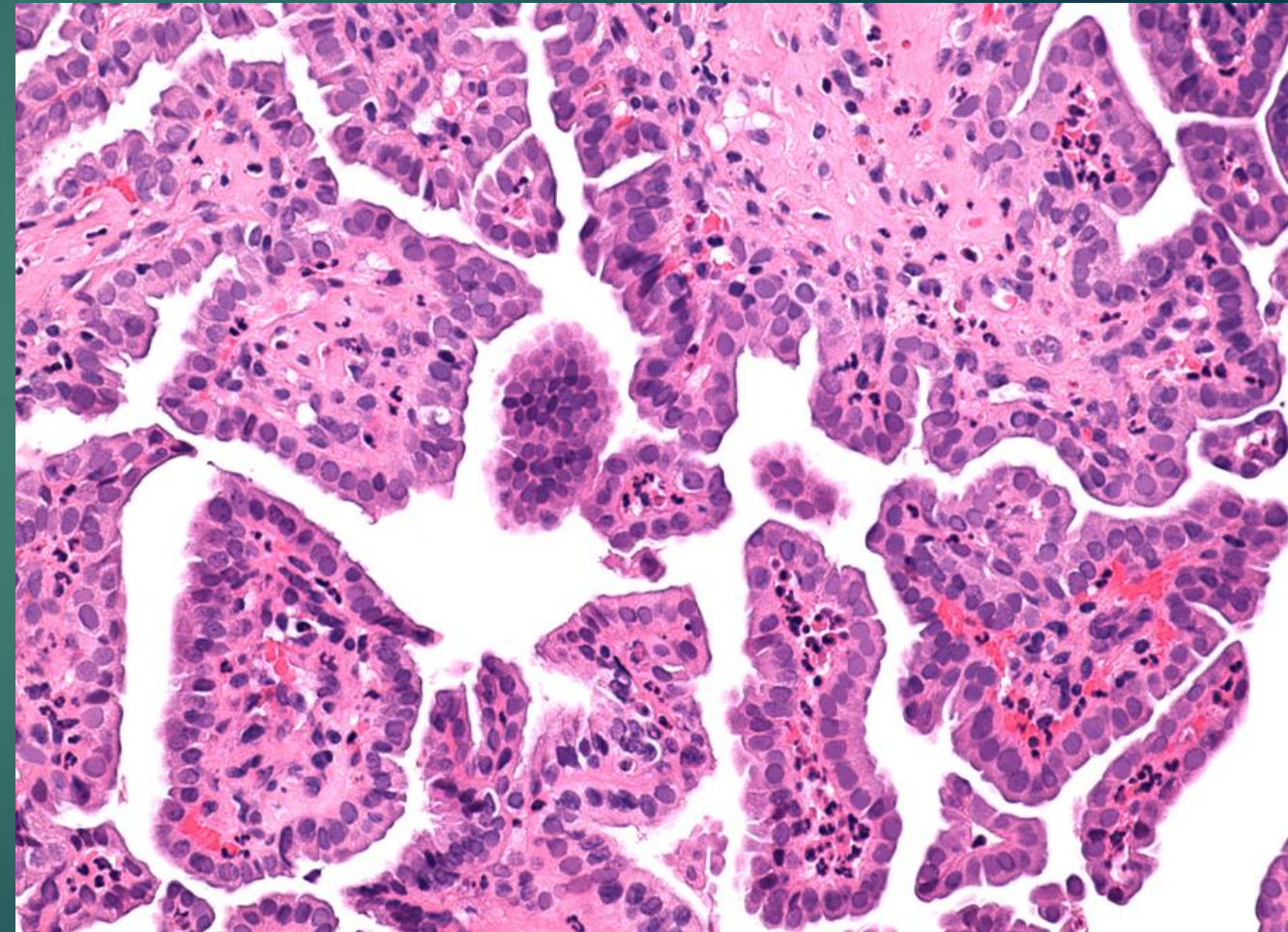
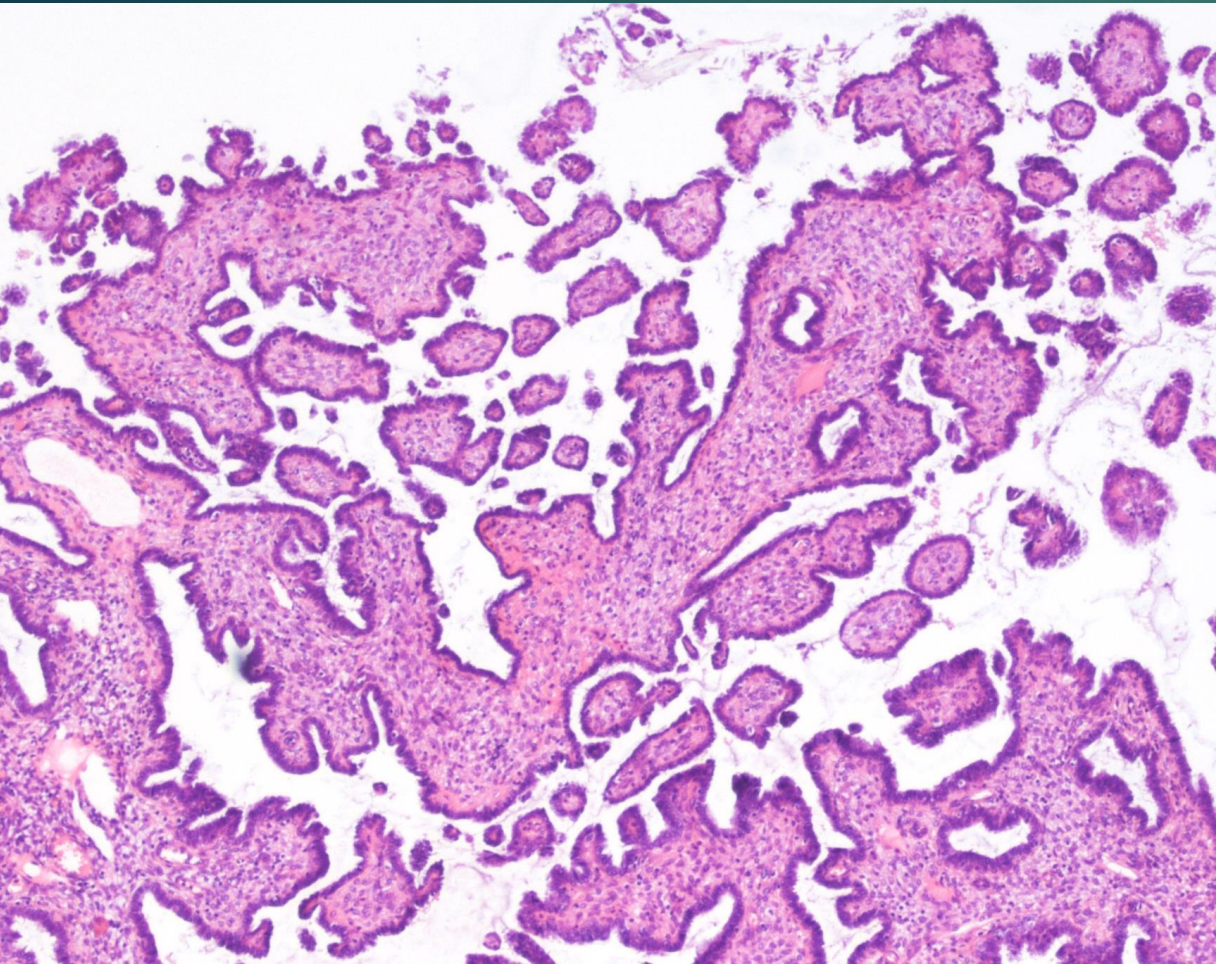


# Simple Papillary Proliferation



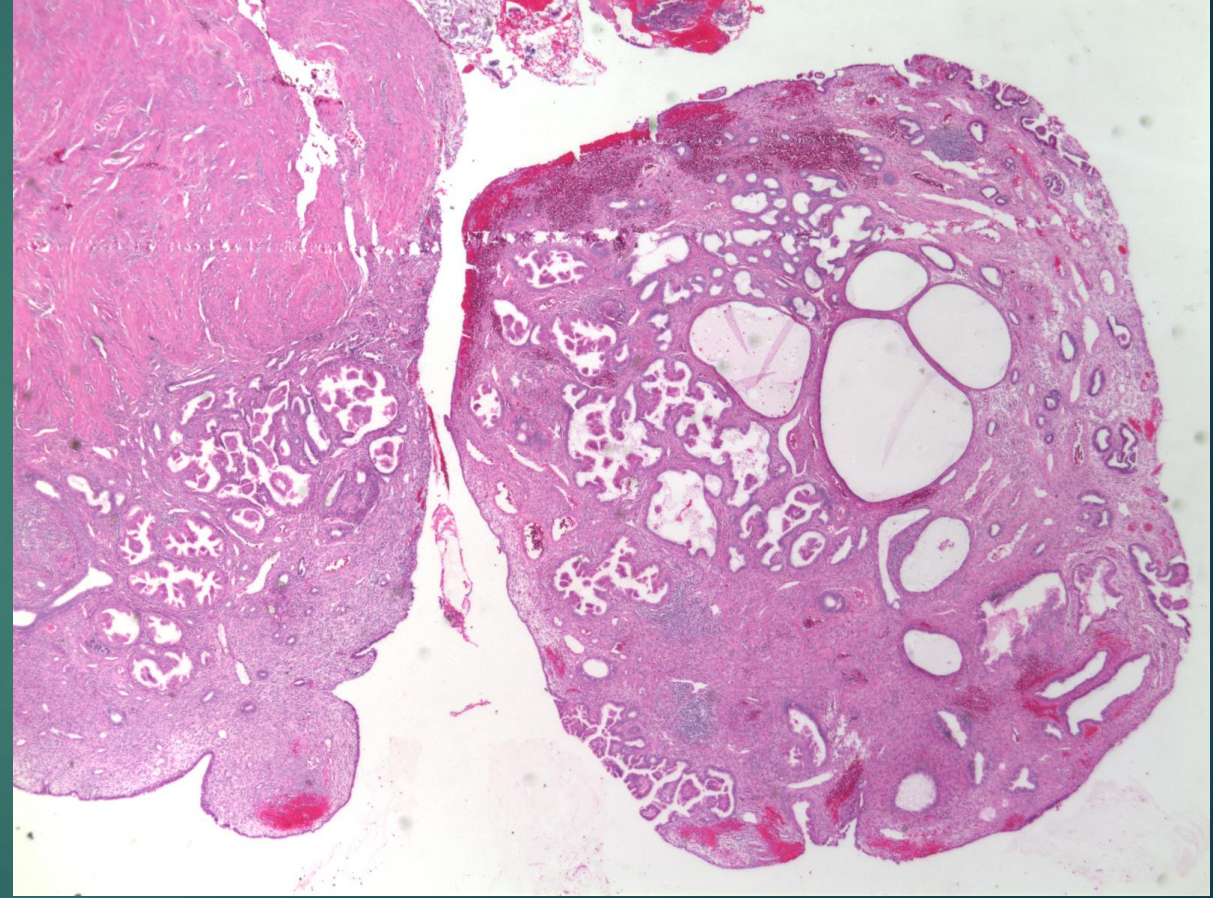
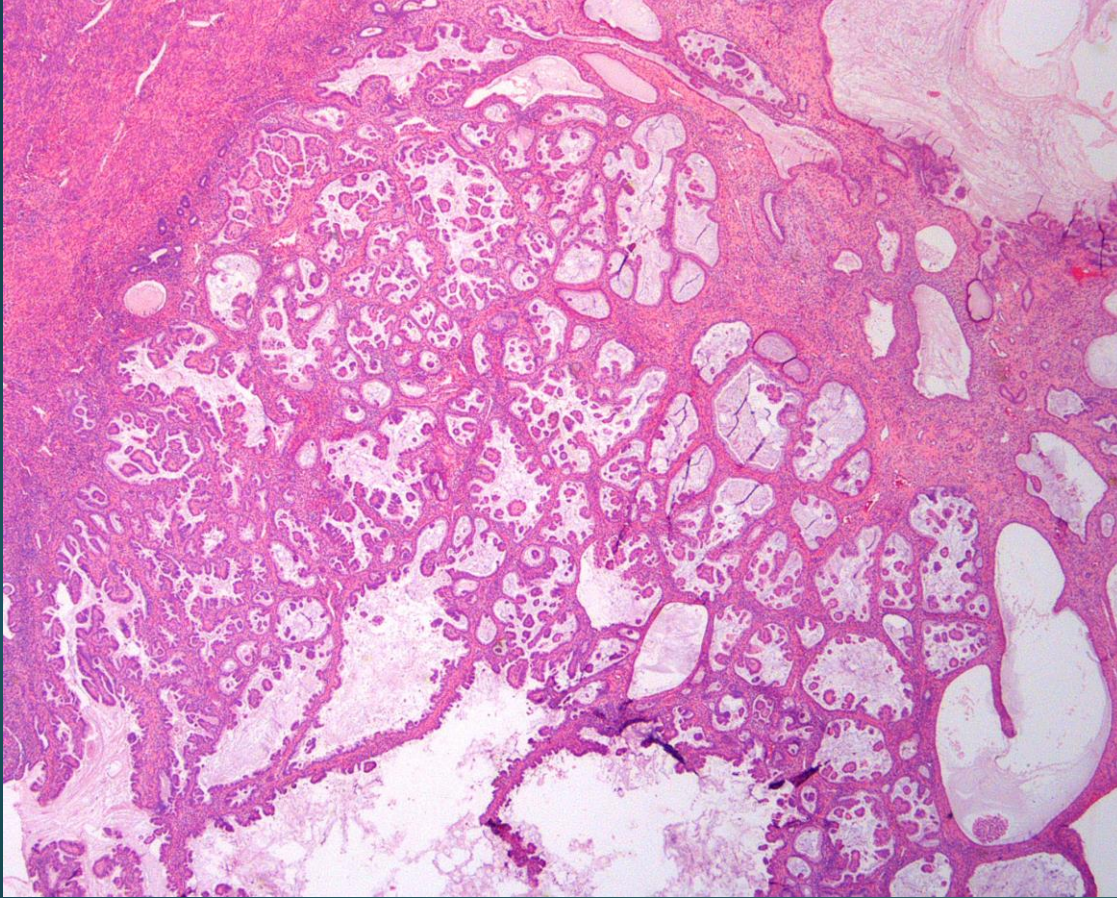


# Complex Papillary Proliferation





# Papillary Proliferation of Endometrium in small biopsies



- ▶ 80% coexisting endometrial polyp.
- ▶ 66% cases, lesion involved the polyp.

Liu Q. et al. Virchow Archiv. 2019  
Ip PP. Virchow Archiv. 2018  
Ip PP. et al. Am J Surg Pathol. 2013



# Papillary Proliferation of Endometrium in small biopsies: other metaplasias

|                            | Lehman & Hart | Ip 2013 | Liu 2019 | Liu 2022 |
|----------------------------|---------------|---------|----------|----------|
| Mucinous                   | 90%           | 39%     | 80%      | 83.6%    |
| Ciliated                   | 70%           | 29%     | 6%       | 10.6%    |
| Eosinophilic               | 89%           | 22%     | 33%      | 1.92%    |
| Syncytial papillary change |               | 15%     | 10%      |          |
| Squamous                   | 22%           | 3%      | 3%       | 116.0%   |
| >1 type                    | 100%          | 39%     |          | 15.5%    |

Liu Q. et al. Virchow Archiv. 2019  
Liu DY. et al. Virch Archiv. 2022  
Ip PP. et al. Am J Surg Pathol. 2013  
Lehman MB, Hart WWR. Am J Surg Pathol. 2001





# Papillary Proliferation of Endometrium: Immunohistochemistry

- ▶ Immunoprofile similar between simple and complex papillae.
- ▶ ER, normal  $\beta$ -catenin, wild-type p53, MMR-p.
- ▶ Loss of expression for PR (84%), PAX2 (57%), PTEN loss (10%).
- ▶ Low MIB1 proliferative index.



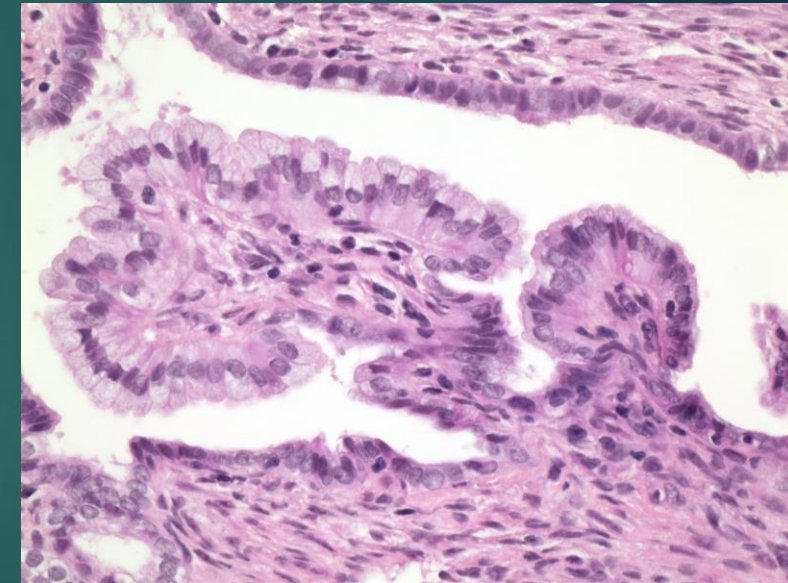
# Papillary Proliferation of Endometrium: Mutational analysis

- ▶ *KRAS* mutations correlated with mucinous metaplasia.

| Gene mutations    | Simple PPE ( <i>n</i> = 22) | CPH ( <i>n</i> = 8) | PPE ( <i>n</i> = 30) |
|-------------------|-----------------------------|---------------------|----------------------|
| <i>KRAS</i>       | 10                          | 4                   | 14                   |
| c.35G>T p.G12V    | 5                           | 1                   | 6                    |
| c.35G>A p.G12A    | 3                           | 3                   | 6                    |
| c.38G>A p.G13D    | 0                           | 0                   | 0                    |
| c.183A>C/T p.Q61H | 2                           | 0                   | 2                    |
| <i>AKT1</i>       |                             |                     |                      |
| c.49G>A p.E17K    | 1                           | 0                   | 1                    |

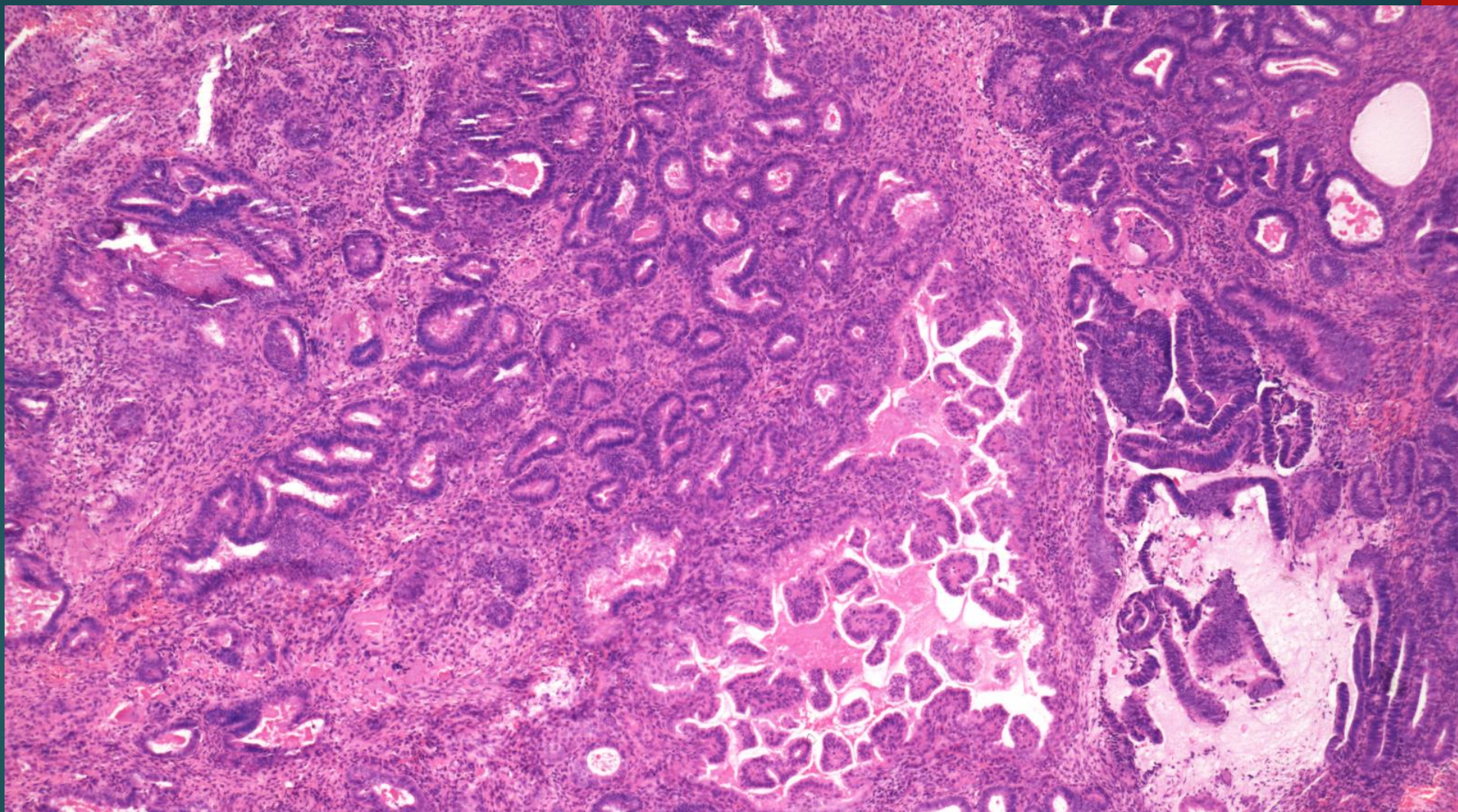
There were no mutations of the three *PI3KCA* hotspots (E542K, E545K, and E546K), *PTEN* (exons 3, 5, and 7), and *ARID1A* (exons 1 and 14) in PPEs

*PPE* papillary proliferation of the endometrium, *CPH* complex papillary hyperplasia





# Simple Papillary Proliferation

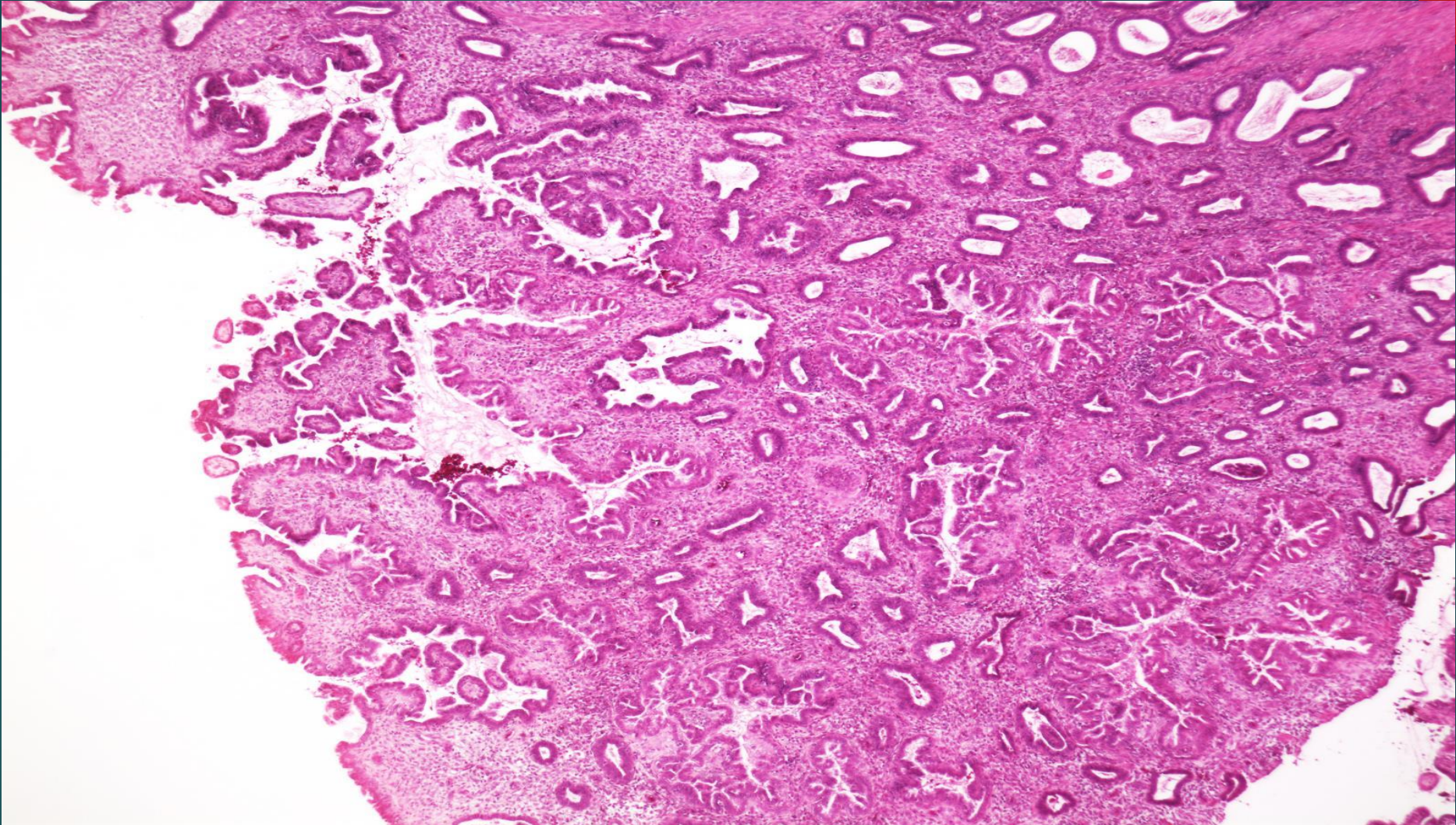


- ▶ 12% simple PPE had concurrent or subsequent atypical hyperplasia, rarely carcinoma.

Liu Q. et al. Virchow Archiv. 2019  
Park CK et al. Oncotarget. 2016  
Ip PP. et al. Am J Surg Pathol. 2013



# Complex Papillary Proliferation



- ▶ 81% complex PPE had concurrent or subsequent nonatypical / atypical hyperplasia, and low-grade endometrioid carcinoma.

Liu Q. et al. Virchow Archiv. 2019  
Park CK et al. Oncotarget. 2016  
Ip PP. et al. Am J Surg Pathol. 2013

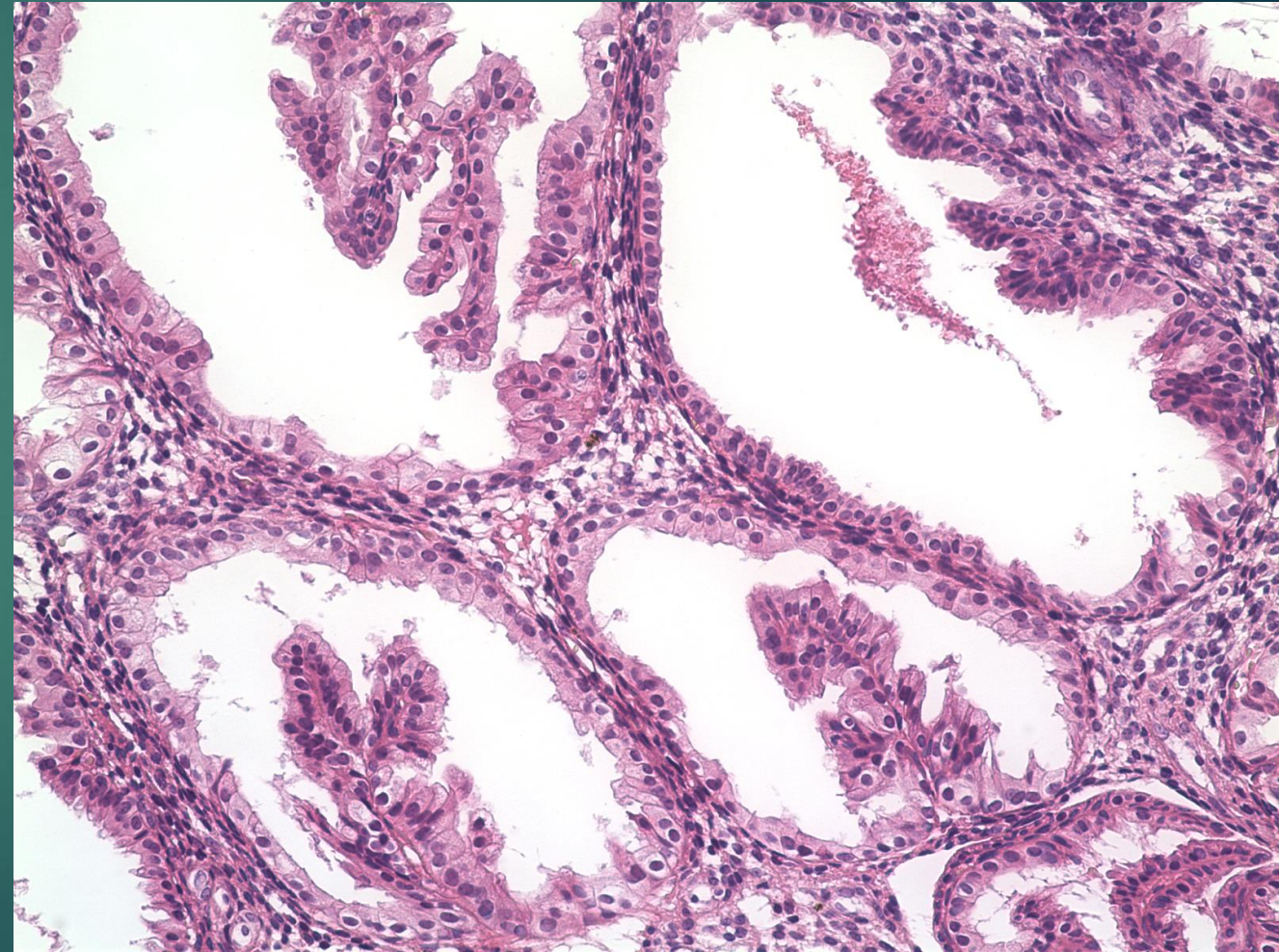
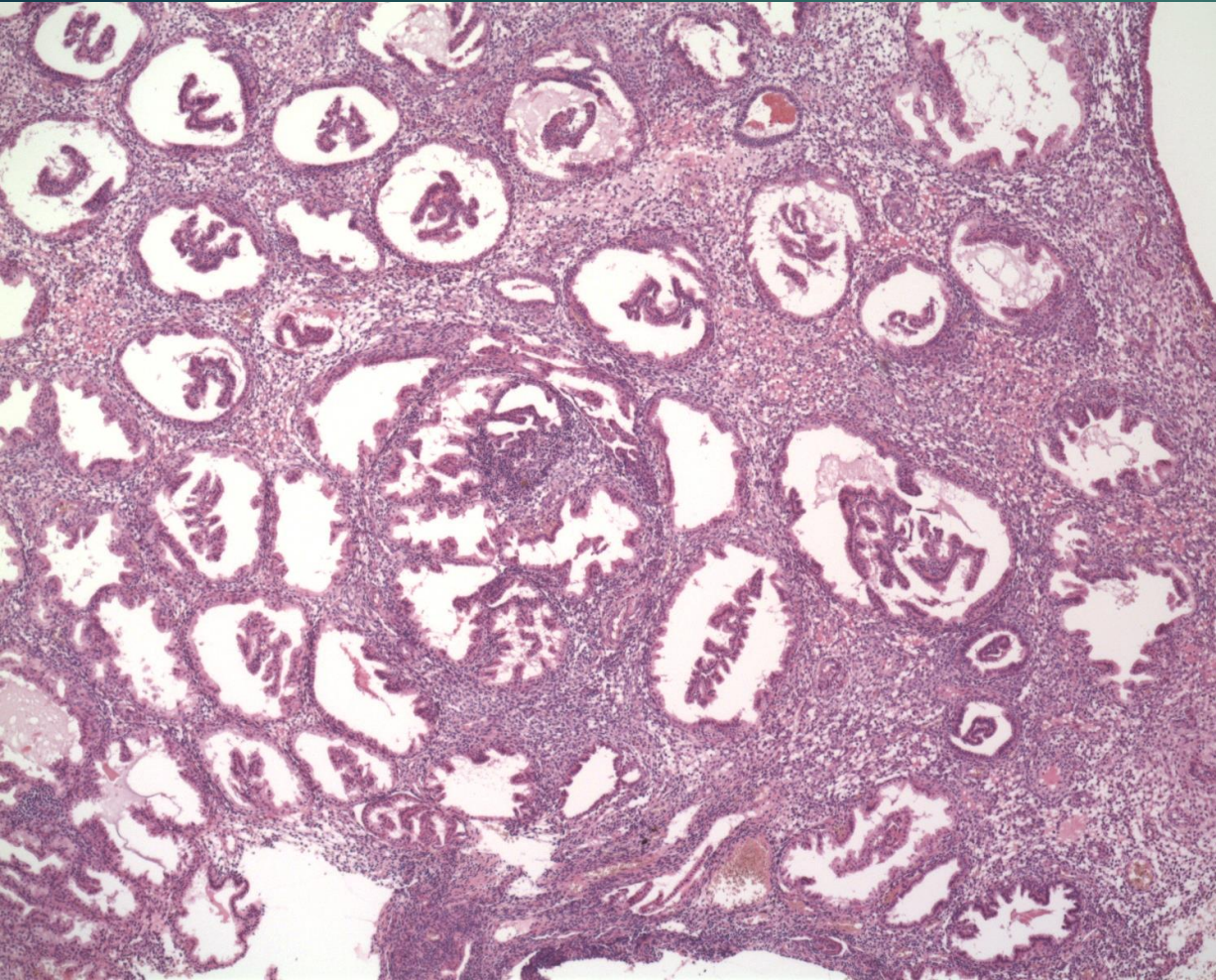


# Papillary Proliferation of Endometrium: Differential Diagnoses

- ▶ Pseudopapillary artifact
- ▶ Syncytial papillary change
- ▶ Carcinomas with papillary pattern
- ▶ Post-hormonal therapy samples



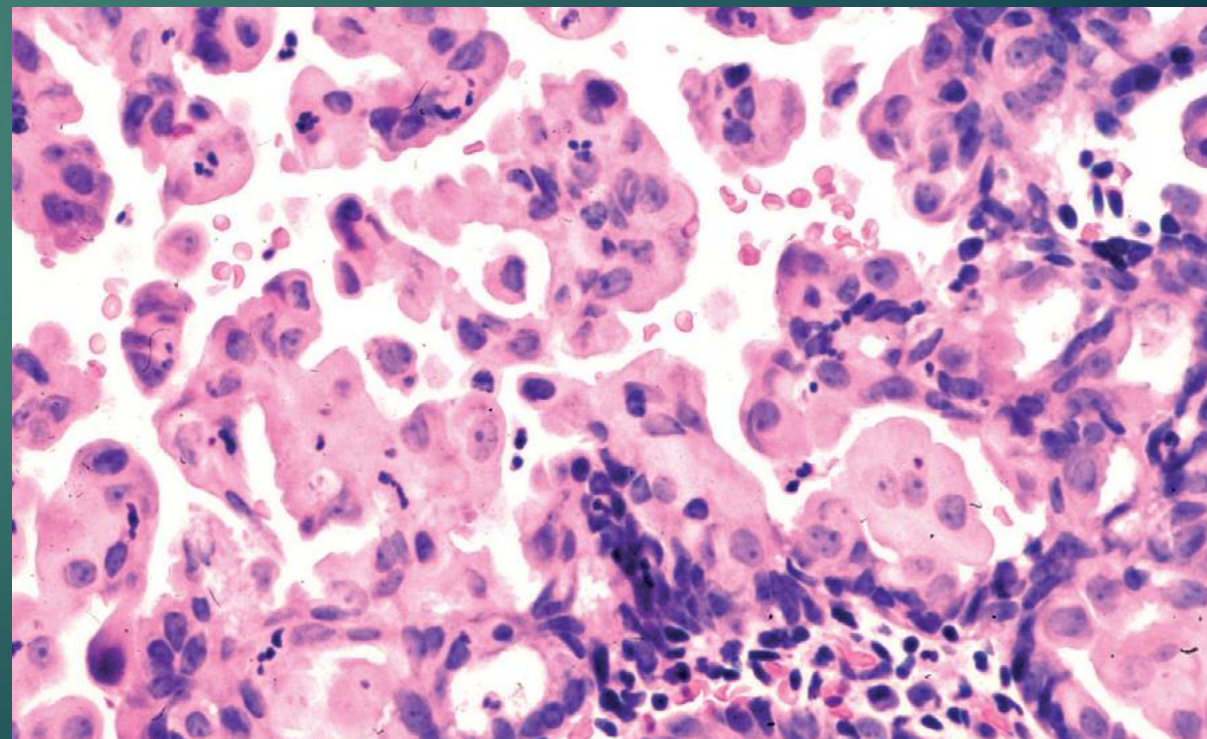
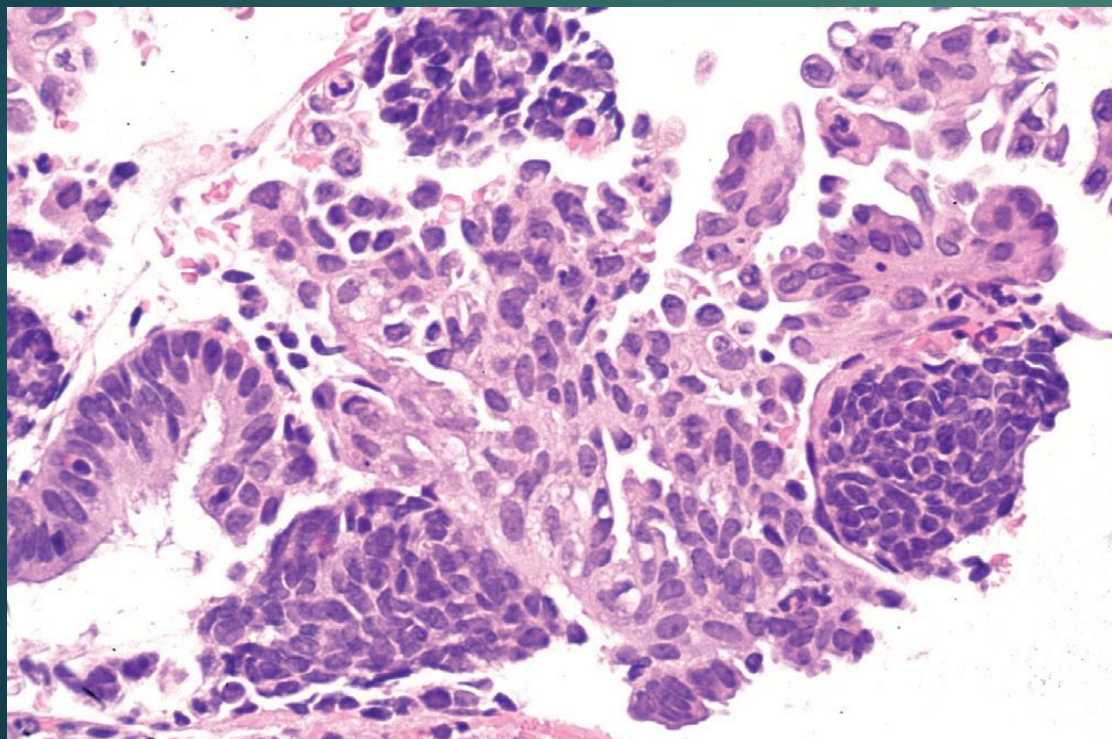
# Pseudopapillary artifact





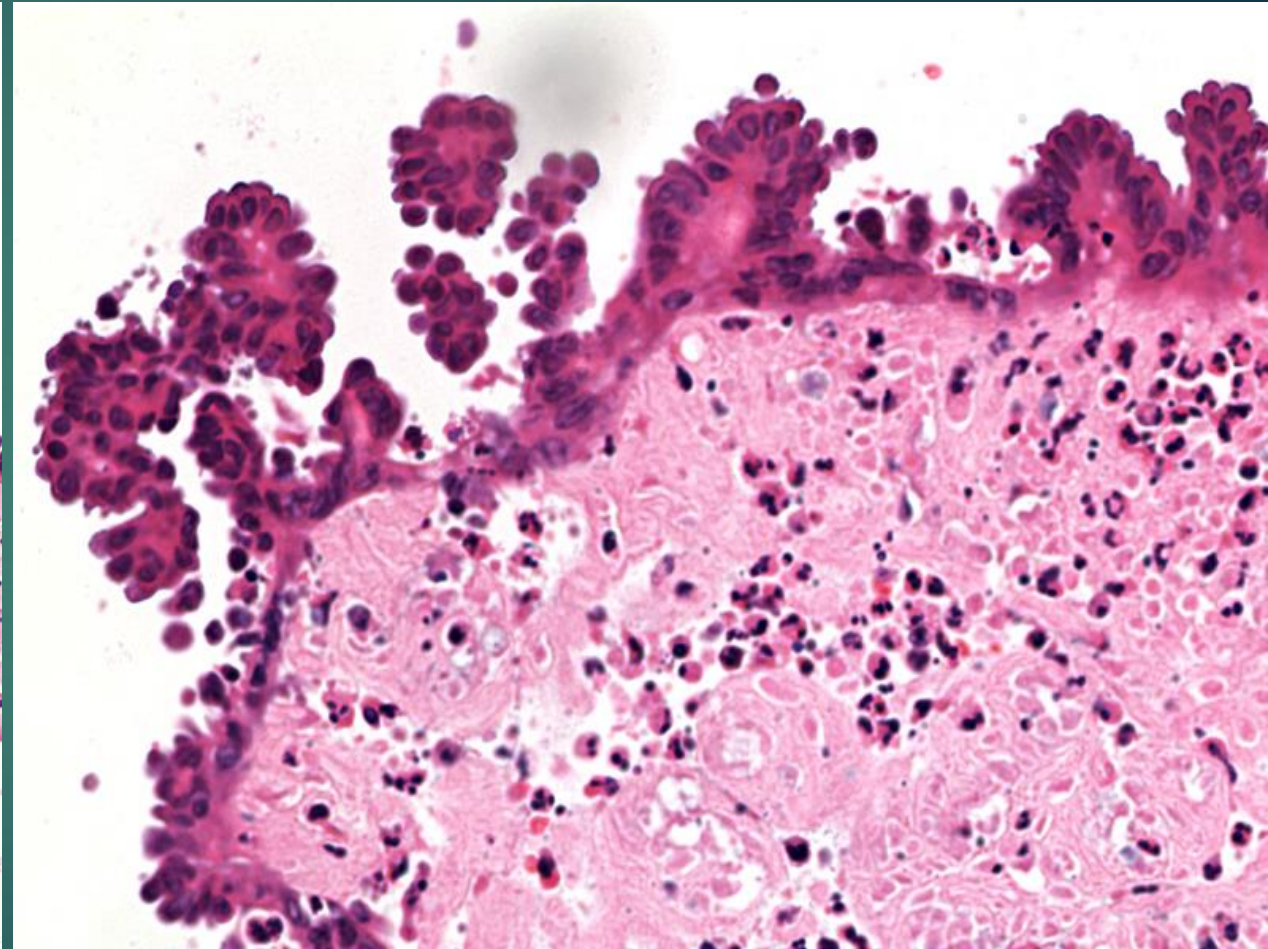
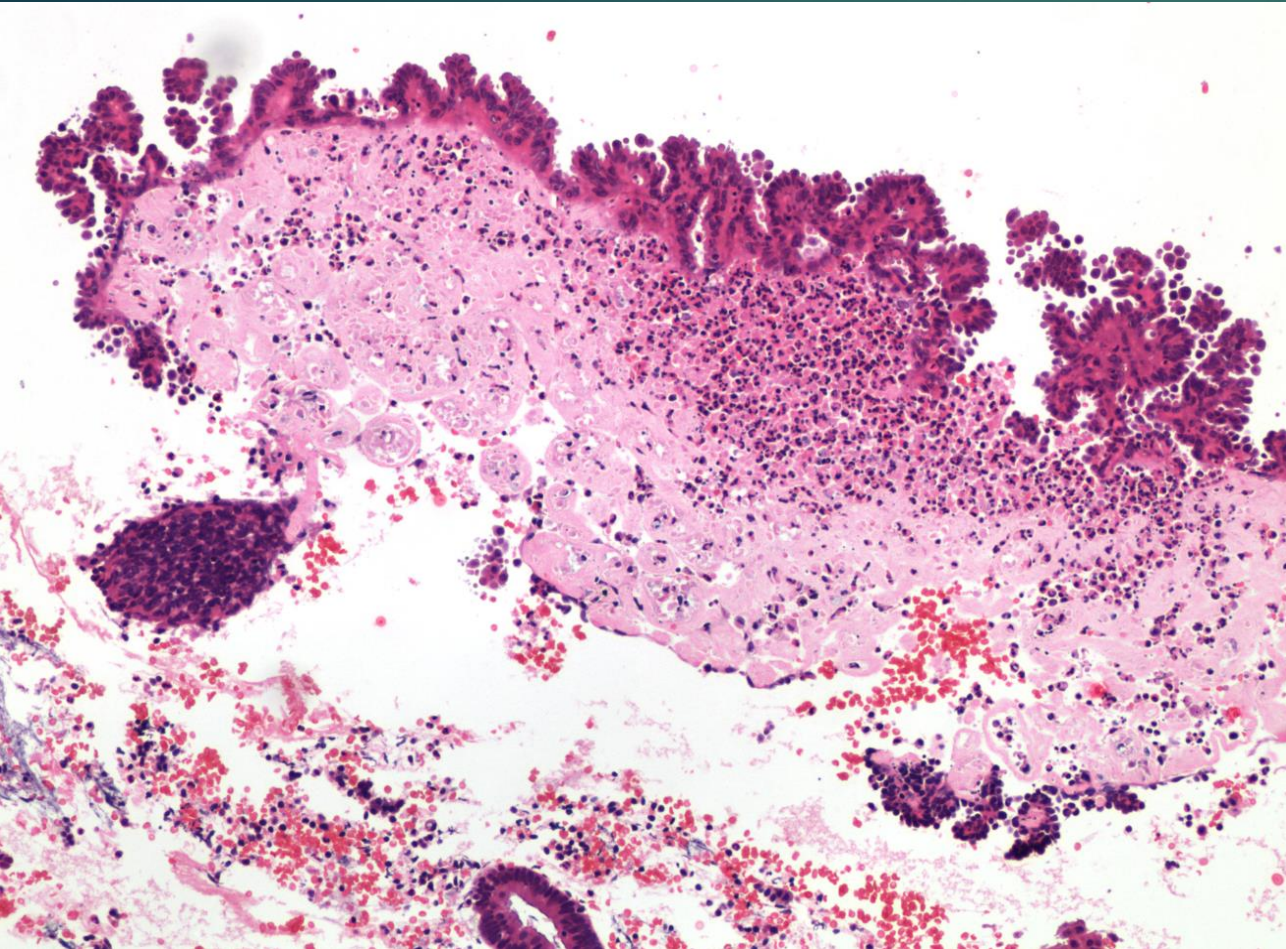
# Syncytial Papillary change

- ▶ A syncytial or bud-like lesion, to more overtly papillary process but lack prominent fibrovascular stromal cores.
- ▶ Regenerative phenomenon: menstrual breakdown, or surface of infarcted polyp.





# Syncytial Papillary change



Ip PPC, Djordjevic B. WHO Classification of Female Genital tumours, 5<sup>th</sup> ed. p.268

Fadare O. et al. Int J Gynecol Pathol. 2017

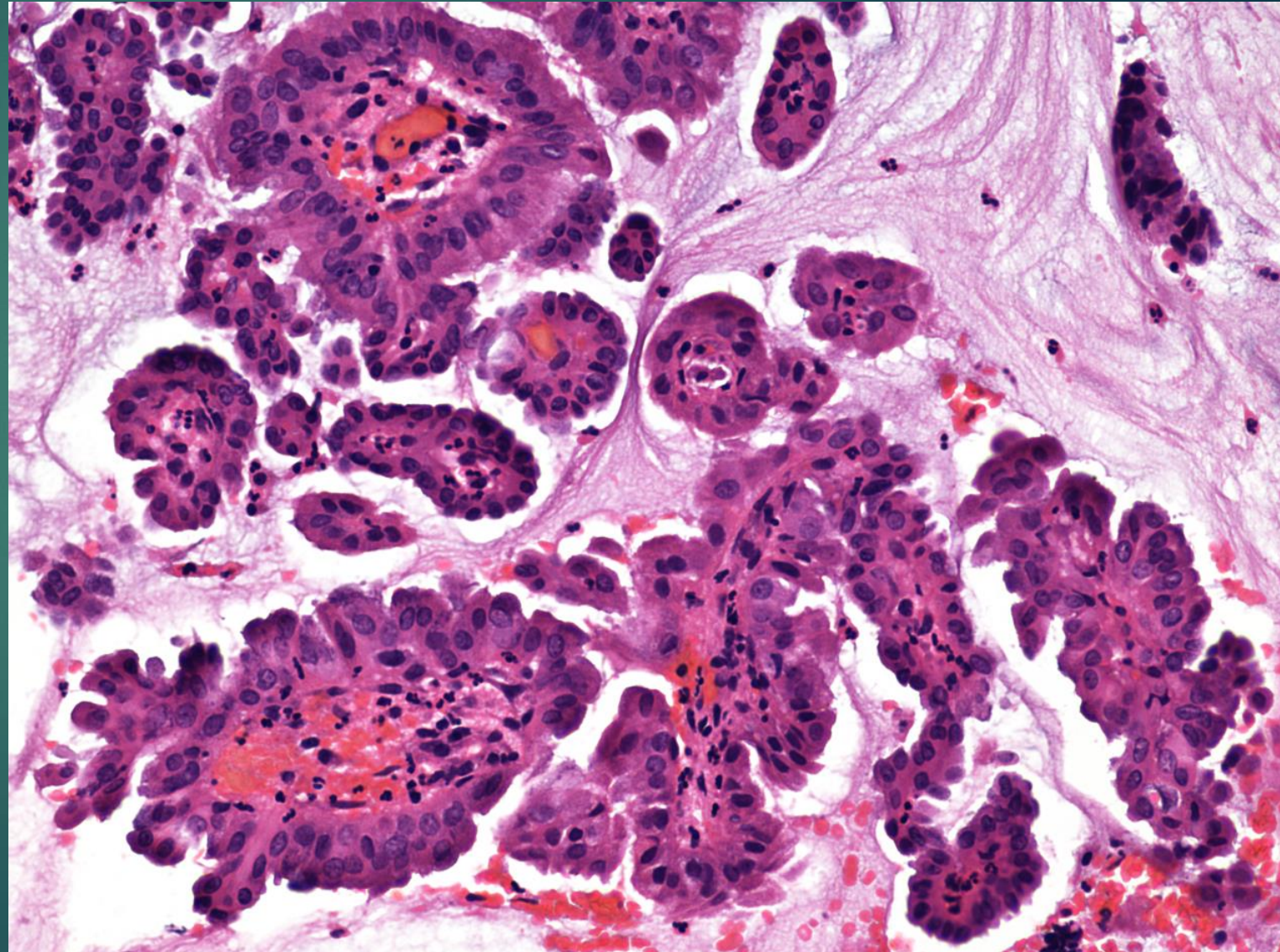
Nicolae A. et al. J Clin Pathol. 2011

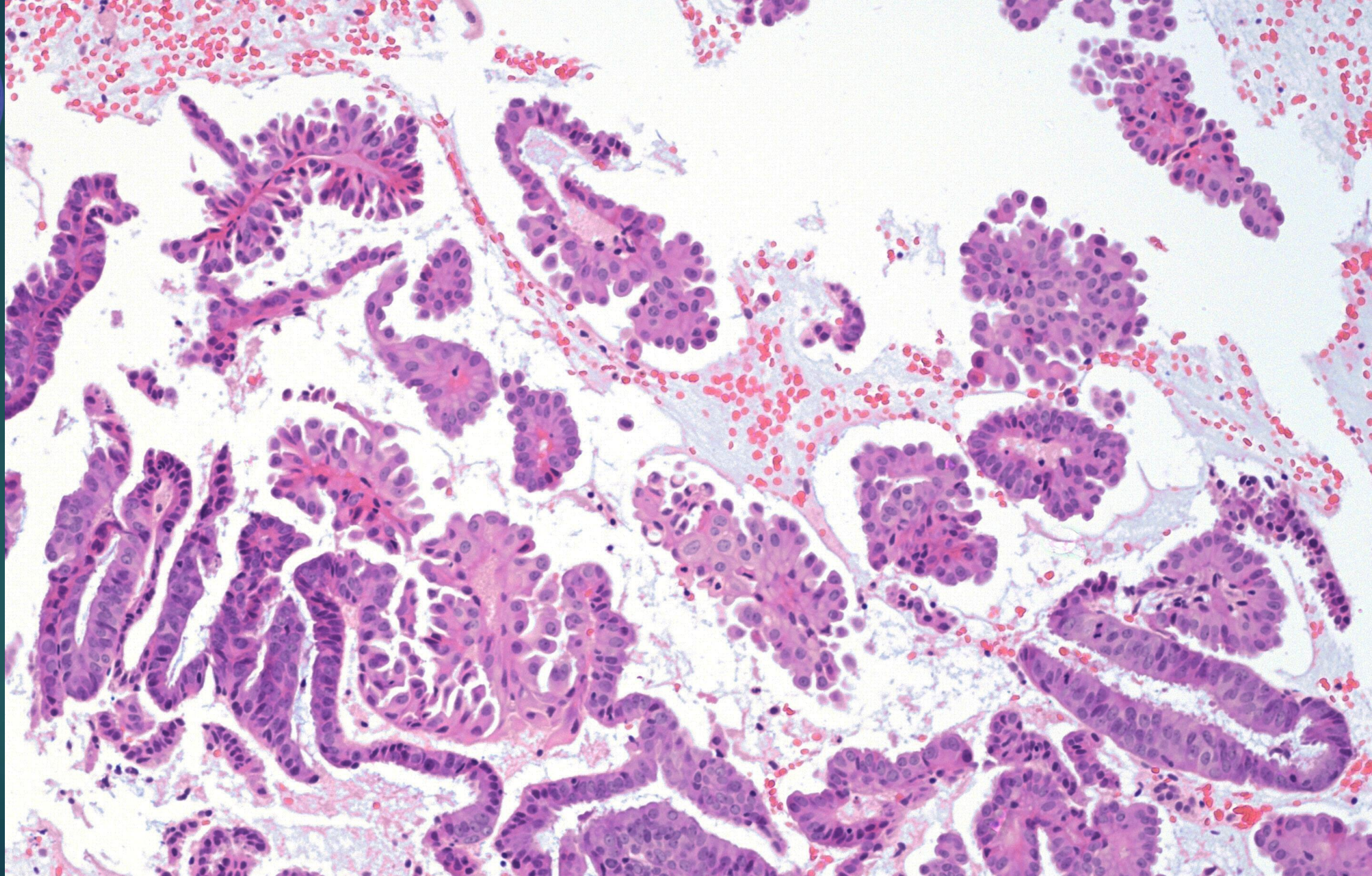


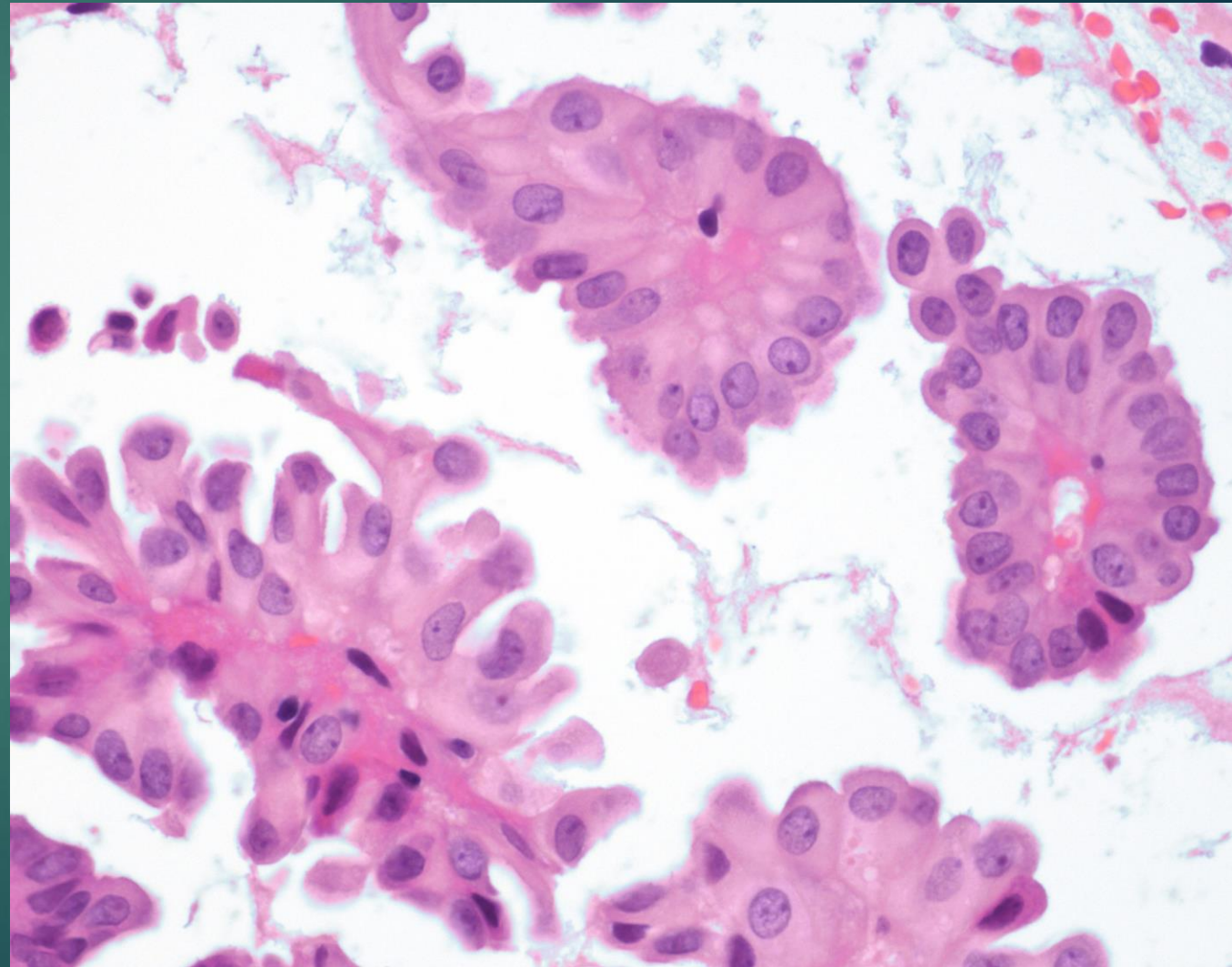
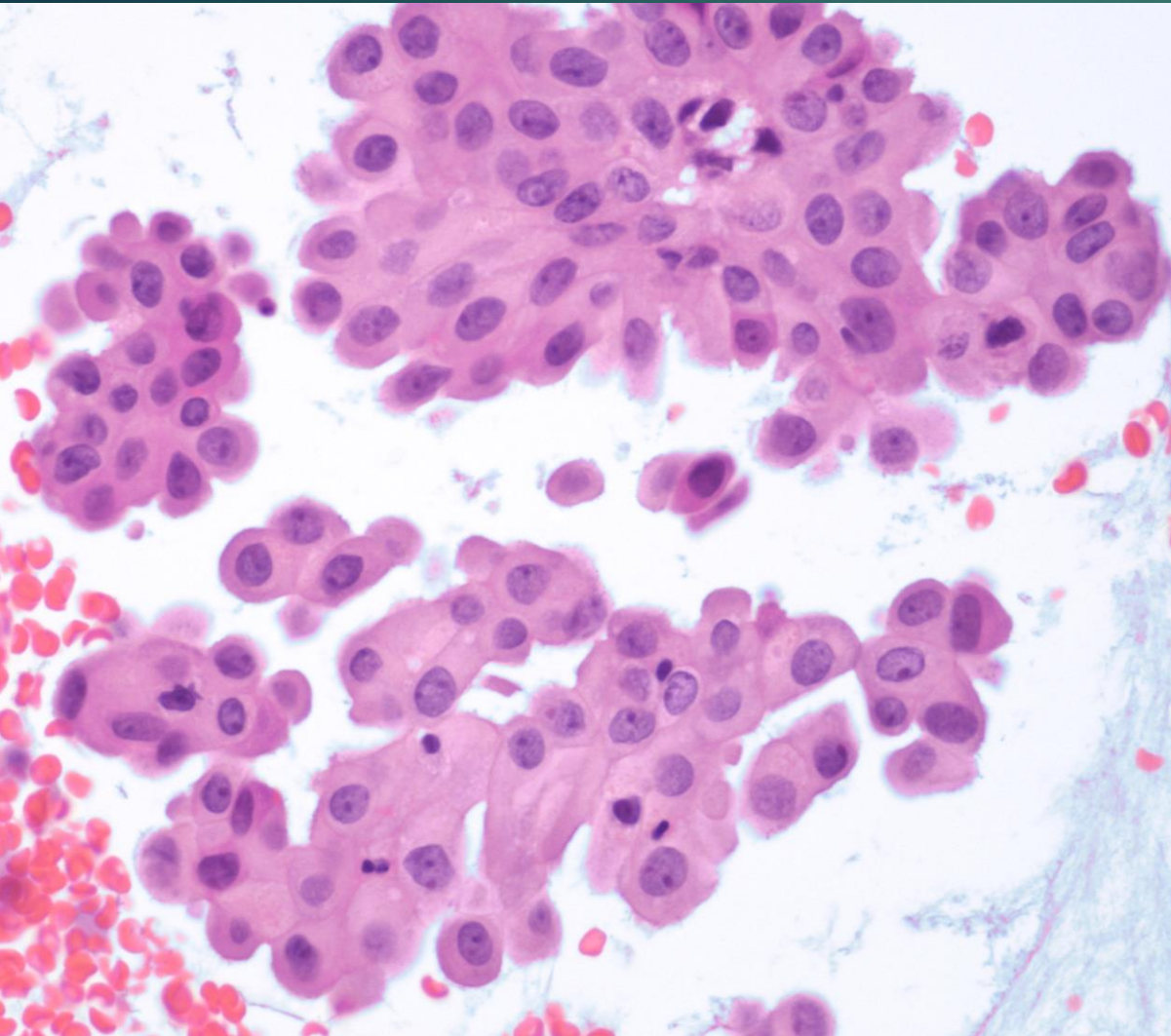


# Syncytial Papillary change

- ▶ Distinction from simple papillary proliferation may not always be clear.
- ▶ They represent a continuum, and often co-exist.



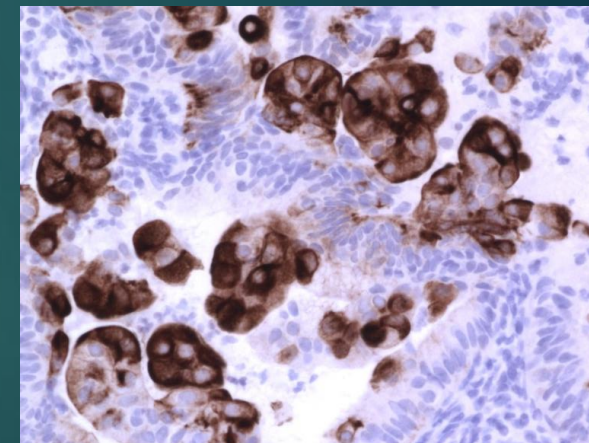
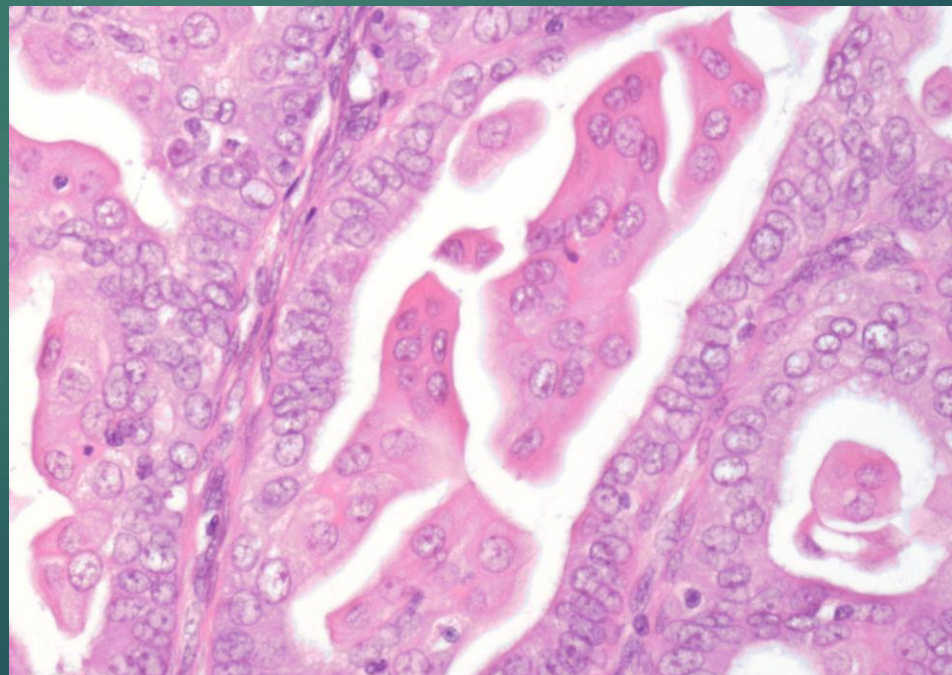
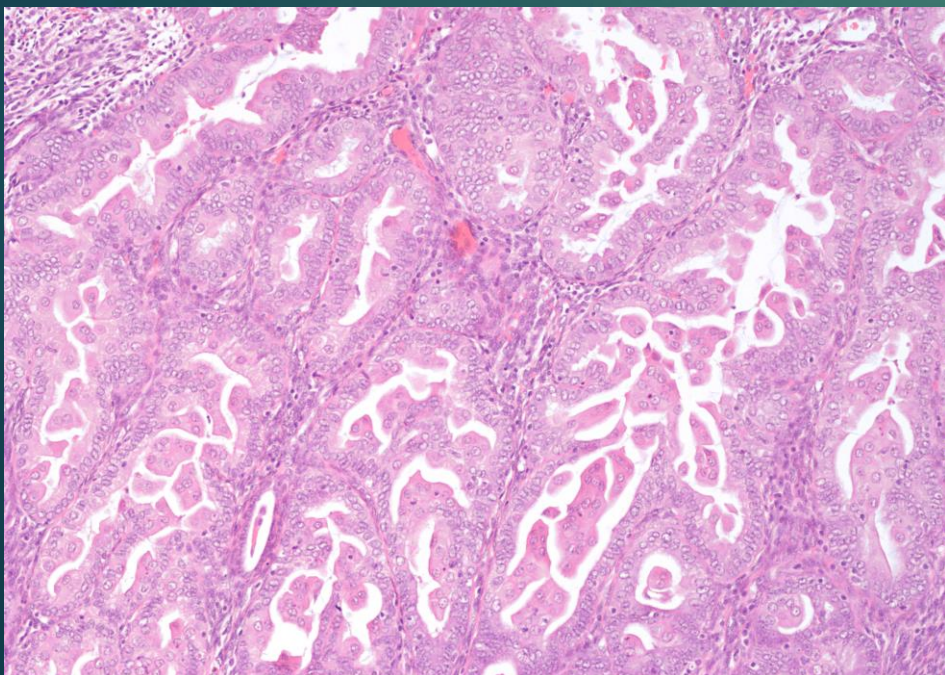


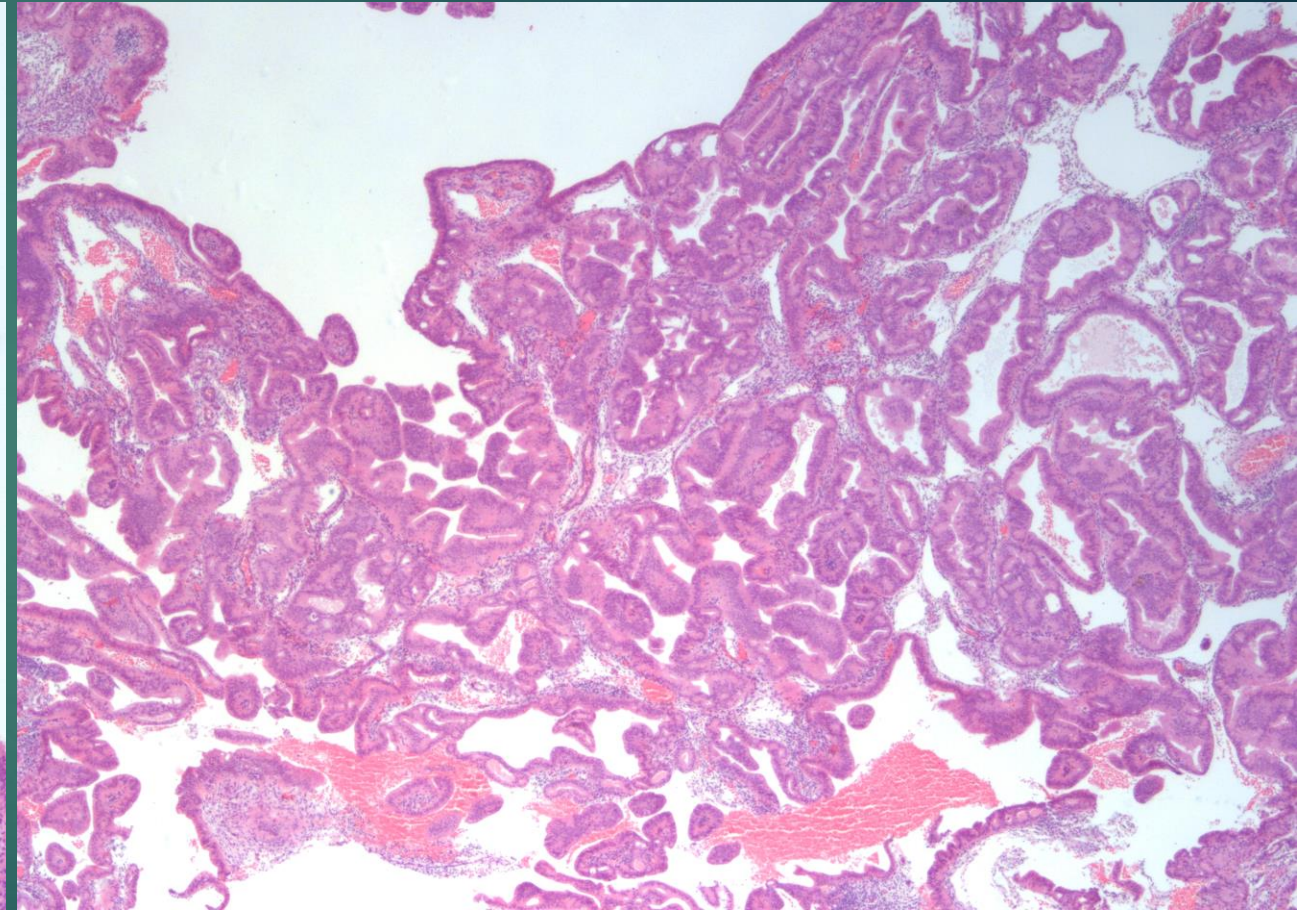
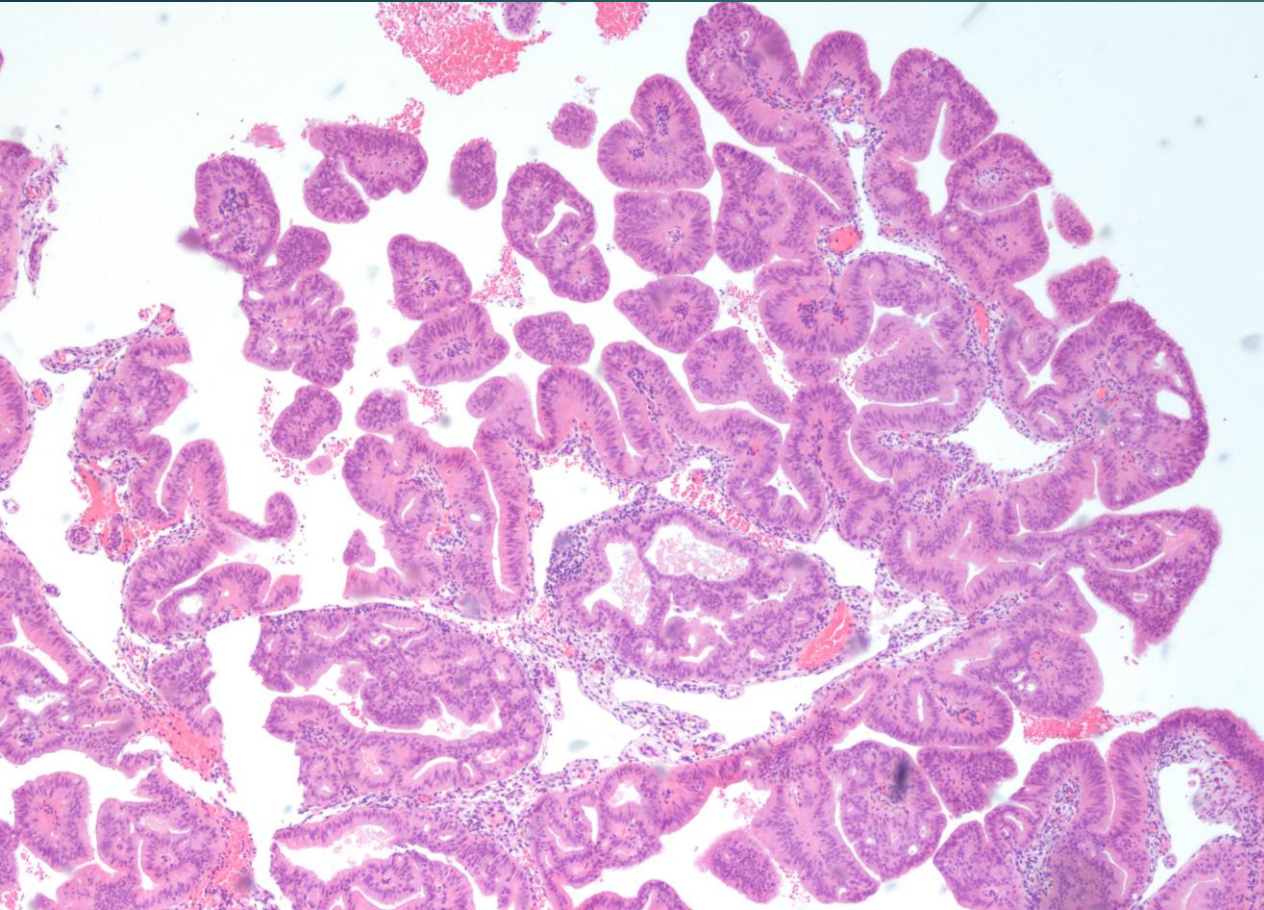


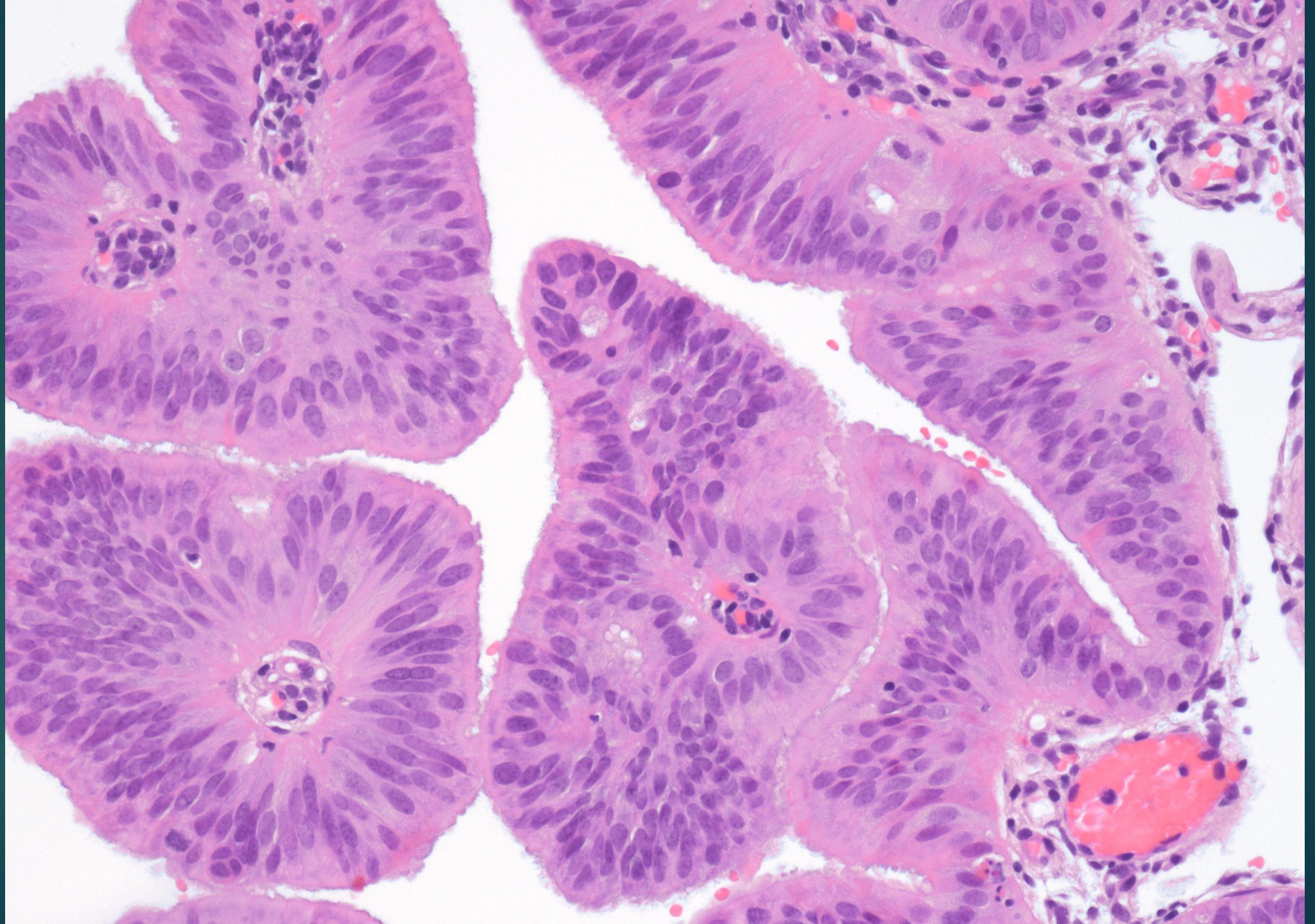


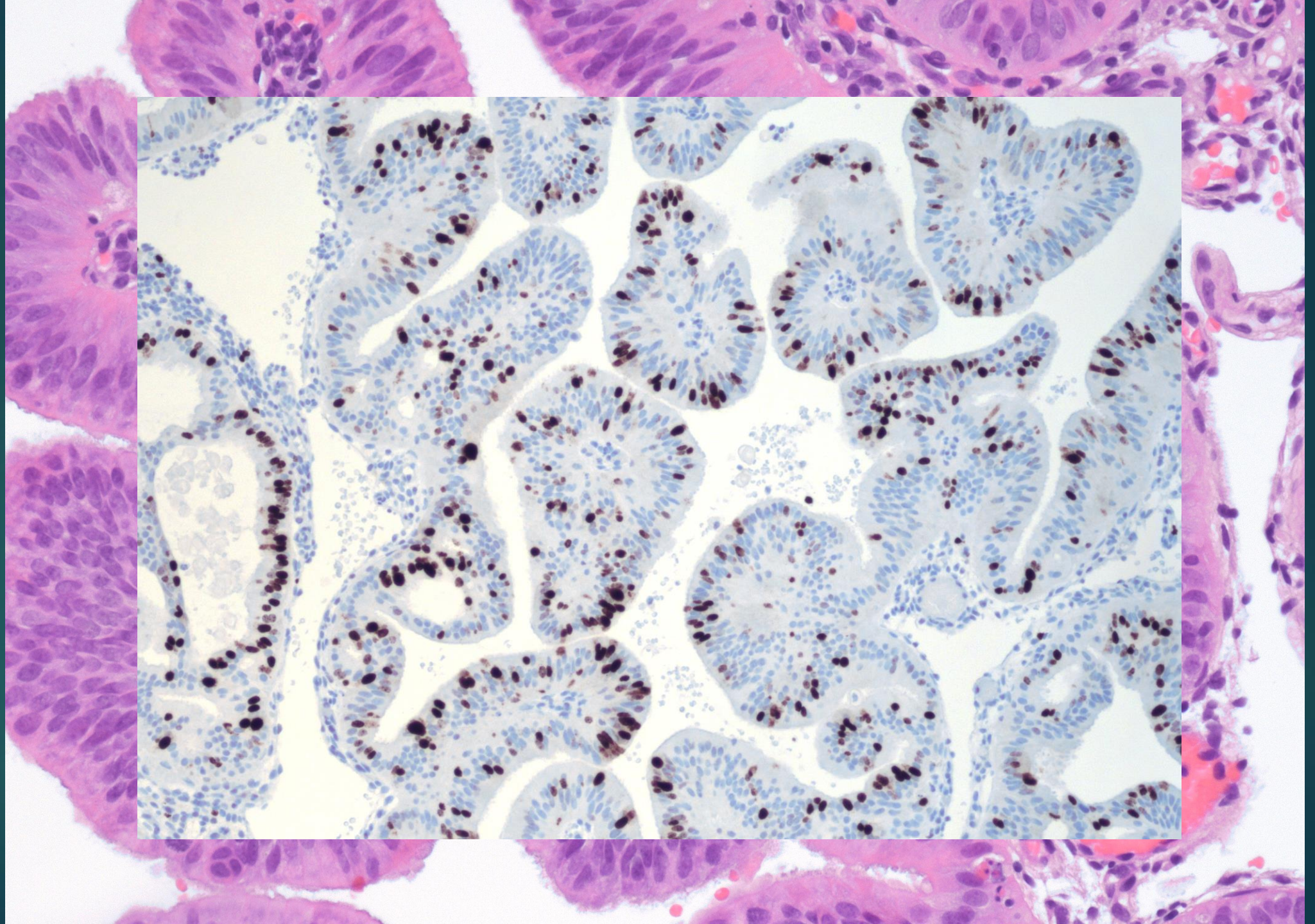
# Endometrioid Ca with small nonvillous papillae

- ▶ Papillae are in the form of buds of rounded cells with ample eosinophilic cytoplasm and a low N : C ratio.
- ▶ Longer papillae may extend across gland lumens resulting in a more complex pattern. More overt cytologic atypia.











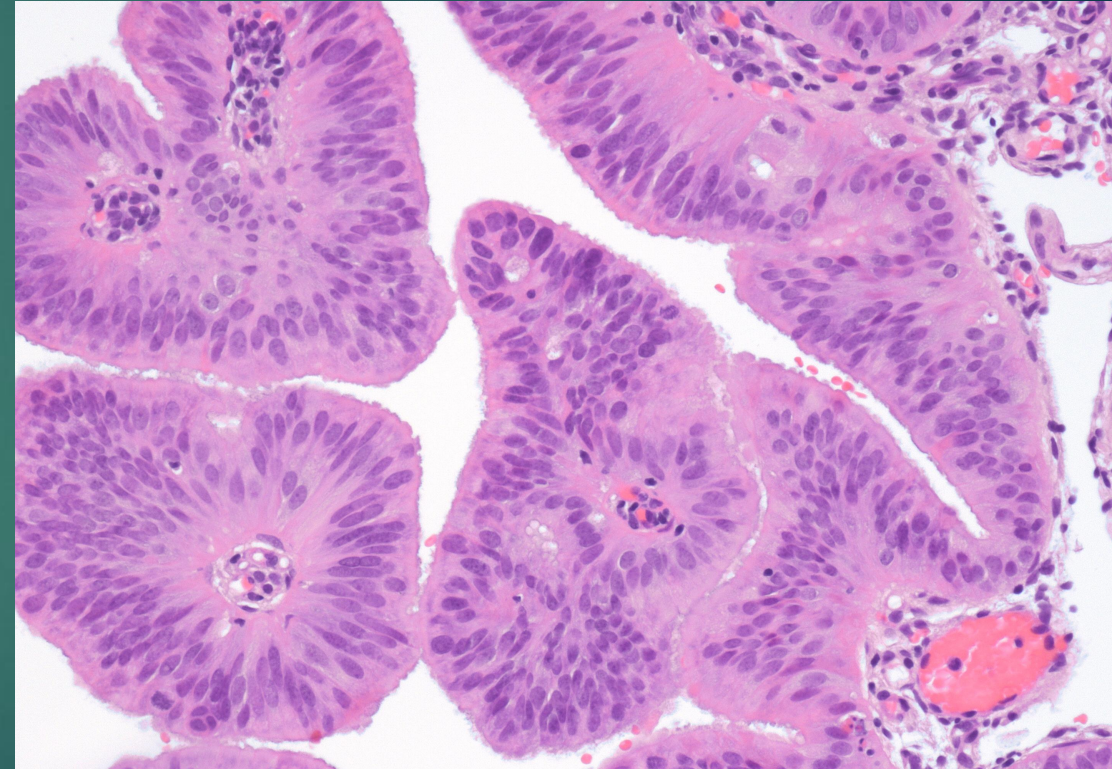
Progesterone-treated  
Endometrioid carcinoma





# Effects of Progesterone Treatment on Atypical hyperplasia or Carcinoma

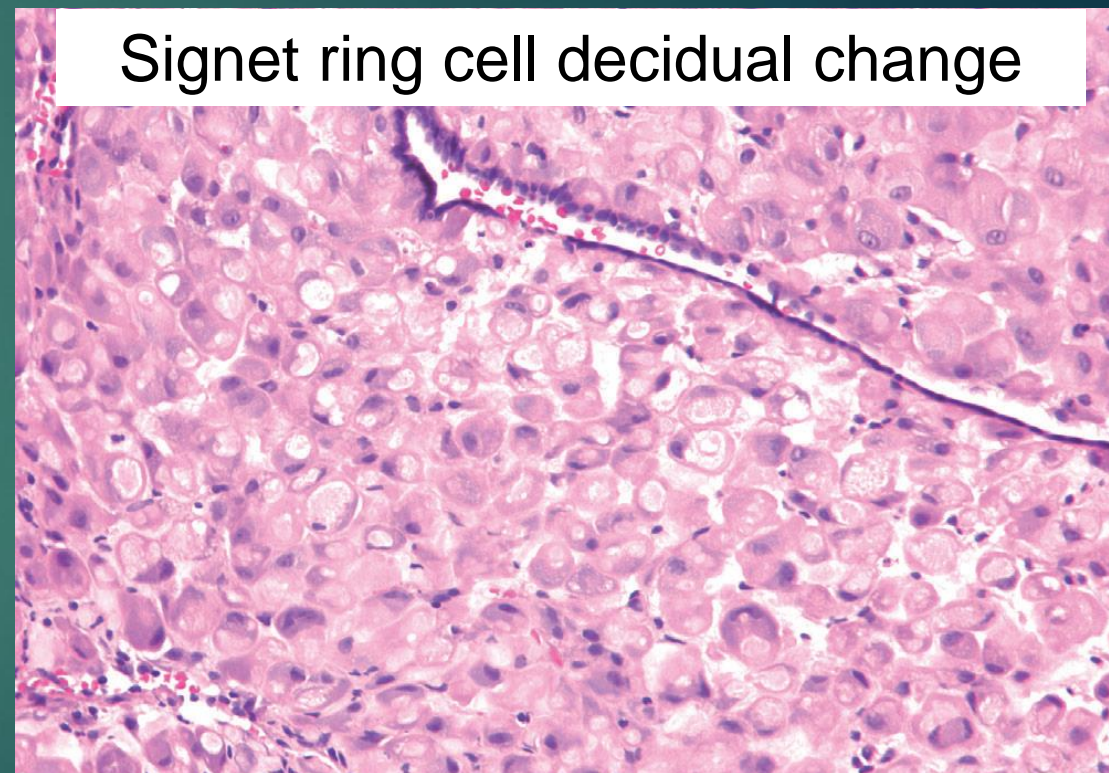
- ▶ Degree of changes is variable (drugs, duration, dosage, compliance).
- ▶ Architecture: Decrease in gland confluence and complexity.
- ▶ Cells: Decreased N/C ratio, cytoplasmic eosinophilia or vacuoles, smaller nuclei with fine chromatin, nucleolus is less prominent.
- ▶ Metaplasias.

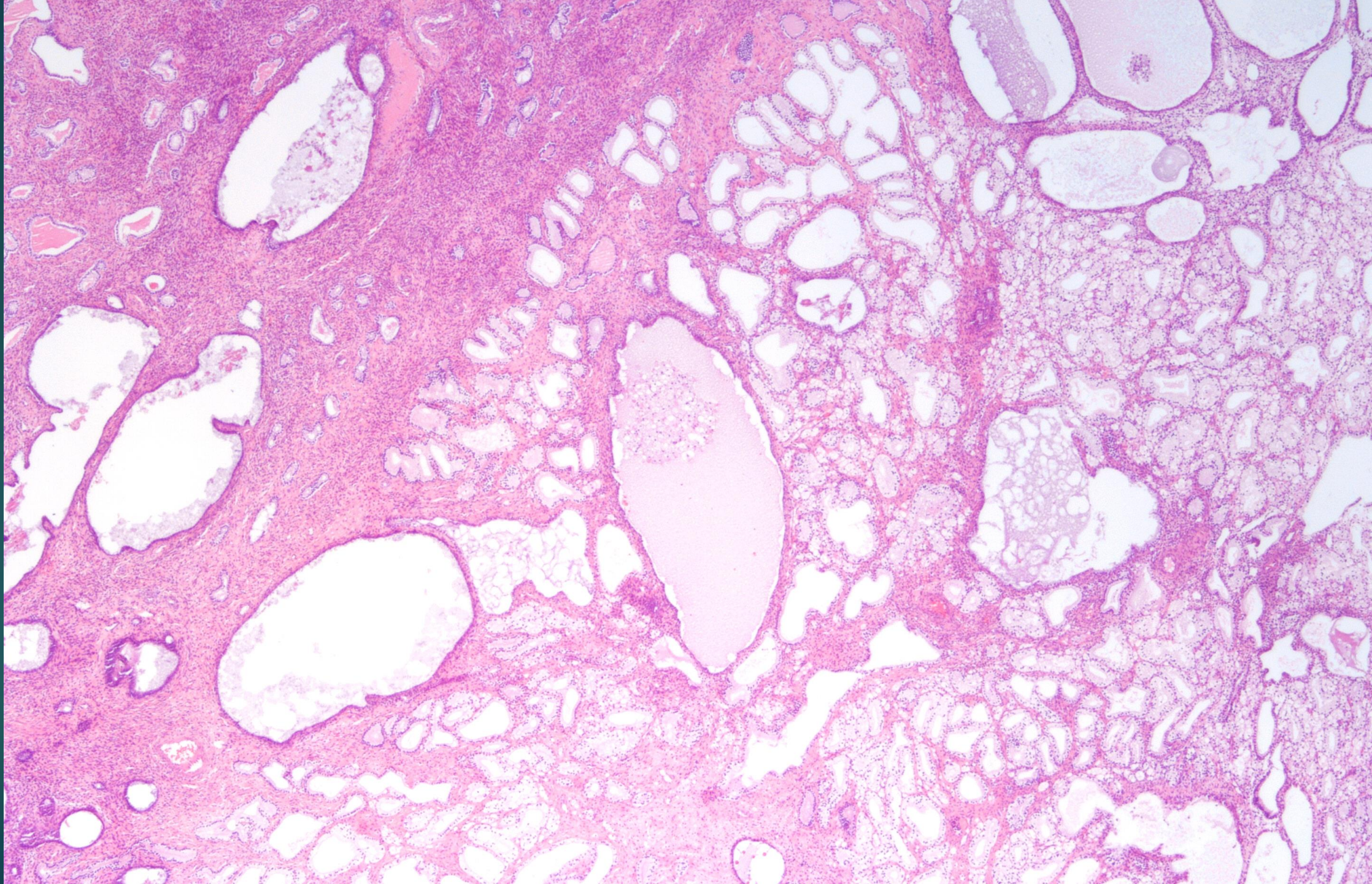




# Effects of Progesterone Treatment on Atypical hyperplasia or Carcinoma

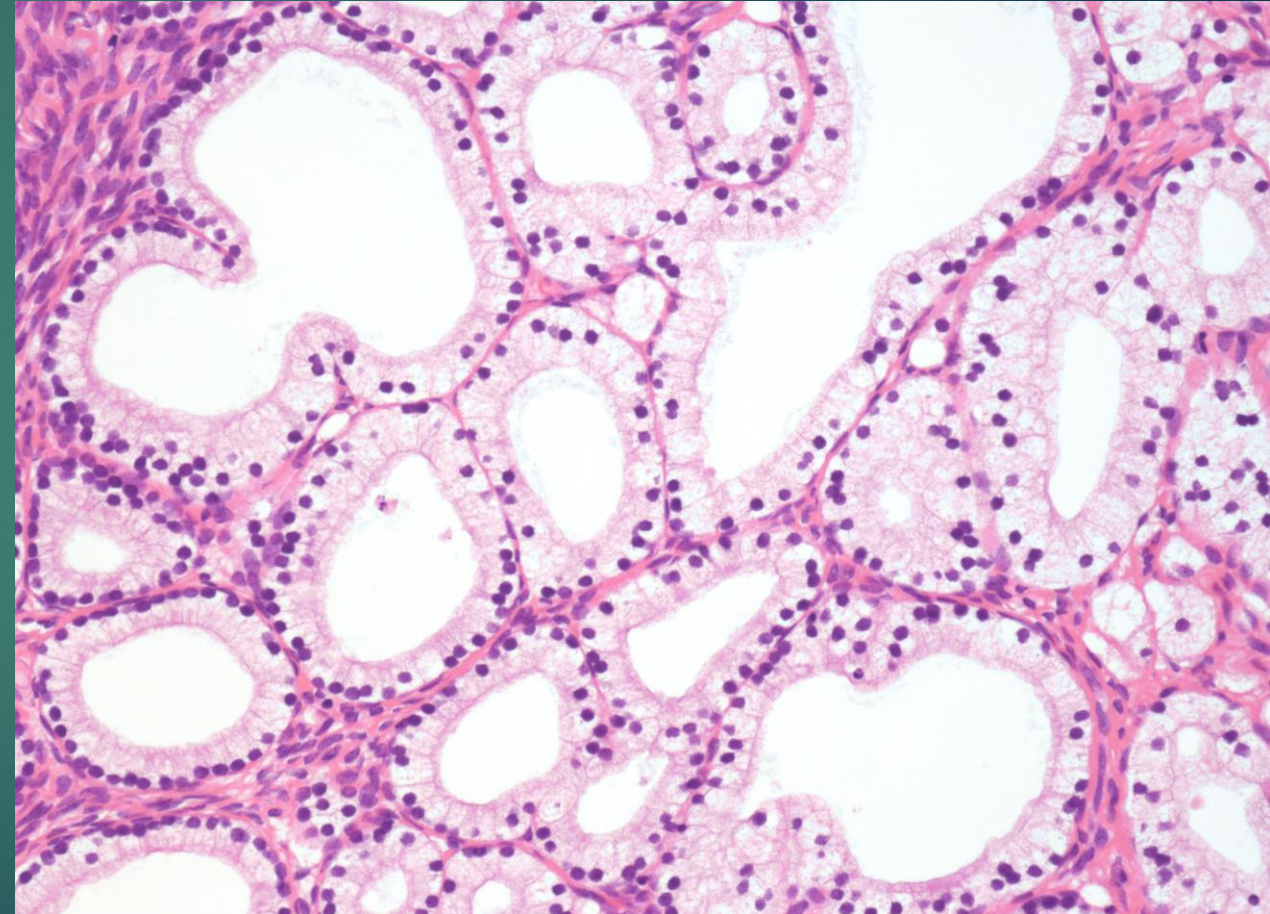
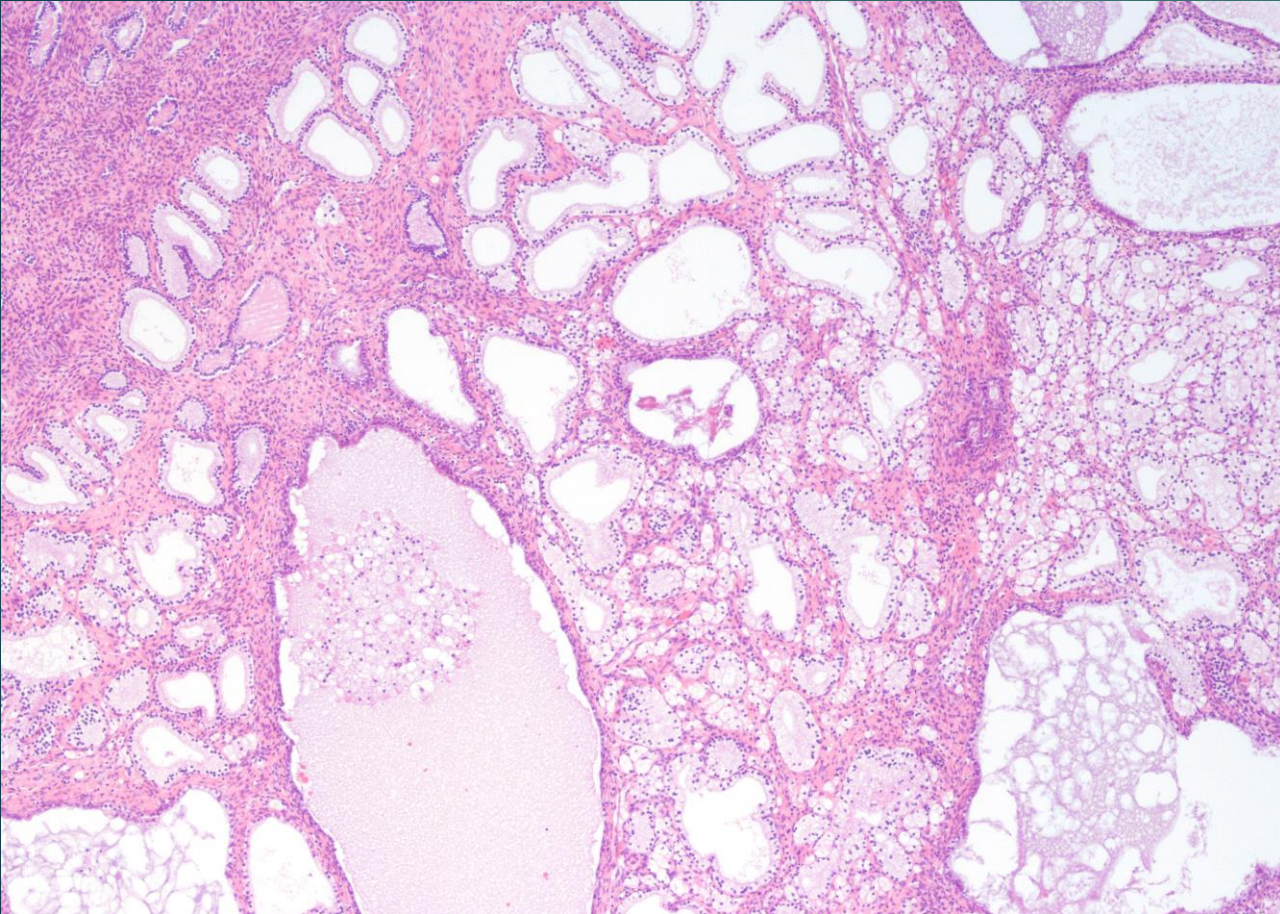
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- ▶ Metaplasias.

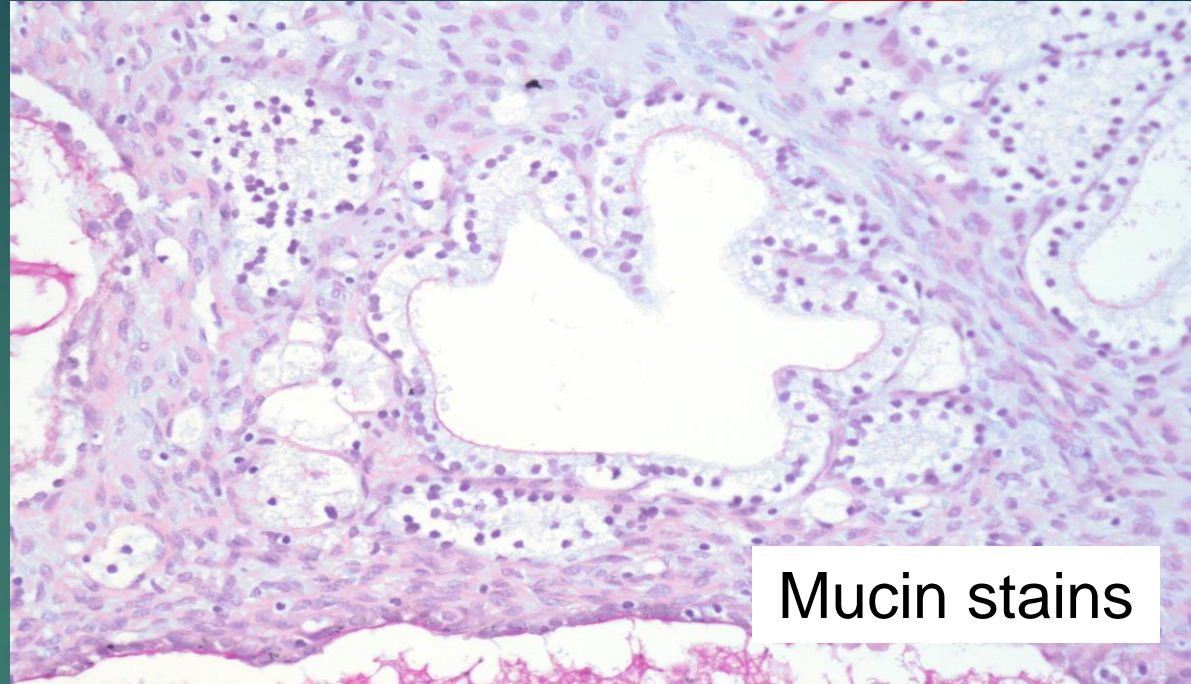
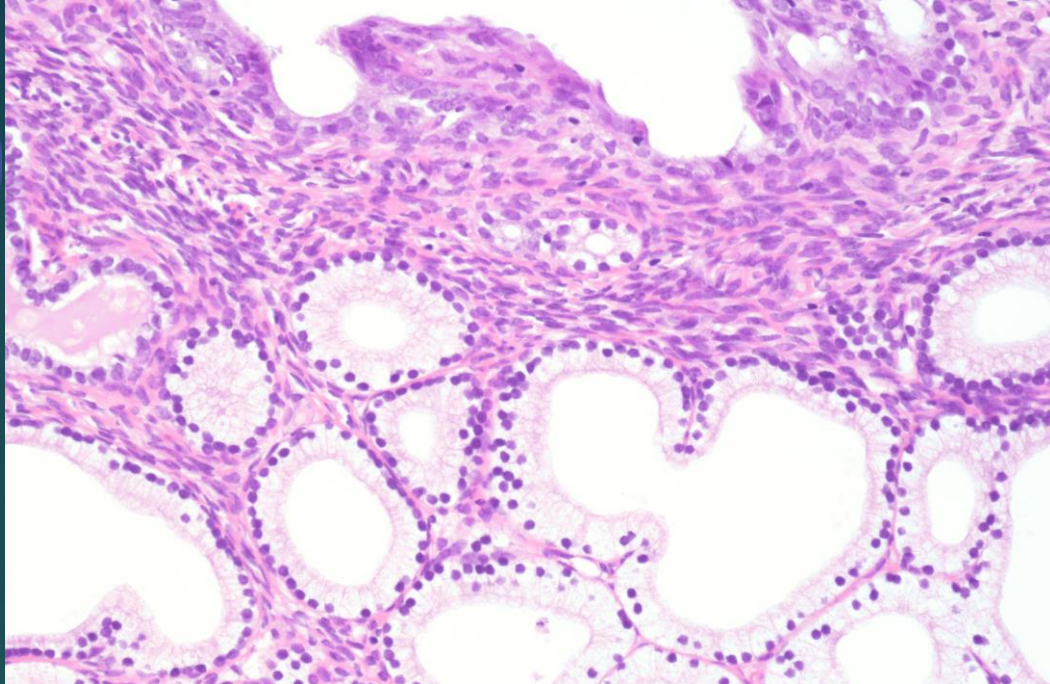




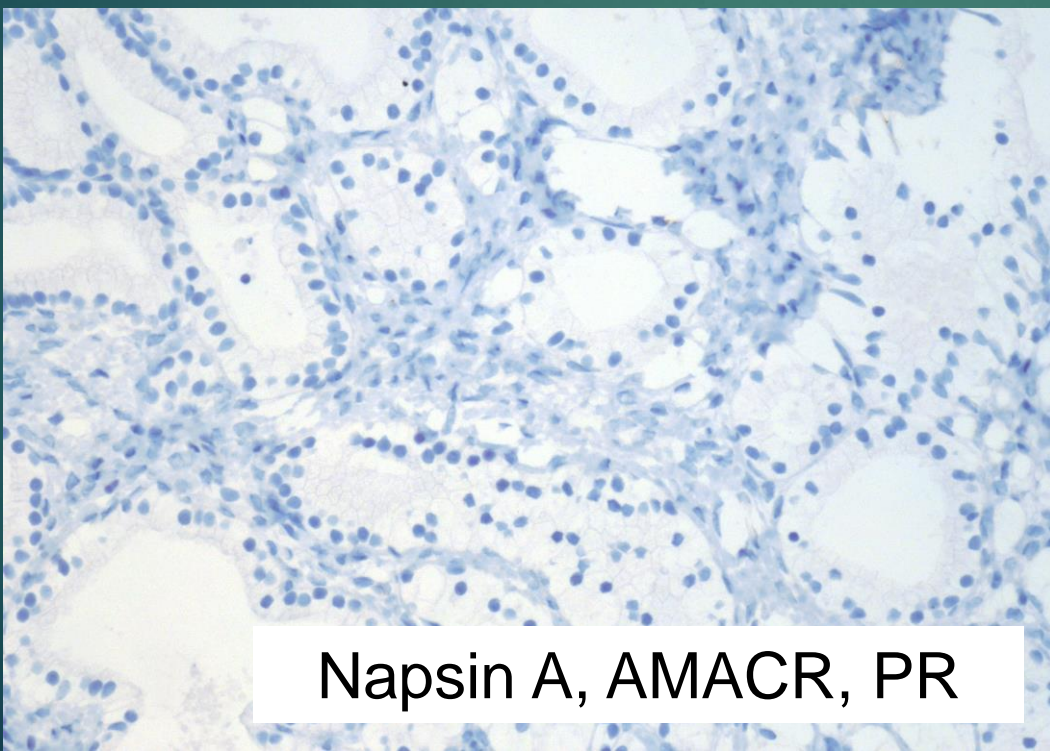


# Clear cell Metaplasia

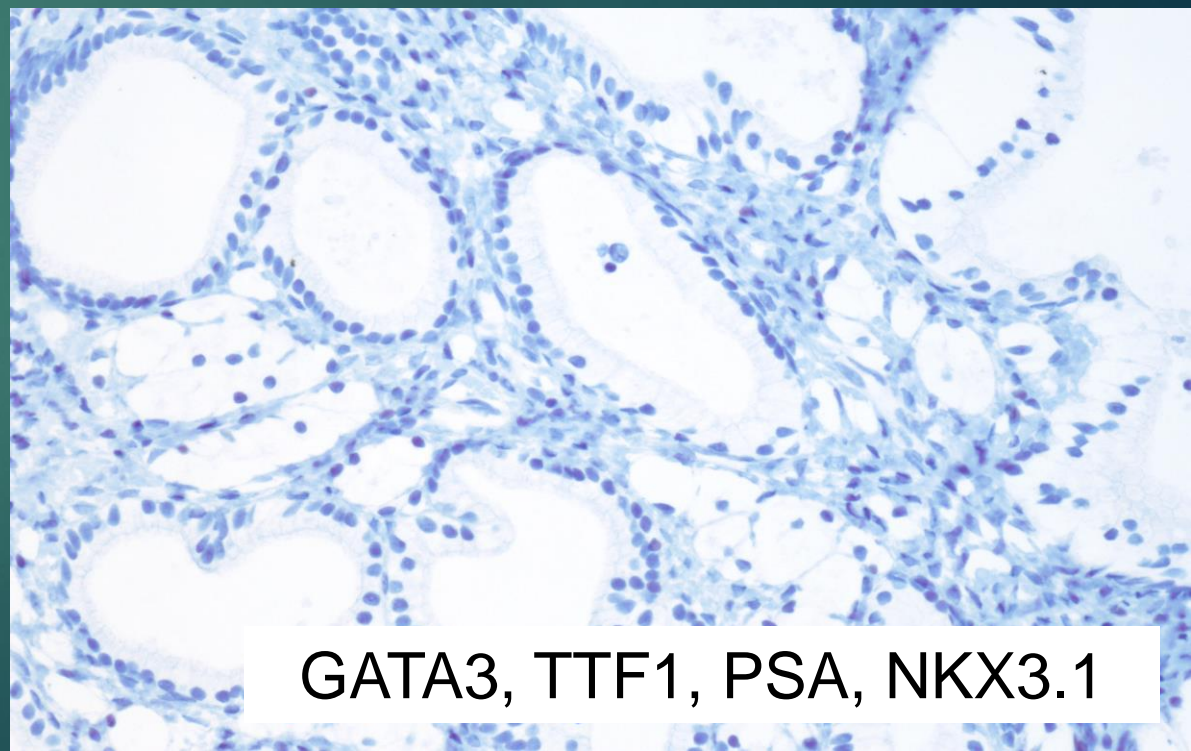




Mucin stains



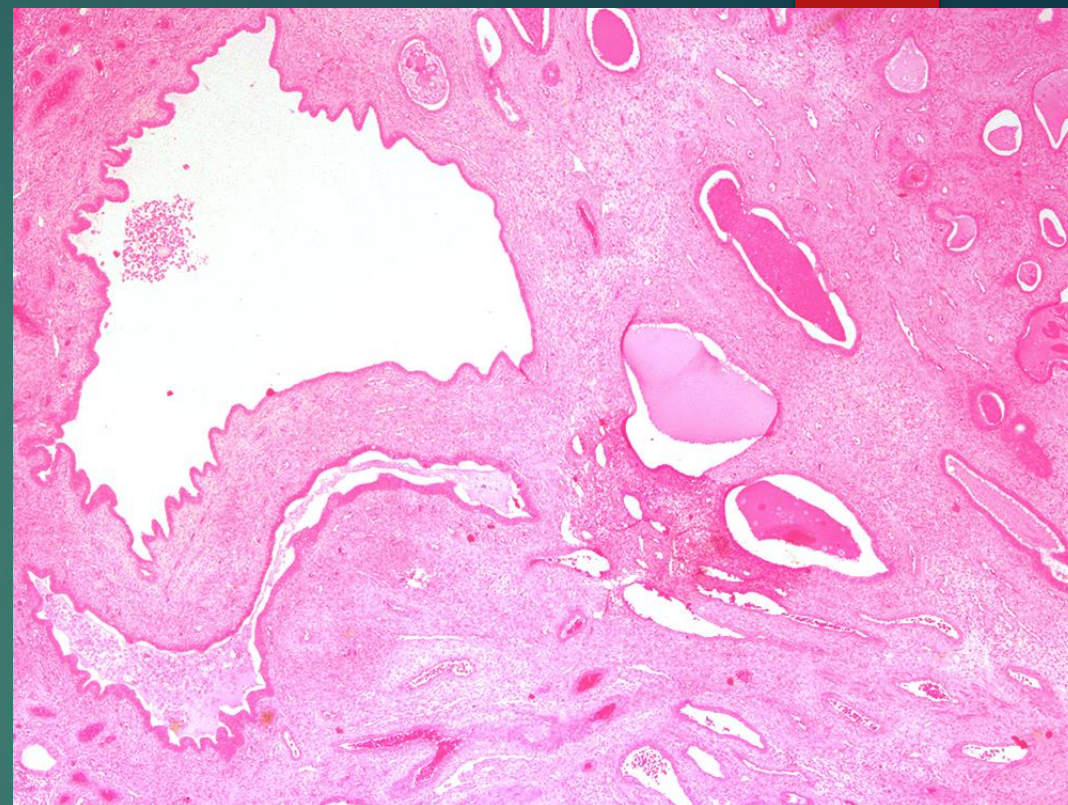
Napsin A, AMACR, PR



GATA3, TTF1, PSA, NKX3.1



# Tamoxifen Polyps



- ▶ Commonest endometrial lesion in tamoxifen-treated patients.
- ▶ 3-10% hyperplasia or Ca.
- ▶ Metaplasias (even clear cell are rare!).

Ip PPC, Djordjevic B. WHO Classification of Female Genital tumours, 5<sup>th</sup> ed. p.268

Deligdisch L. et al. Gynecol Oncol. 2000

Bergman L. et al. Lancet. 2000

Schlesinger C. et al. Int J Gynecol Pathol. 1998



# Arias-Stella Reaction

- ▶ Pregnancy, abortions, gestational trophoblastic diseases, exogenous progestogens.
- ▶ An important mimic of malignancy especially in small biopsies, history maybe nonspecific, and drug history unknown.

Eponyms and Entities

## Javier Arias-Stella and His Famous Reaction

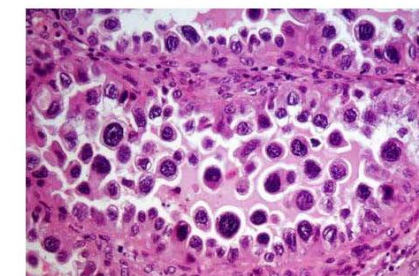
Juan Rosai, M.D. and Robert H. Young, M.D.

**Key Words:** Arias-Stella reaction—Javier Arias-Stella, M.D.—History of Pathology.

There are many eponyms in gynecologic pathology, most of them ancient. Some refer to normal structures of the female genital tract (such as Bartholin, Wolff, Müller), some to clinically insignificant non-neoplastic processes (Naboth), and some to benign primary and metastatic neoplasms of the ovary (Brenner, Krukenberg). Among them stands out an eponym that designates a non-neoplastic lesion that can be easily confused with a malignant tumor, universally known as the Arias-Stella reaction (Fig. 1). This essay is devoted to this phenomenon and to the man whose discovery the eponym celebrates. The man in question is Javier Arias-Stella (Fig. 2), a distinguished pathologist from Lima, Perú, and much of the story recounted here is a synopsis of an account he wrote himself some years ago (1).

Dr Arias-Stella, a native of Lima (Perú), graduated from the School of Medicine of the Universidad Nacional de San Marcos (Lima) in 1951. He began his training in pathology while still in medical school by participating in the activities of the Department of Pathology. Javier took a particular interest in gynecologic pathology and personally handled most of the specimens of that subspecialty. One day he stumbled on an endometrial curettage specimen from a 24-yr-old woman who had had a hydatidiform mole

expelled 5 mo before, followed by a hysterectomy. On pathologic examination, the uterine corpus was involved by an invasive mole (choriocarcinoma destruens), but the most interesting changes were present in the endometrium. Most of the endometrial glands had an unremarkable secretory look, but others were lined by highly atypical cells with large, hyperchromatic, and irregularly shaped nuclei. The appearance was highly suggestive of a malignant tumor, but not one that he or his seniors could recognize. The changes were finally interpreted as most consistent with an early or *in situ* stage of endometrial carcinoma, and their presence was not even mentioned in the final pathology report. Javier was very excited by this finding. He looked in all the books and journals available to him but found nothing similar. The lesion in question was beginning to recede in his memory when a second case appeared, this one in a 34-yr-old woman with an ectopic (tubal) pregnancy.



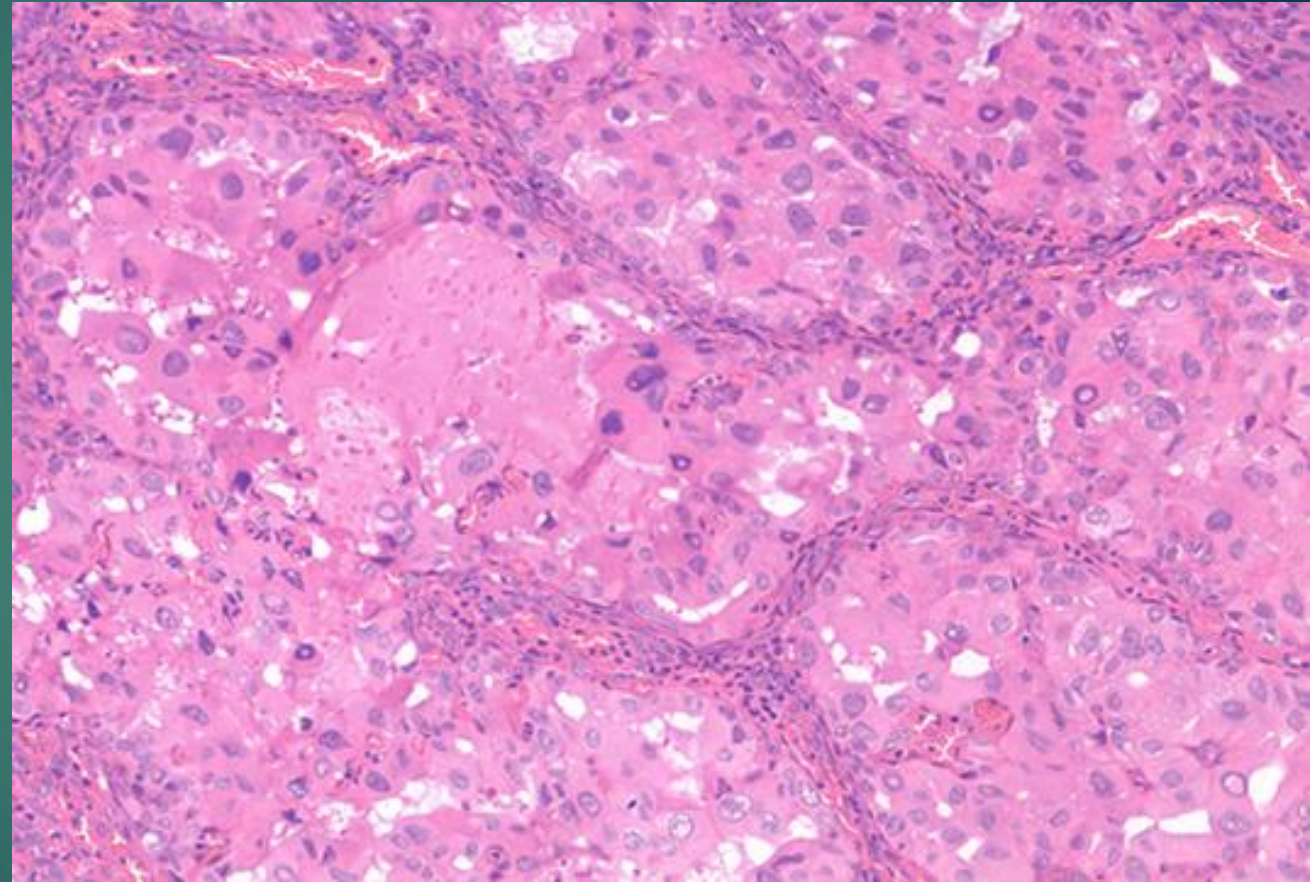
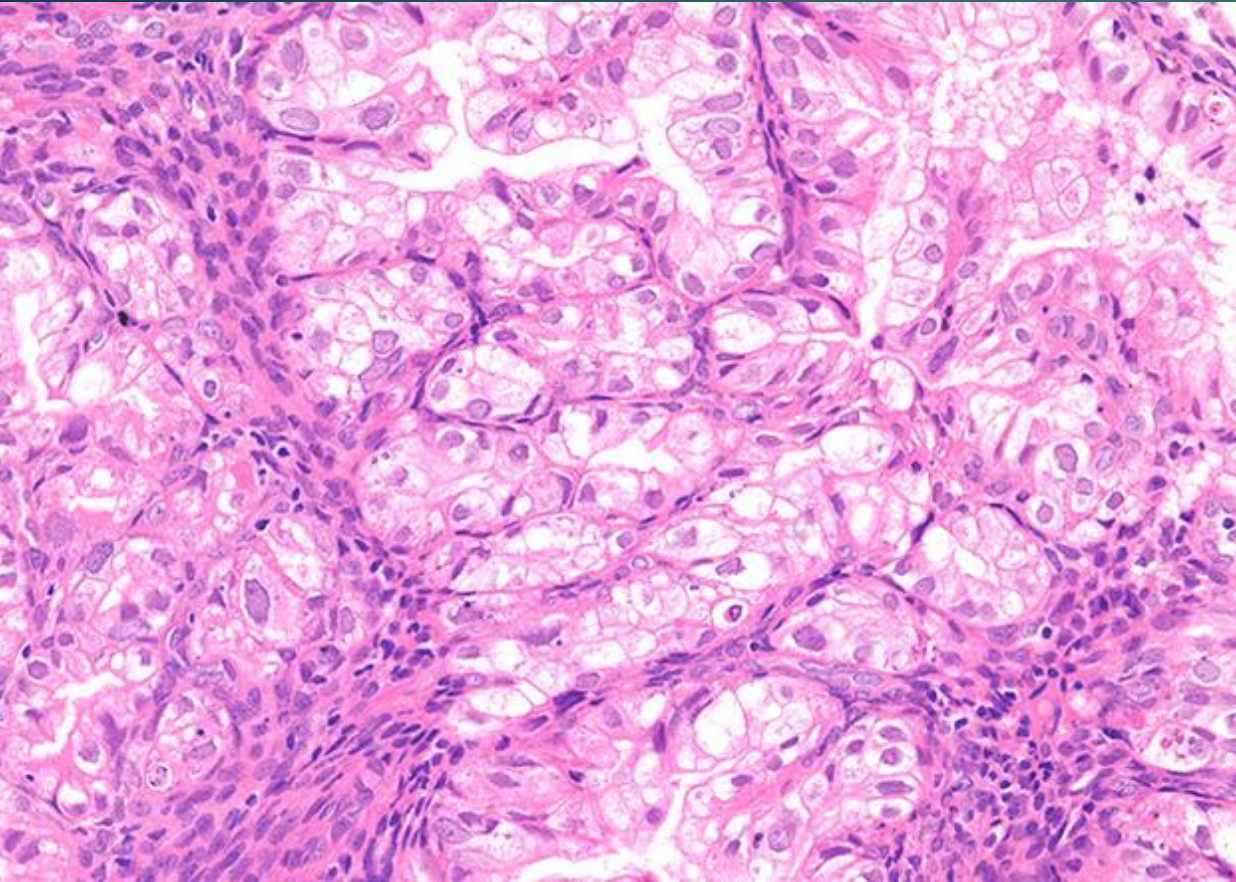
**FIG. 1.** Arias-Stella reaction. Marked nuclear pleomorphism is evident.

From the Centro Diagnostico Italiano, Milan, Italy; Department of Pathology, University of Utah Medical School, Salt Lake City, Utah (J.R.), and The James Homer Wright Pathology Laboratories (R.H.Y.), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

The authors declare no conflict of interest.  
Address correspondence to Robert H. Young, MD, The James Homer Wright Pathology Laboratories, Massachusetts General Hospital, 55 Fruit Street, Boston, MA. E-mail: rhyoung@partners.org.



# Arias-Stella Reaction

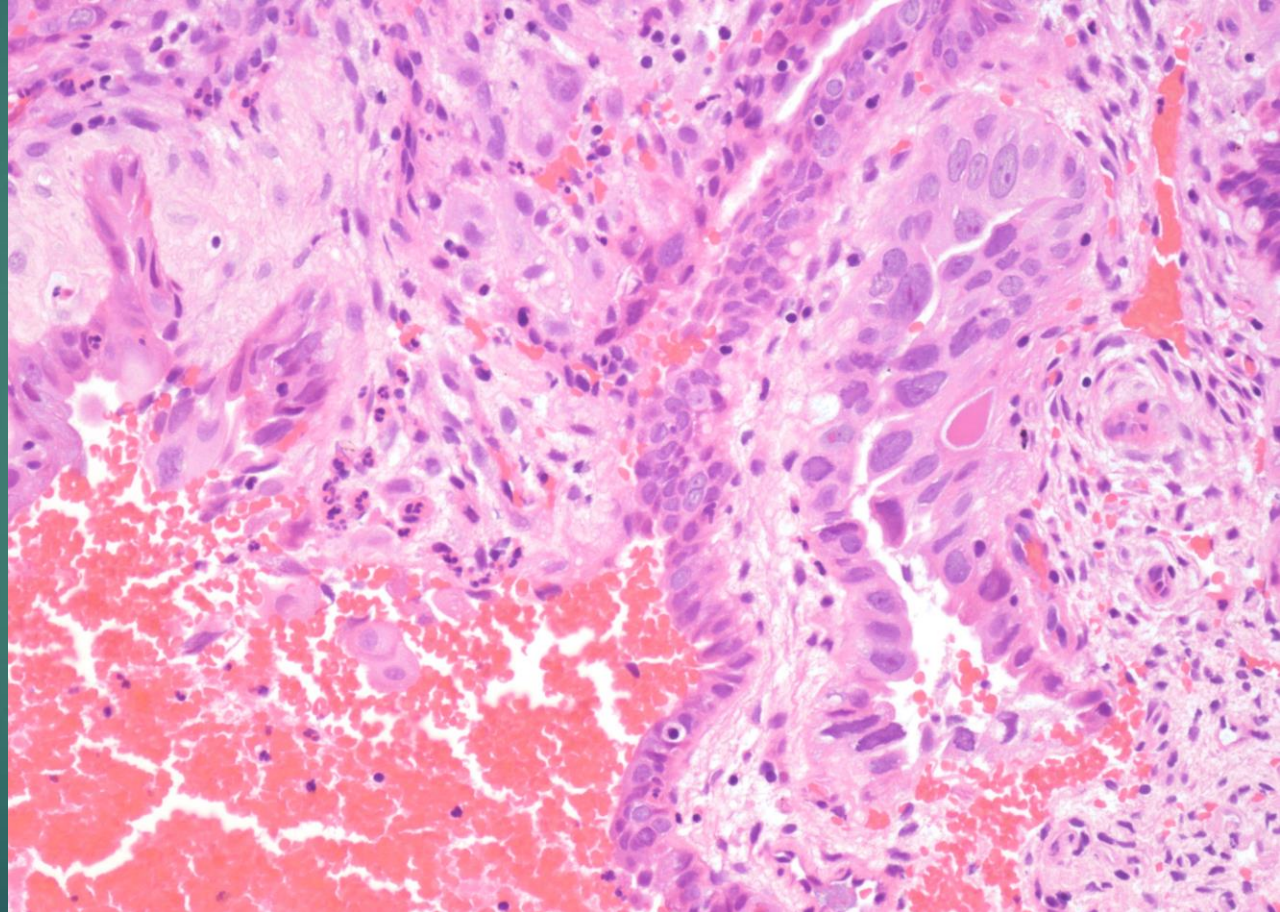
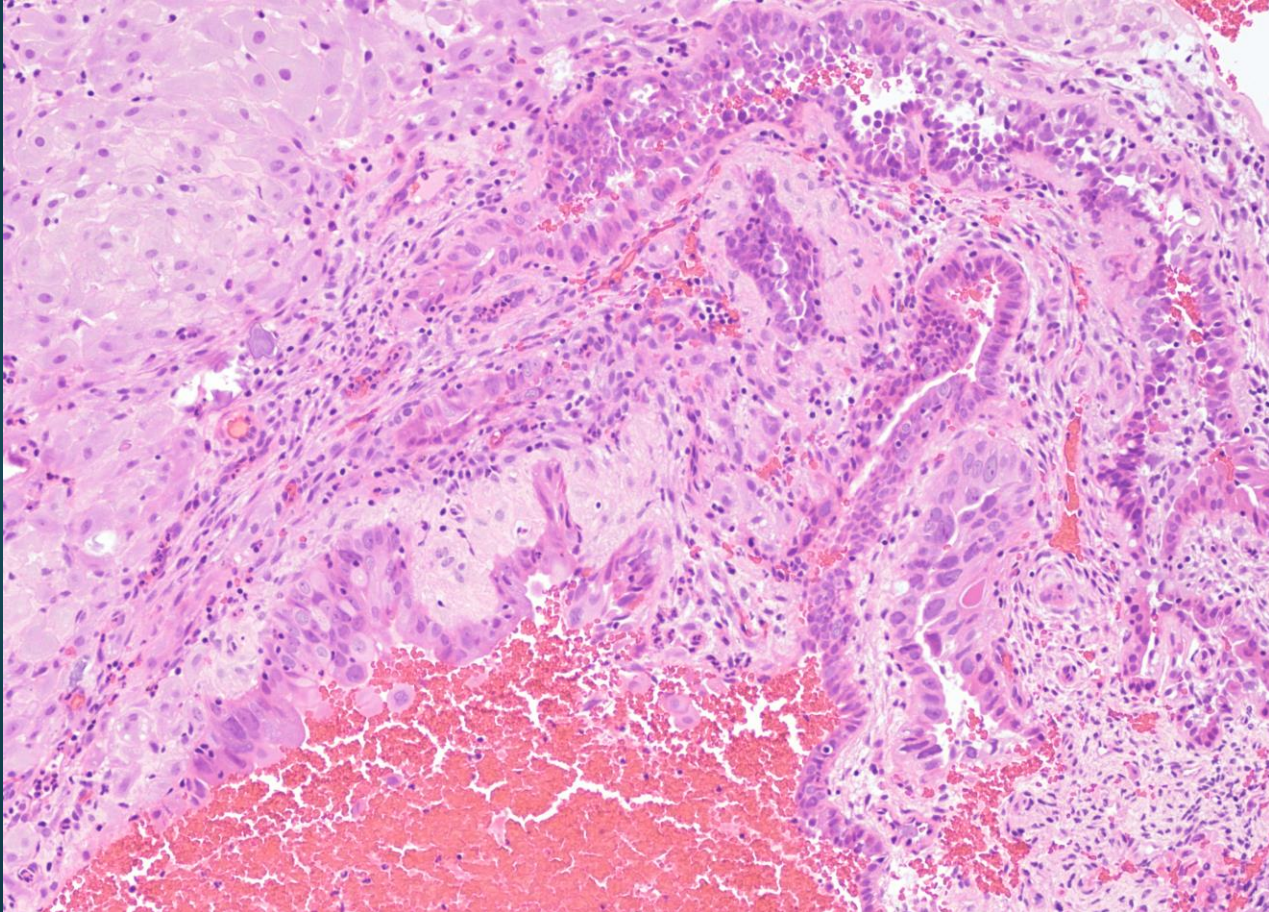


- ▶ Nuclear enlargement and irregularity, smudged nuclear chromatin, pseudonuclear inclusions, clear or eosinophilic cytoplasm.





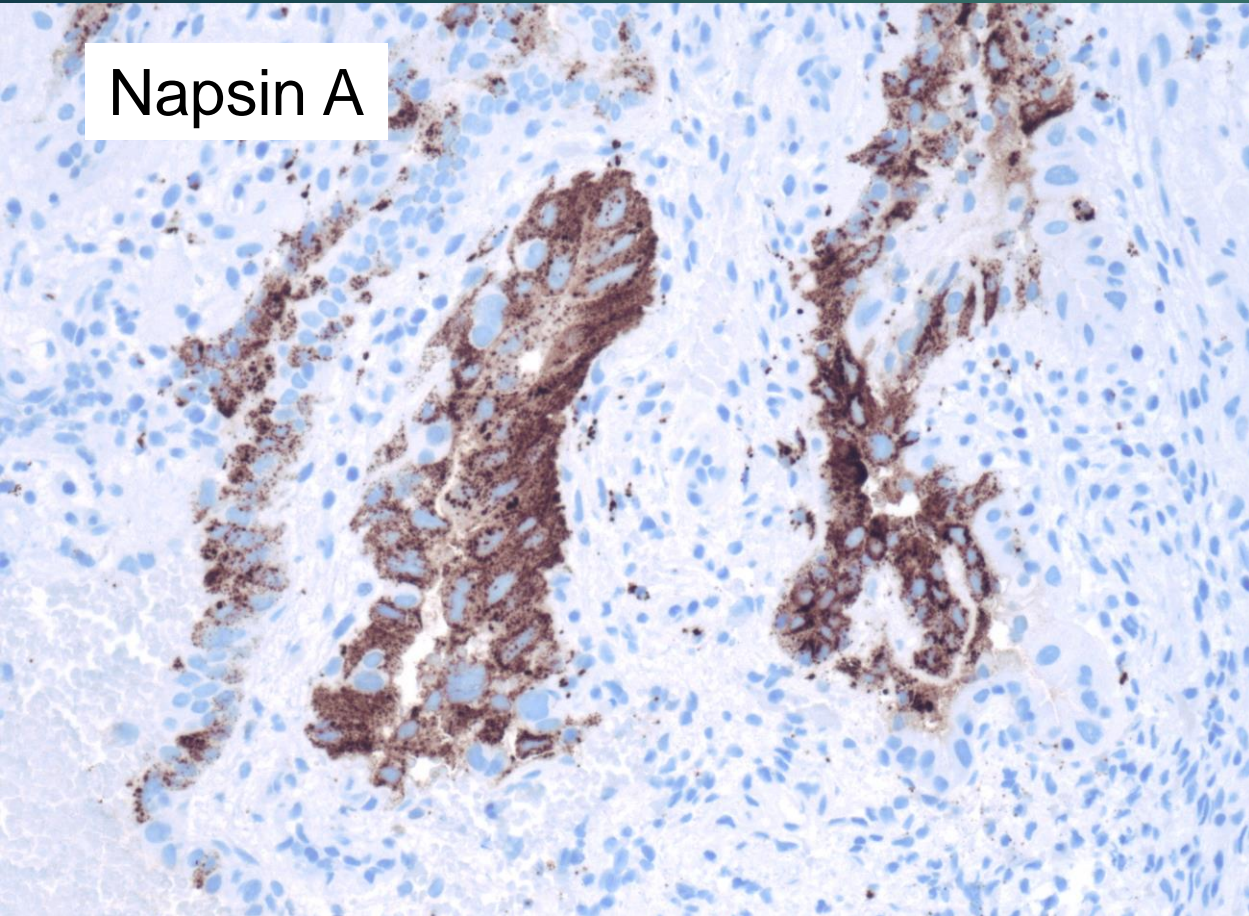
# Arias-Stella Reaction



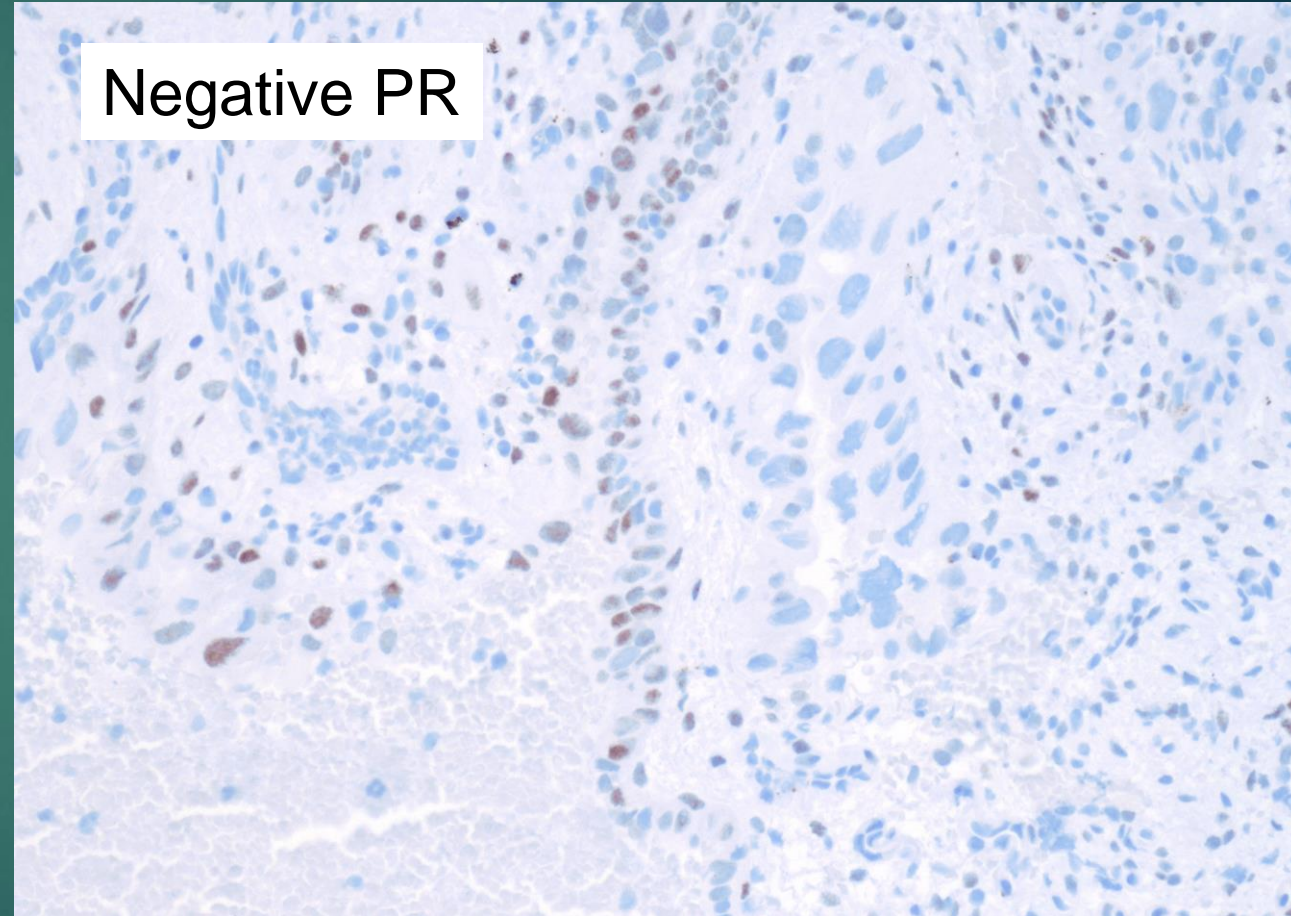


# Arias-Stella Reaction

Napsin A



Negative PR



- ▶ Napsin A, HNF1 $\beta$ , AMACR (P504S Racemase).
- ▶ Overlaps with clear cell carcinoma.



# Arias-Stella

## Clues for Arias-Stella reaction:

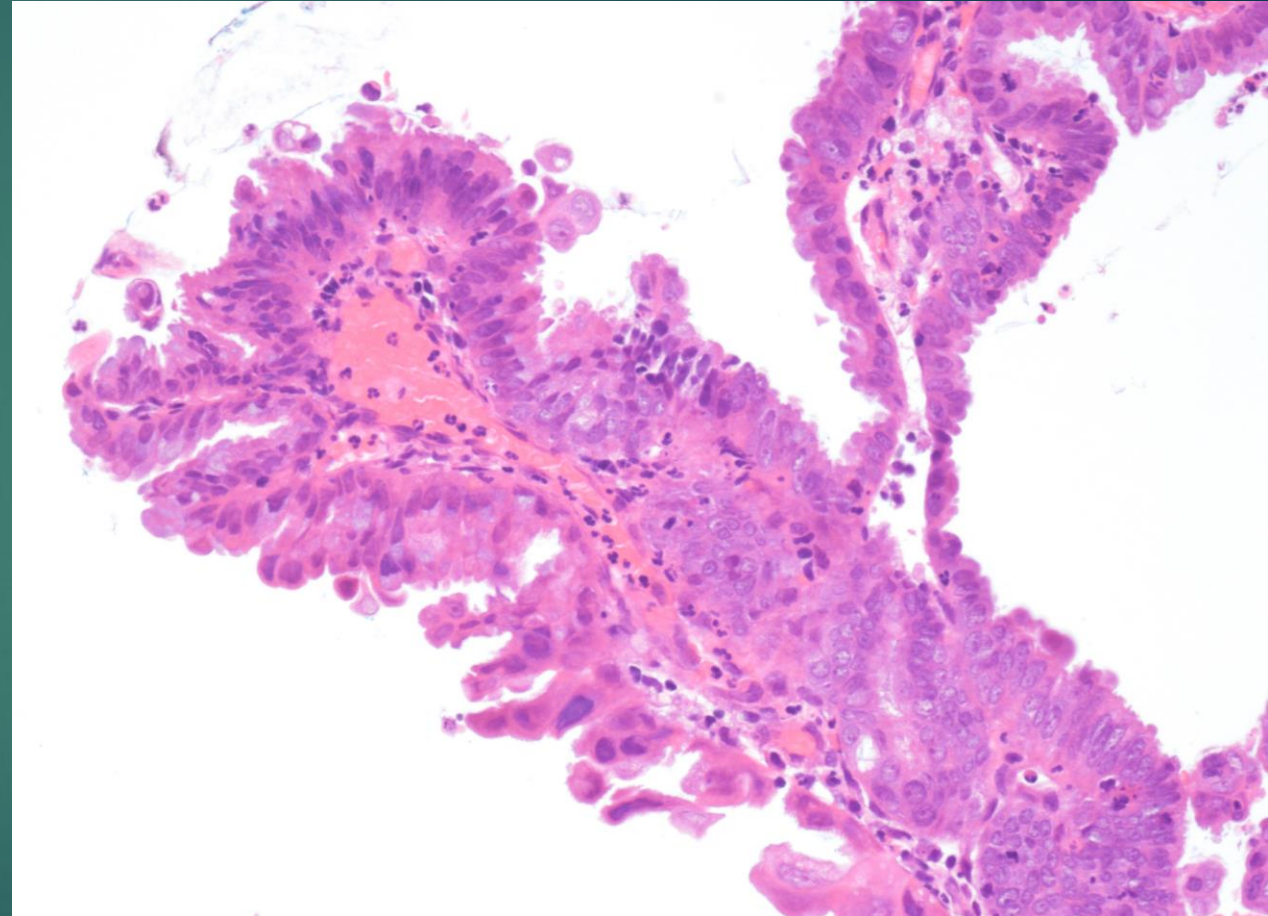
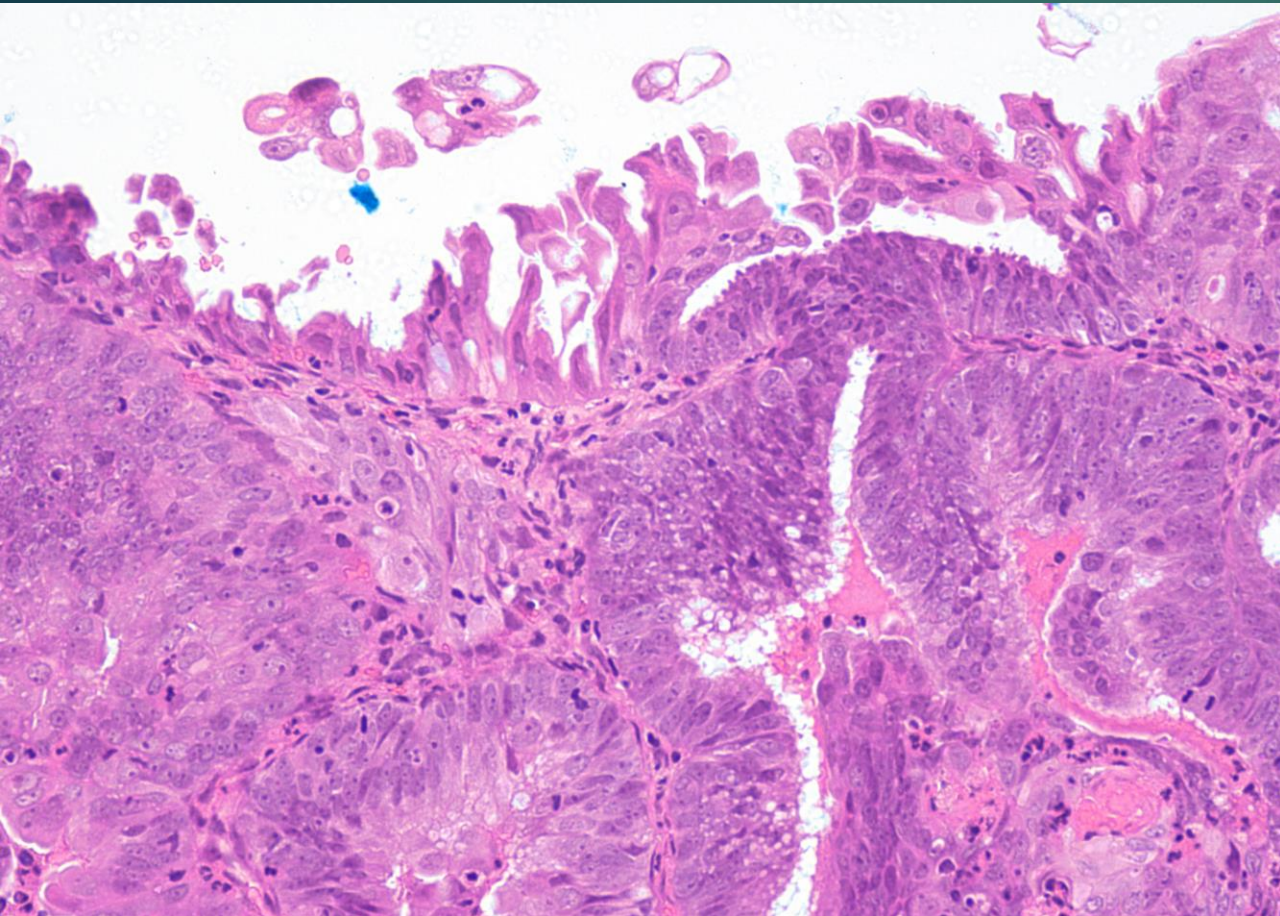
- Variability in number of glands involved.
- Variability of number of cells involved in an involved gland.
  - Stromal predecidual change.

- ▶ Napsin A, HNF1 $\beta$ , AM...
- ▶ Overlaps with clear cell carcinoma.

Ip PPC et al. Am J Surg Pathol. 2019  
Fadare O. Hum Pathol. 2016  
Fadare O. et al. Am J Surg Pathol. 2014



# Arias-Stella Reaction



- ▶ Arias-Stella reaction may involve progesterone-treated carcinomas.
- ▶ Avoid making a diagnosis of mixed carcinoma!



# Learning Outcome: Practical issues of Endometrial Proliferative lesions in small biopsies

- ▶ Improved proficiency in the assessment of endometrial cytologic atypia.
- ▶ Can recognise the different forms of endometrial metaplasias, their significance, and their association with premalignant lesions and carcinomas.
- ▶ Learnt the importance of obtaining a drug history in everyday signouts of small endometrial biopsies.



**THANK YOU!**

