Carlos Parra-Herran MD, Boston MA US



Title: Mimics of pre-invasive and invasive glandular lesions of the cervix

- **Dr. Carlos Parra-Herran is an academic gynecologic pathologist at Brigham and Women's Hospital and Associate Professor of Pathology at Harvard Medical School. He graduated from Universidad Nacional de Colombia and completed his residency at Jackson Memorial Hospital, followed by subspecialty training at Brigham and Women's Hospital and Sunnybrook Health Sciences Centre. His research focuses on the morphologic and molecular characterization of gynecologic tract neoplasia, particularly lower genital tract epithelial lesions, mesenchymal tumors and non-serous ovarian neoplasia. He has authored over 80 peer-reviewed publications and edited one reference textbook in Gynecologic Pathology (Foundations in Diagnostic Pathology series, Elsevier 2020). He has served as teaching faculty for continuing medical education events offered by the United States and Canadian Academy of Pathology (USCAP), the Latin American Pathology Society, the Canadian Association of Pathologists, the European Society of Pathology and the College of American Pathologists. He is also part of the organizing team of the International Society of Gynecological Pathologists (ISGyP) Live Virtual Education program. Dr. Parra-Herran currently serves as a member of the ISGyP board of directors and the USCAP education committee.**

The British Association of Gynaecological Pathologists

17th Annual Meeting

- Title: Mimics of pre-invasive and invasive glandular lesions of the cervix
- Speaker: Carlos Parra-Herran
- Affiliation: Brigham and Women's Hospital, Boston MA US
- Date: June 10th 2021, 11:50-12:30

The British Association of Gynaecological Pathologists

Speaker disclosures

Choose one

- ❑ I have no financial conflicts of interest to disclose

MIMICS OF PRE-INVASIVE AND INVASIVE GLANDULAR LESIONS OF THE CERVIX

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DISCLOSURE OF FINANCIAL SUPPORT

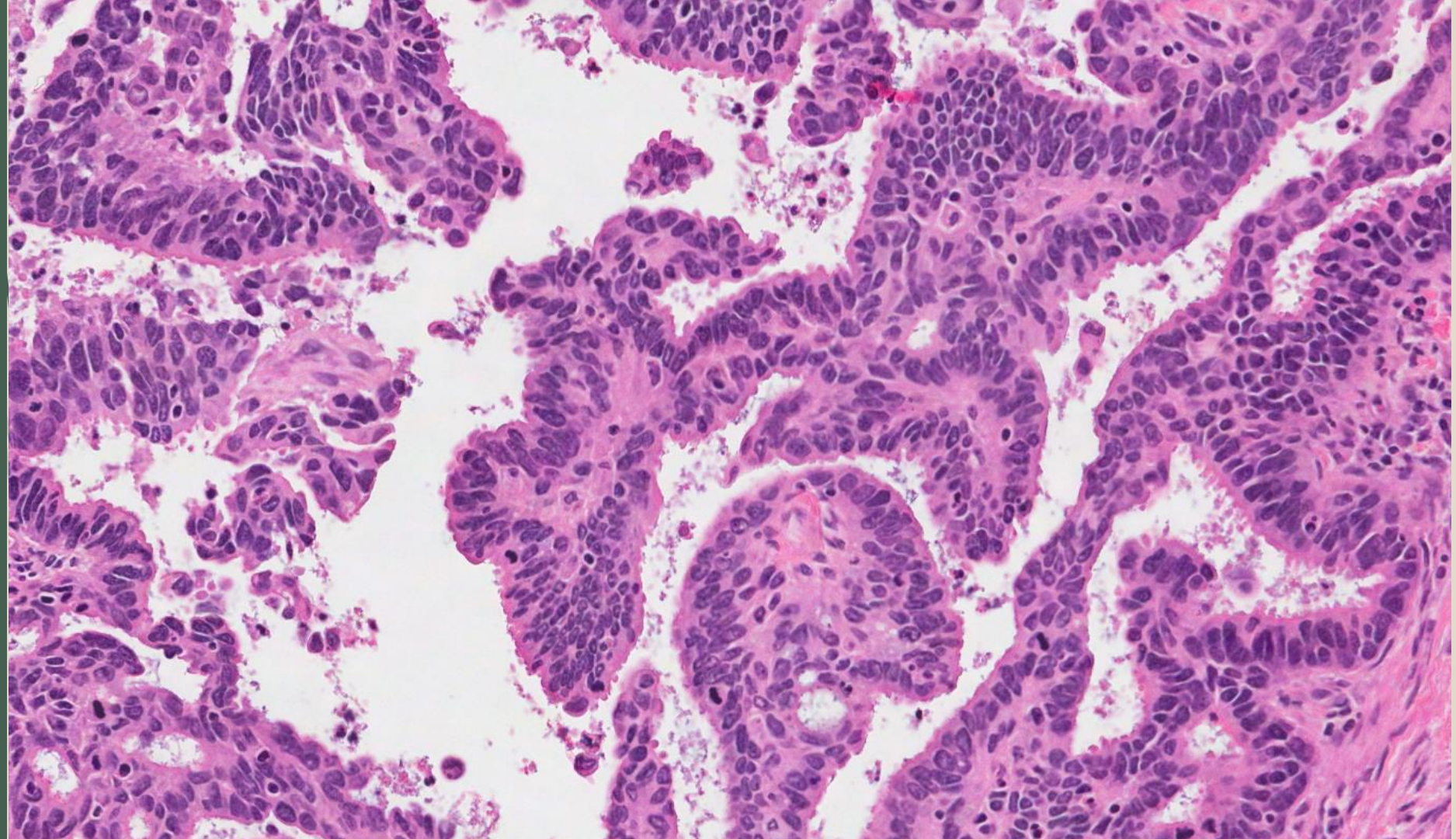
I have no conflicts of interest to disclose related to this academic activity

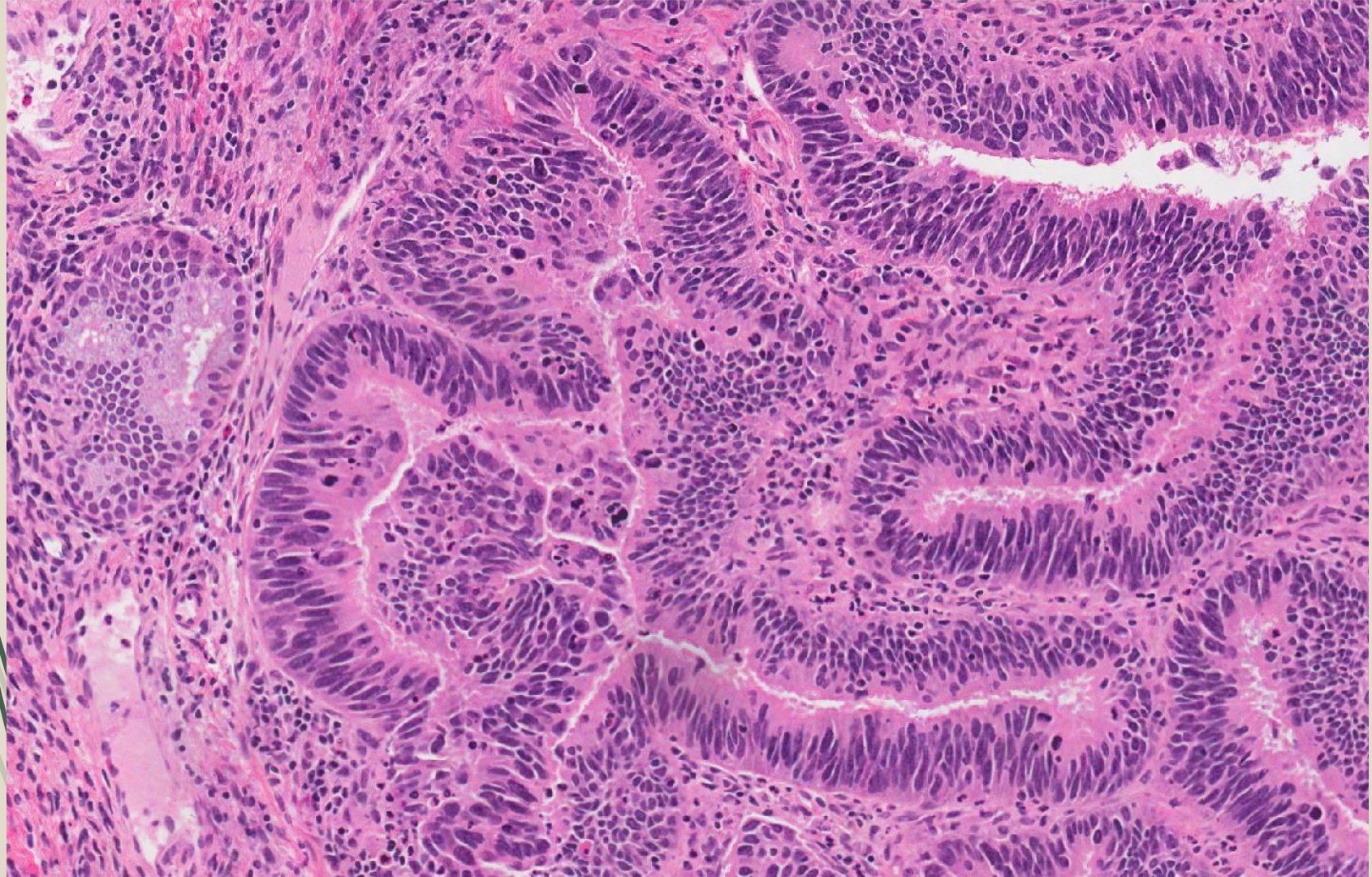
OUTLINE

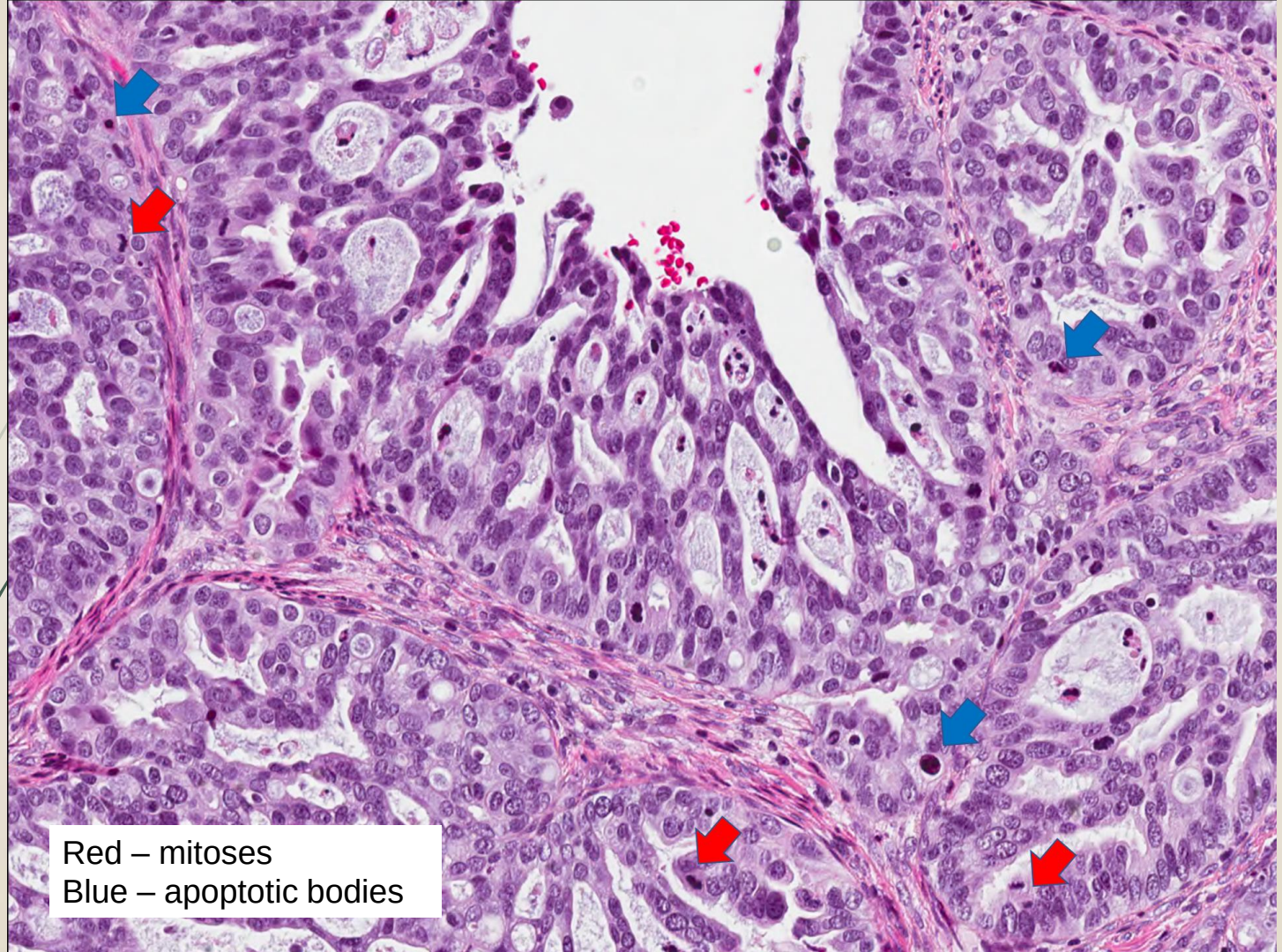
- Mimics of HPV-associated endocervical neoplasia
- Mimics of HPV-independent endocervical neoplasia

HPV-associated endocervical adenocarcinoma

- Apical mitotic figures
- Apoptotic bodies
- Easily recognizable at low power magnification (4x or 10x)
- Most commonly **usual type**
  - ~70-75% of all adenoCAs
  - Non-mucinous cells in most of the tumor (≥50%)






Red – mitoses
Blue – apoptotic bodies

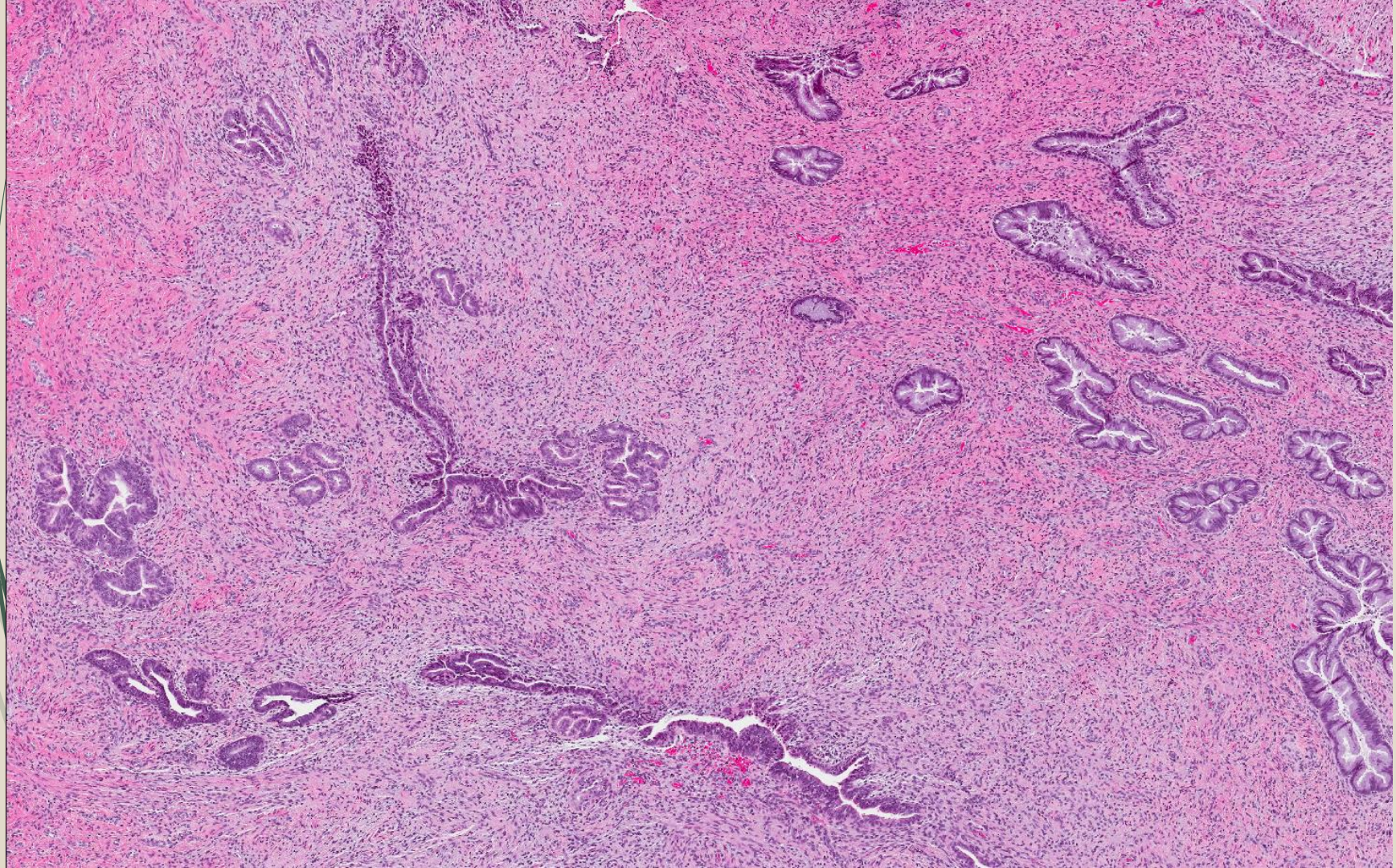
HPV-ASSOCIATED ADENOCARCINOMA MIMICS

- Tubo-endometrioid metaplasia
- Endometriosis
- Microglandular hyperplasia
- High grade squamous intraepithelial lesion
- Endometrial carcinoma & other metastatic carcinomas

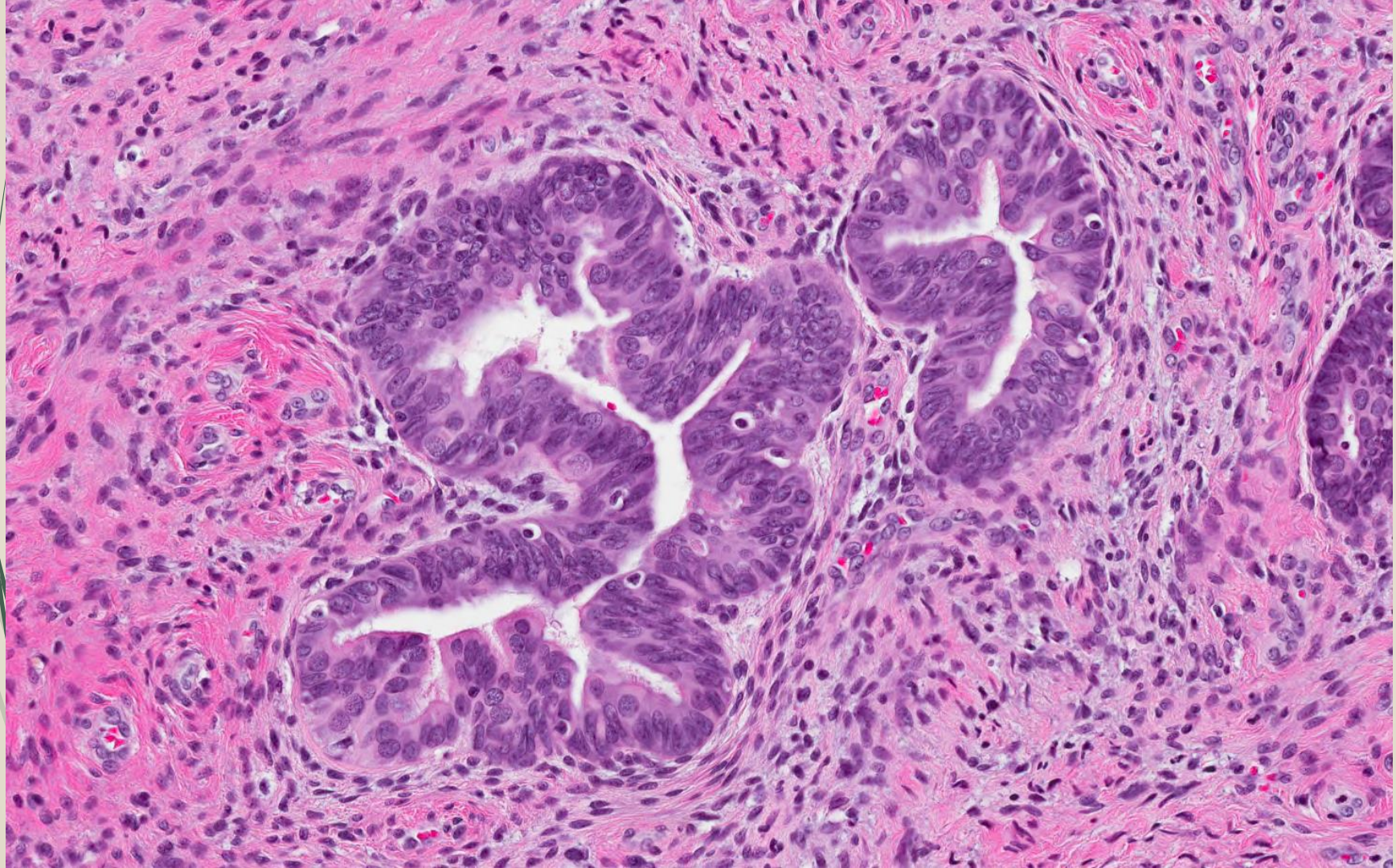
DDx: TUBO-ENDOMETRIOID METAPLASIA

- ~20% cone biopsies, ~60% hysterectomies
- Association with previous Cx procedure (e.g. LEEP)
- Columnar mucin-depleted epithelium
- Cigar-shaped nuclei
- Mitoses may be present
- Reactive "desmoplastic" stroma

Int J Gynecol Pathol 1992;11:89-95
Histopathology 1991;18:107-114





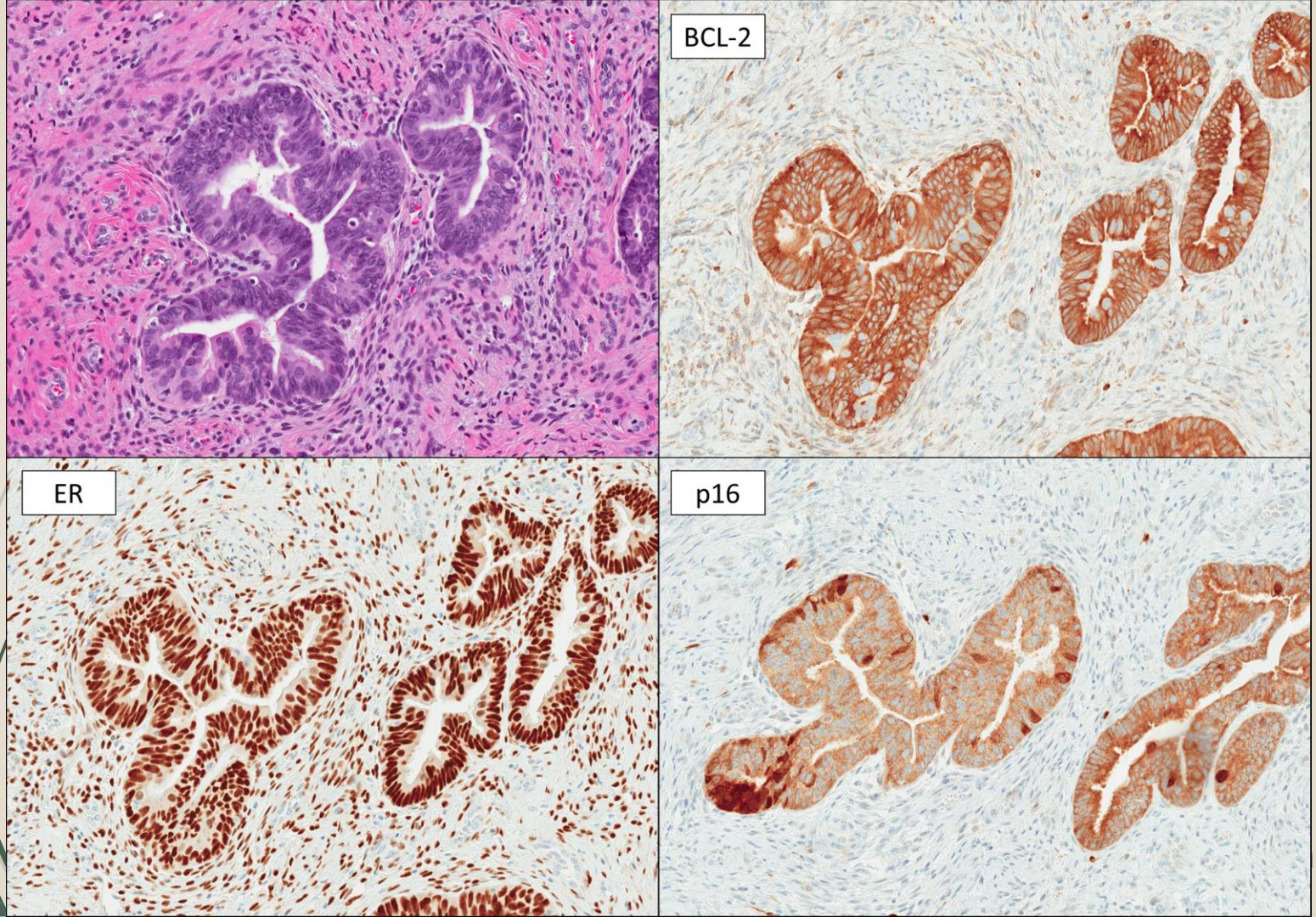


DDx: TUBO-ENDOMETRIOID METAPLASIA

- Tubal morphology: Ciliated and peg cells
- Uniform chromatin distribution
- Overall preservation of polarity

Histopathology 2002;41:313-321
Pathology 2010;42:217-223

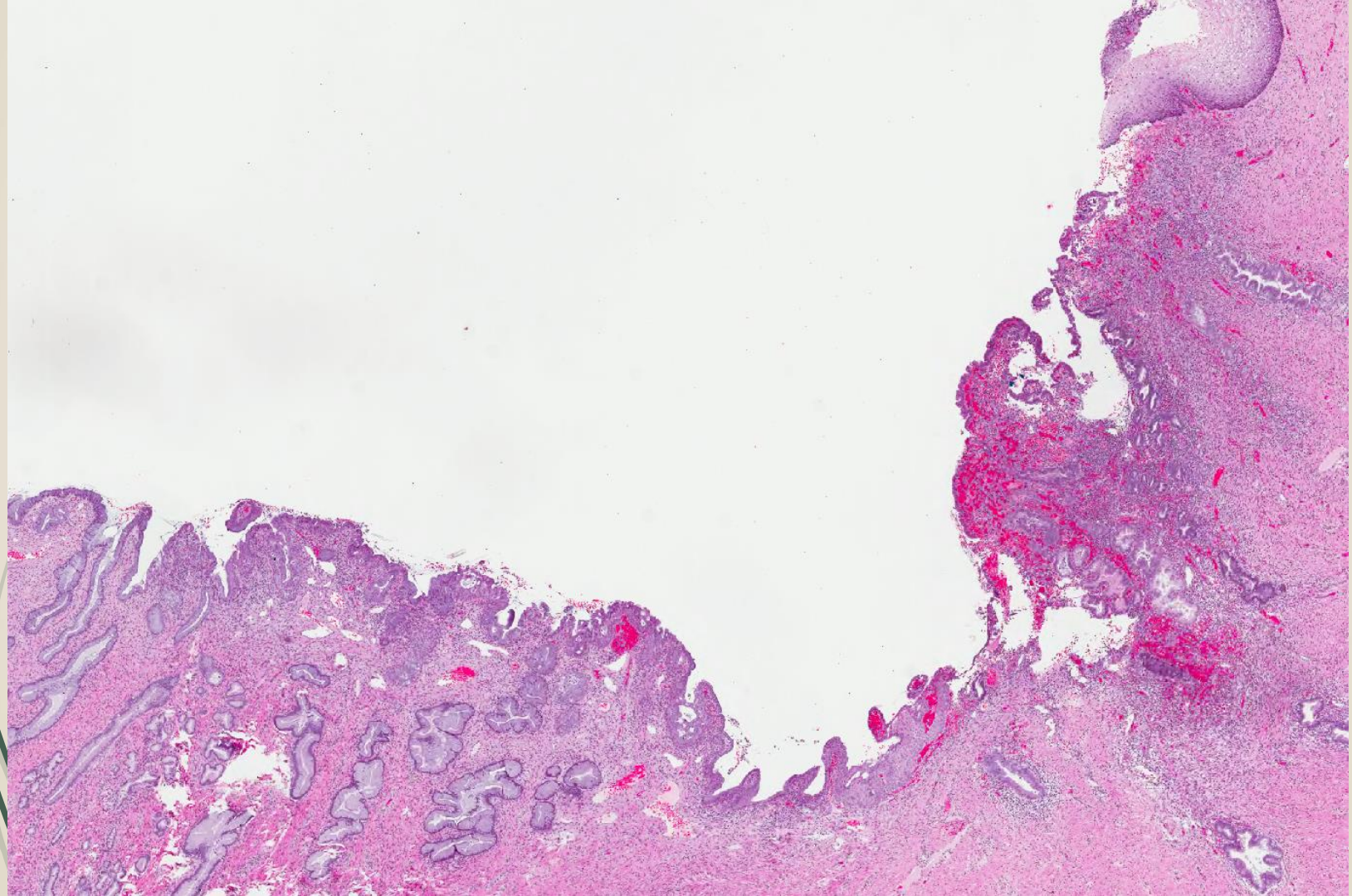
	P16	Vimentin	BCL-2	ER
TEM	Negative or Patchy	Positive	Positive (diffuse)	Positive
Endocervical adenocarcinoma	Overexpressed	Negative	Negative or Focal	Negative

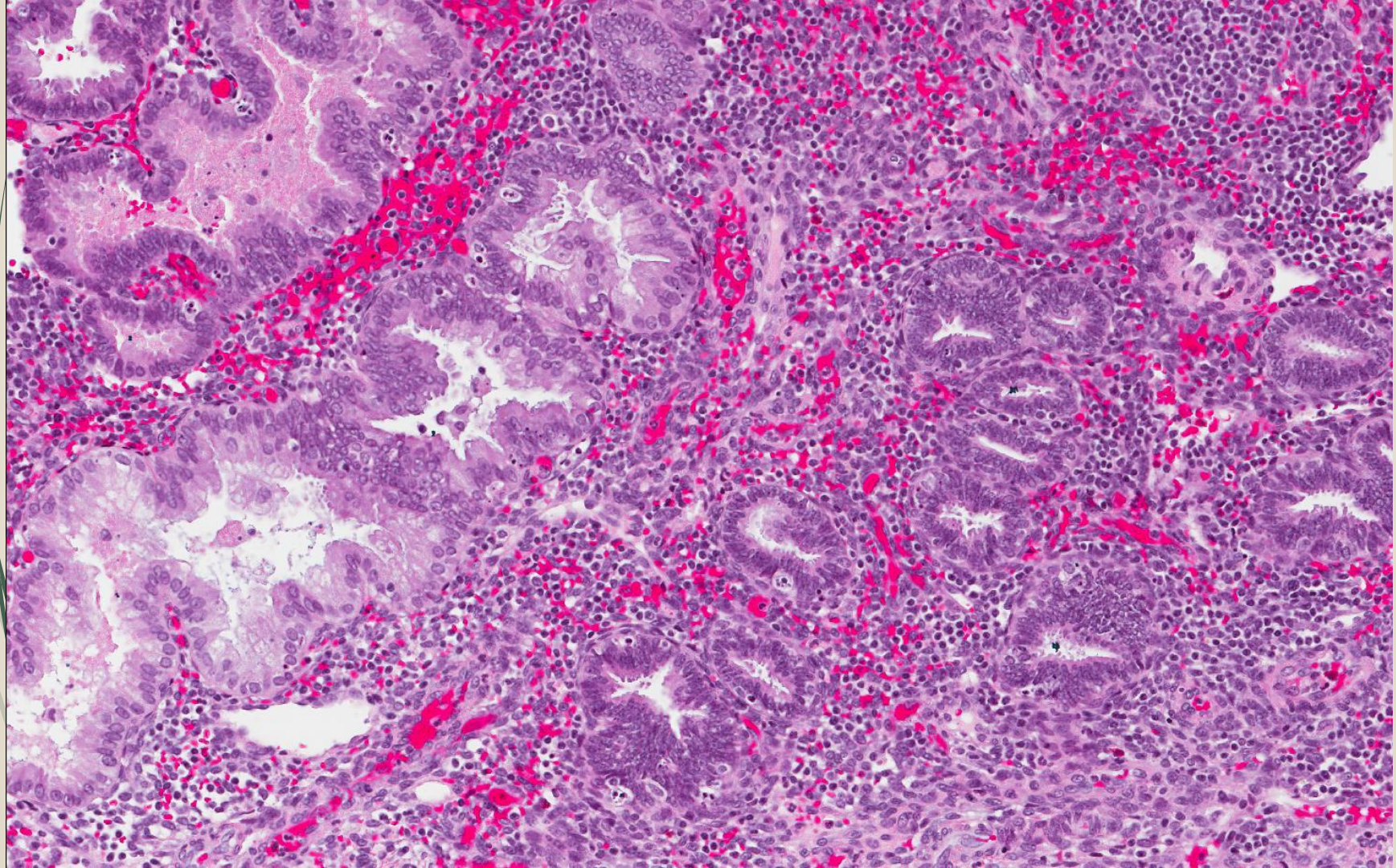

BCL-2
ER
p16

DDx: CERVICAL ENDOMETRIOSIS

- <1% of endometriosis cases
- Previous pregnancy or endometrial curettage
- Usually superficial; can be transmural
- Symptoms in ~50%
- Abnormal cytology

Am J Obstet Gynecol 2011;205:452.e1-5
Diagn Cytopathol 2004;30:88–91





DDx: CERVICAL ENDOMETRIOSIS

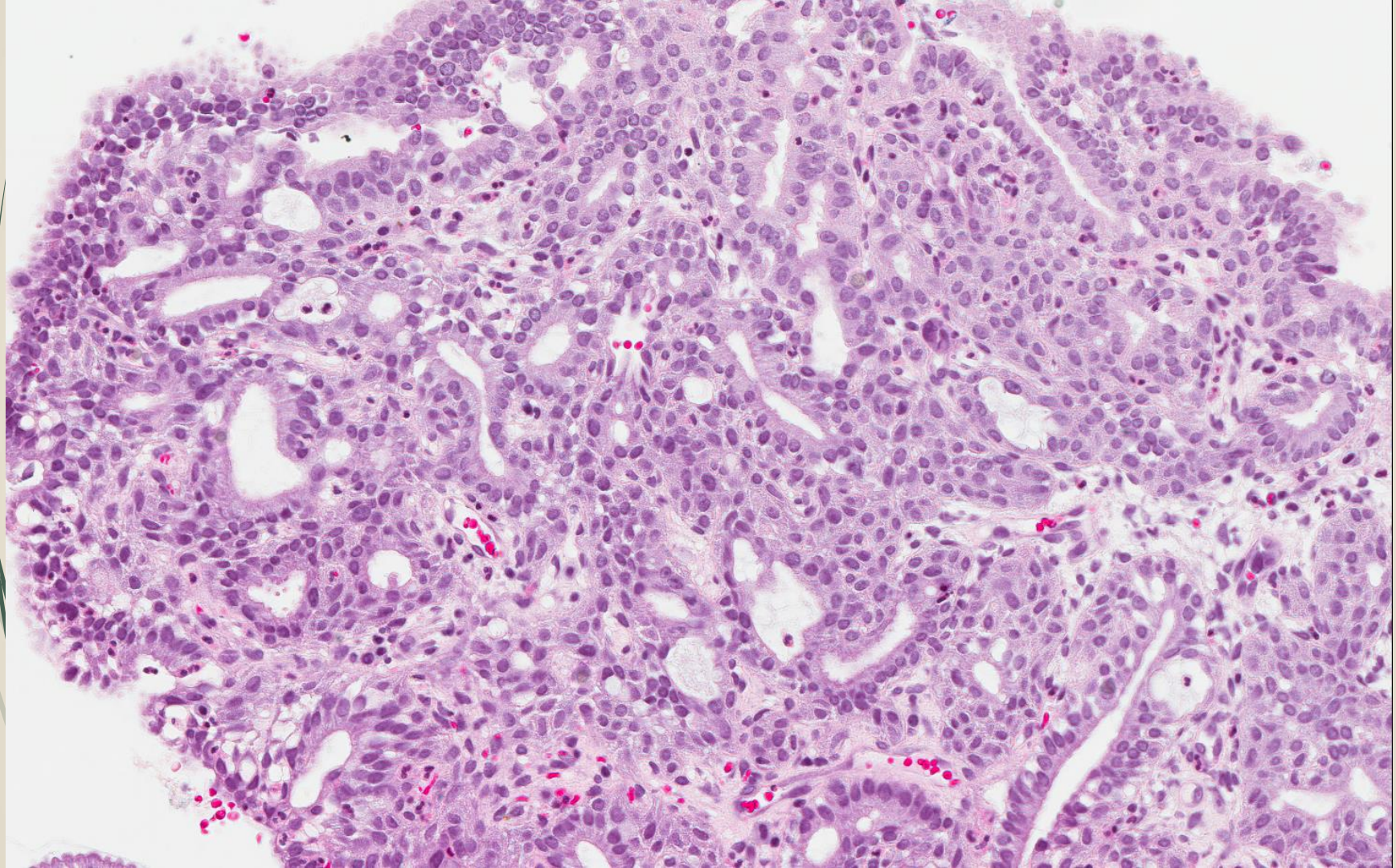
- Columnar mucin-depleted epithelium
- Cigar-shaped nuclei
- Mitoses may be present
- Uniform chromatin distribution ✓
- Overall preservation of polarity ✓
- Endometrial-type stroma ✓
- Hemosiderin-laden macrophages ✓

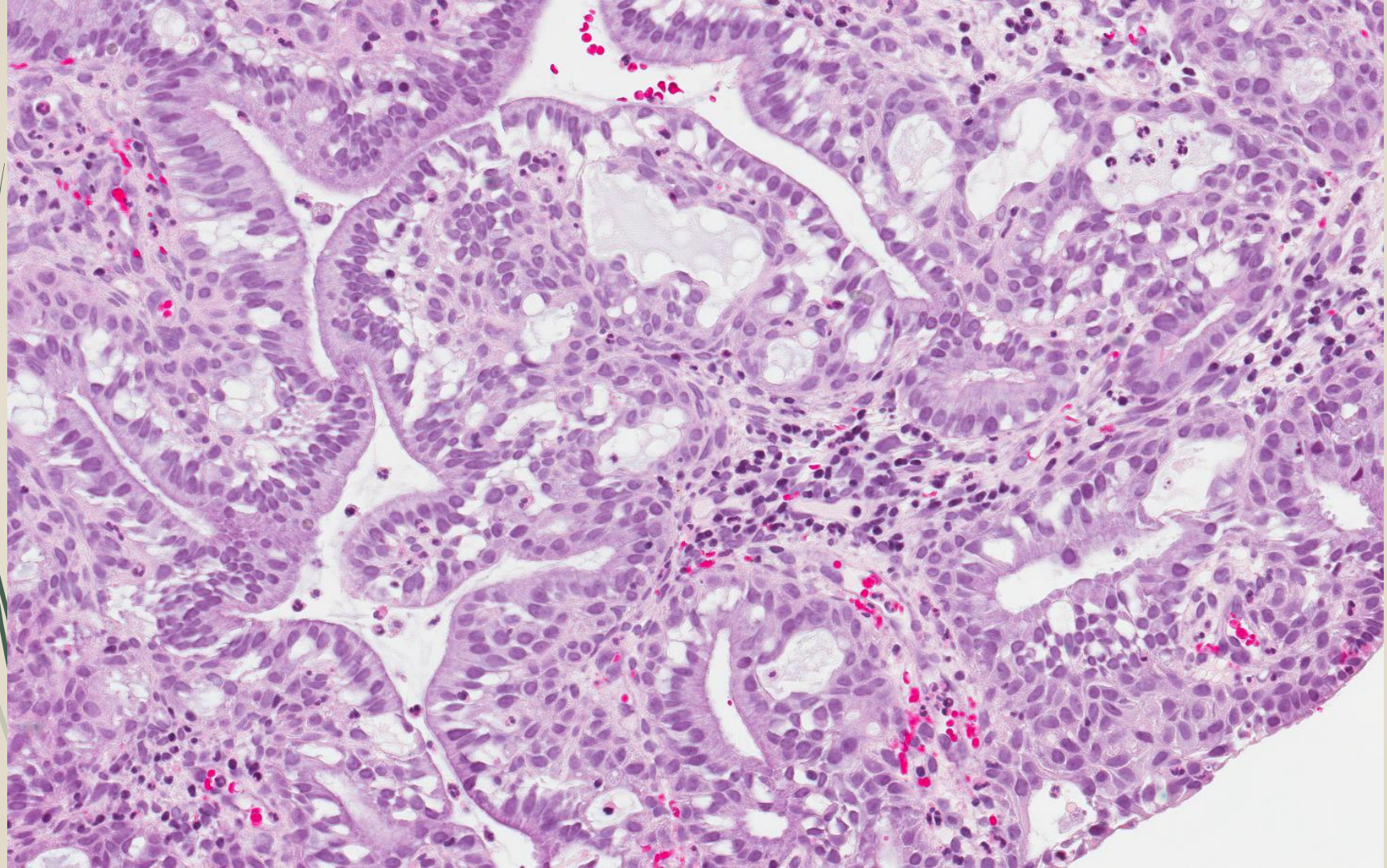
P16 Negative
BCL2 positive
ER positive
VIM positive

DDx: MICROGLANDULAR HYPERPLASIA

- Previously linked to oral contraceptives or pregnancy
- Most patients lack Hx of OCP use
- Reparative / metaplastic process
  - Prominent inflammation
  - Squamous metaplasia

Obstet Gynecol 1976;47:189–195
Int J Gynecol Pathol 1995;14:50–54





DDx: MICROGLANDULAR HYPERPLASIA

- Superficial location
- Crowded and confluent mucinous glands
- Microacinar or cribriform architecture
- Bland cytomorphology
- Vacuolated cytoplasm
- Prominent reserve cell layer
- Low mitotic activity (<3/10 HPFs)





P16 Negative
VIM negative
ER positive
PR negative

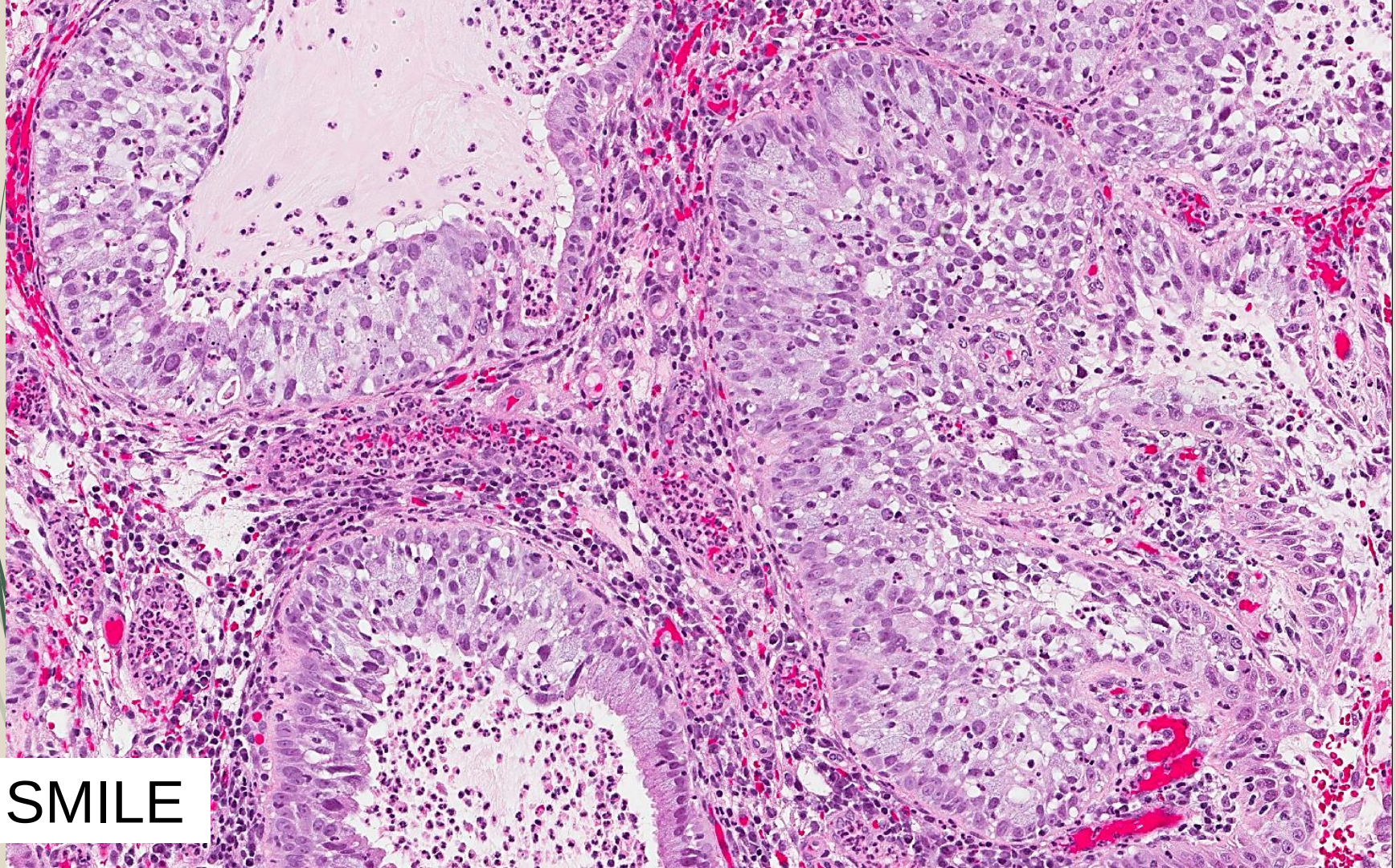
Int J Gynecol Pathol 1997;16:52–59
Int J Gynecol Pathol 2003;22:261–265

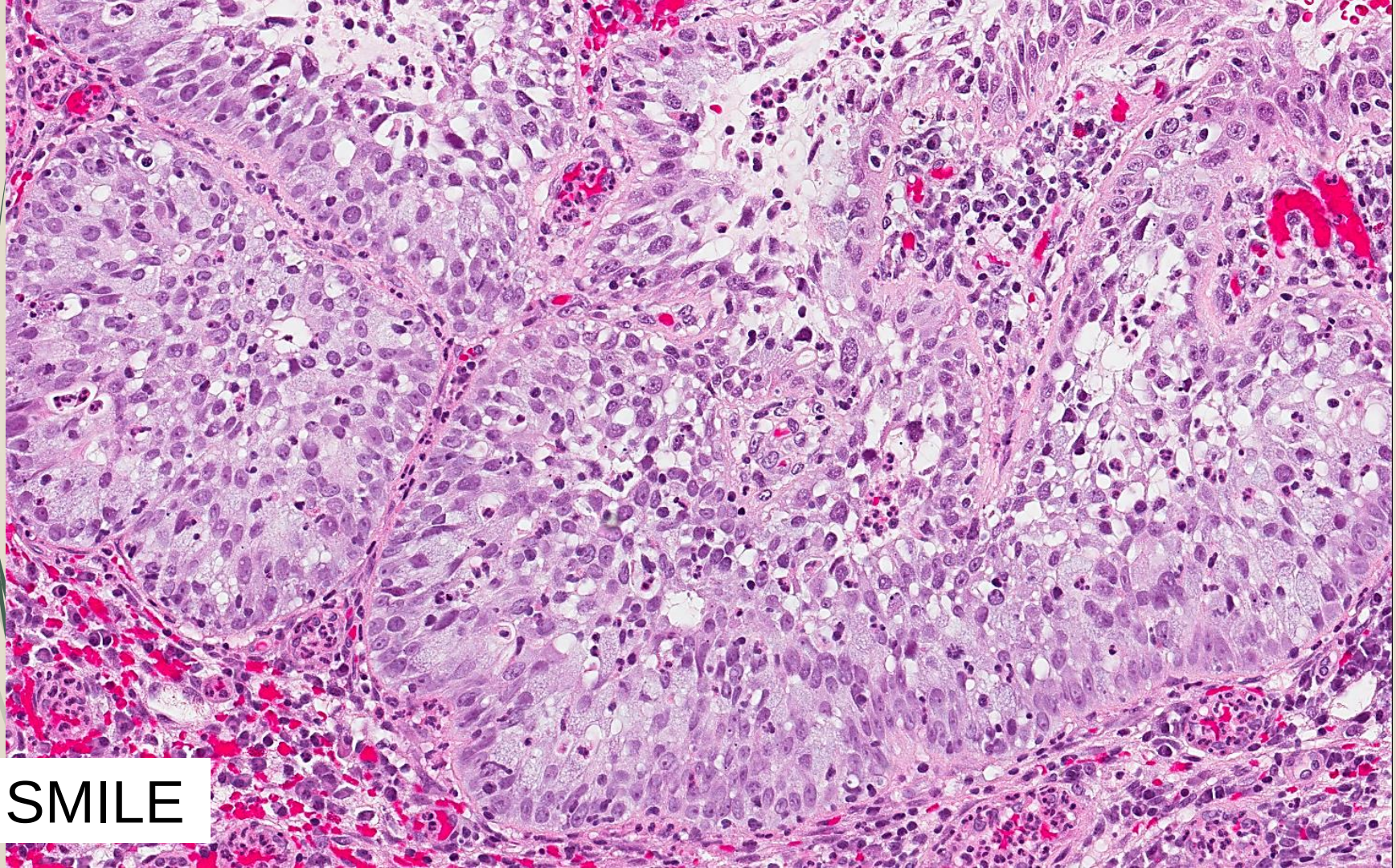
DDx: HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION

- Versus stratified mucin-producing intraepithelial lesion (SMILE)
- Both related to hr-HPV
- Low power appearance of stratified epithelium
- Mucin-containing cells throughout (not just at top)
- Absence of squamous features on high power view

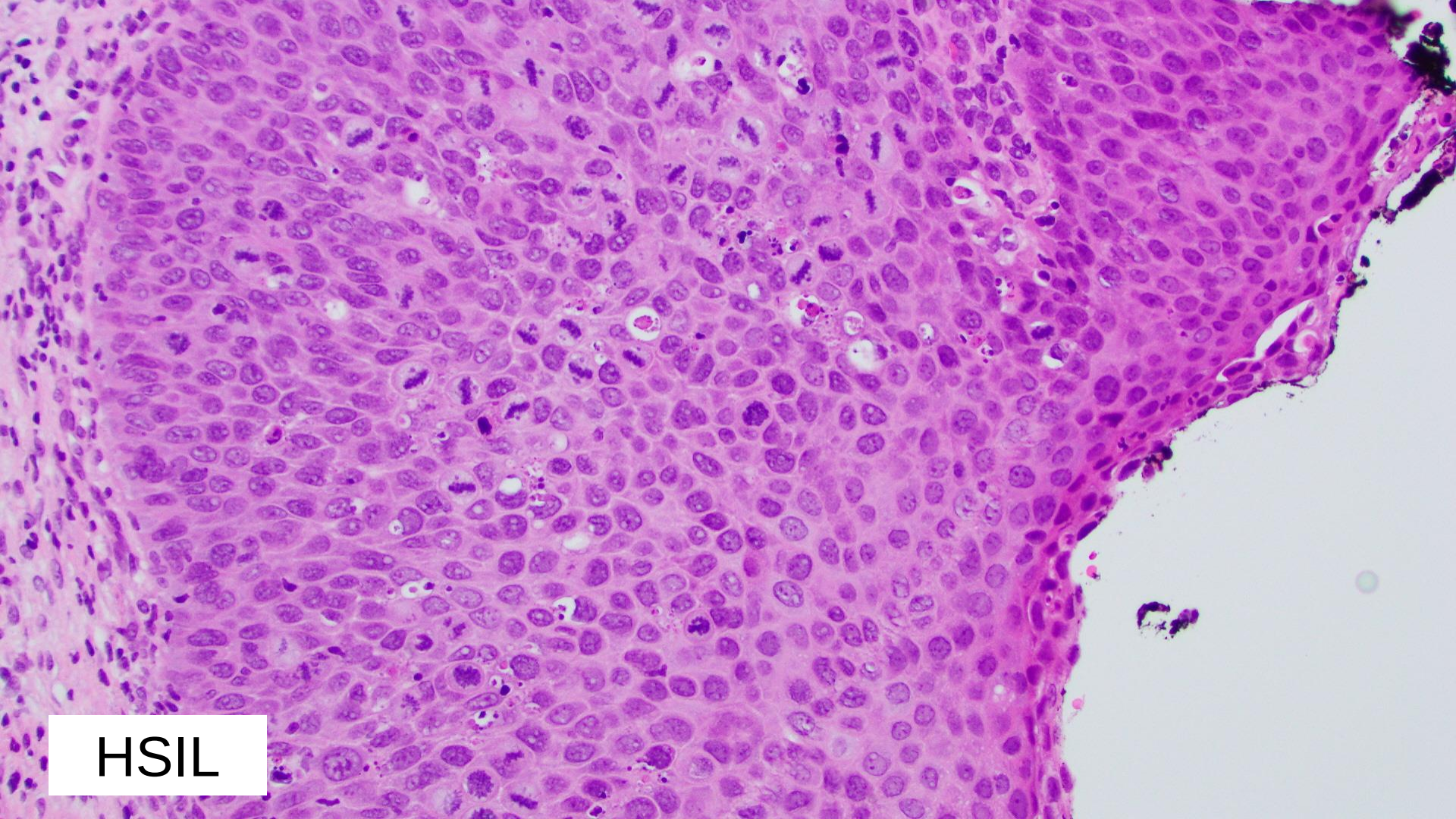


Am J Surg Pathol 2000;24:1414-1419
Hum Pathol 2016;55:174-181


SMILE



SMILE

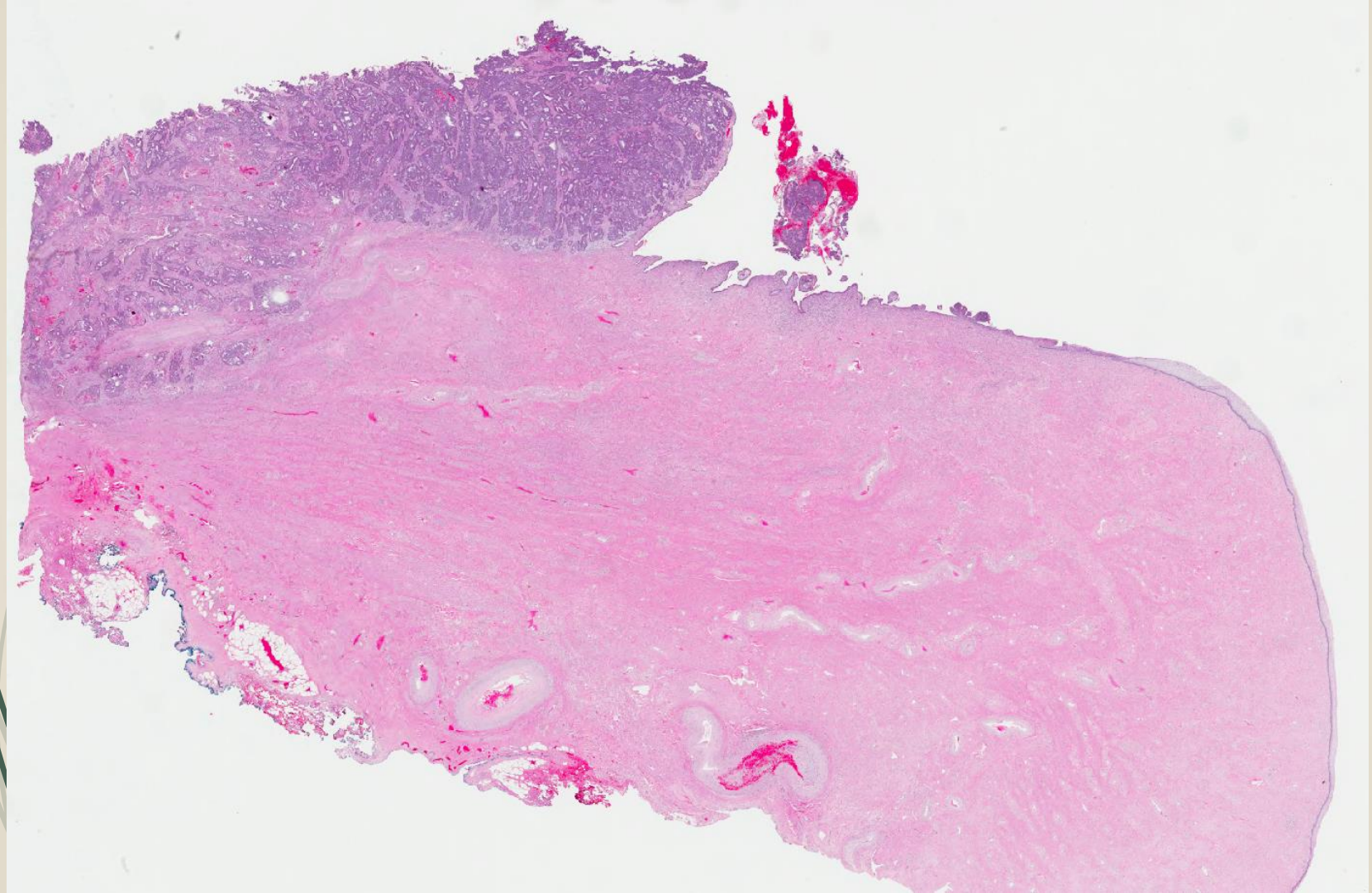

HSIL

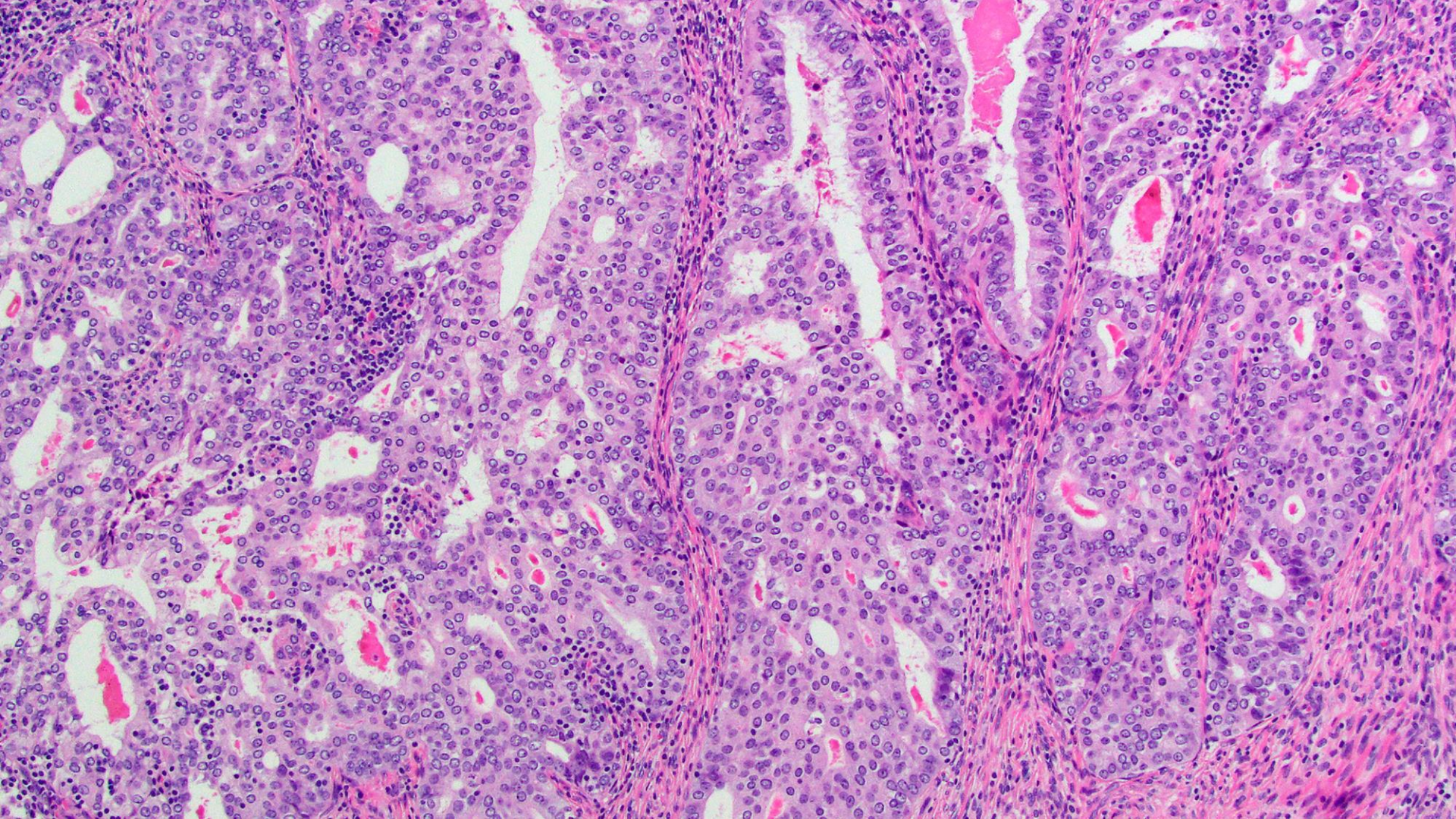
DDx: ENDOMETRIAL CARCINOMA

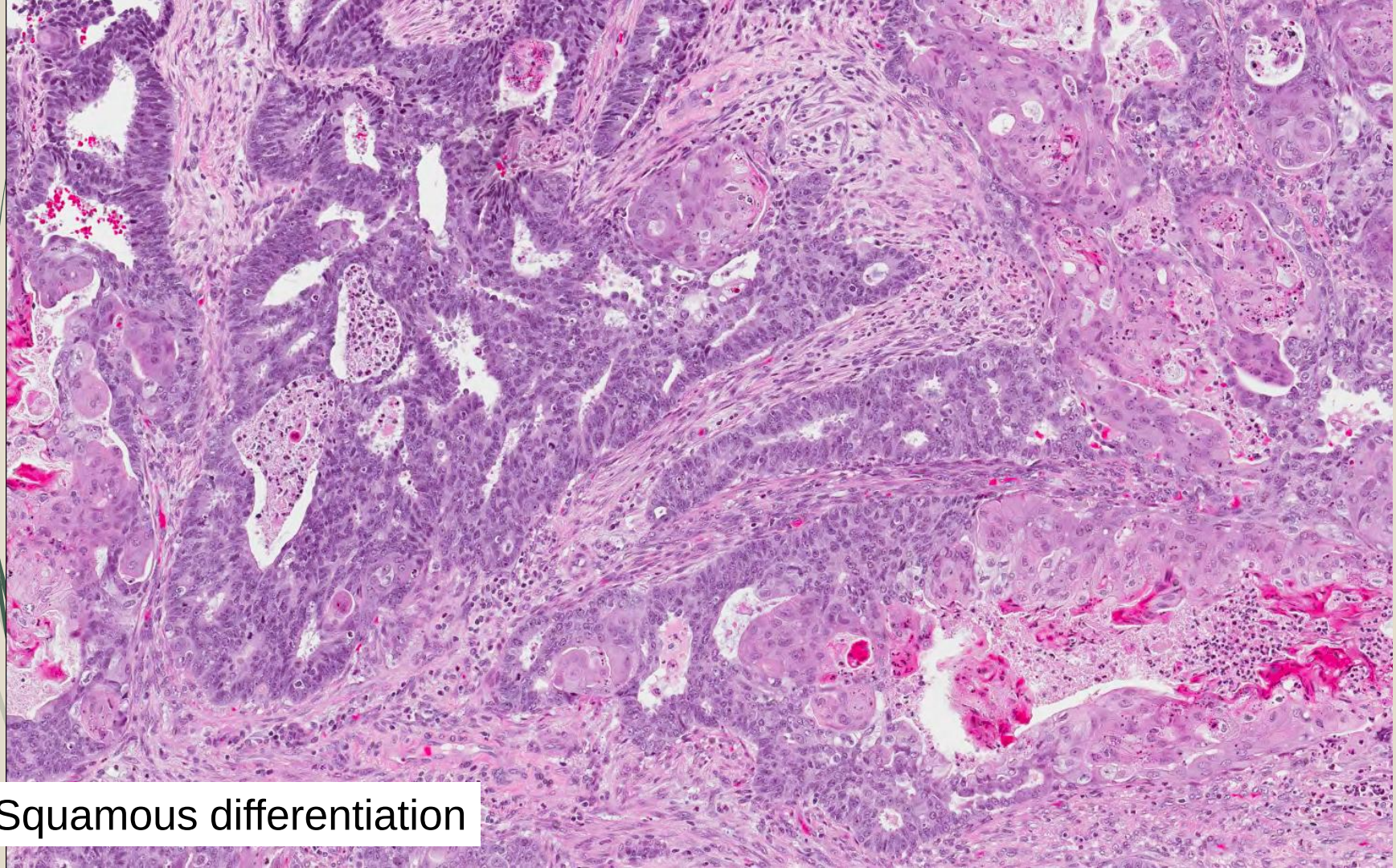
- Commonly involves the cervix
- Endometrioid type most common
  - DDx: HPV-related adenocarcinoma
    Endometrioid adenocarcinoma of the cervix
- Serous, carcinosarcoma, clear cell carcinoma
  - Exceedingly rare or non-existent in the cervix
  - Assume endometrial origin until proven otherwise

DDx: ENDOMETRIAL CARCINOMA

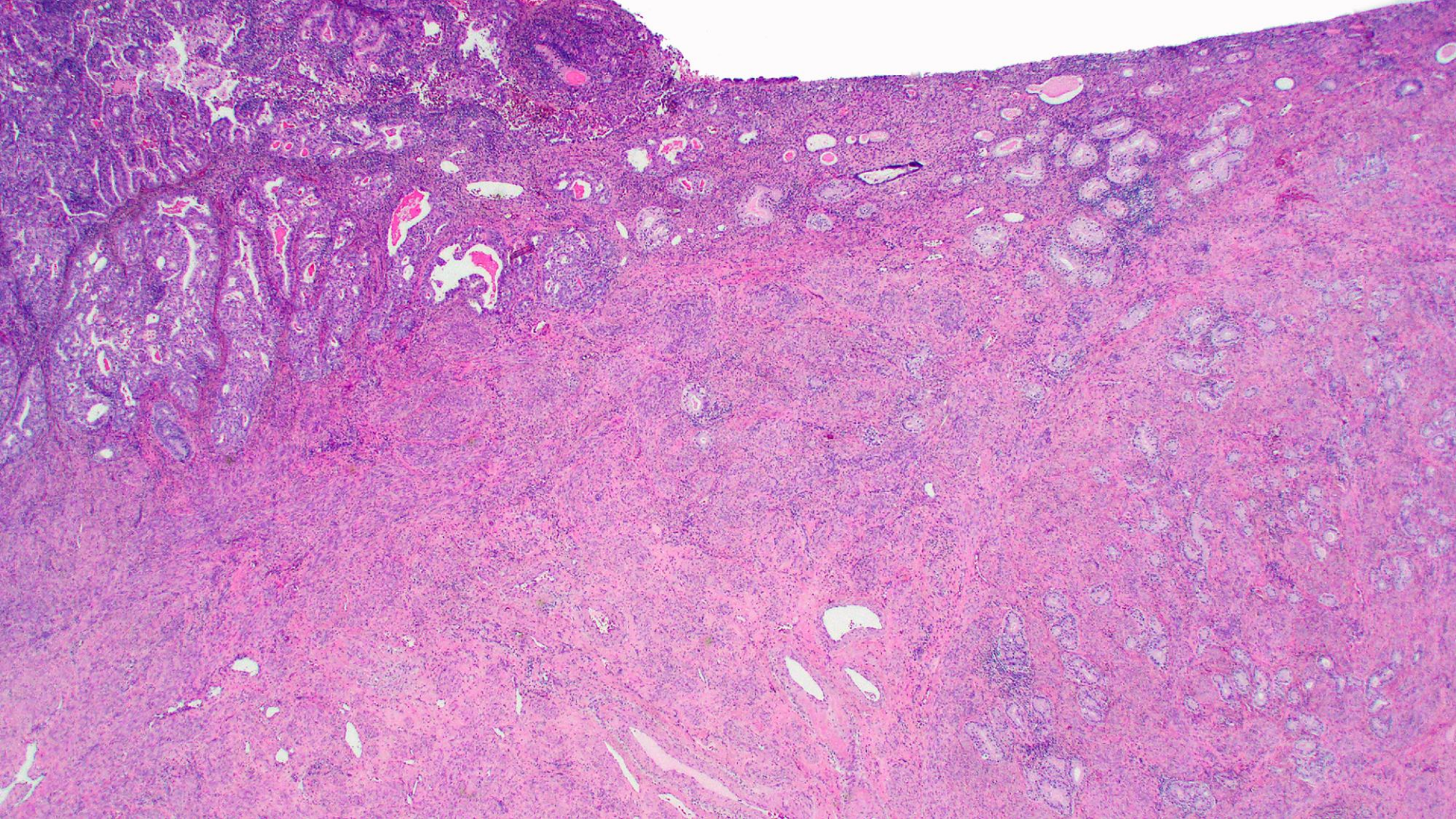
- Endometrioid carcinoma
  - Uniform, round nuclei without pseudostratification
  - Open chromatin
  - Squamous differentiation
    - Morules
    - Bland cytomorphology
  - Secretory differentiation
  - Foamy histiocytes in intervening stroma

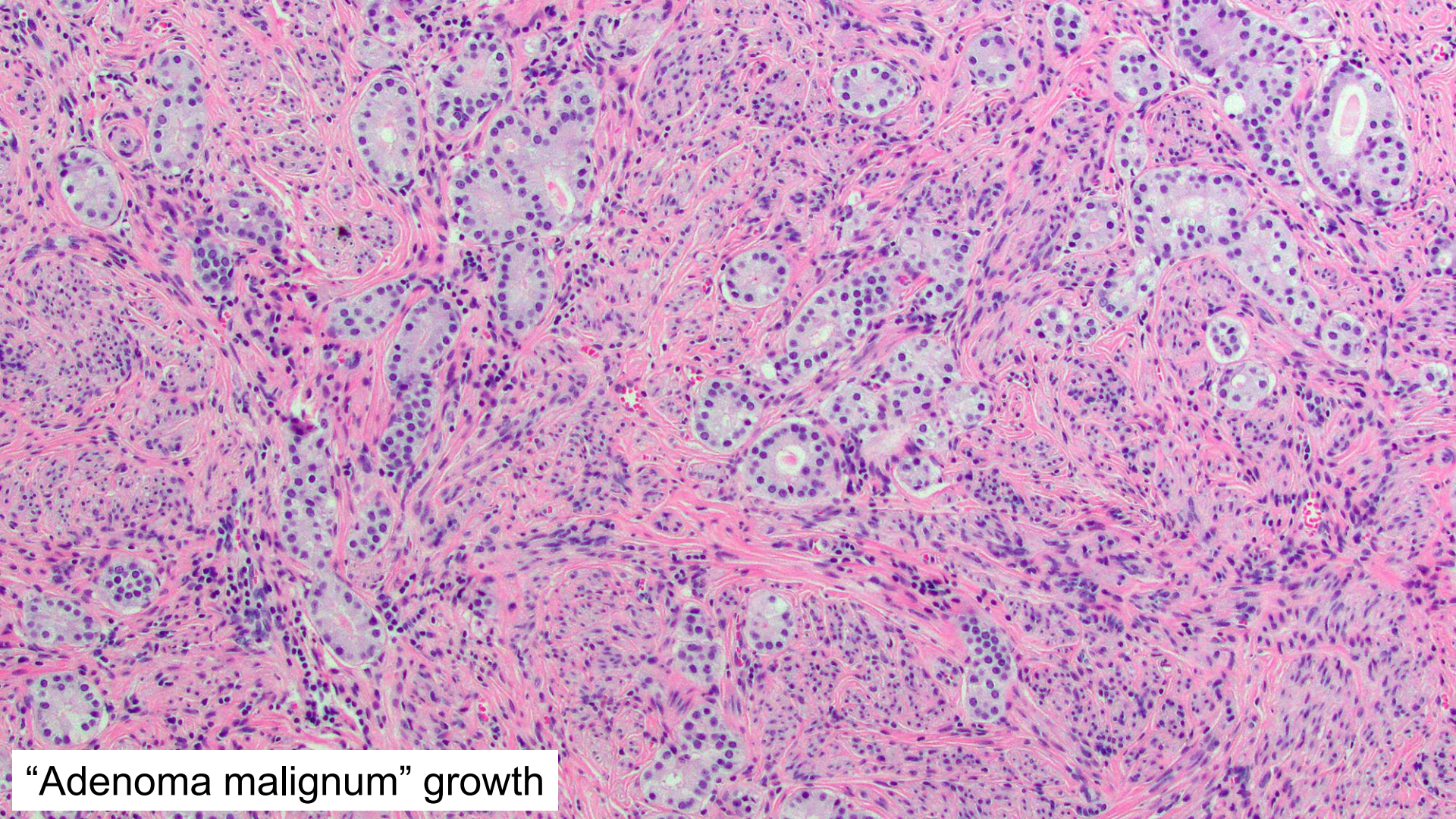


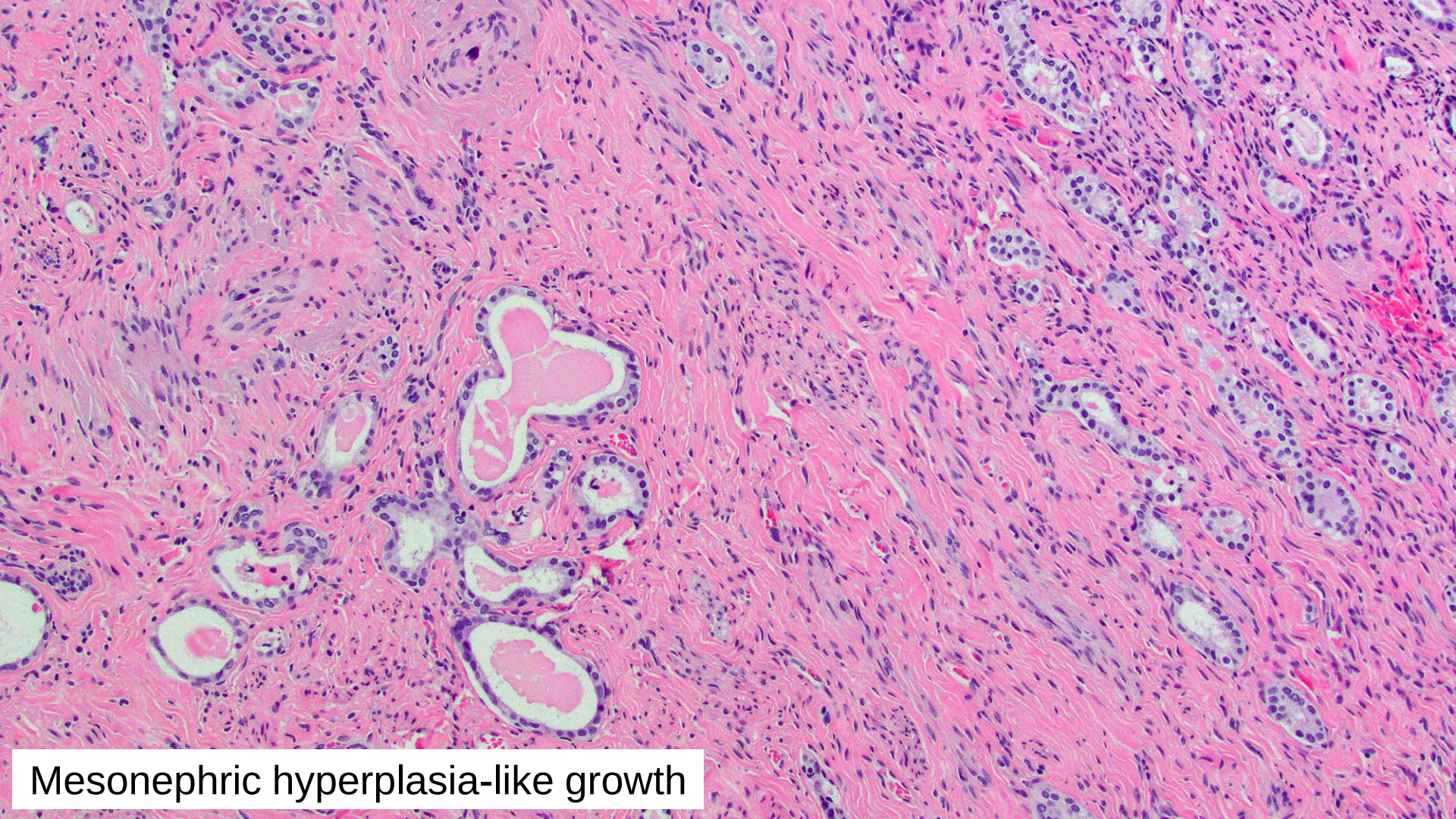




Squamous differentiation




“Adenoma malignum” growth


Mesonephric hyperplasia-like growth

DDx: ENDOMETRIAL CARCINOMA

- Immunohistochemistry of **low-grade endometrioid CA**
  - ER / PR Positive
  - P16 Negative
  - Vimentin Positive (can be patchy)
  - mCEA Negative
  - MMR Intact or lost
- Only seen in ~30% of endometrial endometrioid CAs

Int J Gynecol Pathol 2002;21:4–10
Am J Surg Pathol 2002;26:998–1006
Int J Gynecol Pathol 2009;28:489–496

DDx: ENDOMETRIAL CARCINOMA

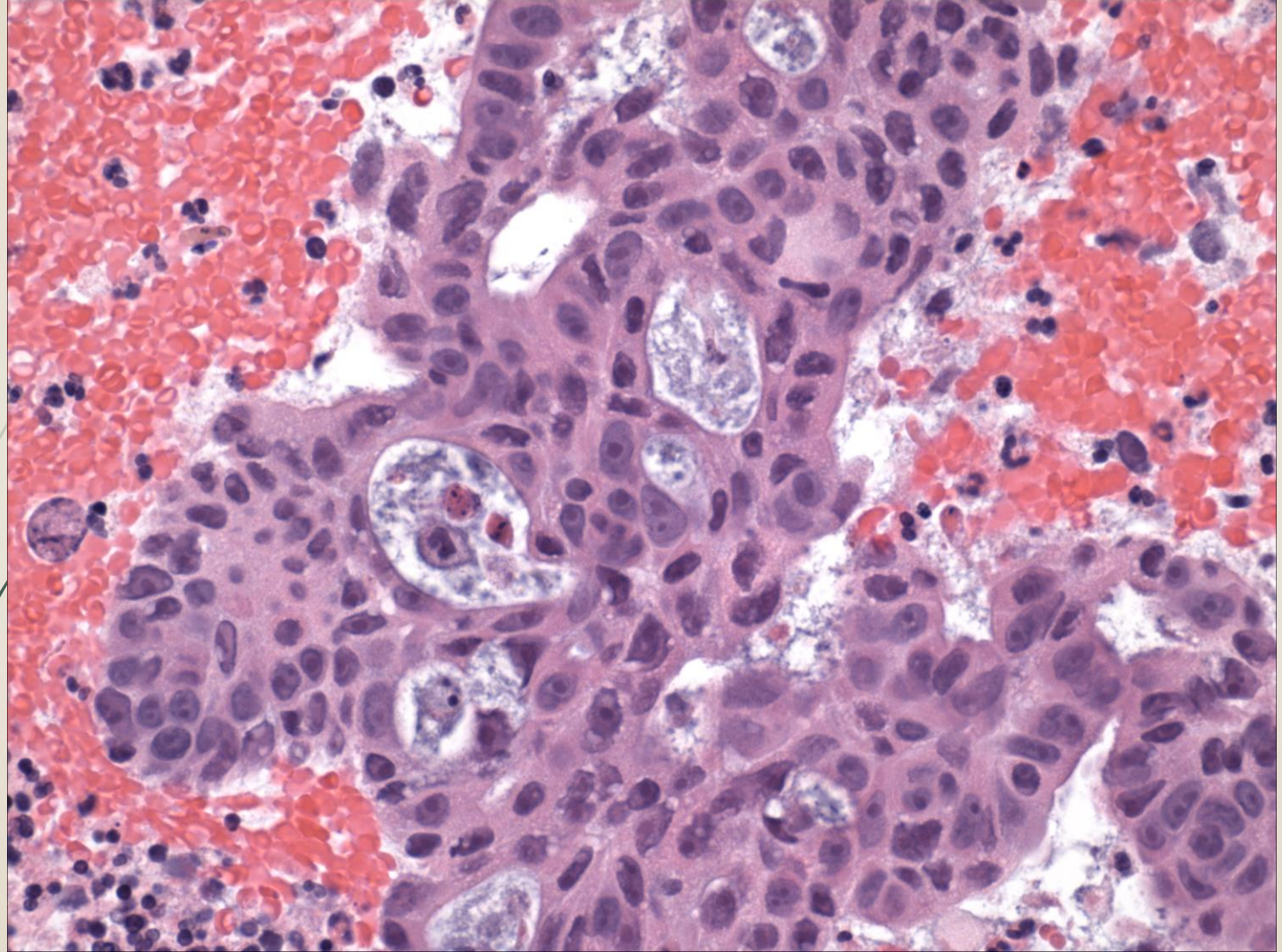
- High-grade endometrial carcinomas are often:
  - ER / PR negative
  - P16 overexpressed
- Correlate with clinical history
- Precursor lesion? AIS or EIN
- Hr-HPV studies

Int J Gynecol Pathol 2002;21:4–10
Am J Surg Pathol 2002;26:998–1006
Int J Gynecol Pathol 2009;28:489–496

DDx: METASTATIC CARCINOMA

- Colorectal carcinoma involving the cervix
  - Post-menopausal women
  - Abnormal uterine bleeding
  - Known history of CRC in most cases
  - Aggressive clinical course (median survival 11 months)

J Obstet Gynaecol Res 2012;38:541–549
Jpn J Clin Oncol 1999;29:640–642
J Gastrointest Cancer 2013;44:231–233



DDx: METASTATIC CARCINOMA

- Colorectal carcinoma involving the cervix
  - Mucinous or mucin depleted glandular proliferation
  - Signet-ring cell morphology in some 
  - Luminal necrosis 
  - Wide cervical wall infiltration, extensive LVI 
  - CK20, CDX2, SATB2 diffusely positive 

J Obstet Gynaecol Res 2012;38:541–549
Jpn J Clin Oncol 1999;29:640–642
J Gastrointest Cancer 2013;44:231–233

DDx: METASTATIC CARCINOMA

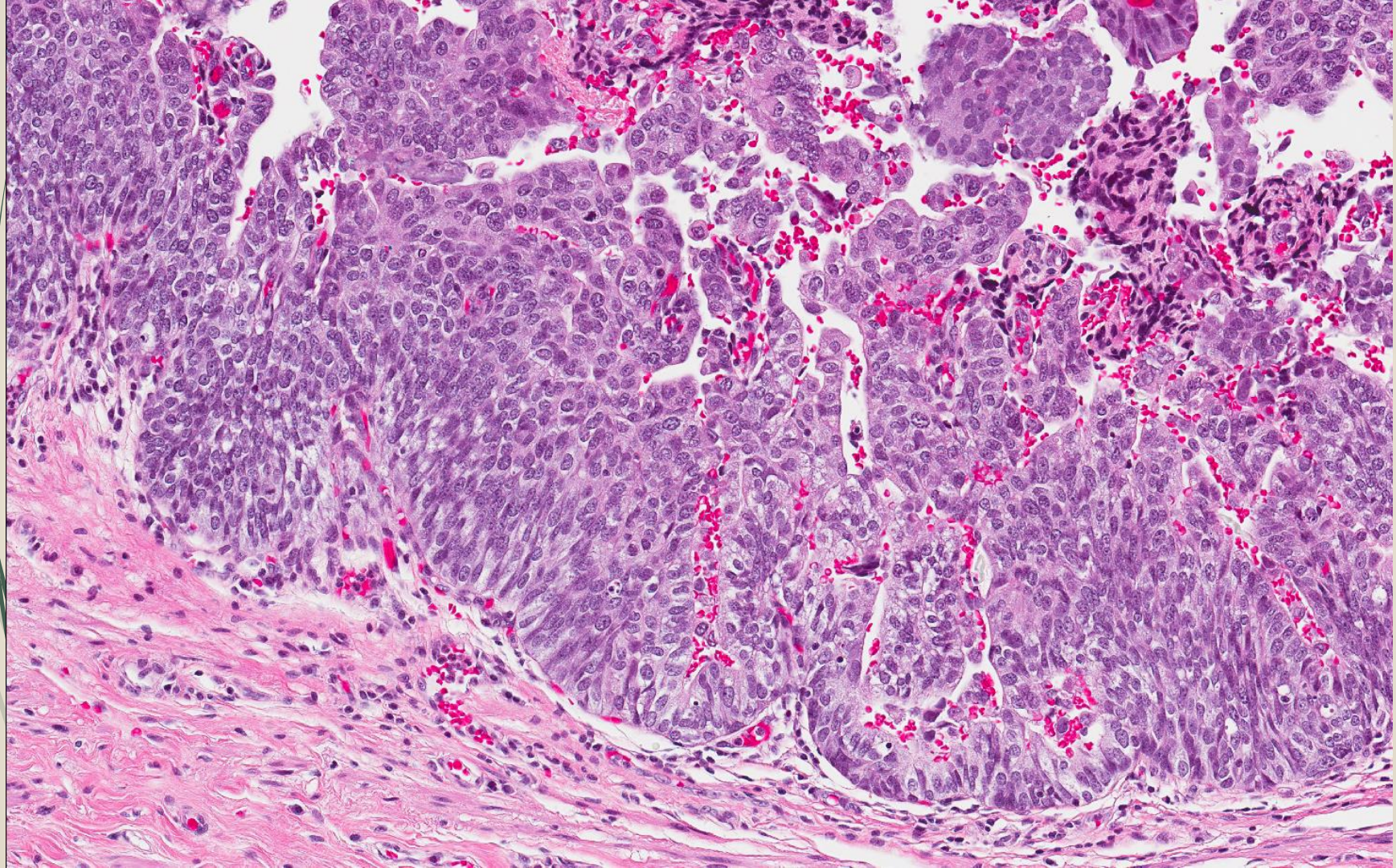
- Urothelial carcinoma with spread to cervix
  - More common in vagina
  - Primary usually in bladder (it can be non-invasive)
  - Simulate an in-situ lesion
  - Architecture: Papillary of flat
  - Cytomorphology: Urothelial carcinoma (low grade or high grade)

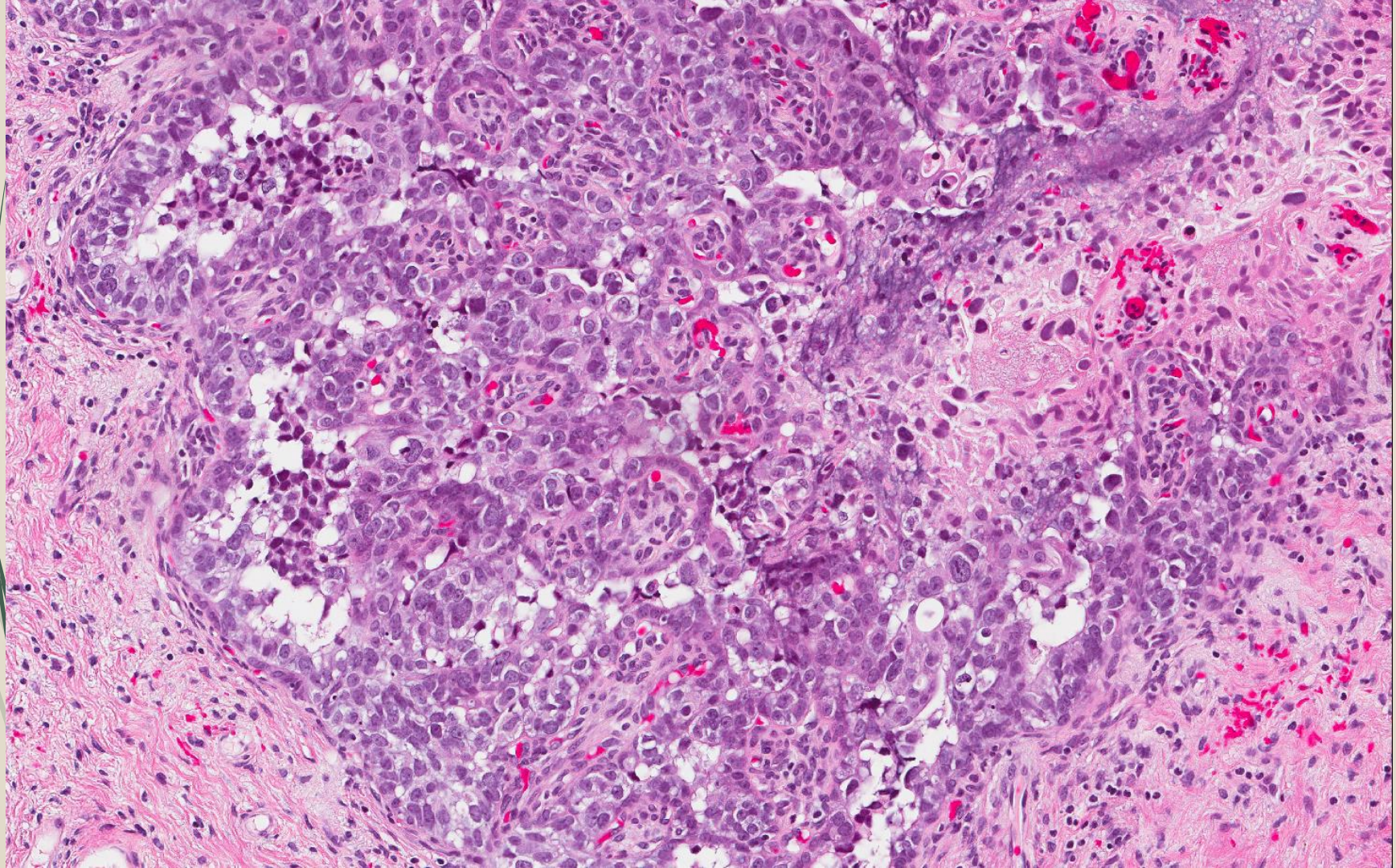
    Squamous or glandular differentiation
  - Known history

PAGETOID SPREAD



Am J Surg Pathol 2012;36:1058-1065
Ann Diagn Pathol 2011:15:422-426





DDx: METASTATIC CARCINOMA

- Urothelial carcinoma with spread to cervix
  - P16 can be overexpressed in high grade urothelial CAs
  - HPV negative
  - GATA3 is strong and diffuse
  - GATA3 has lower expression in carcinomas with squamous (20%) and glandular (50%) differentiation
  - S100 is positive in these variants

Cancer Cytopathol 2014;122:760-769
Hum Pathol 2014;45:1473-1482
Appl Immunohistochem Mol Morphol 2016;24:509-513

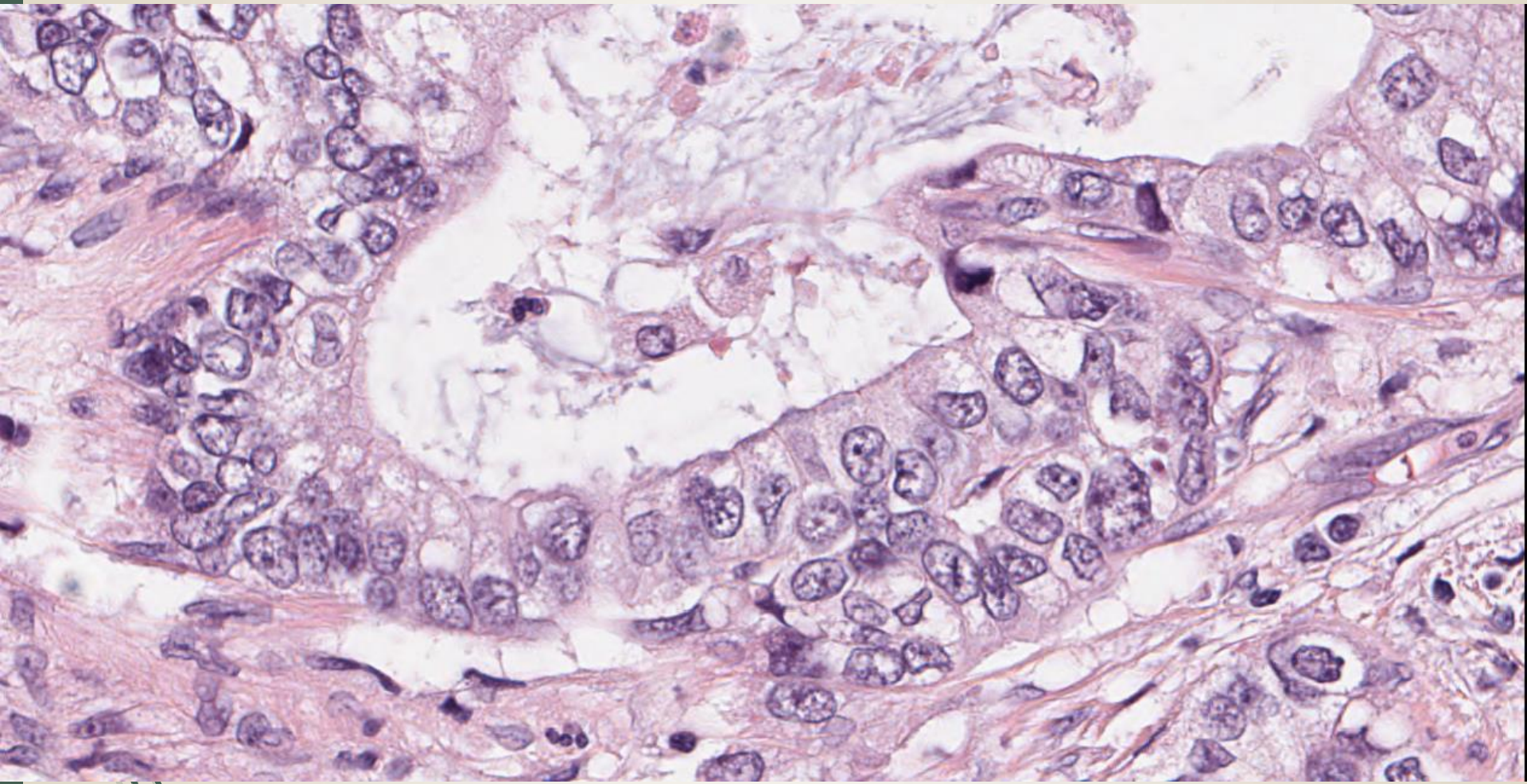
HPV-independent endocervical adenocarcinoma

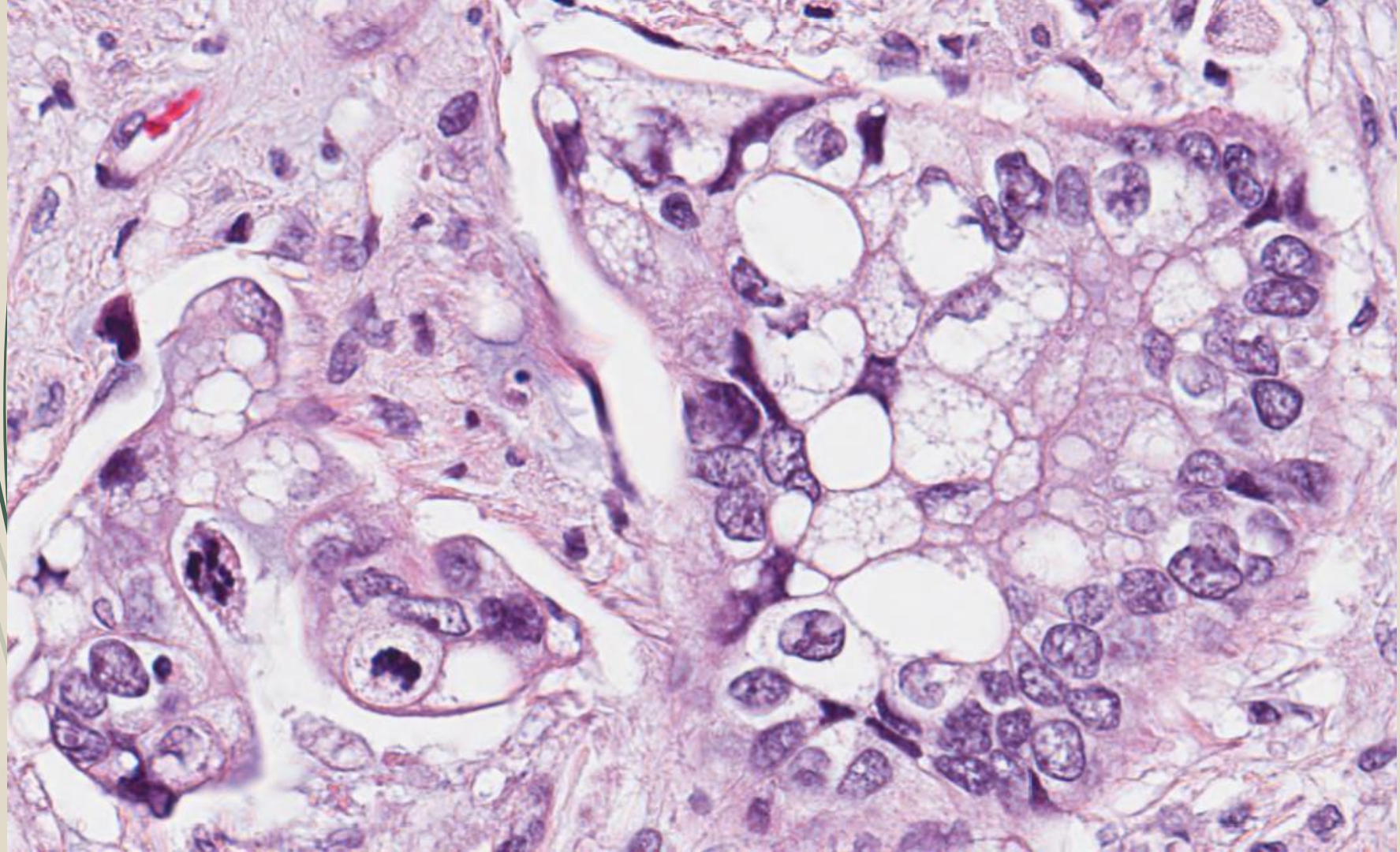
- Gastric type adenocarcinoma
- Clear cell carcinoma
- Mesonephric carcinoma
- Endometrioid carcinoma

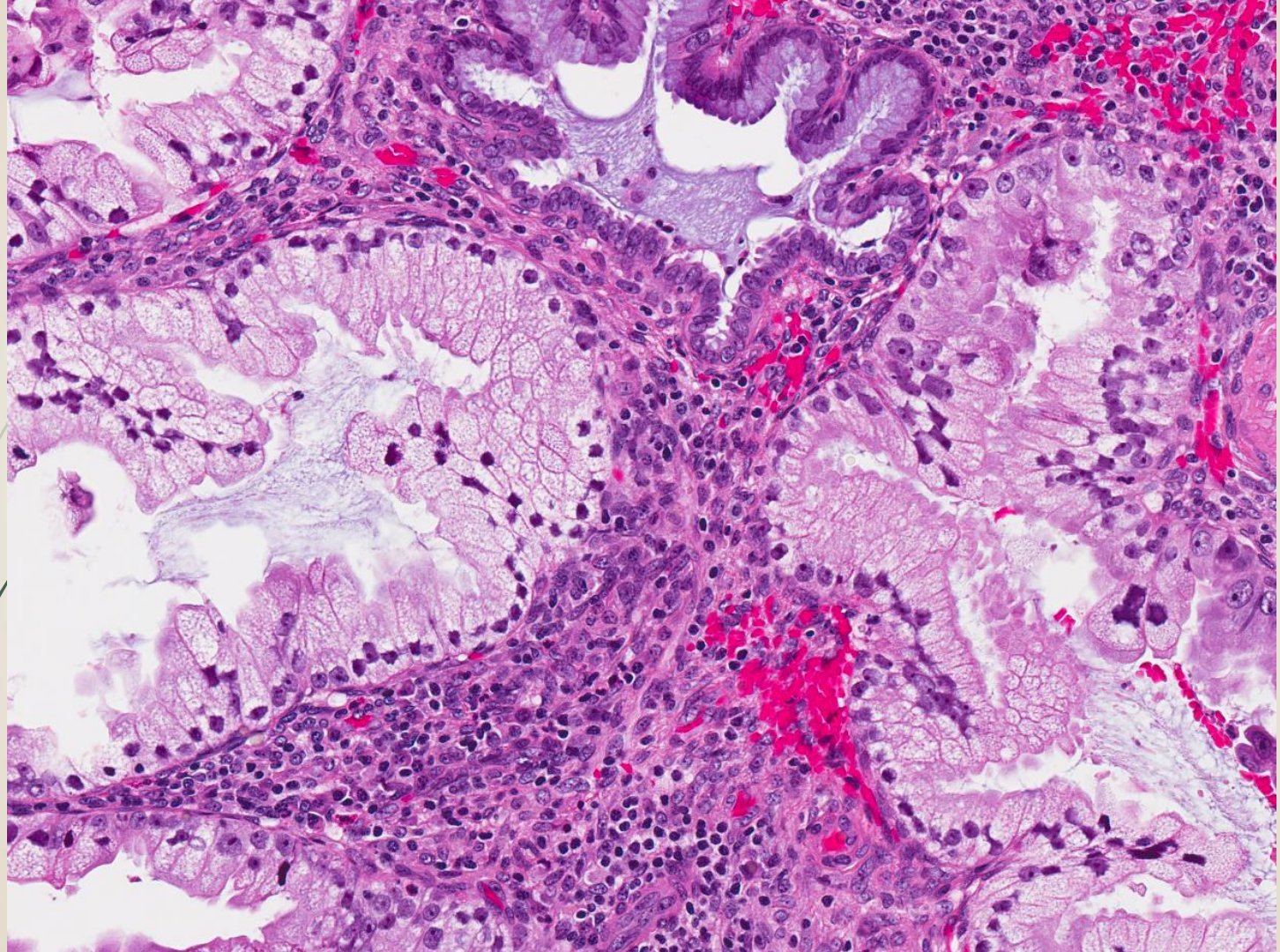
GASTRIC TYPE ADENOCARCINOMA

- Cells with clear and/or pale eosinophilic cytoplasm
- Foamy / frothy appearance
- Distinct cell borders
- HIK1083 and MUC6 expression: Gastric (pyloric) differentiation

Am J Surg Pathol 2007;31:664-72
Methods Mol Biol 2015;1249:213-9







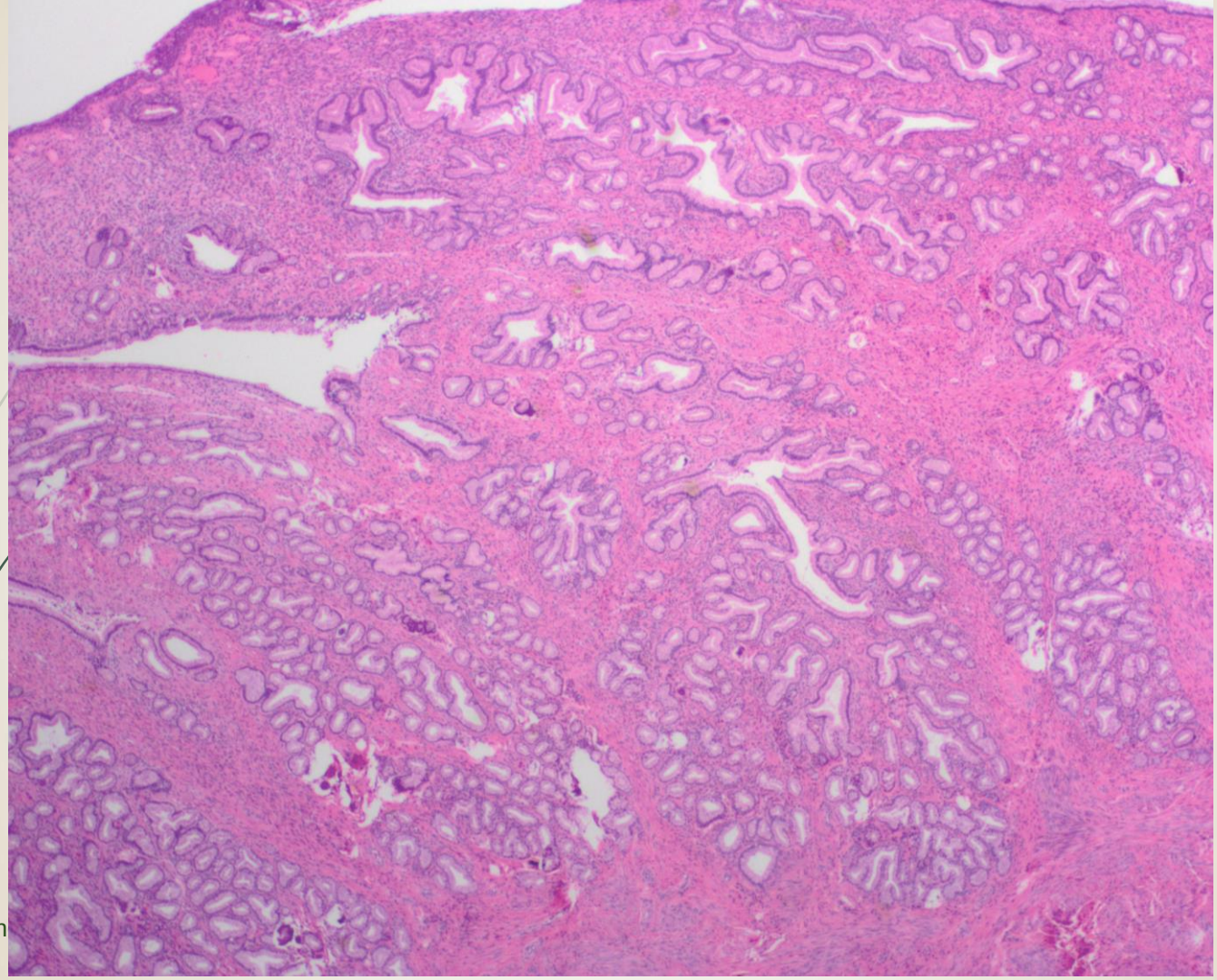
DIFFERENTIAL DIAGNOSIS

- Lobular endocervical glandular hyperplasia
- Tunnel clusters
- Diffuse laminar endocervical hyperplasia
- Deep florid glands
- Metastatic carcinoma from upper gastrointestinal tract

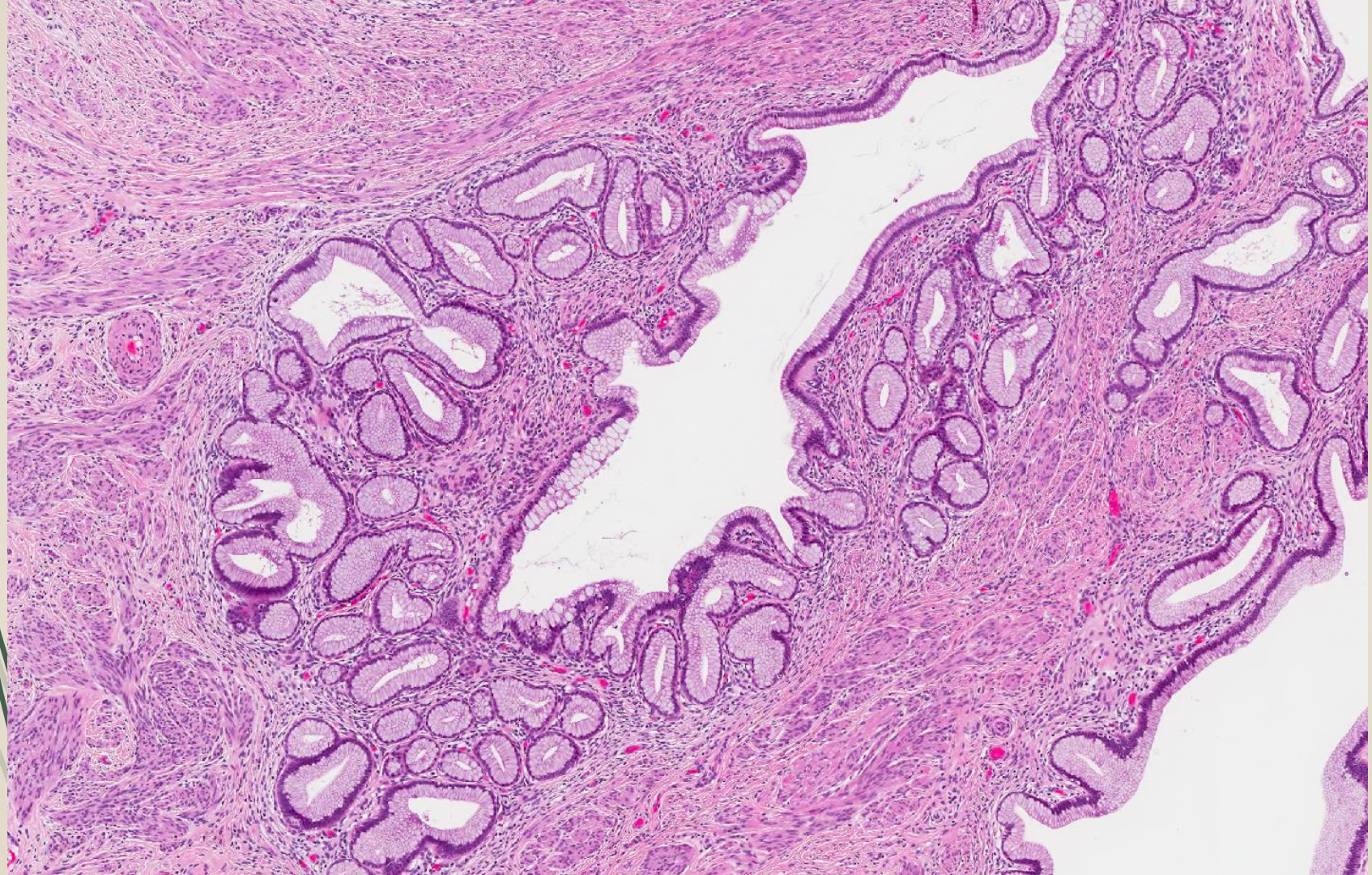
LOBULAR ENDOCERVICAL GLANDULAR HYPERPLASIA (LEGH)

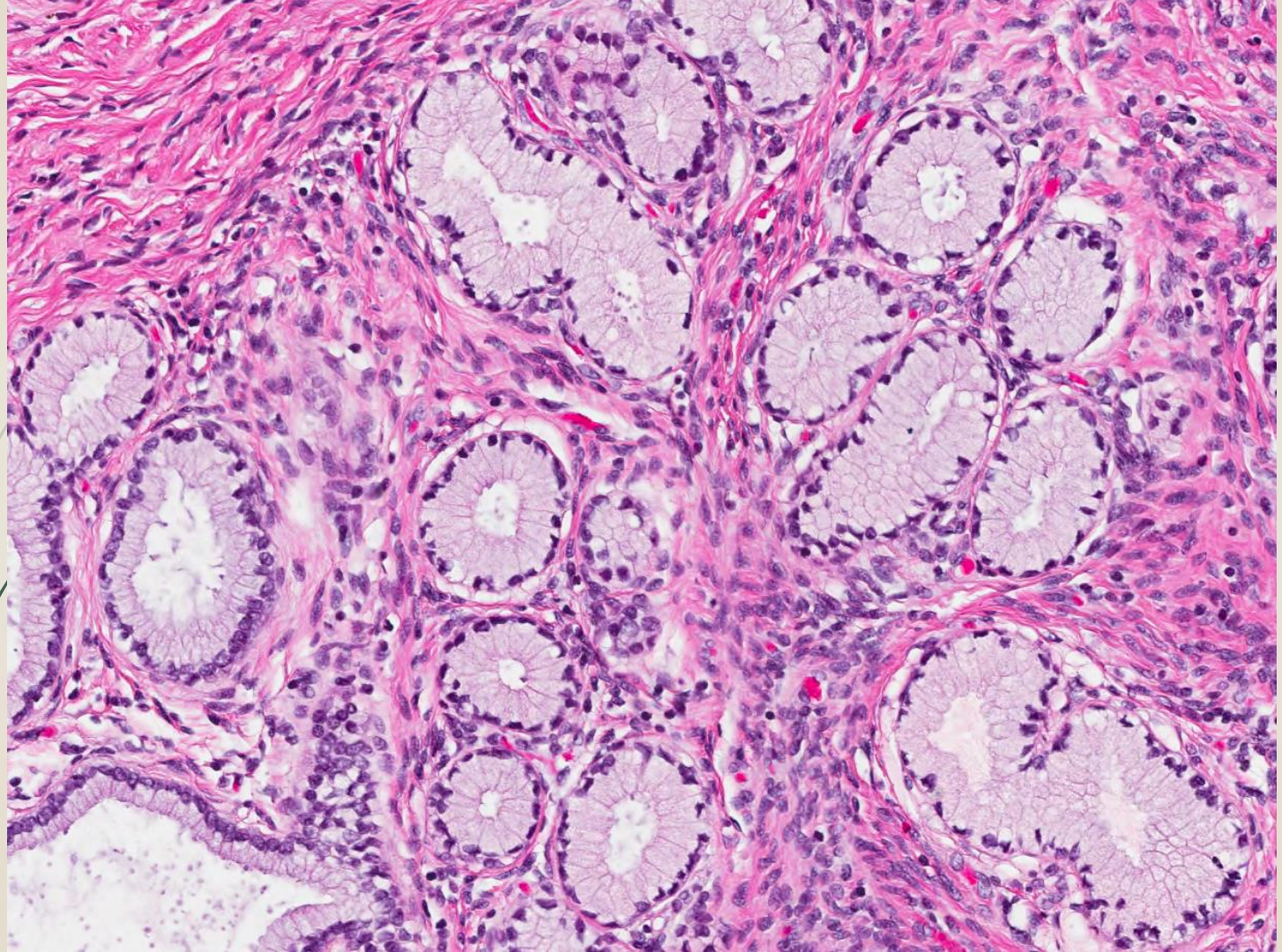
- Complex gastric (pyloric) metaplasia
- Prevalence 0.7% (in Japan)
- 20-25% of gastric-type adenocarcinomas
  - 50% of MDA adenocarcinomas
  - 3.8% of non-MDA adenocarcinomas

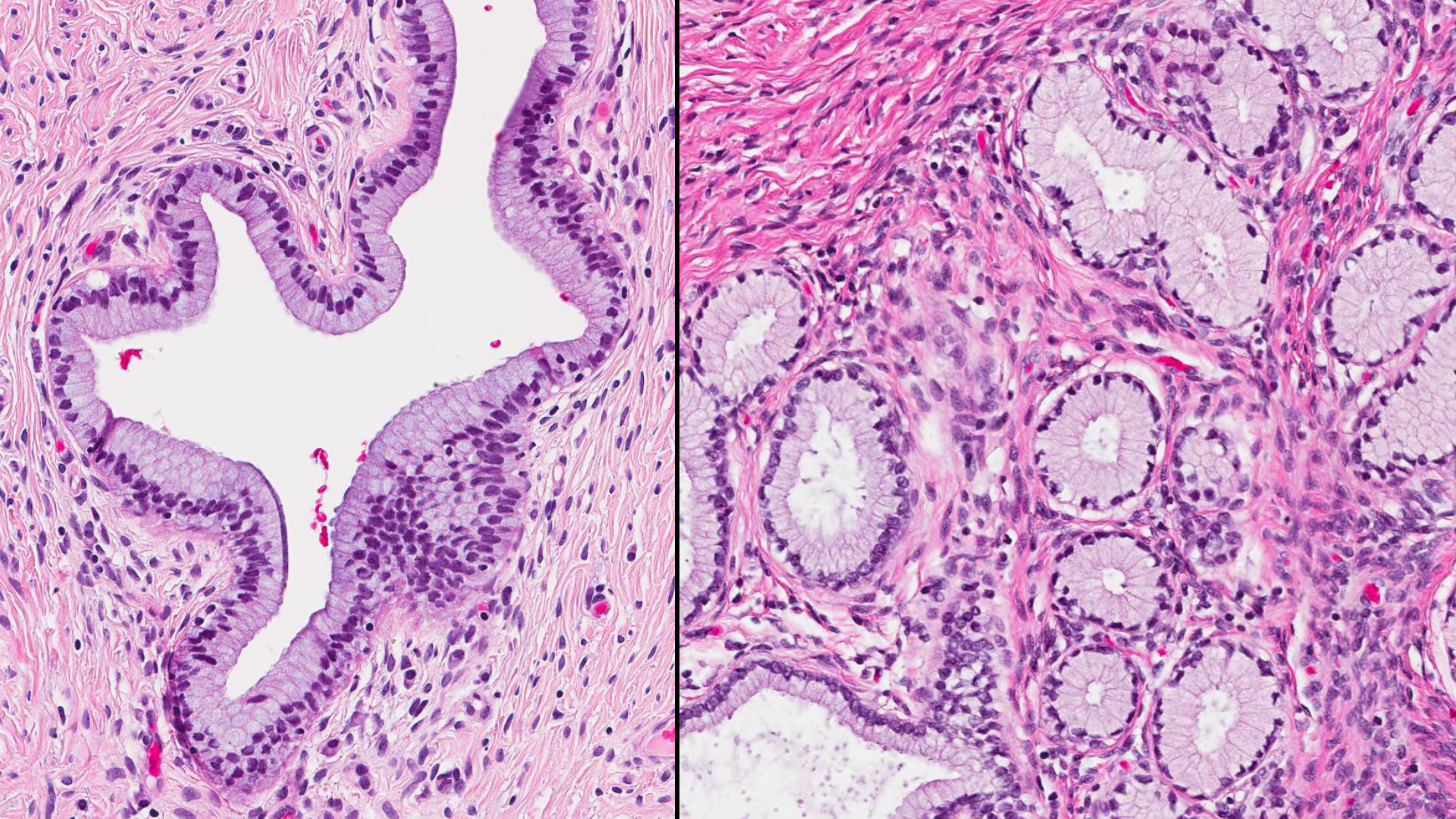
Histopathol 2001;39:364-72
Am J Surg Pathol 2015;39:1449-57



Jun

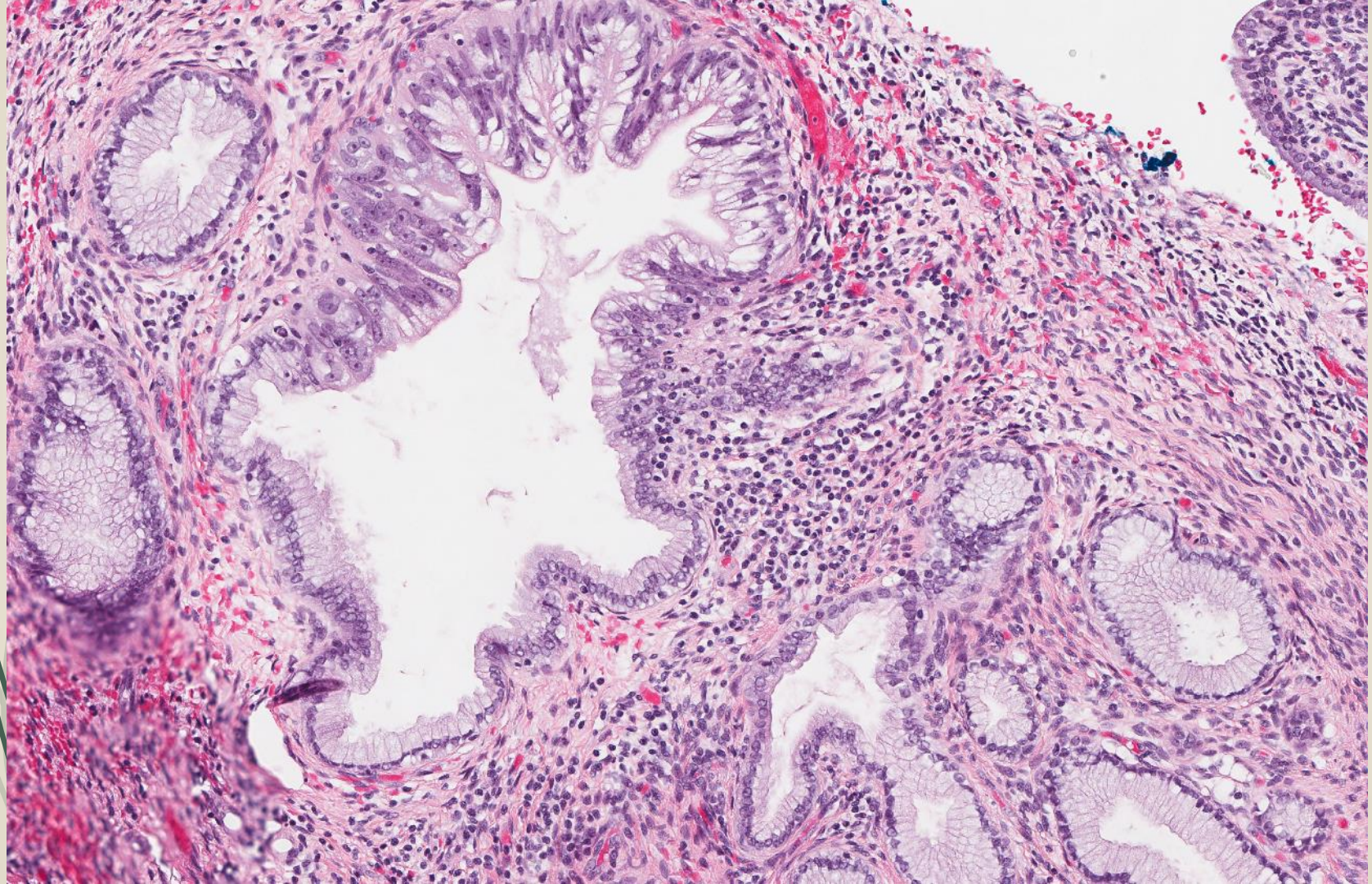


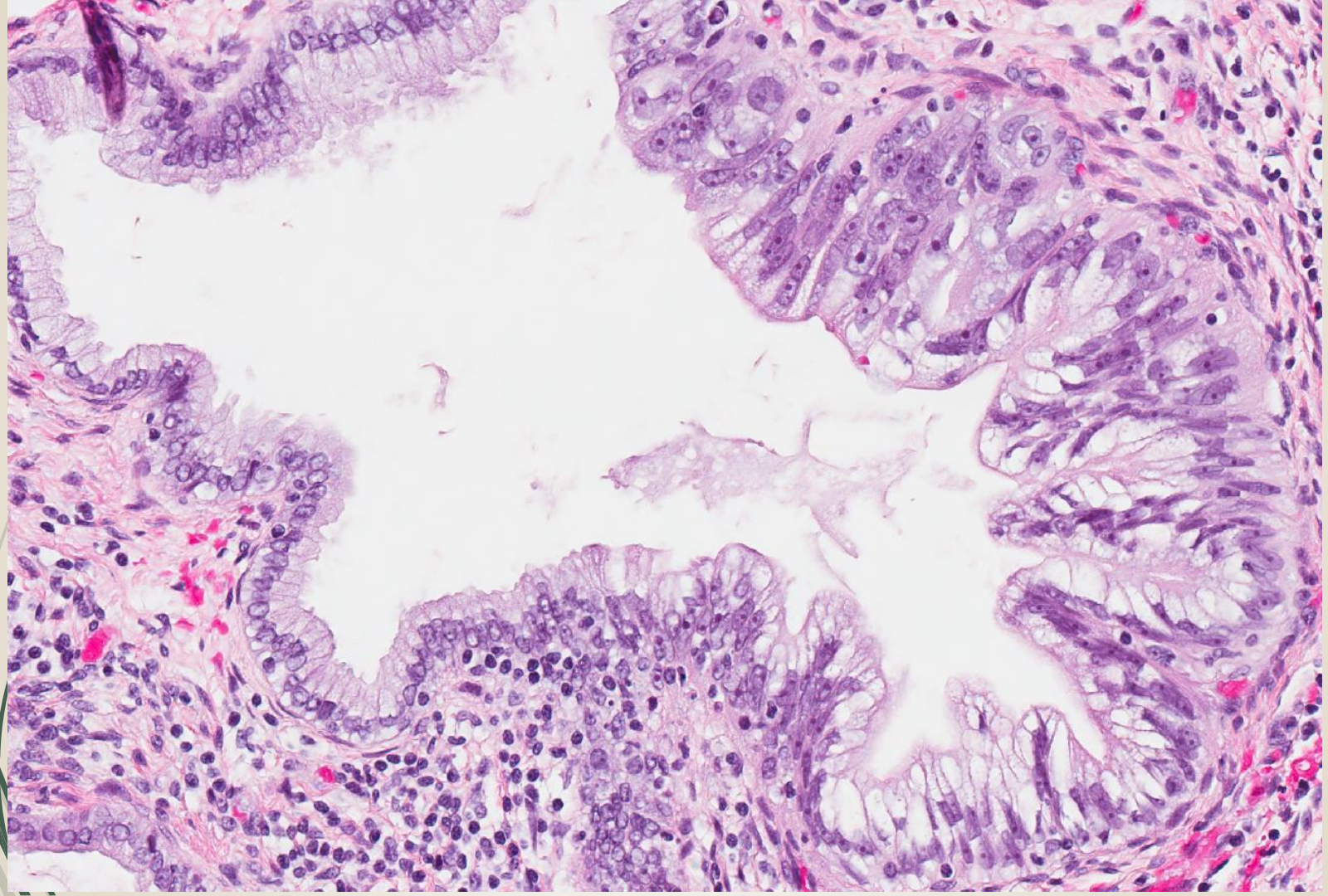


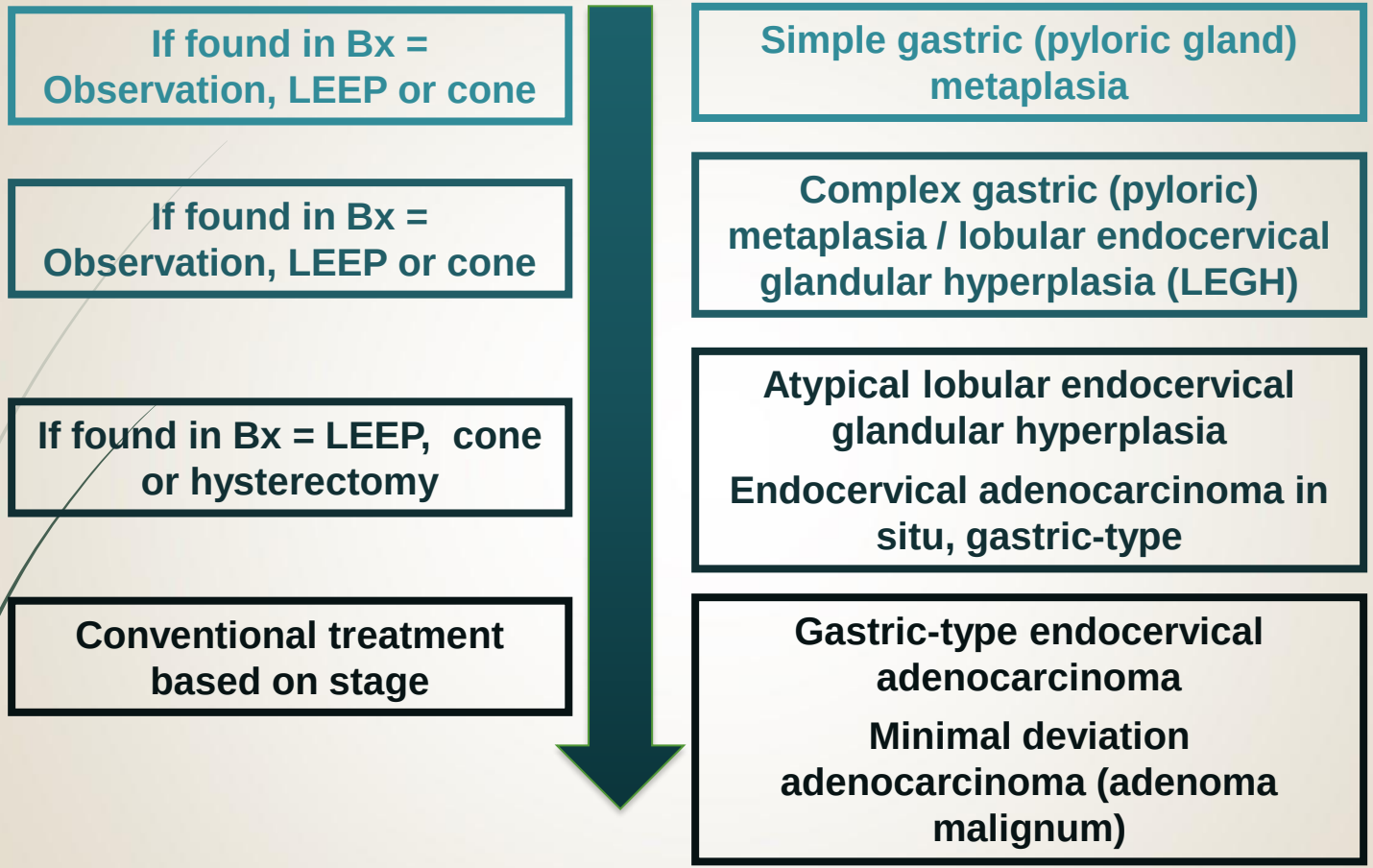


ATYPICAL LEGH

- Lesion architecturally consistent with LEGH, with (*4 or more*):
  - Nuclear enlargement
  - Irregular nuclear contours
  - Distinct nucleoli and coarse chromatin
  - Loss of polarity
  - Mitotic figures (occasional)
  - Apoptotic bodies or luminal nuclear debris
  - Intraluminal papillary projections
- Atypical LEGH identified in 30% of MDAs






If found in Bx = Observation, LEEP or cone
If found in Bx = Observation, LEEP or cone
If found in Bx = LEEP, cone or hysterectomy
Conventional treatment based on stage
Simple gastric (pyloric gland) metaplasia
Complex gastric (pyloric) metaplasia / lobular endocervical glandular hyperplasia (LEGH)
Atypical lobular endocervical glandular hyperplasia
Endocervical adenocarcinoma in situ, gastric-type
Gastric-type endocervical adenocarcinoma
Minimal deviation adenocarcinoma (adenoma malignum)

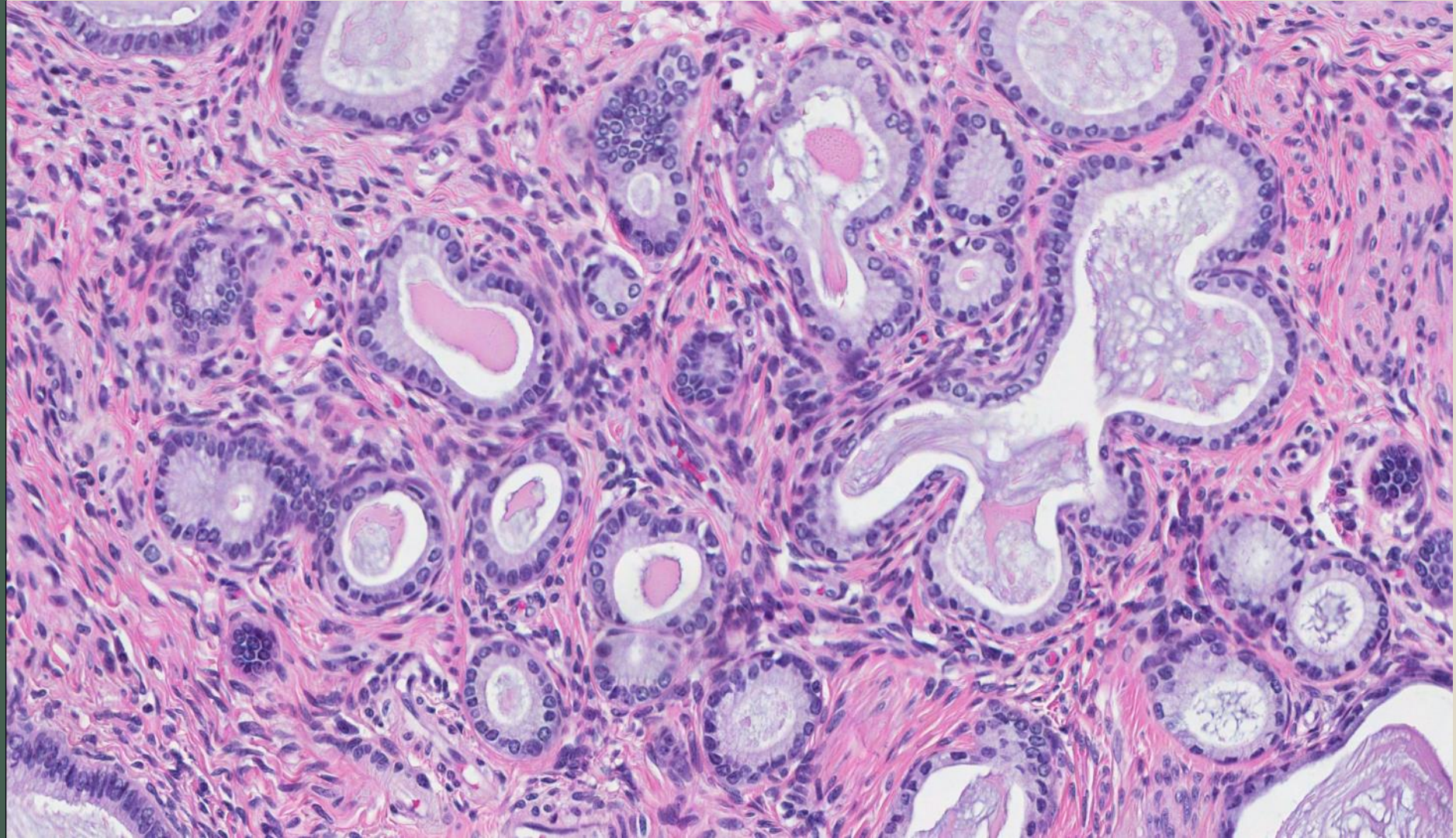
DDx: TUNNEL CLUSTERS

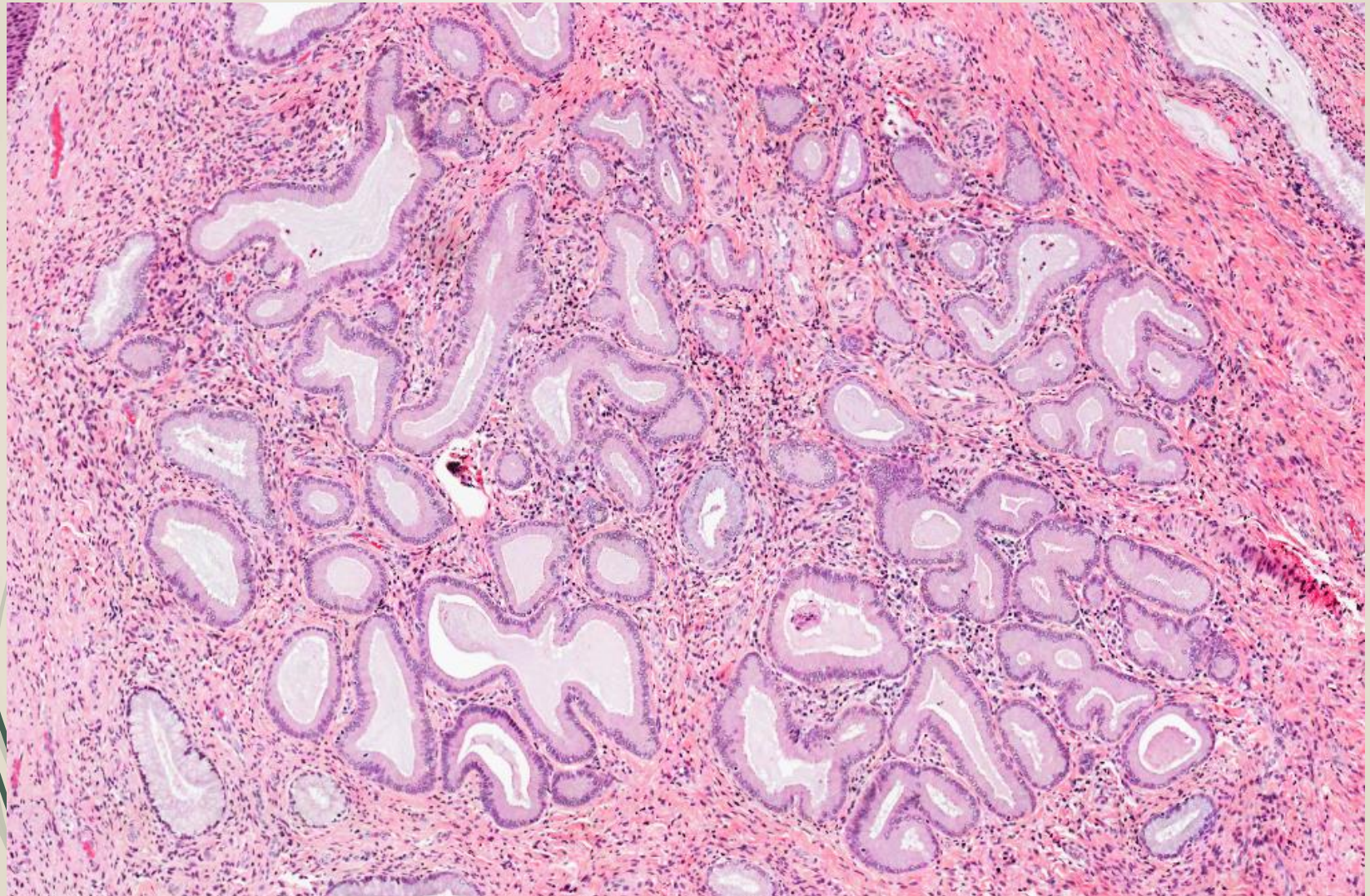
- Well-demarcated, round and densely packed aggregates of glands 
- Typically confined to the inner wall 
- Typically in multiparous women
  - Residual complex infoldings from previous pregnancies
- May cause mucoid discharge
- Most are asymptomatic

DDx: TUNNEL CLUSTERS

- Type-A = non-cystic
  - Small glands arranged around a central cleft
  - Simple, low cuboidal mucinous epithelium
  - Some have a gastric phenotype

Obstet Gynecol 1961;17:206–214
Am J Surg Pathol 1996;20:1312–1318



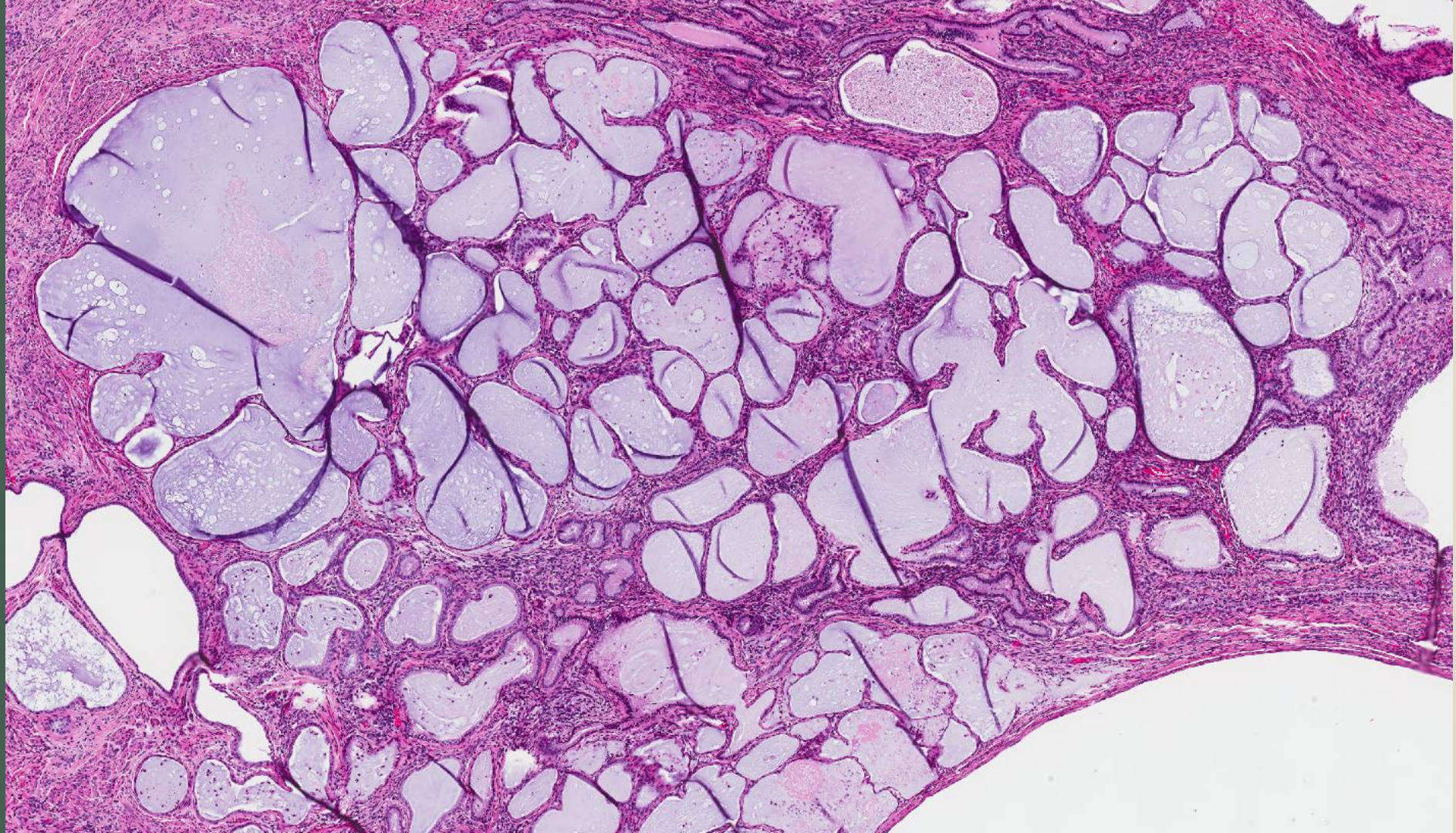


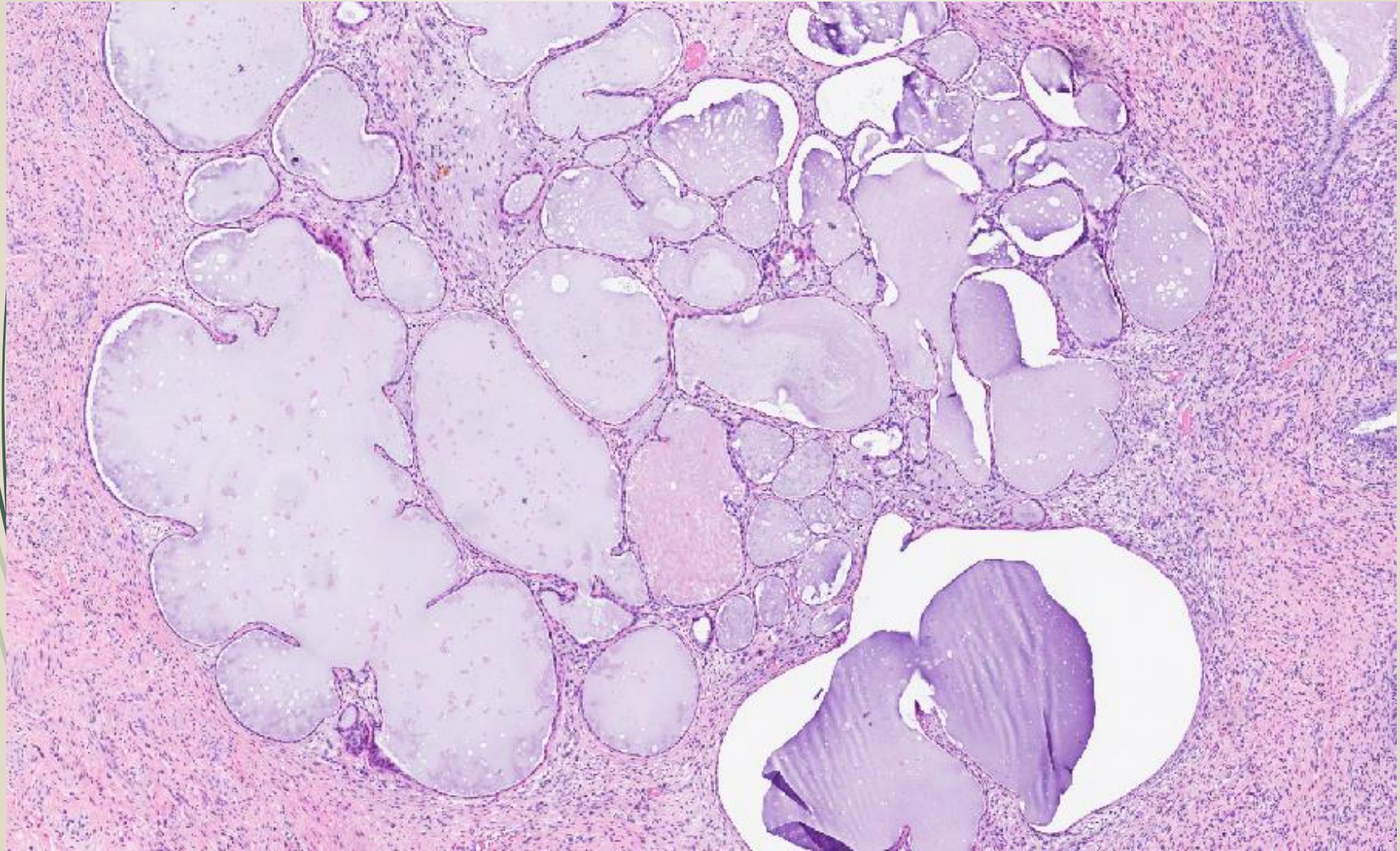
DDx: TUNNEL CLUSTERS

- Type-B = cystic
  - Usually multiple
  - May cause distortion of the mucosal surface
  - Dilated round glandular structures
  - Flattened epithelium
  - Abundant luminal mucin (acid type)

ER / PR positive

Obstet Gynecol 1961;17:206–214
Am J Surg Pathol 1990;14:895–903



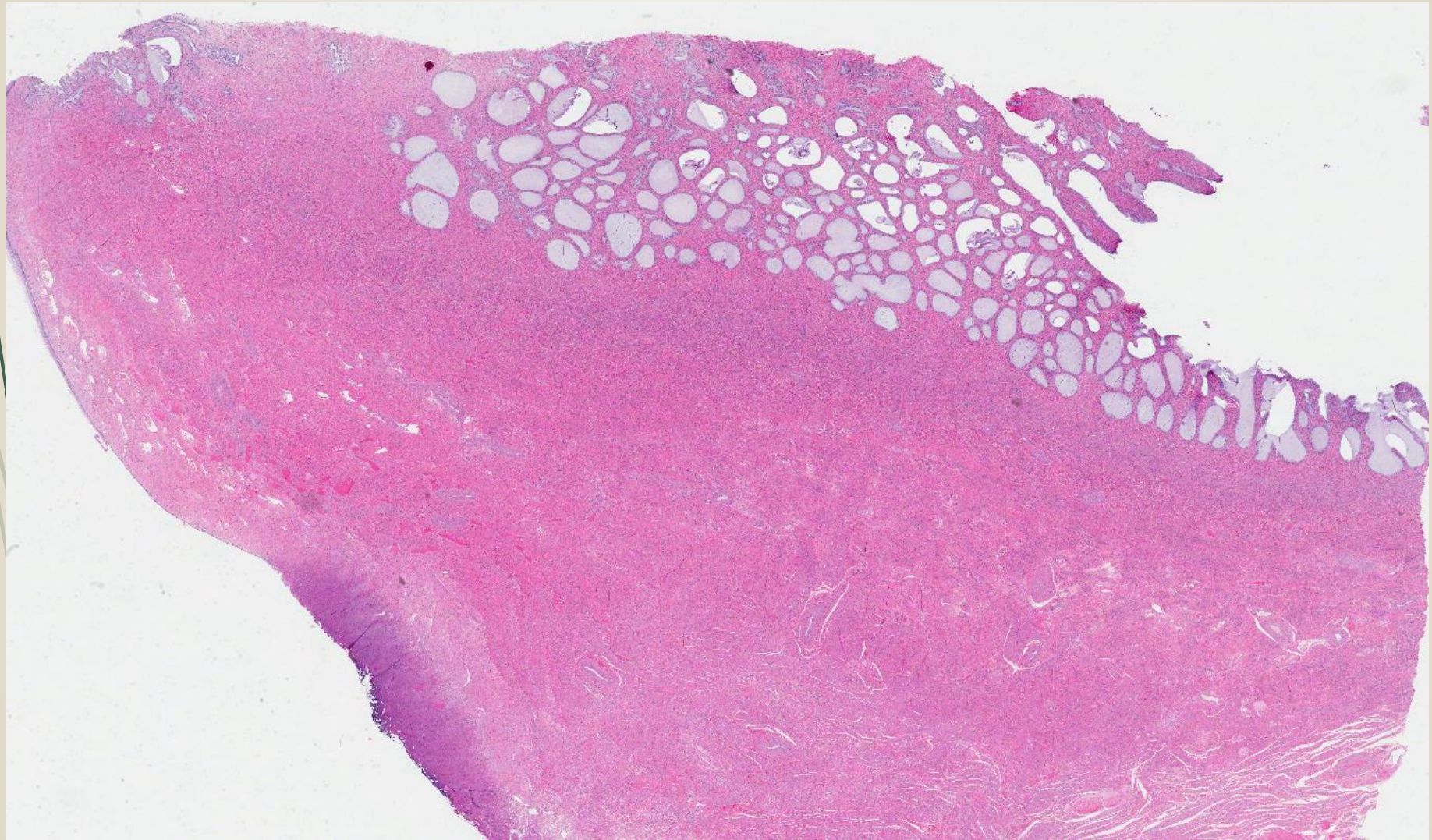


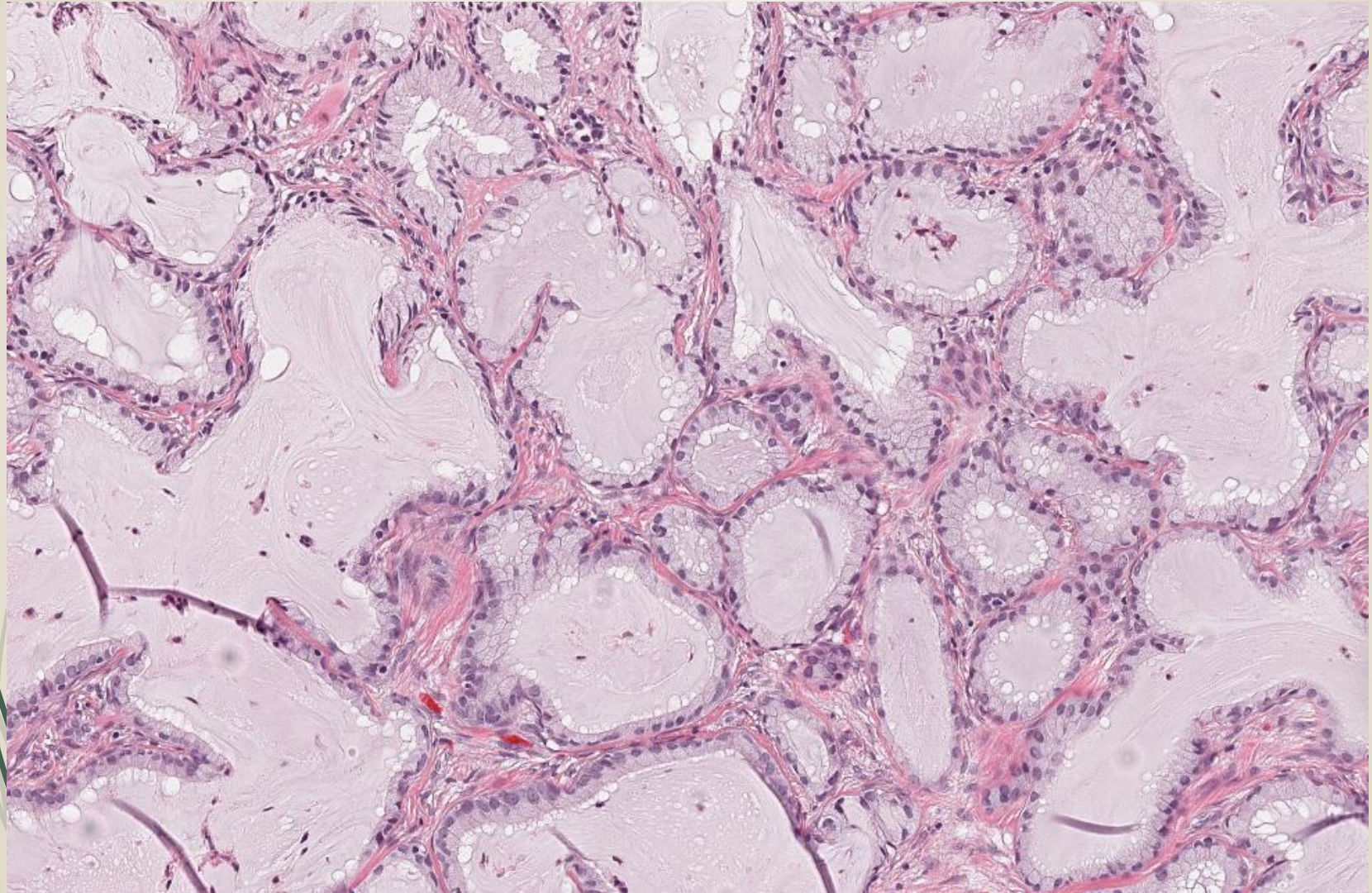
DDx: DIFFUSE LAMINAR HYPERPLASIA

- Very rare
- Densely packed glands and clefts 
- Band-like configuration
- Superficial 1/3 of the cervical wall thickness 
- Lining epithelium has bland endocervical-type features

ER / PR positive

Am J Surg Pathol 1991;15:1123–1129
Pathol Int 1995;45:283–286
Int J Gynecol Cancer 2009;19:1091–1093



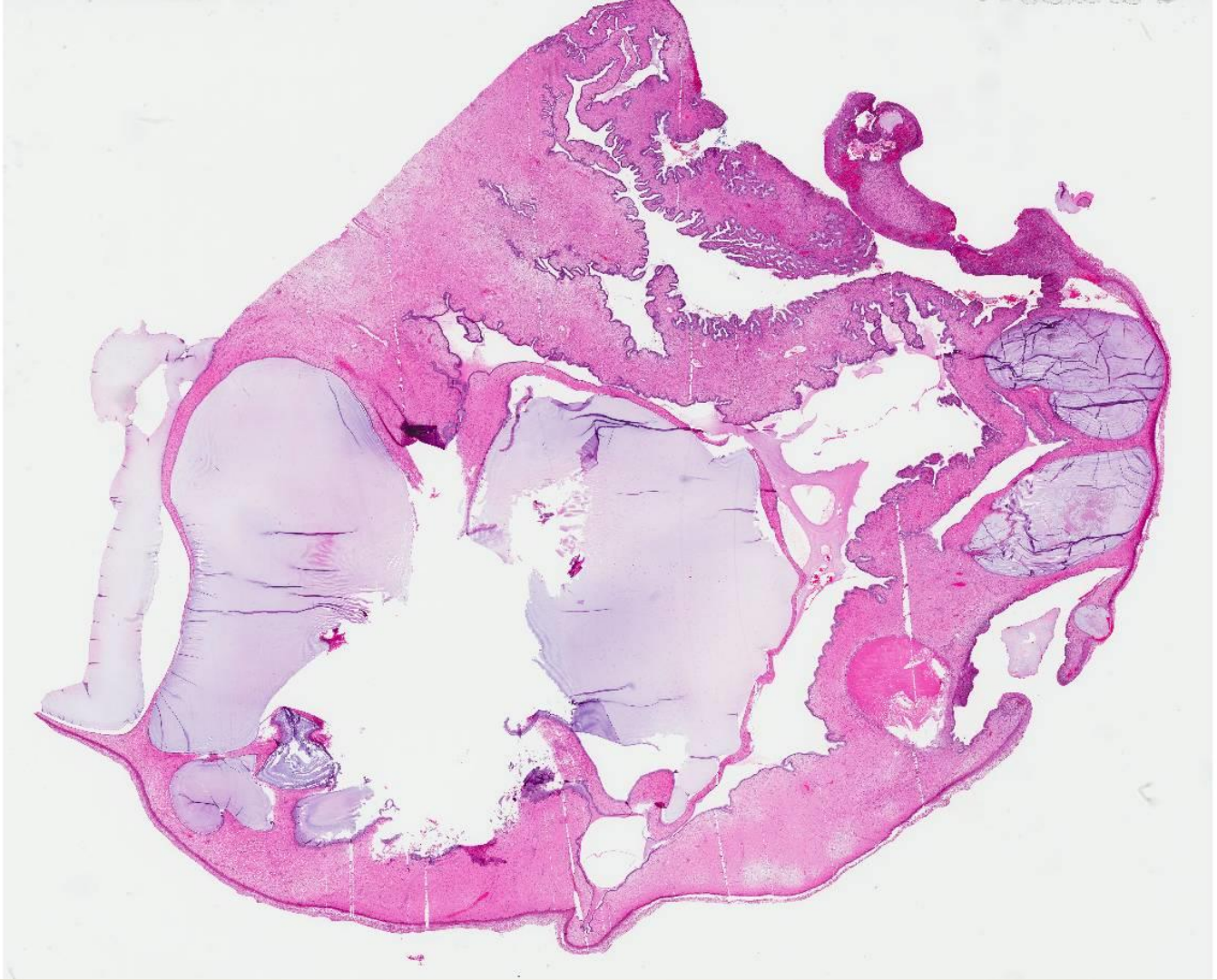


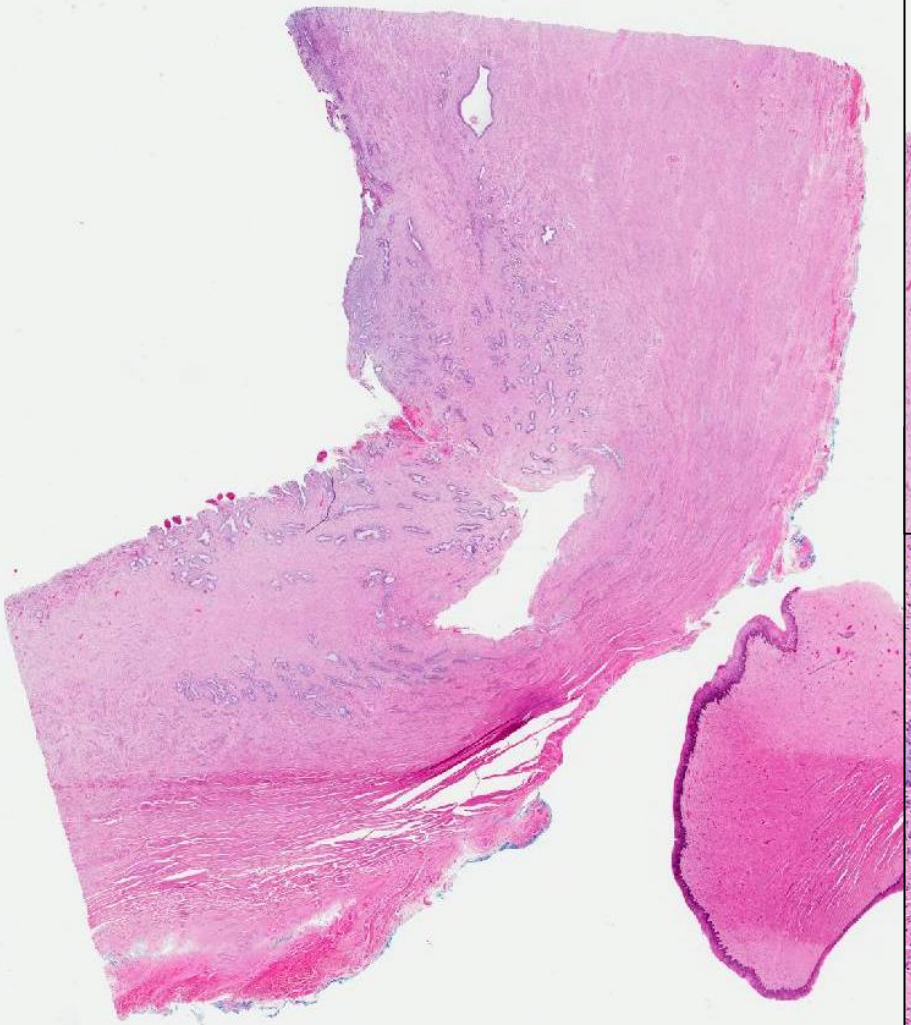
DDx: DEEP FLORID GLANDS

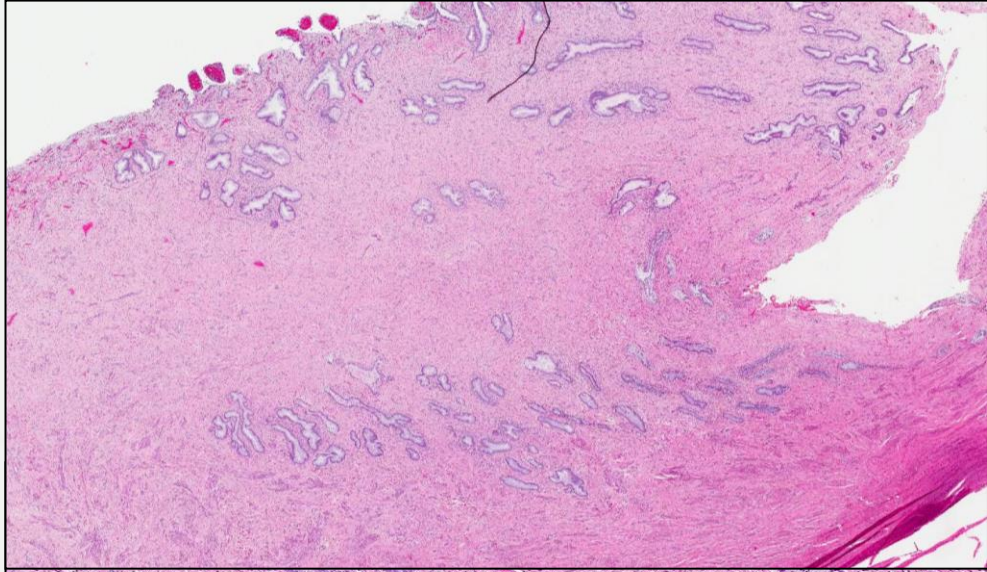
- Usually cystic = Deep Nabothian cysts
- Deep infoldings that become obstructed
- Can cause cervical enlargement
- Glands and cyst are haphazardly distributed
- Round, well-defined shape 
- Single, bland, endocervical type epithelium 

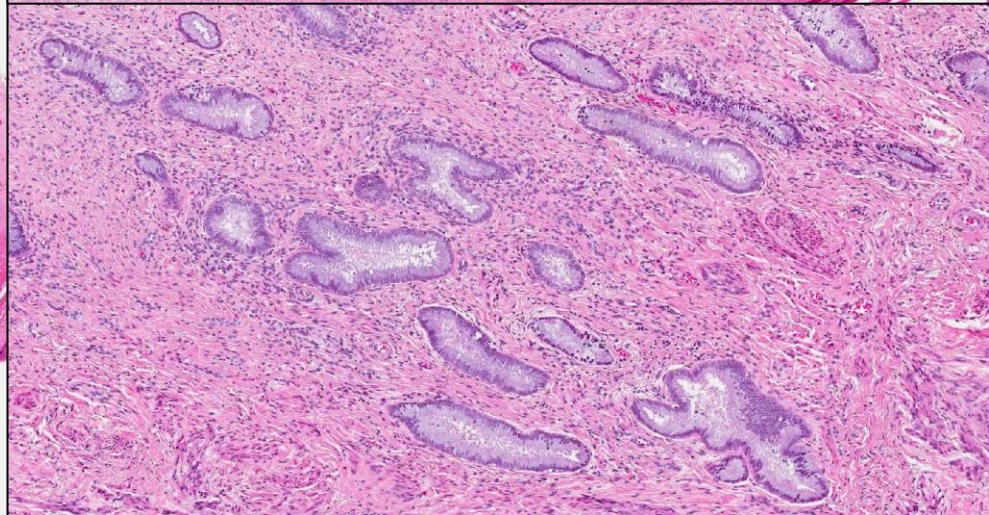
ER / PR positive

Semin Diagn Pathol 1991;8:234-249





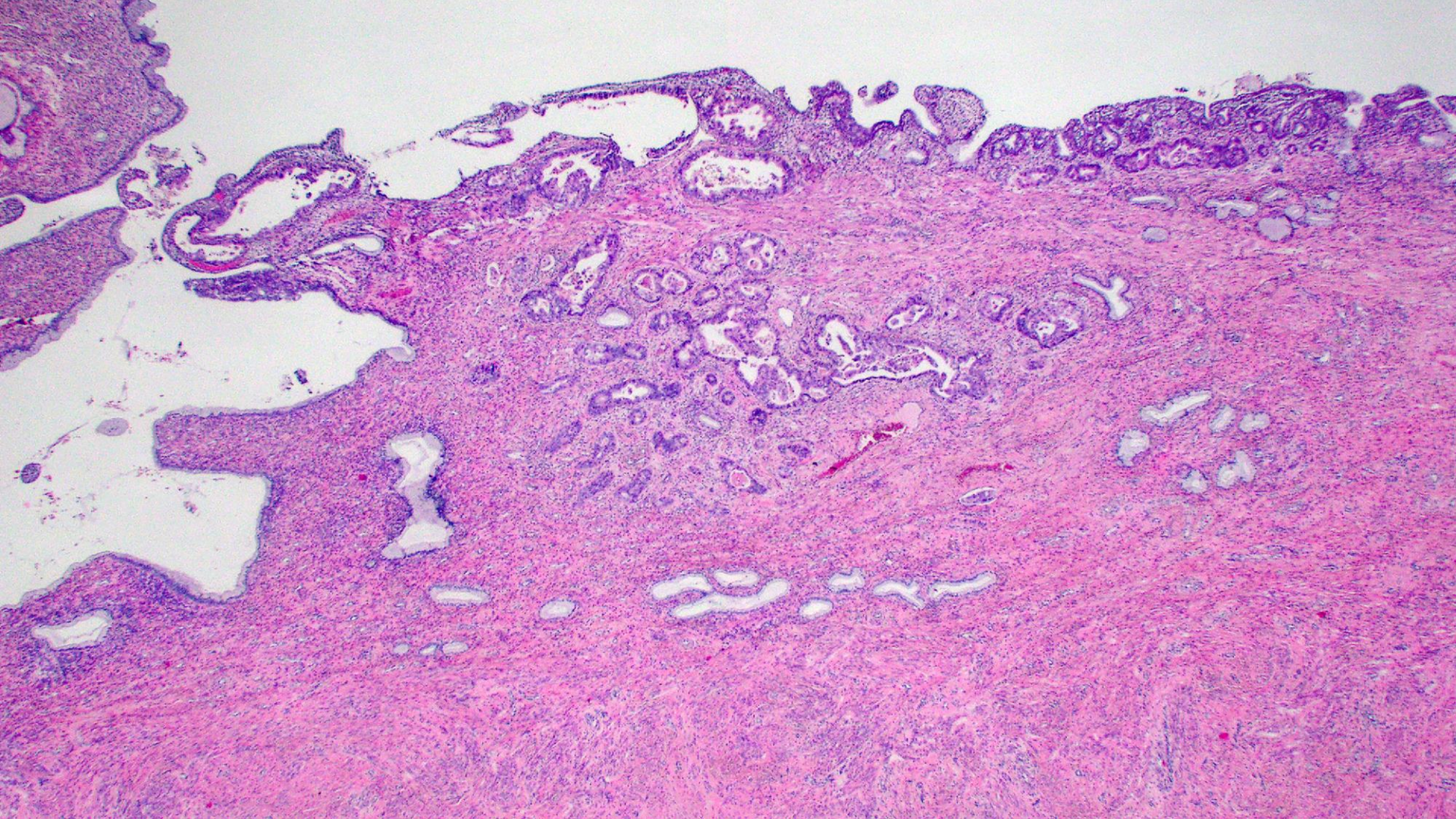


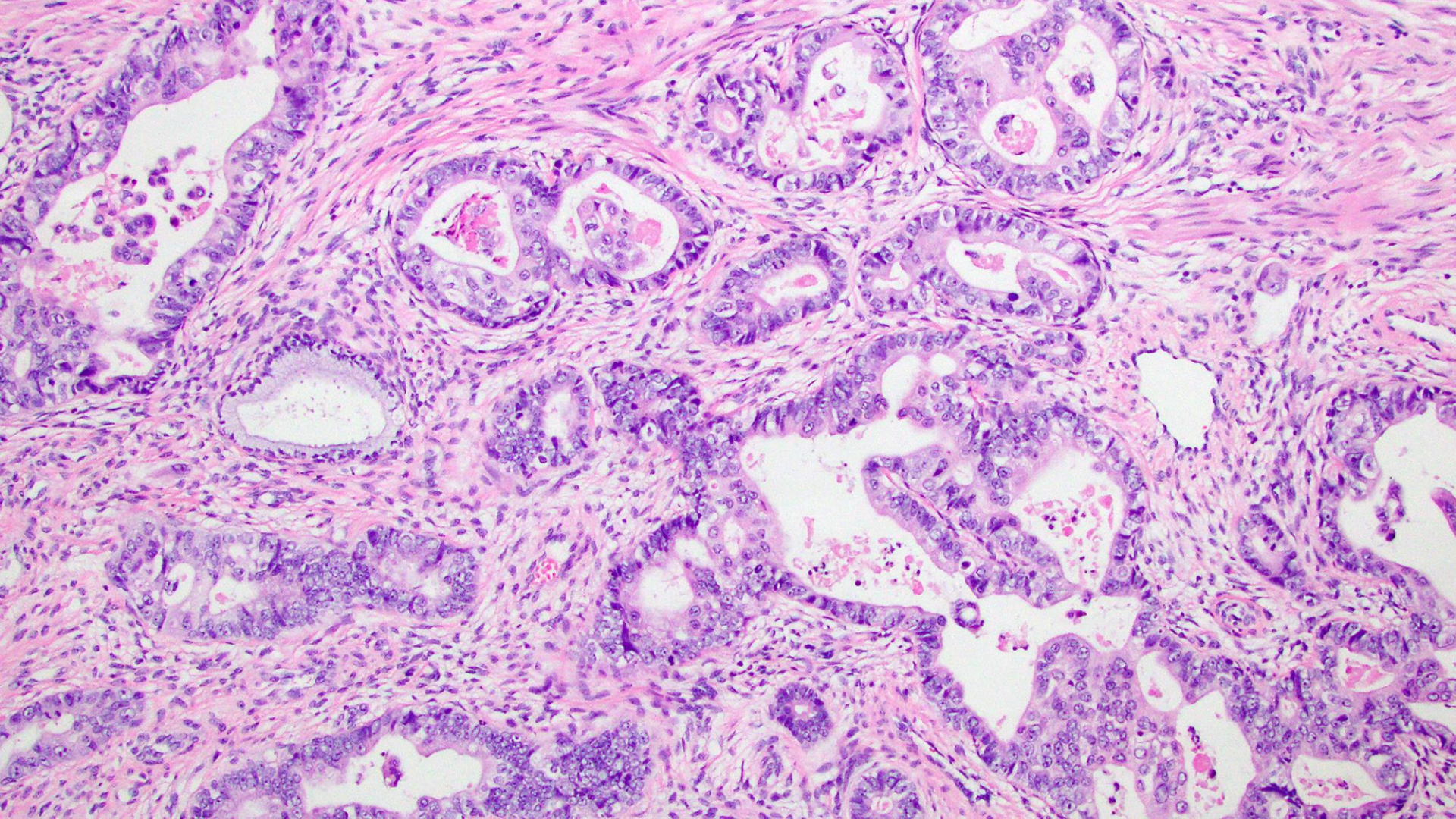


DDx: METASTATIC CARCINOMA

- Upper gastrointestinal tract
  - Primary gastric
  - Pancreato-biliary
- Only ~50% have a previous history of GI primary cancer
- Most are poorly differentiated (signet-ring cell type)

Cancer 1993;71:3472–3477
Int J Gynecol Pathol 2007;26:254–258
J Obstet Gynaecol Res 2012;38:541–549





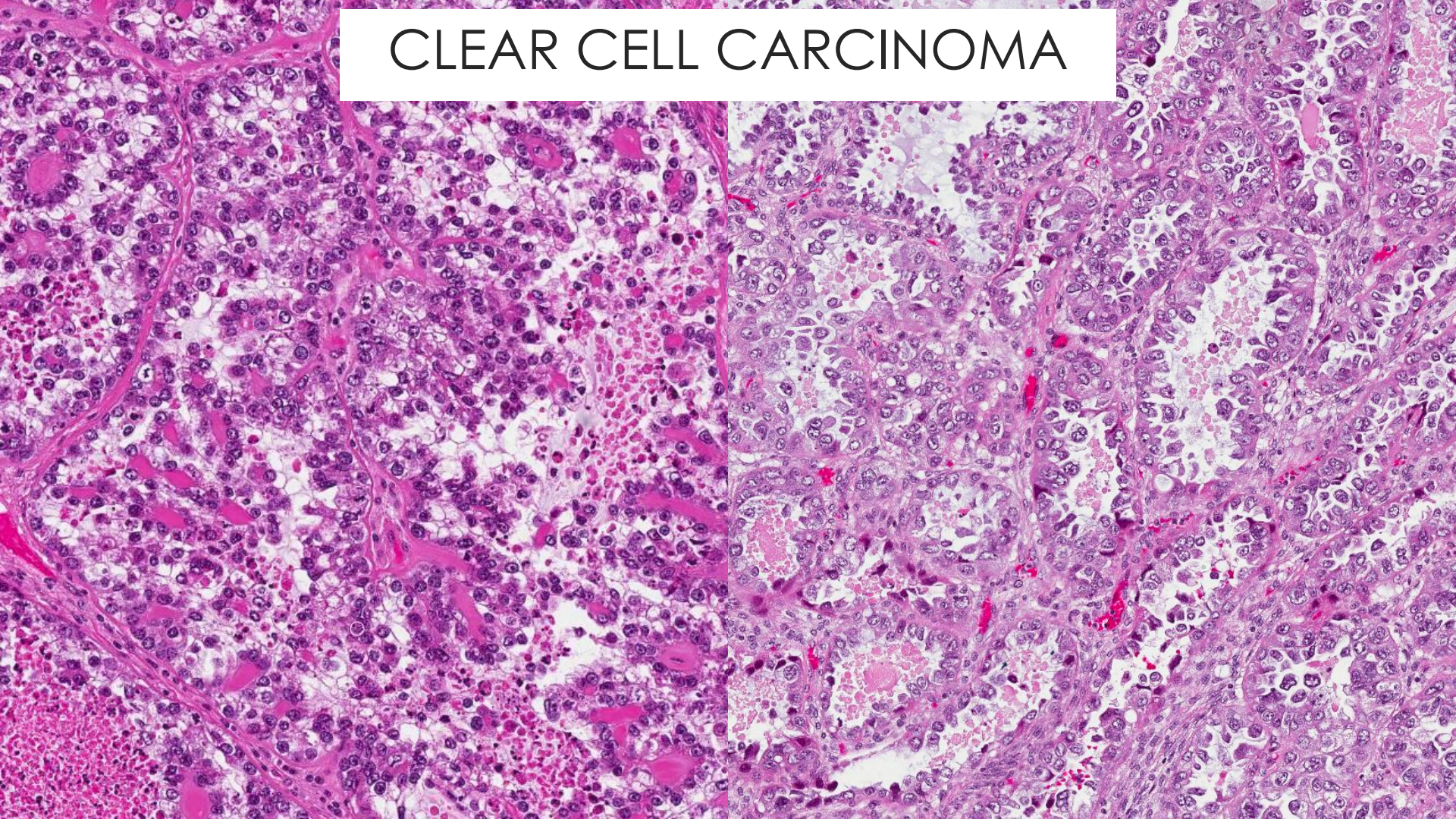
DDx: METASTATIC CARCINOMA

- Signet-ring cell differentiation
  - If diffuse, exclude metastases
- Extensive cervical wall involvement
- Extensive LVI
- Multi-organ involvement
- Gastric-type adenoCA

Consider mets if Cx is not the predominant site

Cancer 1993;71:3472–3477
Int J Gynecol Pathol 2007;26:254–258
J Obstet Gynaecol Res 2012;38:541–549

CLEAR CELL CARCINOMA



DIFFERENTIAL DIAGNOSIS

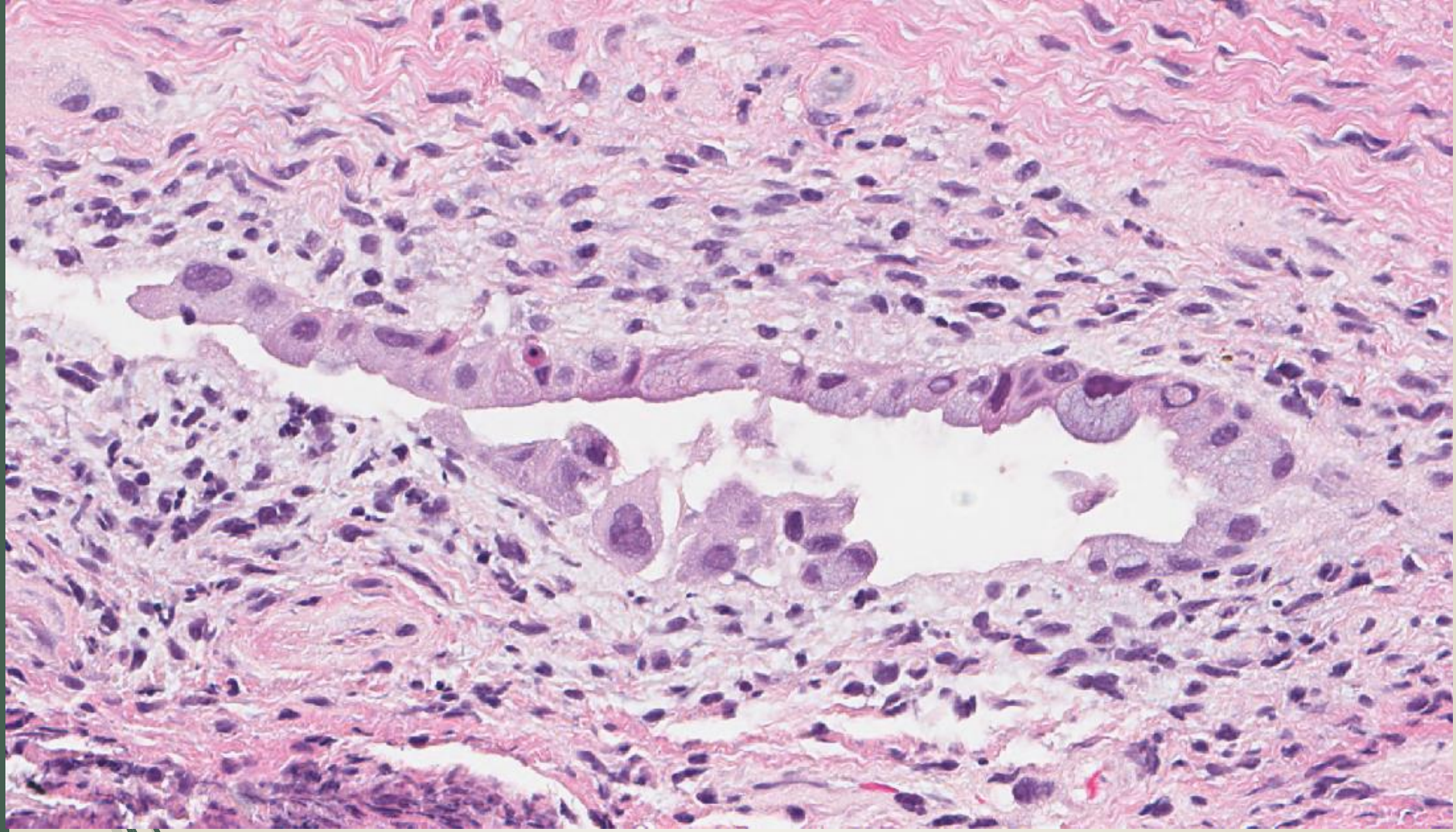
- **Radiation-induced atypia**
- **Arias-Stella reaction**
- **Mesonephric remnants and hyperplasia**
- Serous carcinoma
- HPV-related adenocarcinoma
- Endometrial or ovarian clear cell carcinoma

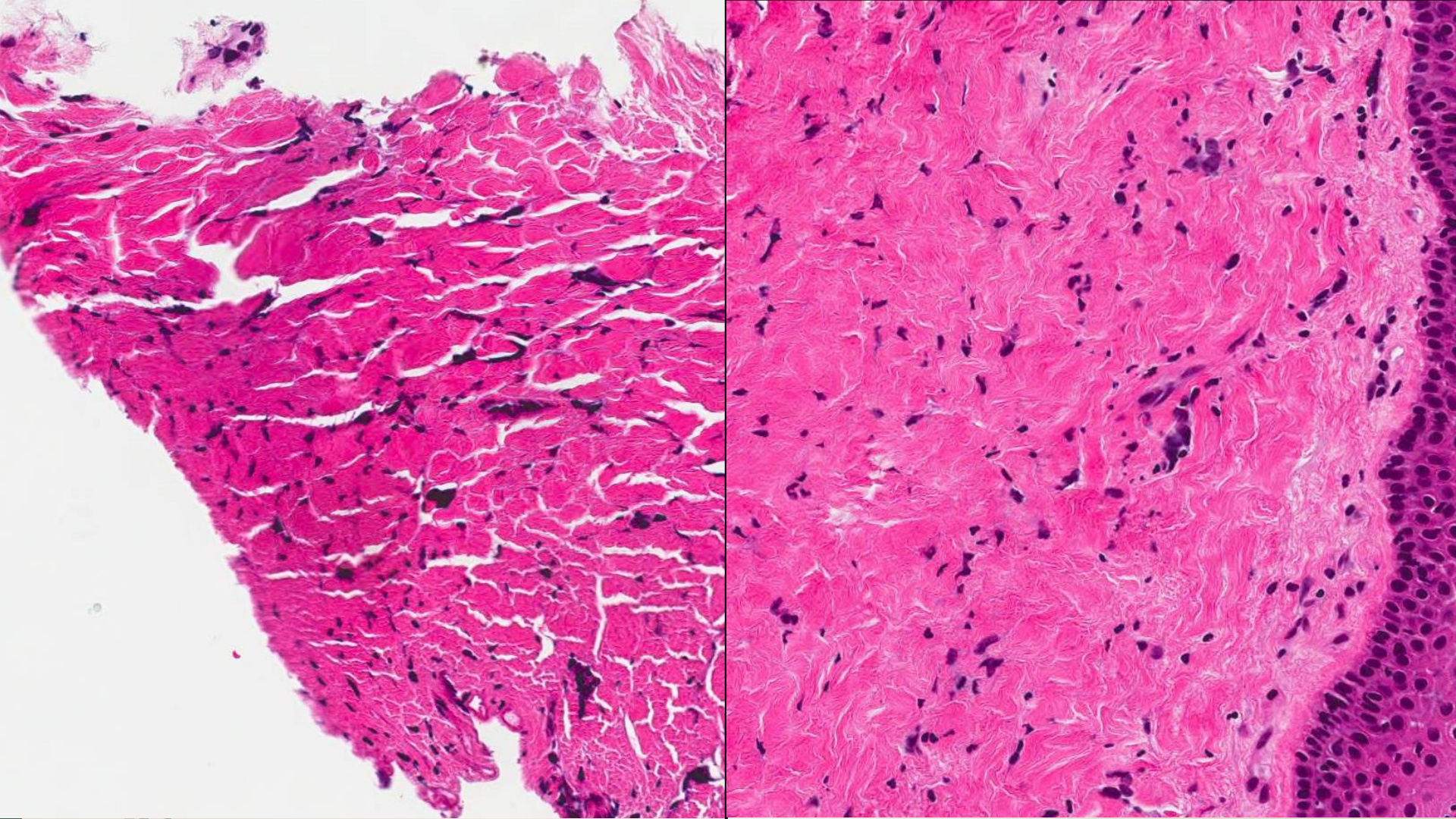
DDx: RADIATION-INDUCED ATYPIA

- Weeks to years after radiation exposure
- Enlarged hyperchromatic nuclei
- May protrude towards the lumen
- Smudged chromatin
- Abundant vacuolated cytoplasm
- Low N/C ratio





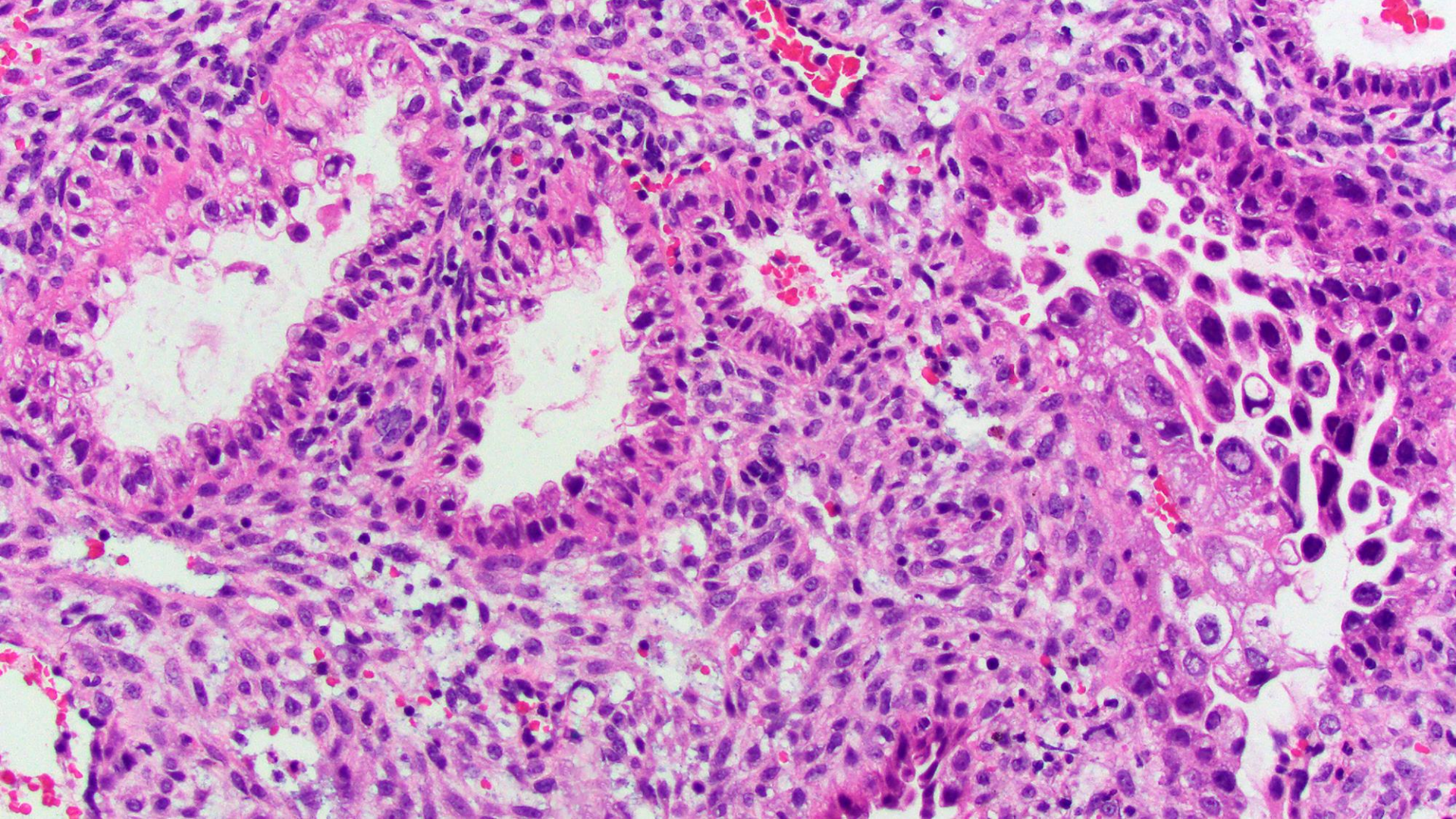


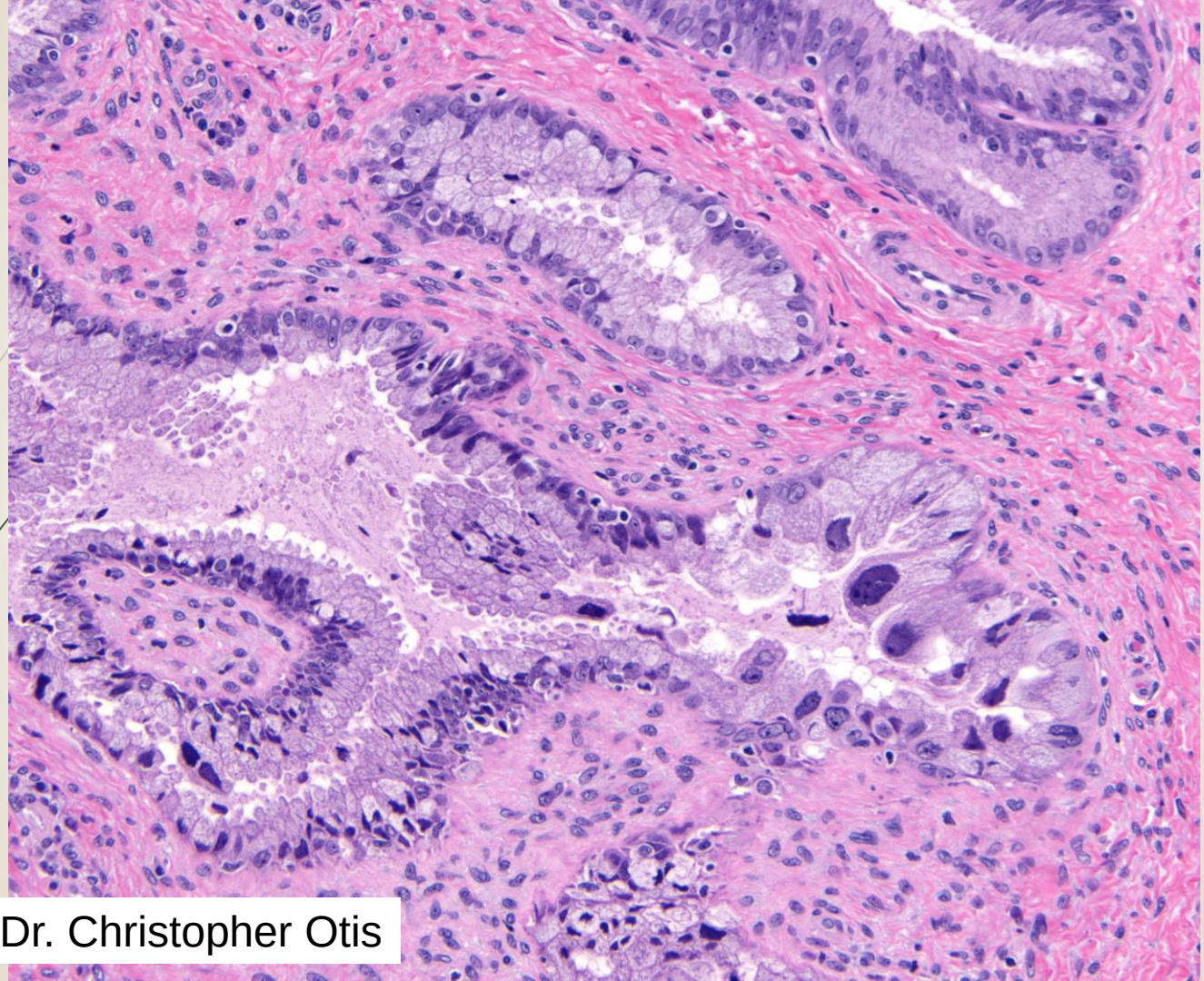


DDx: ARIAS-STELLA REACTION

- Characteristic change secondary to progesterone
  - Pregnancy
  - Progestin or OCP use
- Usually incidental; may appear polypoid
- Multifocal

Am J Surg Pathol 2004;28:608–612
Acta Cytol 1981;25:224–228





Courtesy of Dr. Christopher Otis

DDx: ARIAS-STELLA REACTION

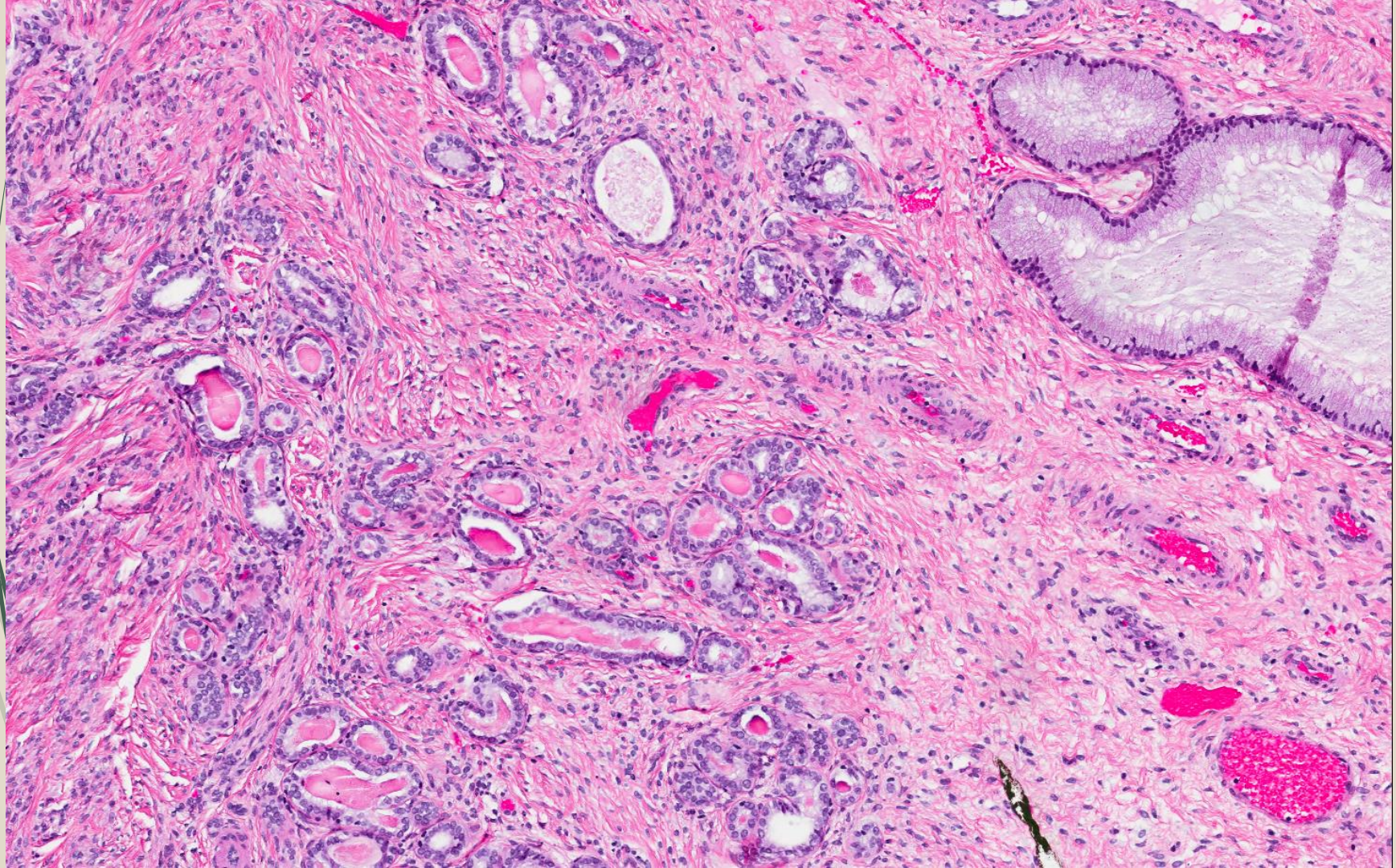
- Enlarged, hyperchromatic, irregular nuclei
- Can protrude towards the lumen (hobnail)
- Tortuous, hypersecretory glands in EMBx ✓
- Abundant clear (secretory) cytoplasm ✓
- Low N/C ratio ✓
- Napsin-A can be positive

Am J Surg Pathol 2004;28:608–612
Hum Pathol. 2016;54:202
Int J Gynecol Pathol 2004;23:223–233

DDx: MESONEPHRIC REMNANTS

- Mesonephric duct remnants
  - Lateral walls of the cervix
  - Superficial (submucosal) – common in LEEP / cone
- Clusters of round glands and tubules
- Lined by simple flat to low cuboidal epithelium
- Indistinct cytoplasm
- Dense eosinophilic PAS+, diastase resistant secretions

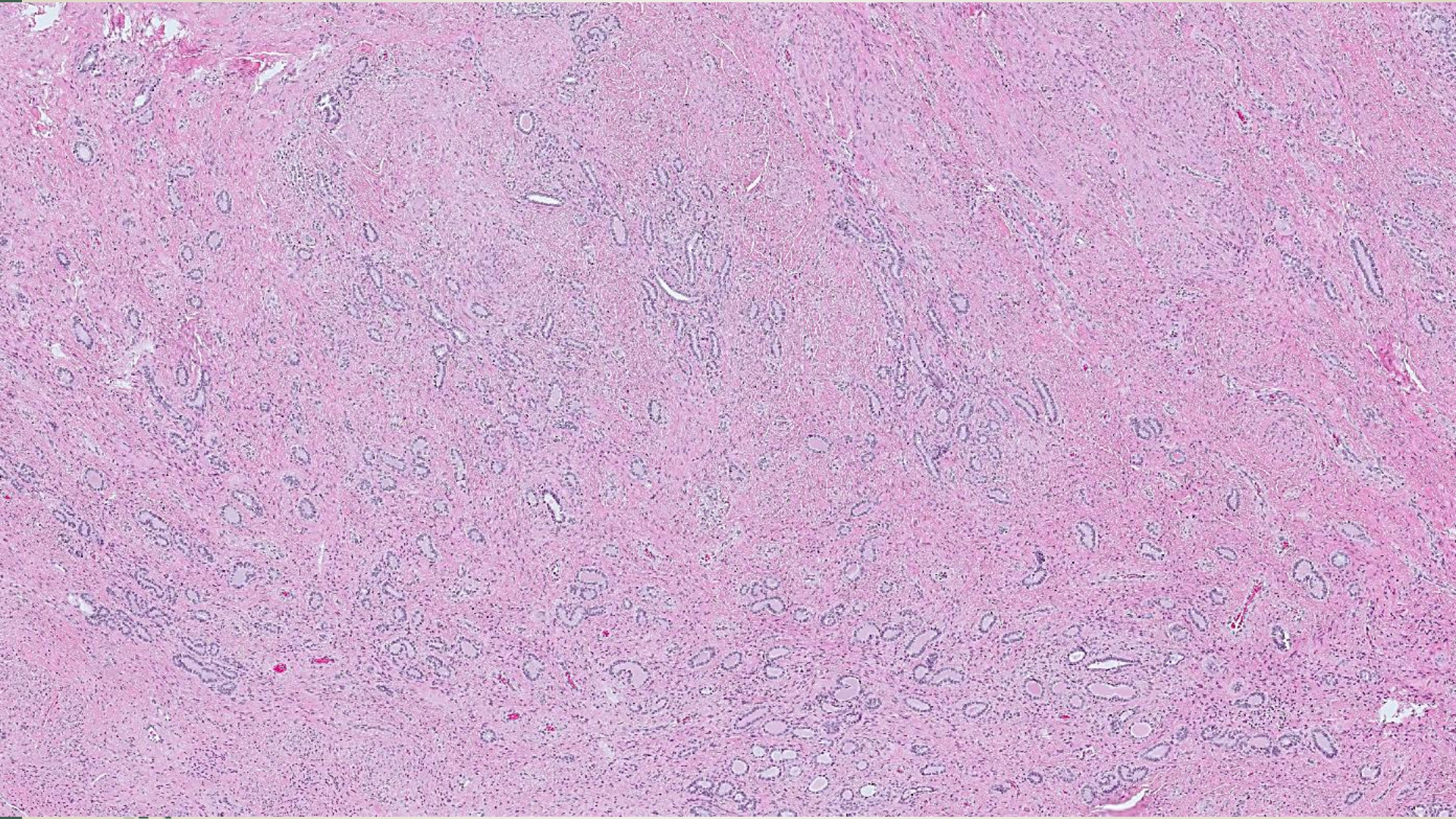
Am J Surg Pathol 1990;14:1100-1111

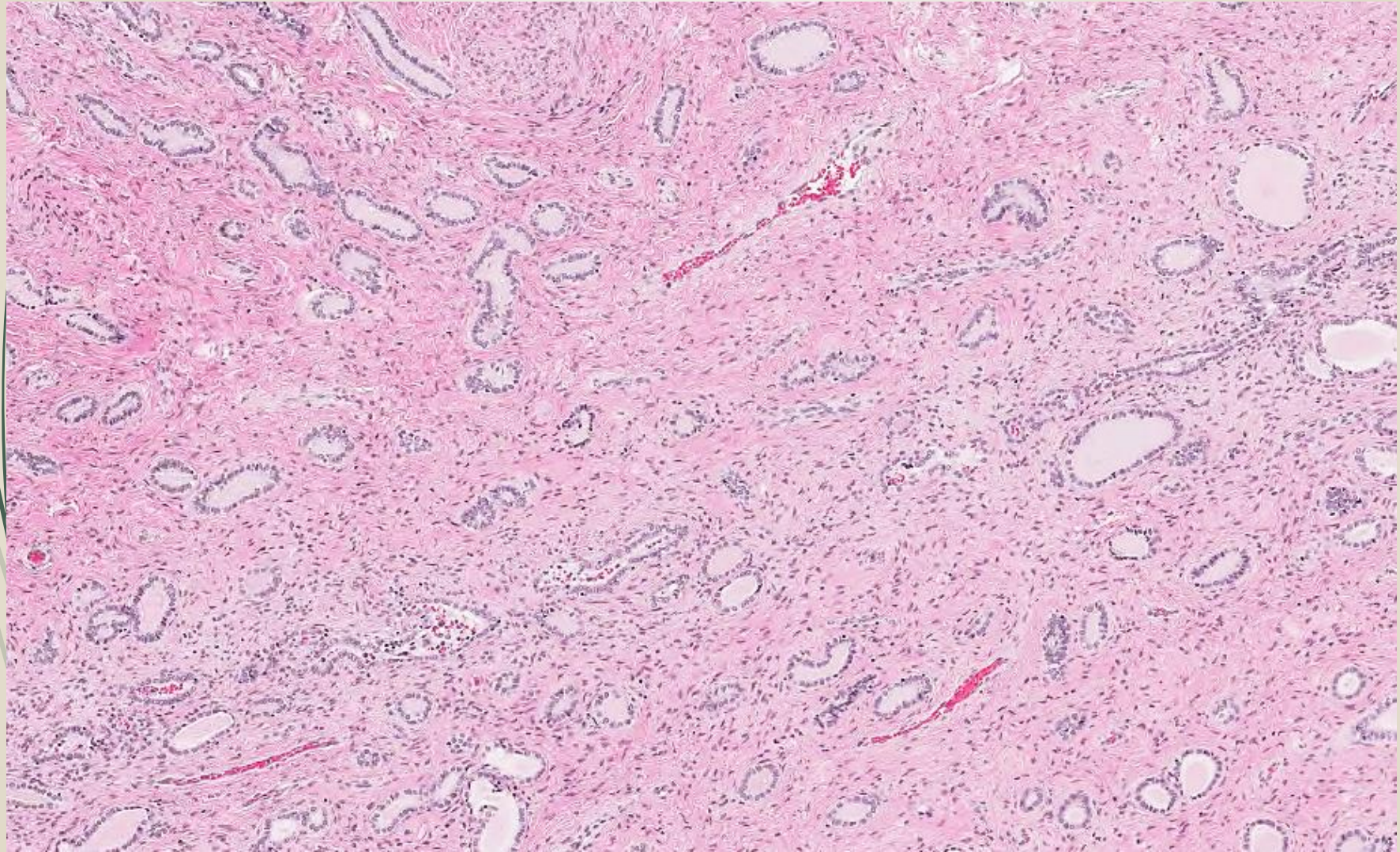


DDx: MESONEPHRIC HYPERPLASIA

- Florid and more extensive ductular proliferation
  - Some authors use size (> 6 mm)
- Lobular, diffuse and ductal types
- Irregular and haphazard distribution
- Involve the outer cervical wall
- Non-destructive and non-confluent growth 
- Bland cytomorphology 

Am J Surg Pathol 1990;14:1100-1111
Int J Gynecol Pathol 1995;14:293-299
Am J Surg Pathol 2001;25:379-387





THANK YOU!!

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