# Endometrioid Intraepithelial Neoplasia (EIN)

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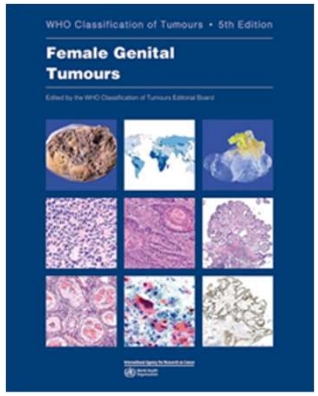
# Overview

1. Current definition of EIN
2. The hyperplasia / neoplasia spectrum
    - PE – DPE/NAH - EIN - Cancer
3. Approaching metaplasia
    - Secretory change
4. Biomarkers in EIN diagnosis

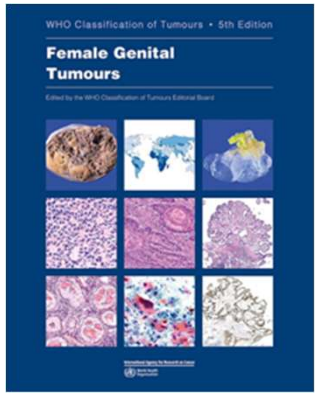
# Current Definition of EIN




# Tumors of the uterine corpus
# Precursor lesions

**Morphology:**

- “The lesion must be of sufficient size (admittedly a subjective measure) that artefact can be excluded and coincident change of architectural and cytological alterations is evident.
- Nuclear appearance varies between patients but is always distinct from that of the background from which the lesion has emerged.
- Cytoplasmic changes (various types of metaplasia) may accompany nuclear atypia in EAH/EIN (Carlson et al.). Common mimics (basalis, polyp, dyssynchronous-phase endometrium) must be excluded.”




# Tumors of the uterine corpus
# Precursor lesions (cont)

**Essential and desirable diagnostic criteria:**

*Essential:* morphologically defined endometrial changes with crowded glandular architecture and altered epithelial cytology, distinct from the surrounding endometrium and/or entrapped non-neoplastic glands.

*Desirable:* loss of immunoreactivity for PTEN, PAX2, or mismatch repair proteins.

# Definition of EIN

*Essential*

1. Altered epithelial cytology, distinct from surrounding
2. Crowded glandular architecture (Gland:stroma ratio >1)
3. No explicit size cutoff
    - Previously > 1mm in the EIN literature
4. Exclude benign mimics
5. Exclude cancer

*Desirable:*

Loss of biomarkers PTEN, PAX2 or mismatch repair proteins

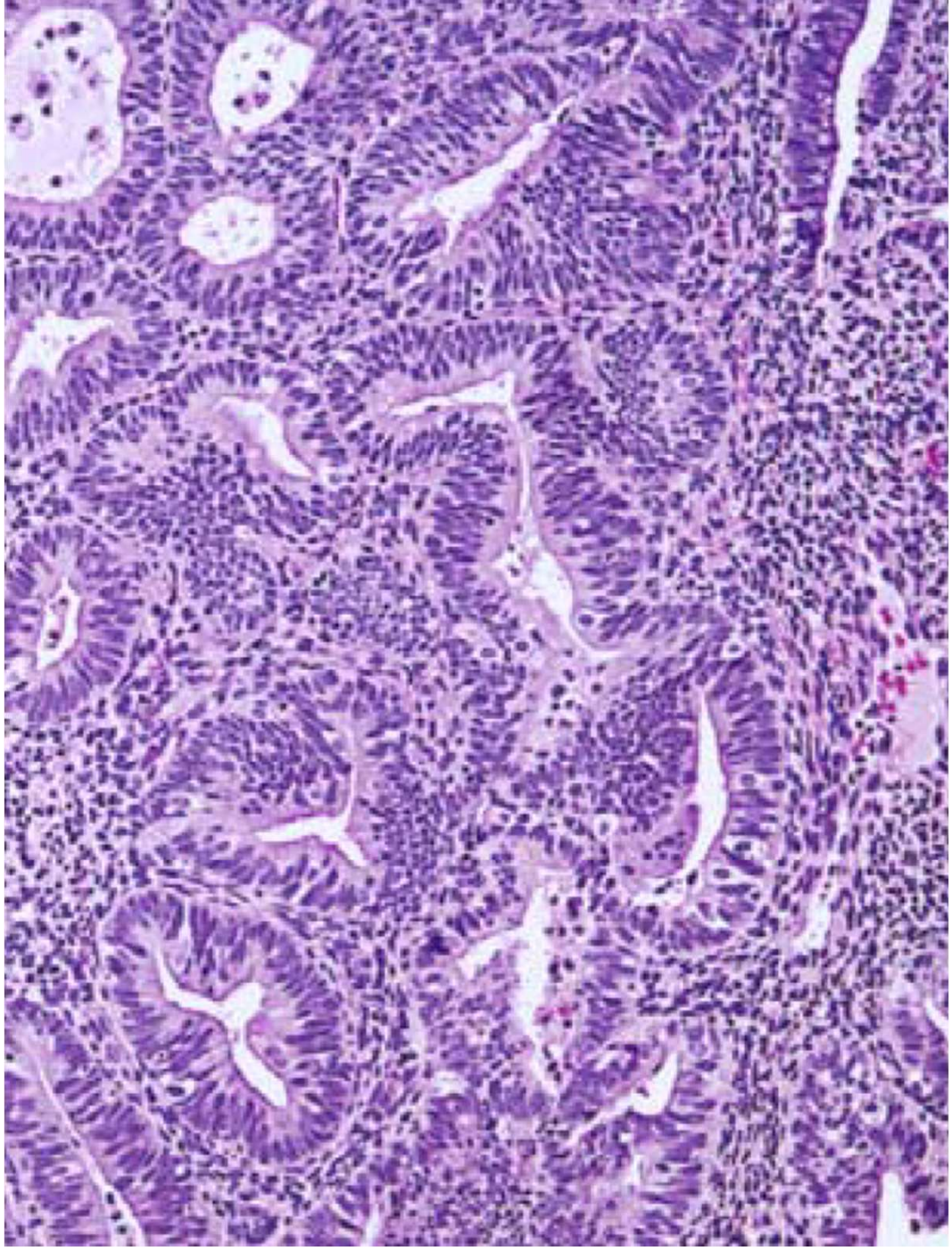
# Altered epithelial cytology

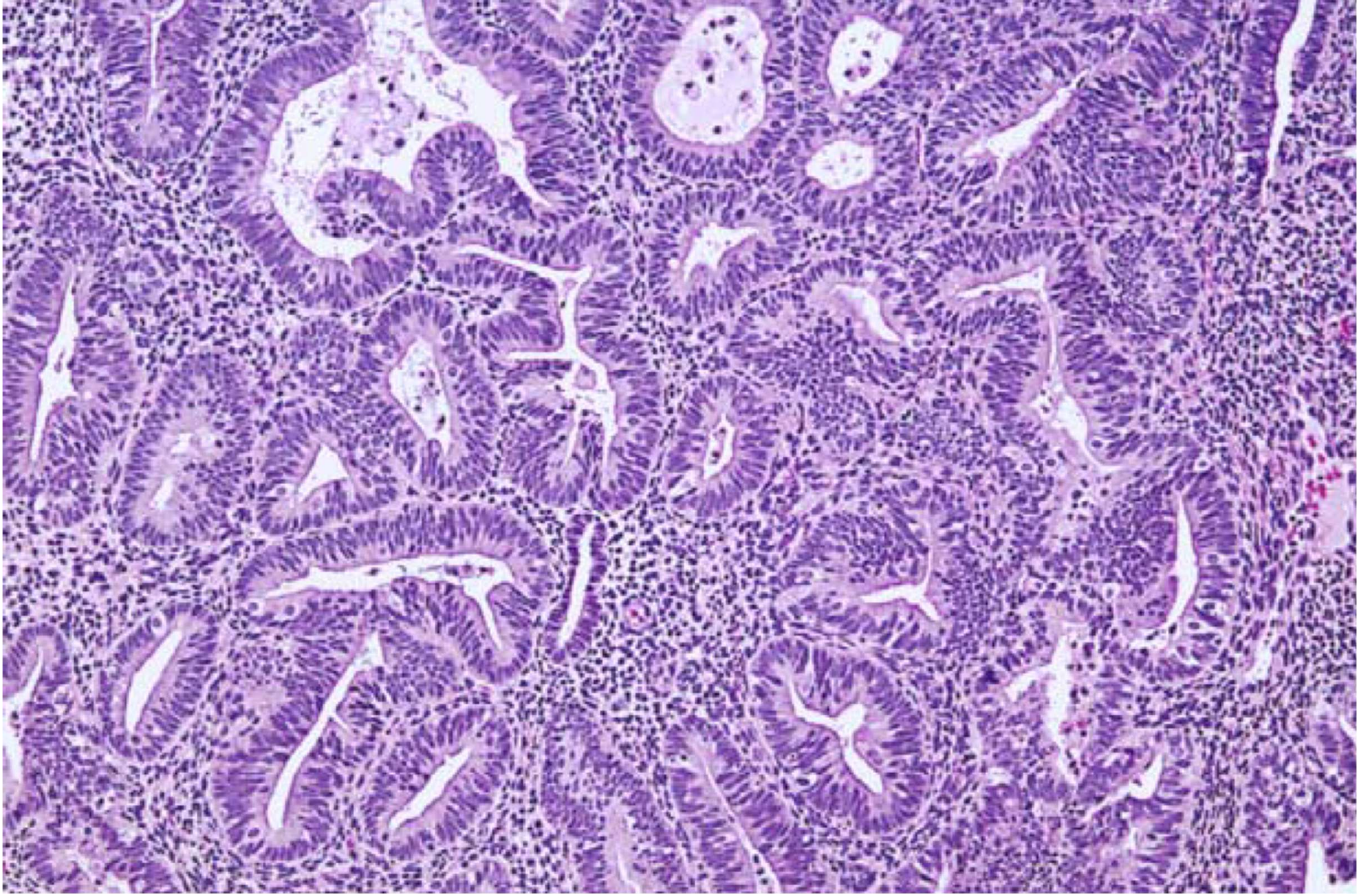
The definition of “atypia” has changed over the past 2 decades, causing confusion.

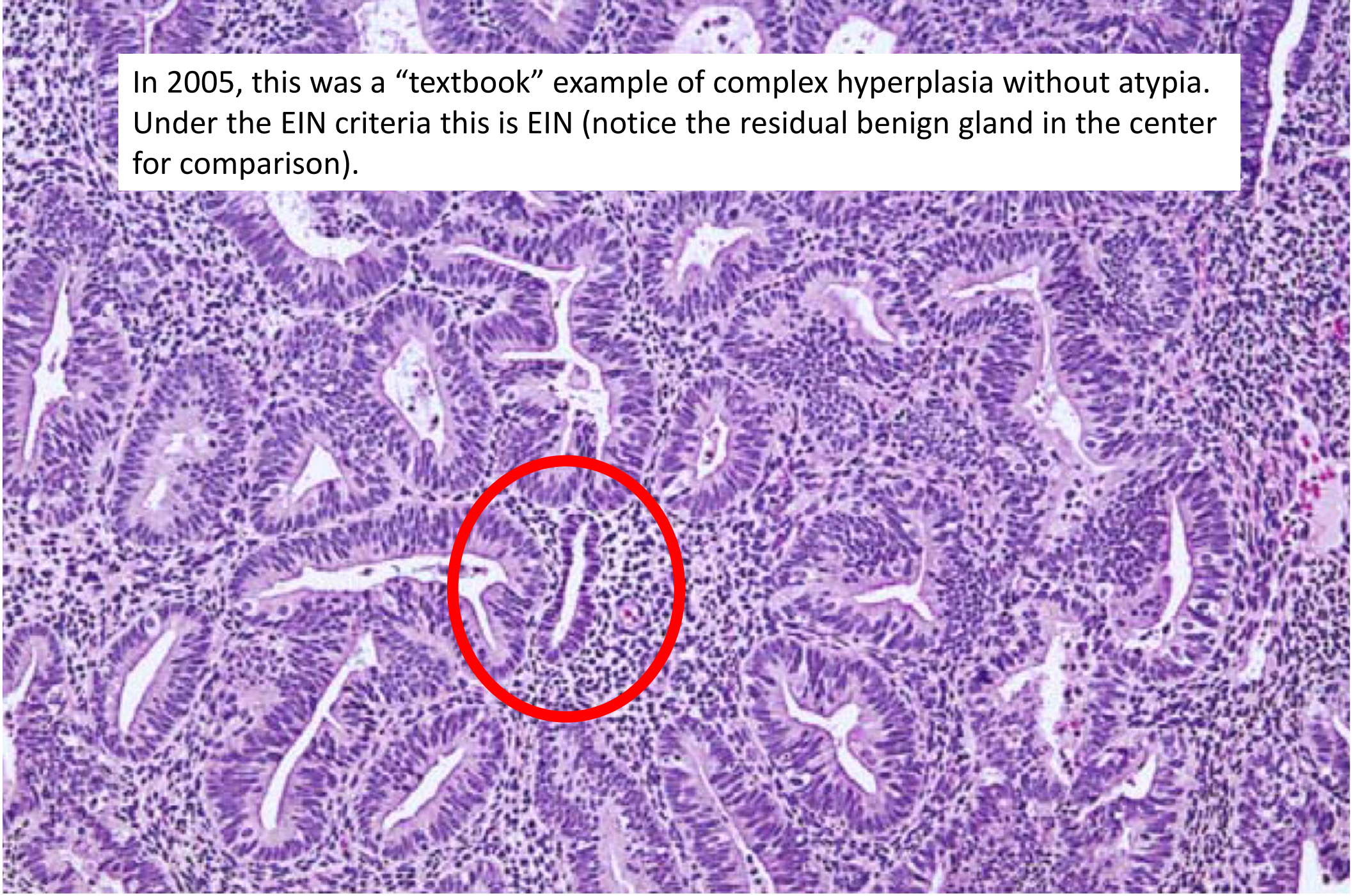
| 2005 | 2020 |
|---|---|
| Absolute definition | Relative definition |
| The diagnosis of atypia is based mainly on specific nuclear features. Many of the nuclei are enlarged and rounded rather than oval and may have irregular nuclear membranes. The nuclear irregularities usually are accompanied by true stratification of 2 to 4 cells with loss of polarity in relation to the basement membrane. In addition, the chromatin is centrally dispersed and forms clumps along the nuclear membrane… | …altered epithelial cytology, distinct from the surrounding endometrium and/or entrapped non-neoplastic glands. |

Mazur MT. Endometrial hyperplasia/adenocarcinoma. a conventional approach. Ann Diagn Pathol. 2005 Jun;9(3):174-81. doi: 10.1016/j.anndiagpath.2005.03.001. PMID: 15944963.

# Is this atypical?





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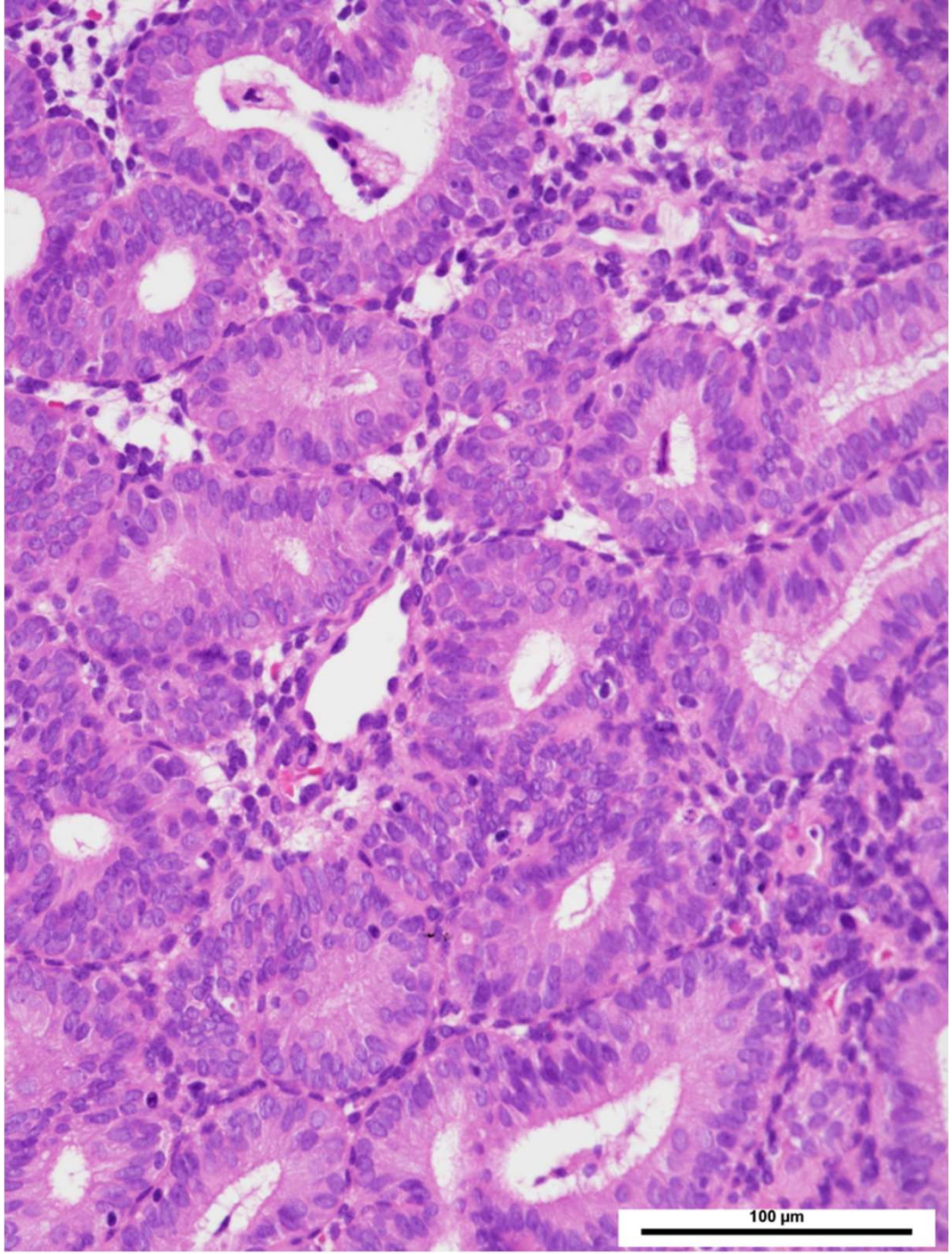


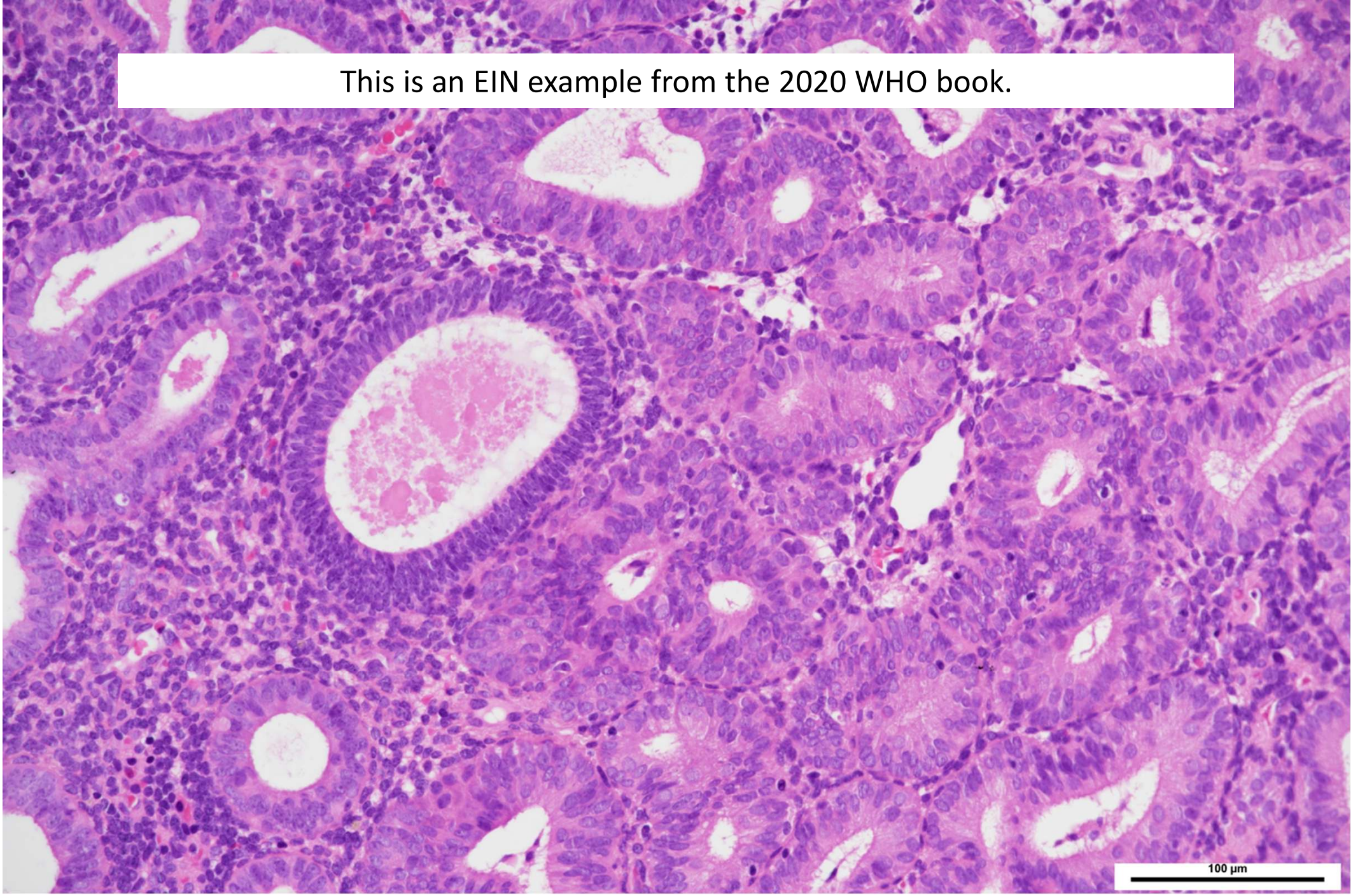
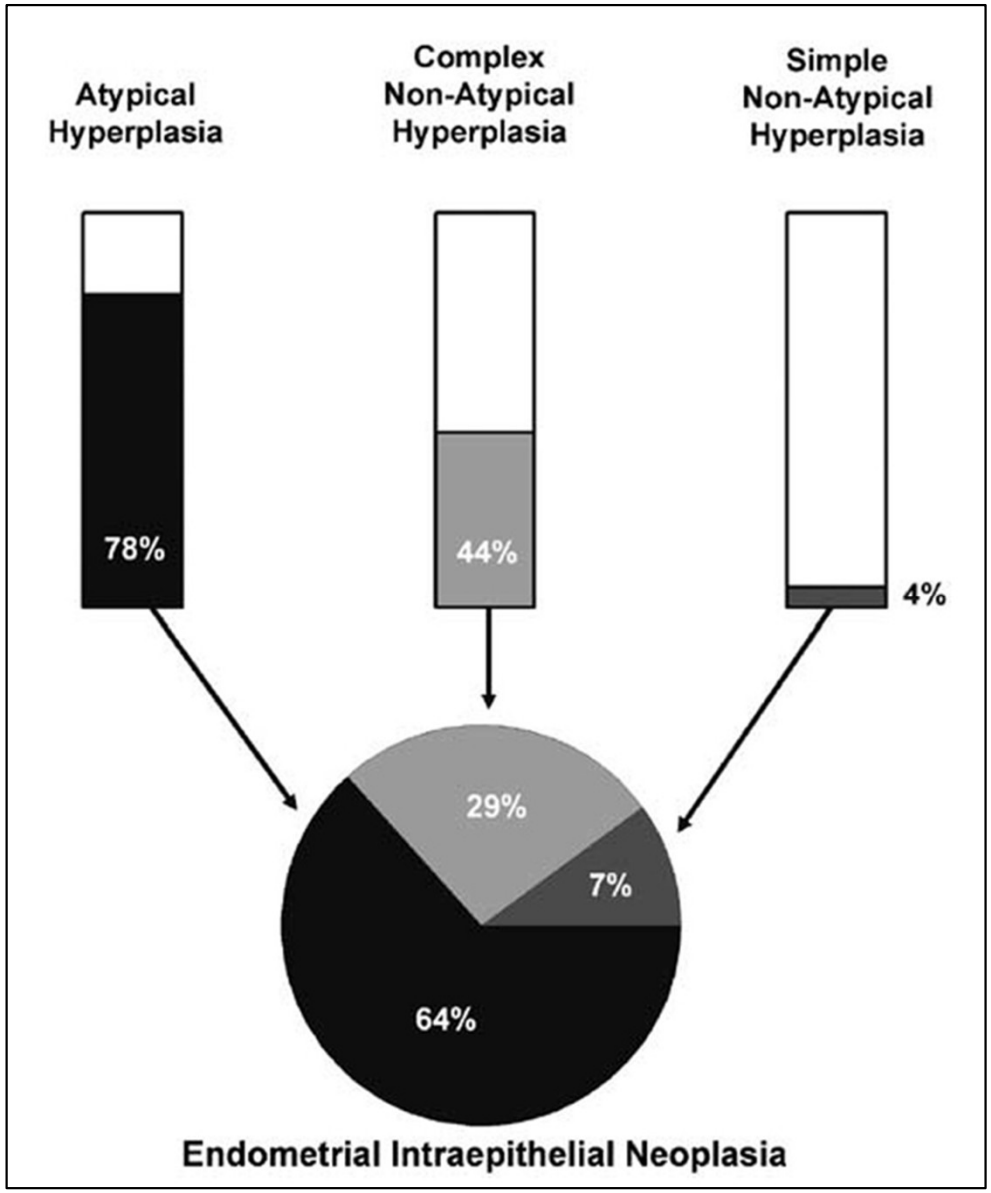

This is an EIN example from the 2020 WHO book.
100 µm

**Table 1** Reclassification of WHO hyperplasias using EIN criteria

| *WHO hyperplasia diagnosis* | *EIN diagnosis* n *(%)* | *Total* |
|---|---|---|
| Complex with atypia | 18 (78) | 23 |
| Simple with atypia | 0 (0) | 0 |
| Complex without atypia | 8 (44) | 18 |
| Simple without atypia | 2 (4) | 56 |
| Total | 28 (29) | 97 |




Hecht JL, Ince TA, Baak JP, Baker HE, Ogden MW, Mutter GL. Prediction of endometrial carcinoma by subjective endometrial intraepithelial neoplasia diagnosis. Mod Pathol. 2005 Mar;18(3):324-30. doi: 10.1038/modpathol.3800328. PMID: 15529181; PMCID: PMC2573865.

# Take Home Messages

1. The diagnosis of AH/EIN has changed over time, especially the identification of “atypia”
2. The criteria for EIN are relatively straightforward, with a high reproducibility.
3. Biomarkers are now suggested as part of EIN diagnosis in the WHO (more on that later!)

# The hyperplasia / neoplasia spectrum

**Proliferative Endometrium (PE)**

**Disordered Proliferative Endometrium (DPE)**

**Non-Atypical Hyperplasia (NAH)**

**EIN**

**Endometrioid Carcinoma (ECa)**

# Proliferative Endometrium

Abundant tubular glands

Evenly spaced

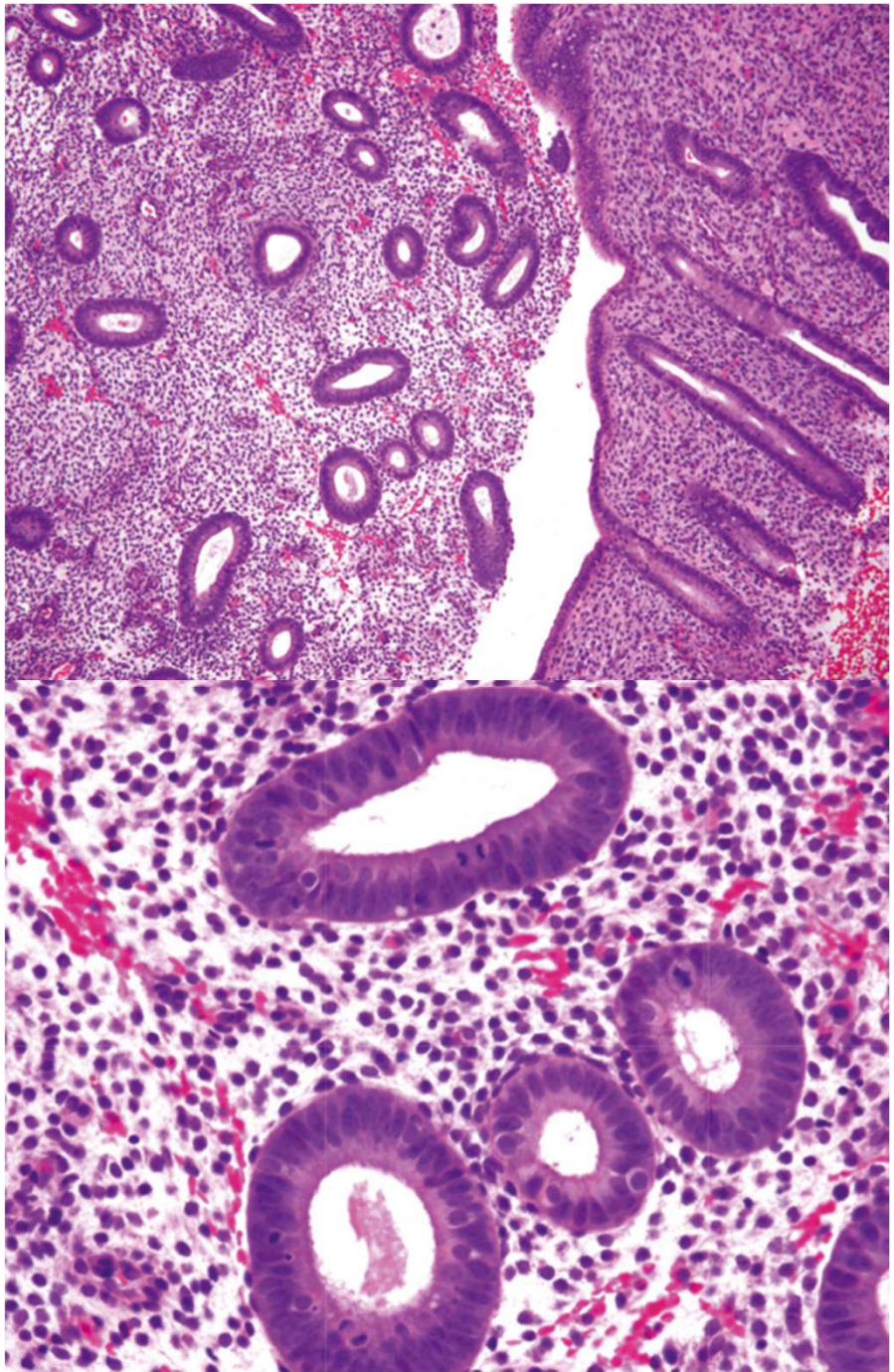
Little to no cystic dilatation

No crowding

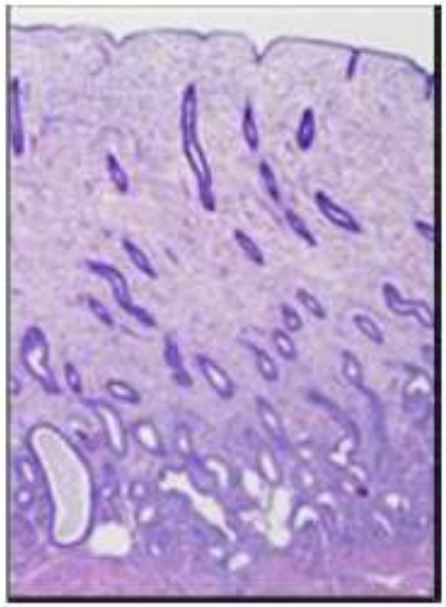
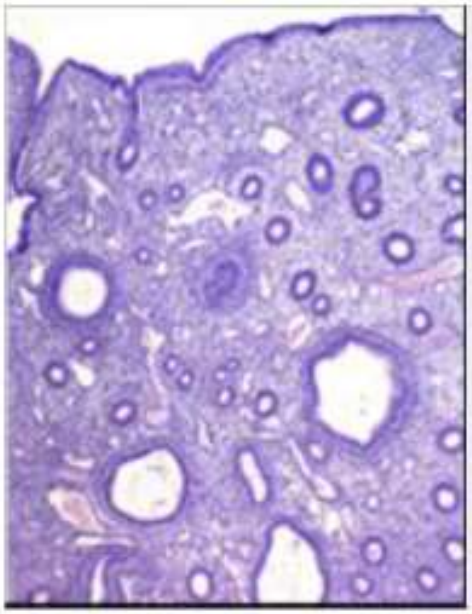
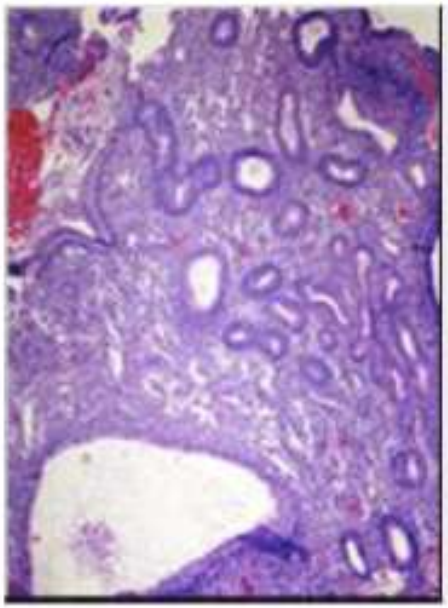
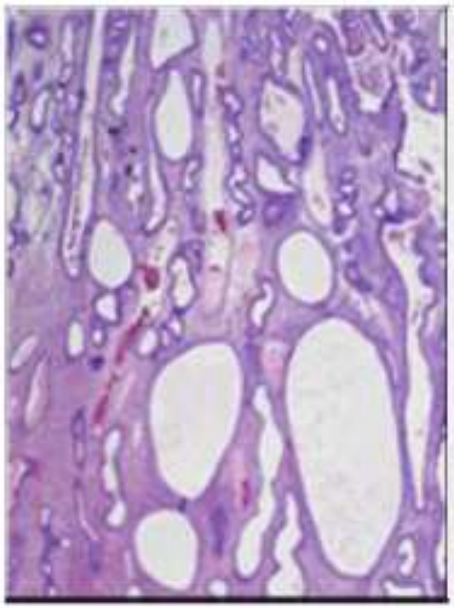
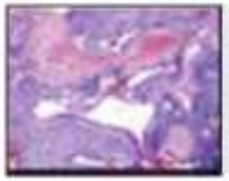
Pseudostratified epithelium

Oval nuclei

Prominent nucleoli



# Unopposed estrogen effect

**Proliferative** → cysts → **Disordered Proliferative** → remodeling, thrombi, variable density → **Benign Endometrial Hyperplasia**

**Estrogen over Time**

From: Dr. George Mutter, online lectures.

# Disordered Proliferative Endometrium
# Non-Atypical Hyperplasia

Multiple, medium to large, intact tissue fragments

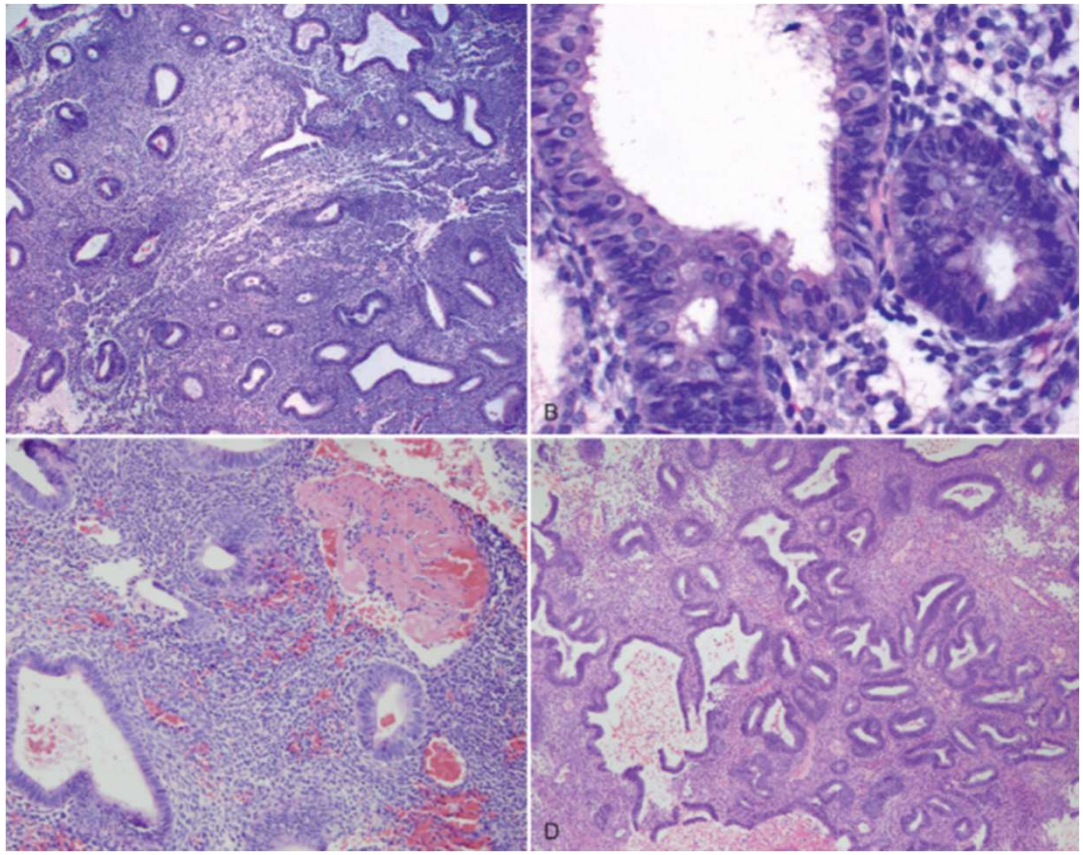
Randomly scattered cysts and branching glands

Gland density is irregular throughout the compartment

No or only focal areas of ”normal PE” encountered

Increased crowding can be seen with increased estrogen duration.

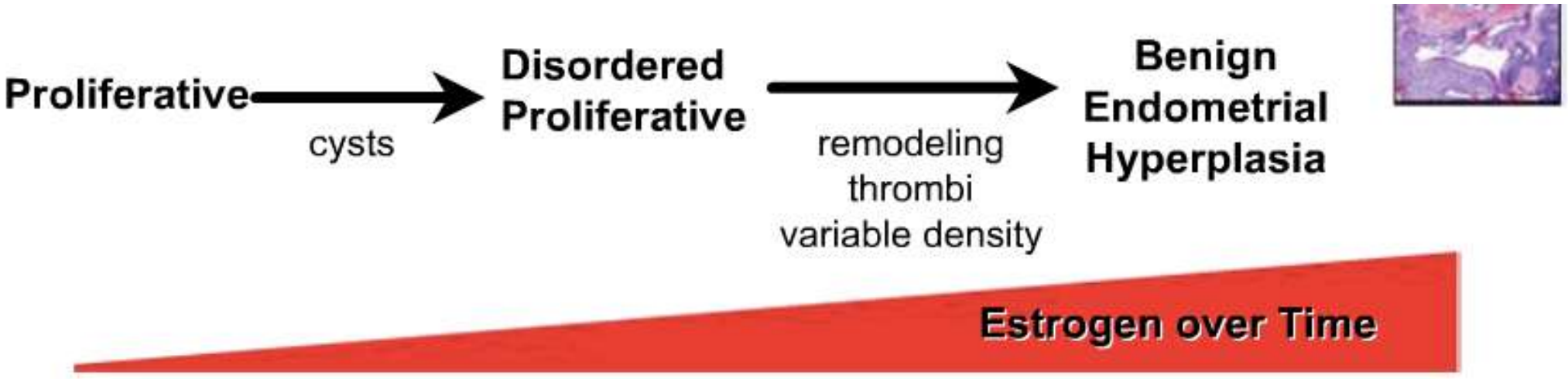
No altered cytology!



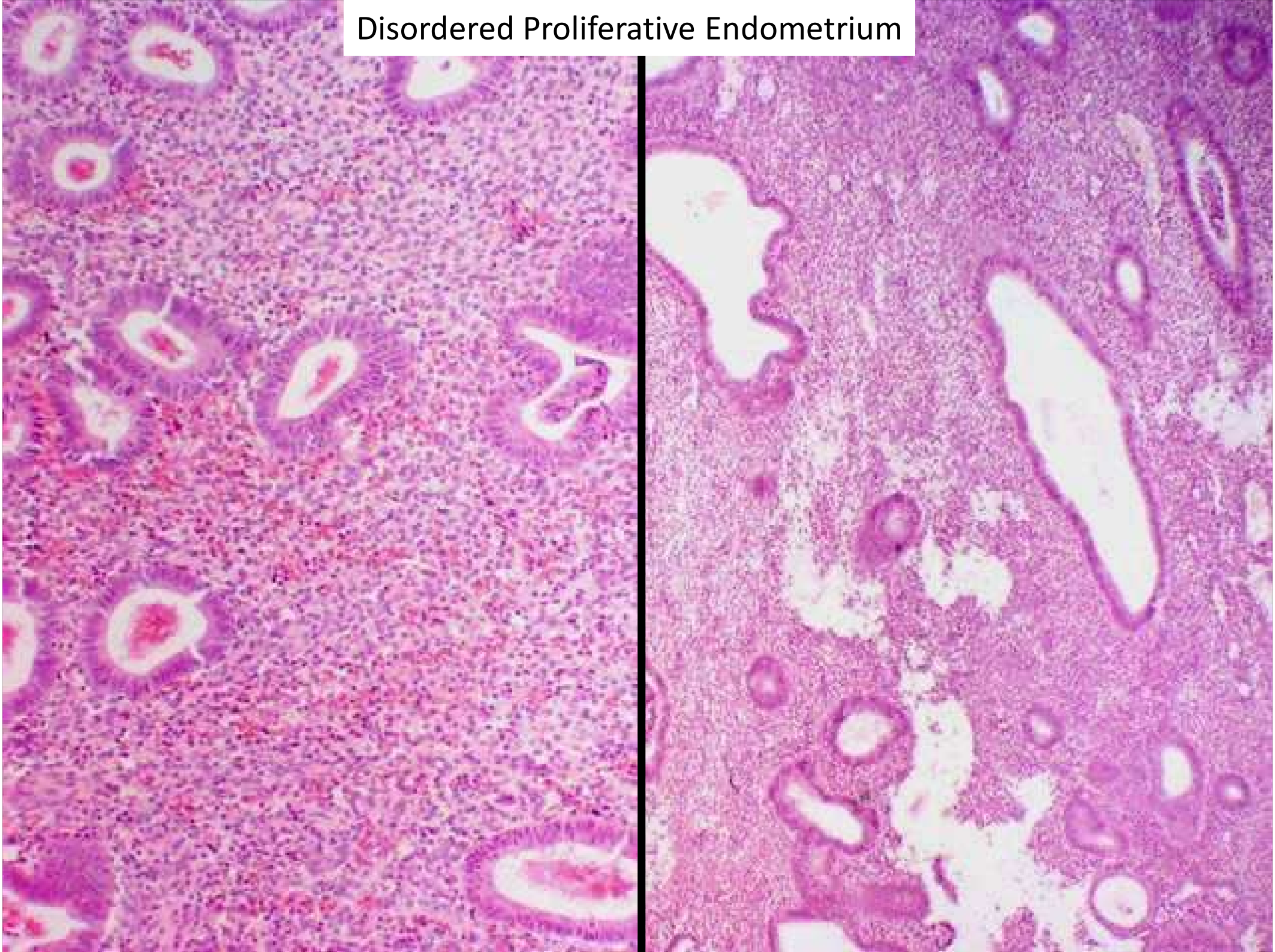
# Where is the line between DPE and NAH?

"Disordered Proliferative Endometrium": well-spaced, cystically dilated/enlarged glands without cribriforming or epithelial stratification, resembling the pattern that is typical in the perimenopausal state.

"Non-Atypical Hyperplasia": the presence of more significant and/or diffuse gland crowding but falling short of the criteria for AH/EIN, with no cribriforming, epithelial stratification, or definitive cytologic distinctiveness/atypia.

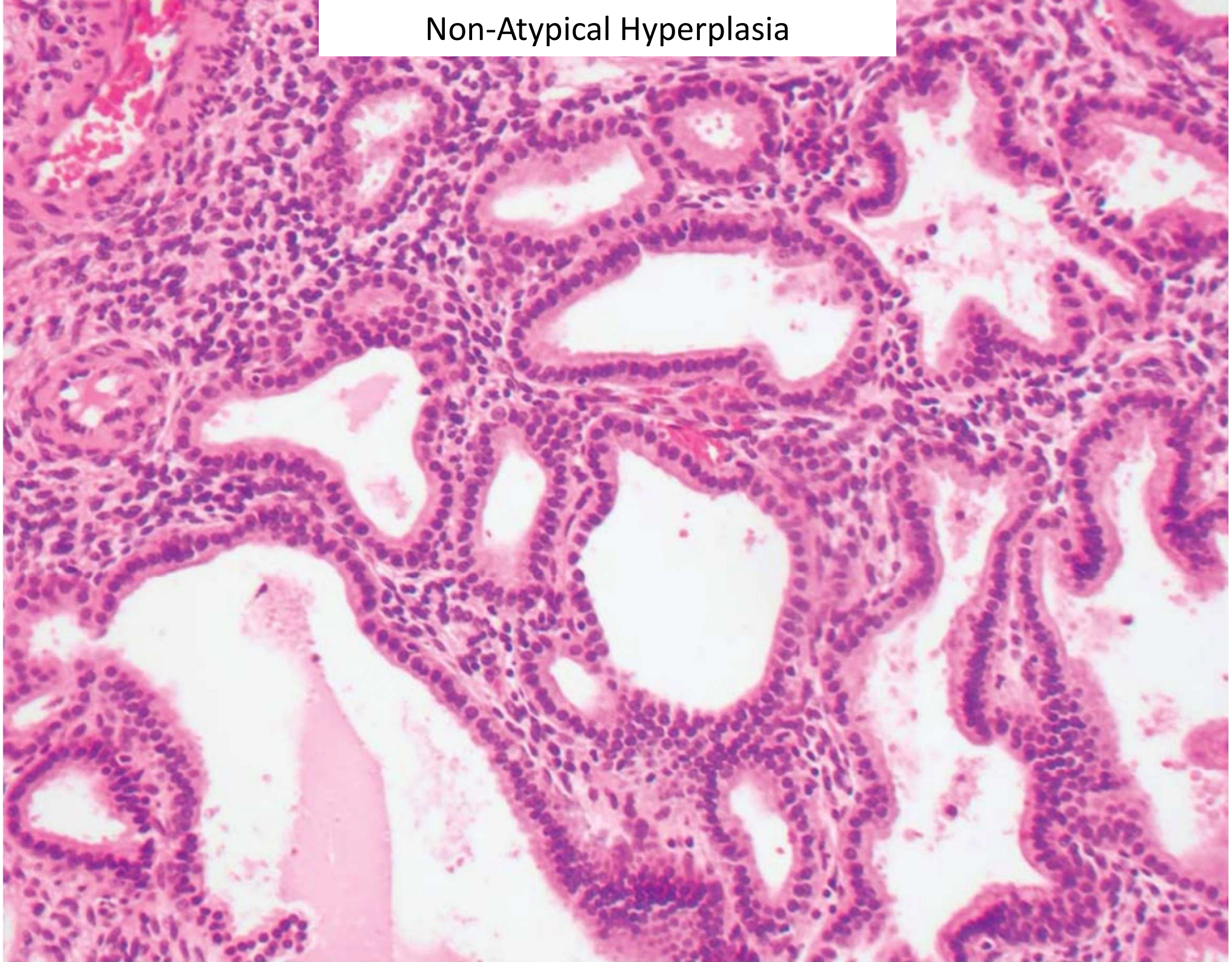



Monte NM, Webster KA, Neuberg D, Dressler GR, Mutter GL. Joint loss of PAX2 and PTEN expression in endometrial precancers and cancer. Cancer Res. 2010 Aug 1;70(15):6225-32. doi: 10.1158/0008-5472.CAN-10-0149. Epub 2010 Jul 14. PMID: 20631067; PMCID: PMC2912978.


Disordered Proliferative Endometrium

Disordered Proliferative Endometrium

Non-Atypical Hyperplasia



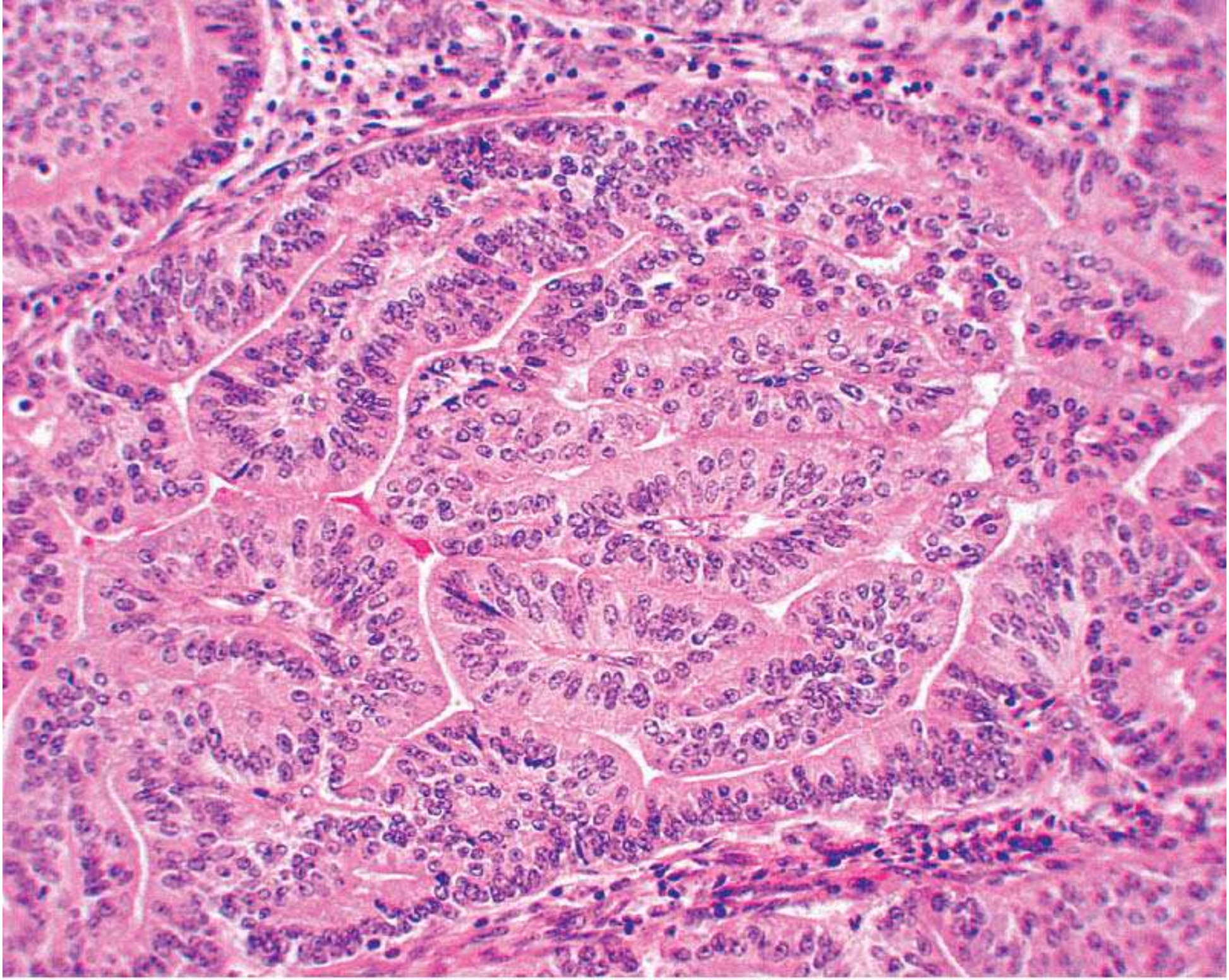
# Carcinoma

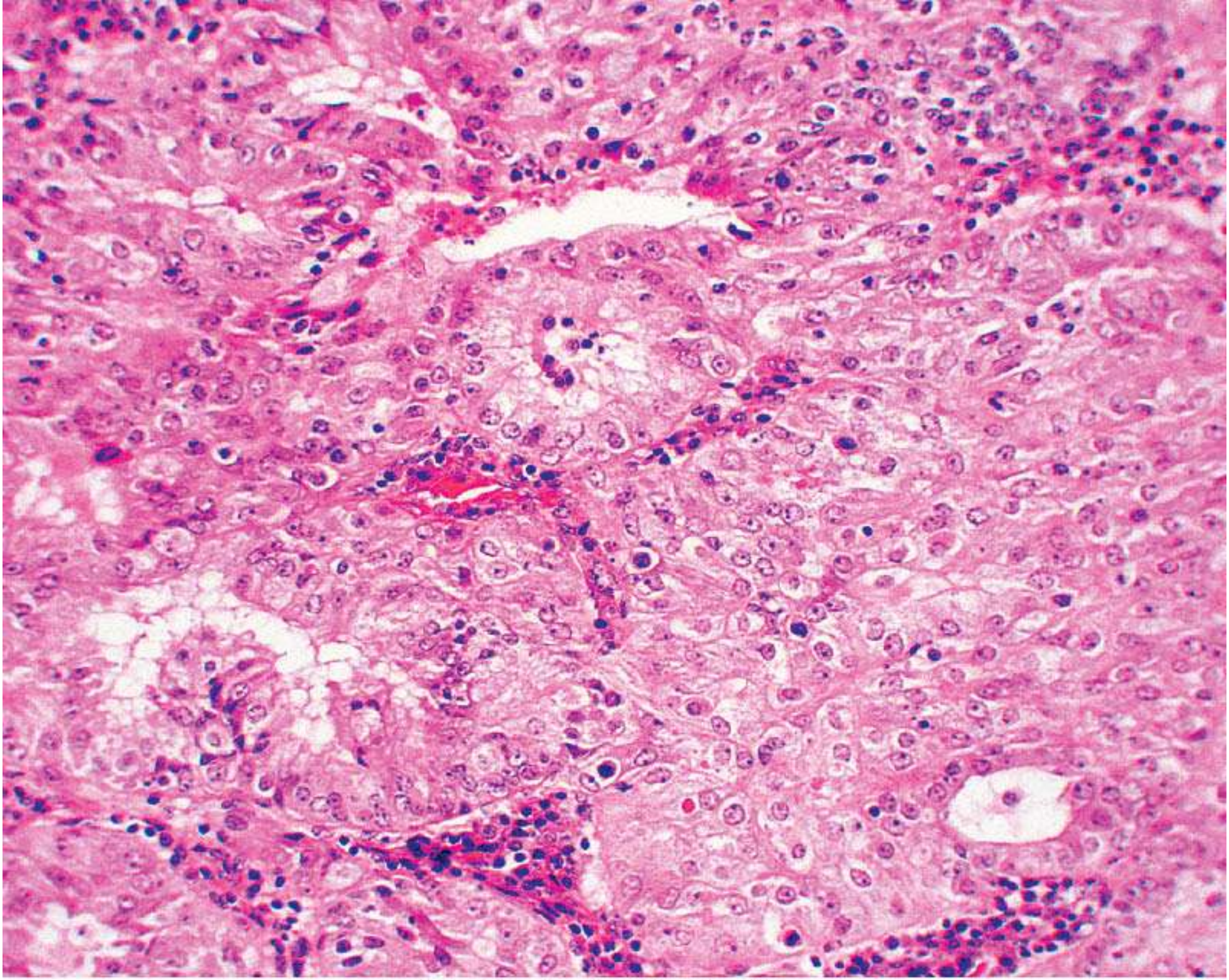
Maze-like (“Labyrinth-like”) growth

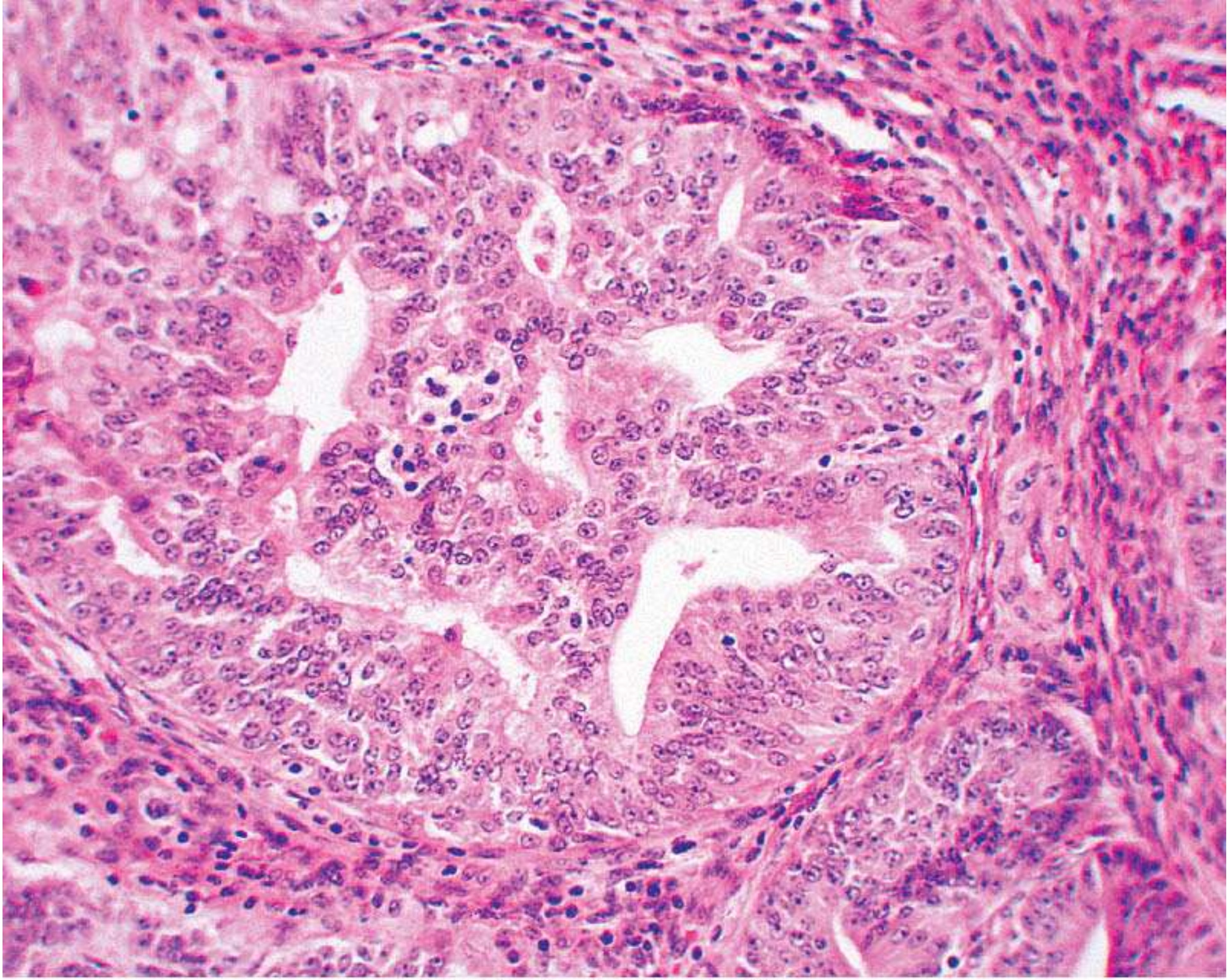
Solid

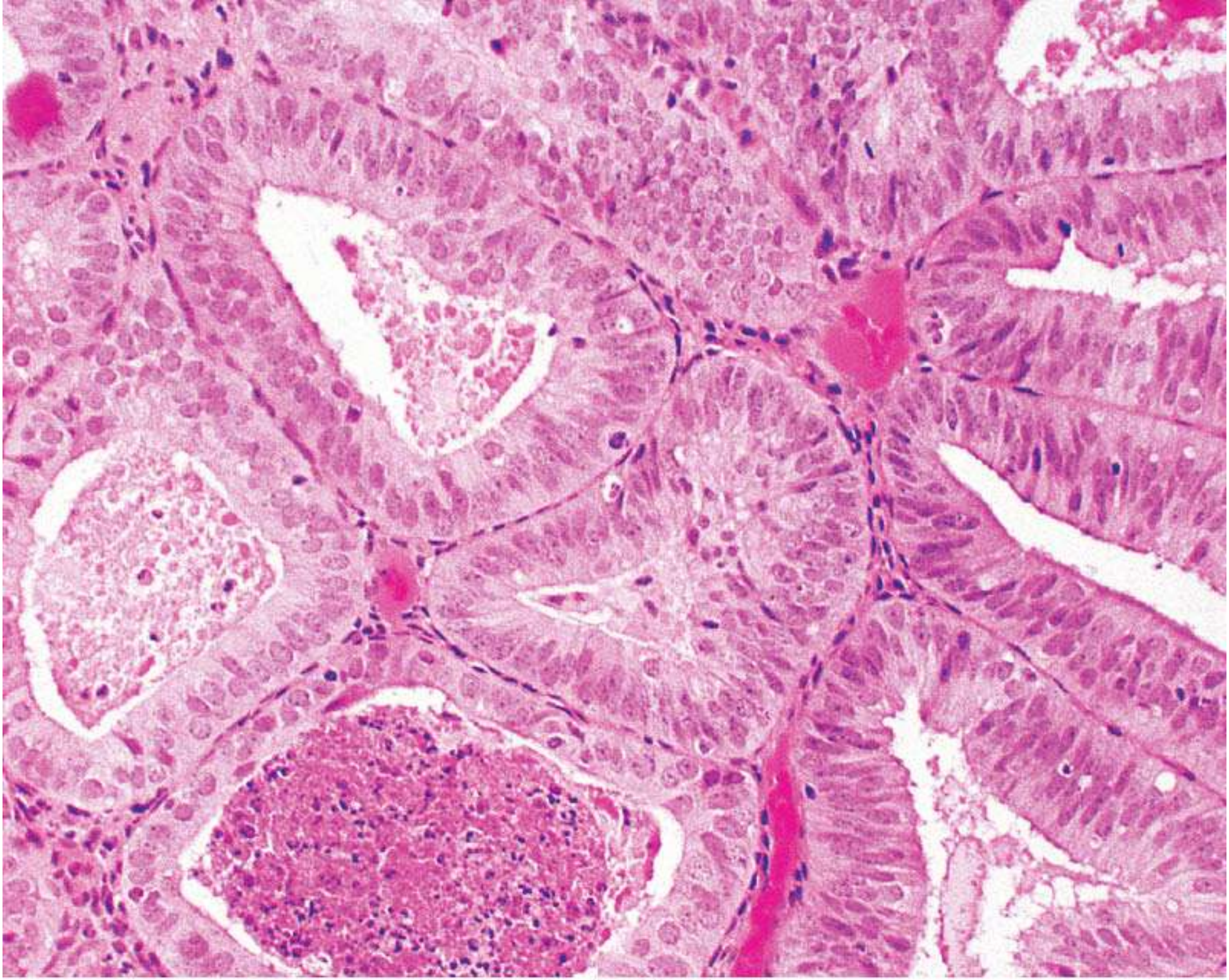
Cribriform

“Gaping gland”









# Take Home Messages

1. DPE and NAH represent a spectrum of mucosal changes in response to estrogen.
2. The exact dividing point between these two diagnoses is unclear, and probably has poor reproducibility.
3. A key aspect of EIN is excluding benign mimics, and excluding overt carcinoma.

# Approaching Metaplastic Changes

# Metaplasias do not exclude EIN

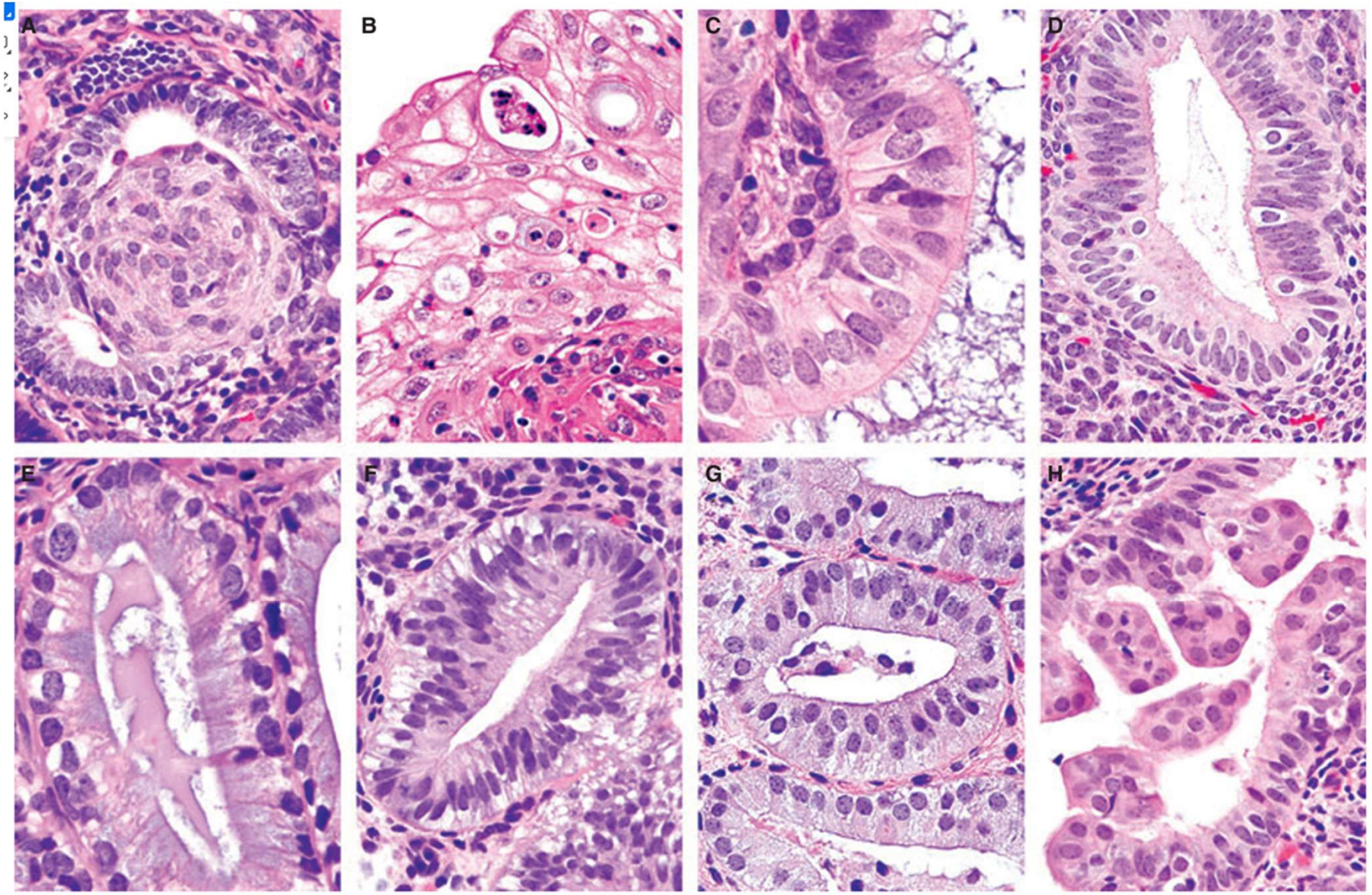
Metaplasias are challenging because they typically remove any “classical, objective atypia”.

Two issues to consider:

1) Does the lesion fulfill the criteria for EIN?
   Dx: EIN or suspicious for EIN
2) What is the architectural complexity of the lesion?
   Dx: Suspicious for neoplasia (EIN and/or cancer)

Carlson JW, Mutter GL. Endometrial intraepithelial neoplasia is associated with polyps and frequently has metaplastic change. Histopathology. 2008 Sep;53(3):325-32. doi: 10.1111/j.1365-2559.2008.03104.x. Epub 2008 Jul 15. PMID: 18637968; PMCID: PMC2574678.

# Metaplasia in EIN

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# EIN frequently displays metaplasia

39/83 (47%) in one study

- 18% squamous morular
- 14% tubal secretory
- 5% each of secretory, mucinous or ciliated change

Of all these, secretory often presents the greatest diagnostic difficulty.

Carlson JW, Mutter GL. Endometrial intraepithelial neoplasia is associated with polyps and frequently has metaplastic change. Histopathology. 2008 Sep;53(3):325-32. doi: 10.1111/j.1365-2559.2008.03104.x. Epub 2008 Jul 15. PMID: 18637968; PMCID: PMC2574678.

# Secretory changes can present a unique problem

Secretory endometrium (SE) changes every day

History is often not provided

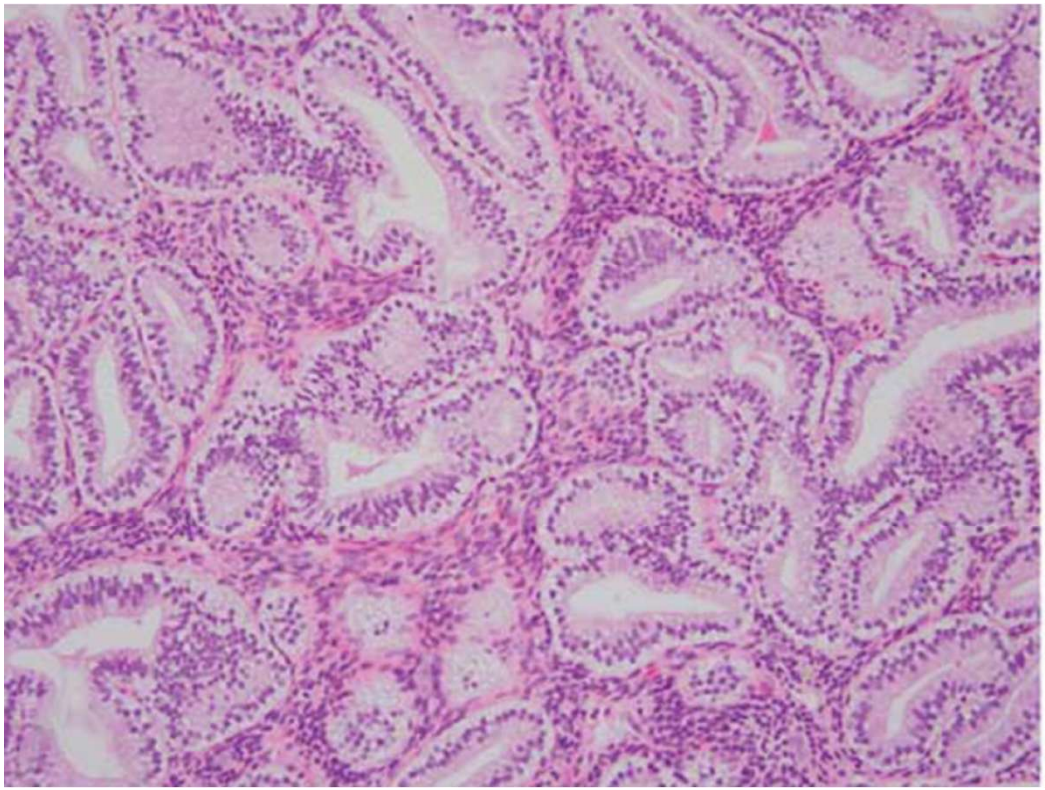
Late secretory endometrium can show crowded glands

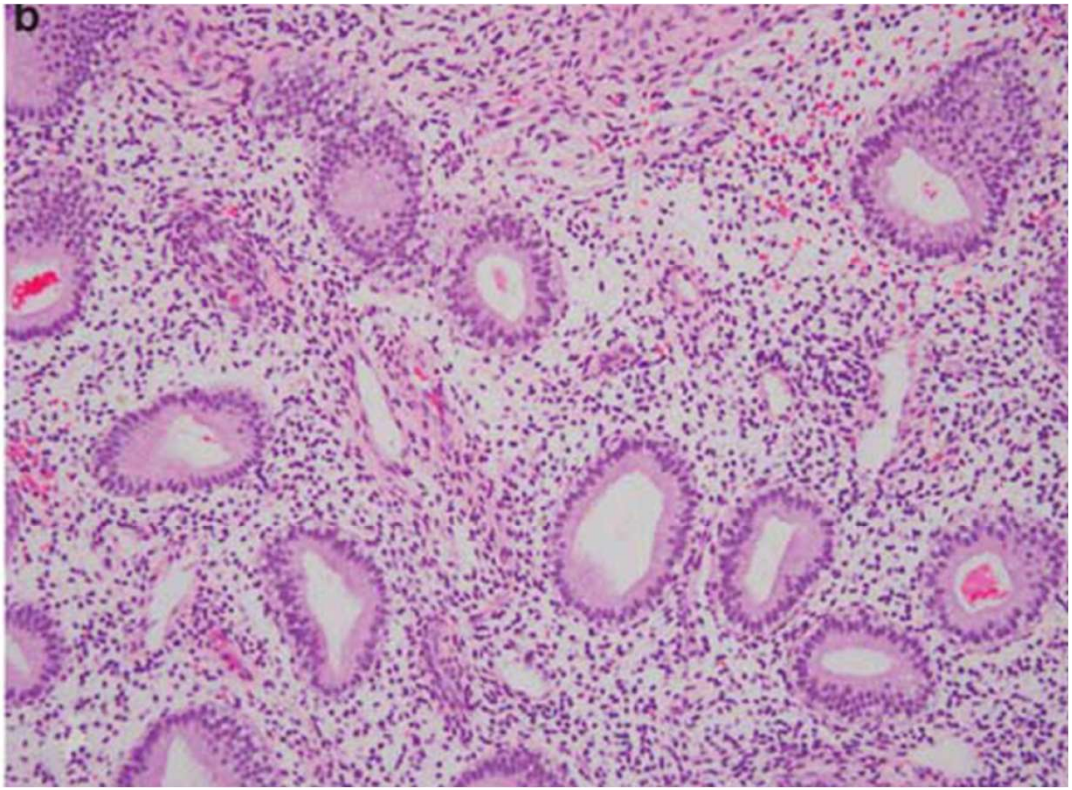
The patient can may have either endogenous progesterone due to ovulation or exogenous due to hormonal therapy.


- Truskinovsky AM, Lifschitz-Mercer B, Czernobilsky B. Hyperplasia and carcinoma in secretory endometrium: a diagnostic challenge. Int J Gynecol Pathol. 2014 Mar;33(2):107-13. doi: 10.1097/PGP.0b013e3182a2945d. PMID: 24487463.
- Gurda GT, Baras AS, Kurman RJ. Ki-67 index as an ancillary tool in the differential diagnosis of proliferative endometrial lesions with secretory change. Int J Gynecol Pathol. 2014 Mar;33(2):114-9. doi: 10.1097/PGP.0000000000000092. PMID: 24487464.
- Parra-Herran CE, Monte NM, Mutter GL. Endometrial intraepithelial neoplasia with secretory differentiation: diagnostic features and underlying mechanisms. Mod Pathol. 2013 Jun;26(6):868-73. doi: 10.1038/modpathol.2012.231. Epub 2013 Jan 18. PMID: 23328979.

## Secretory EIN

## Background endometrium



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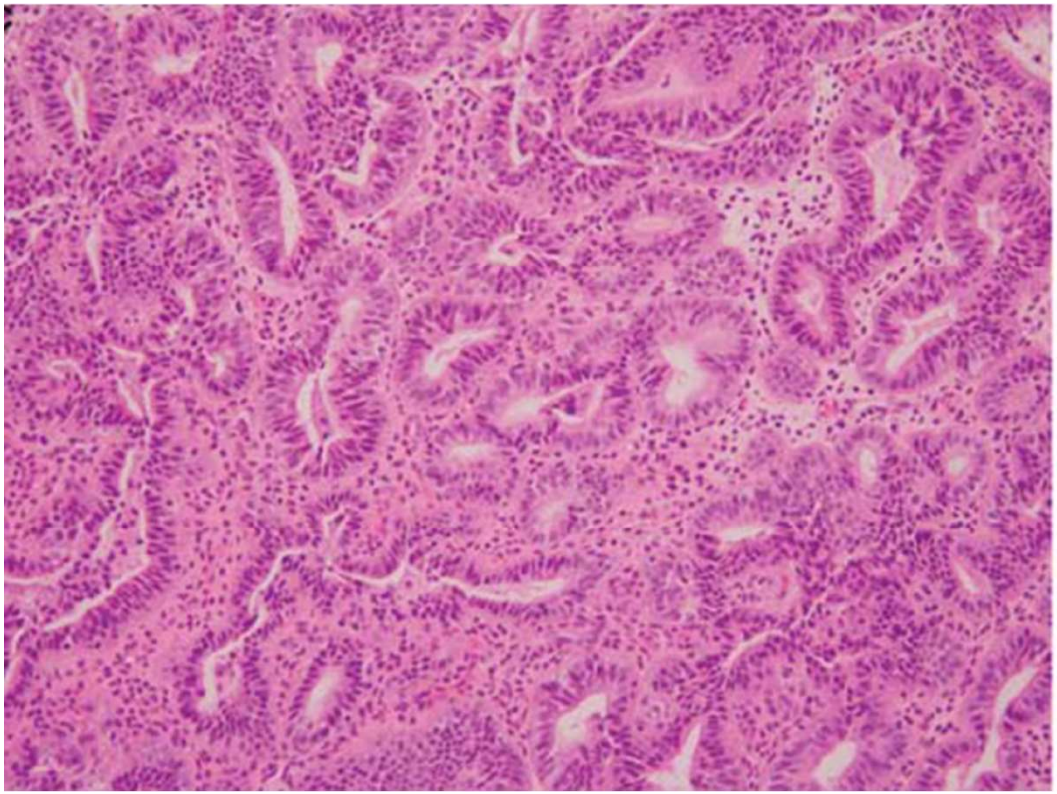

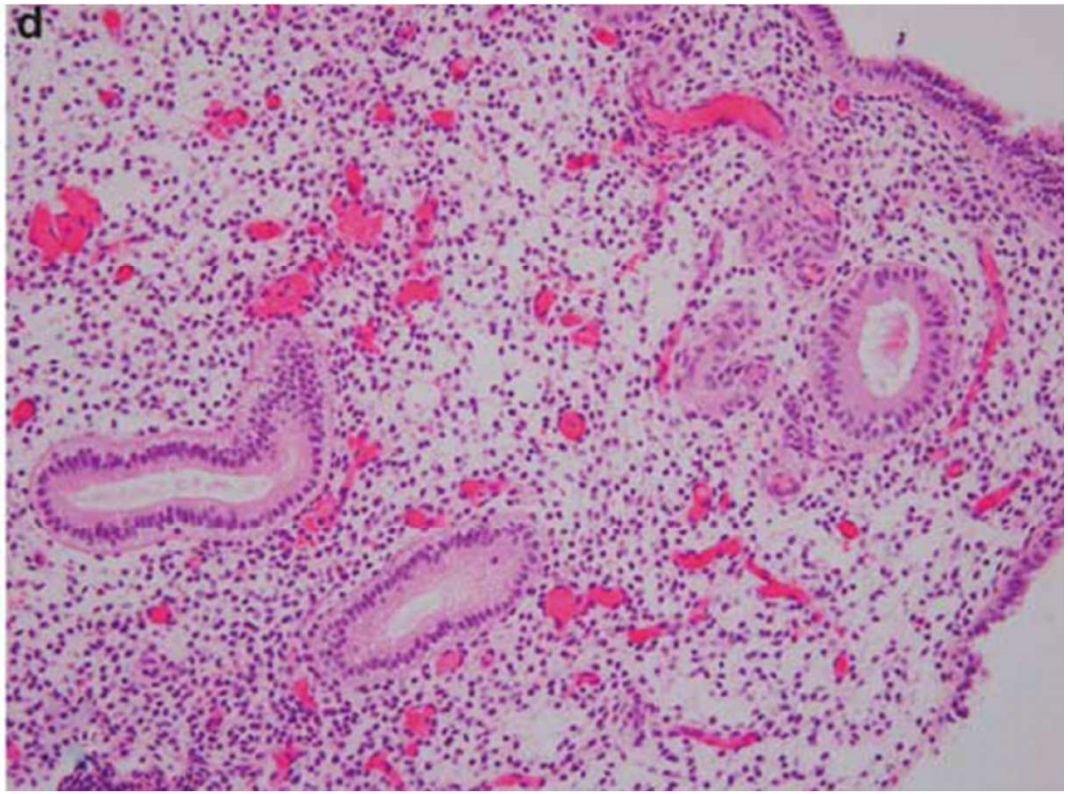


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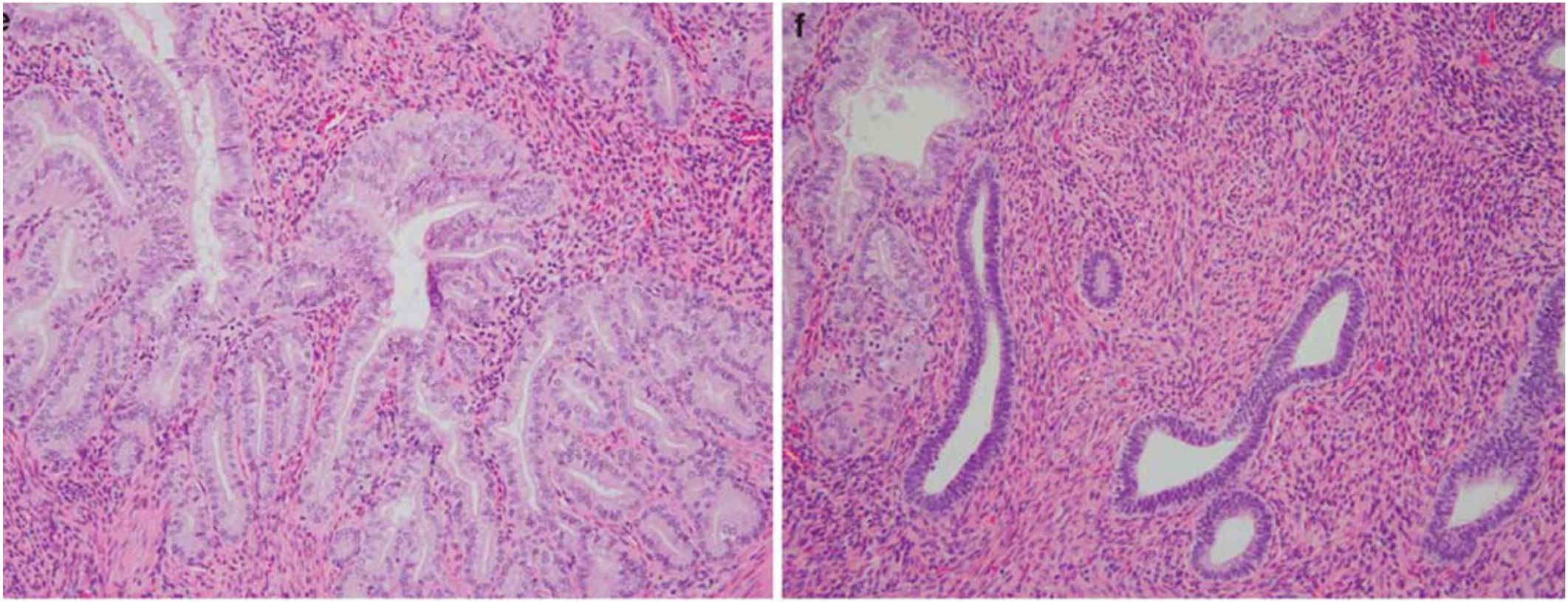
Secretory EIN

Background endometrium



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The majority (93%) of secretory EIN occur in patients with evidence of circulating progestins, as seen in the background endometrium.

“contrast between lesion and background cytology is generally maintained throughout and thus more informative than fixed definitions of cytological atypia.”

# Architecture and Ki-67

Morphologic features that best distinguish hyperplasia or carcinoma from the secretory endometrium include

- Glandular crowding “that should stand out from the background”
- Dilated, irregularly shaped glands, including budding or branching,
- Stroma in the case of an endometrial polyp,
- Cribriform or confluent glands in cases of carcinoma.

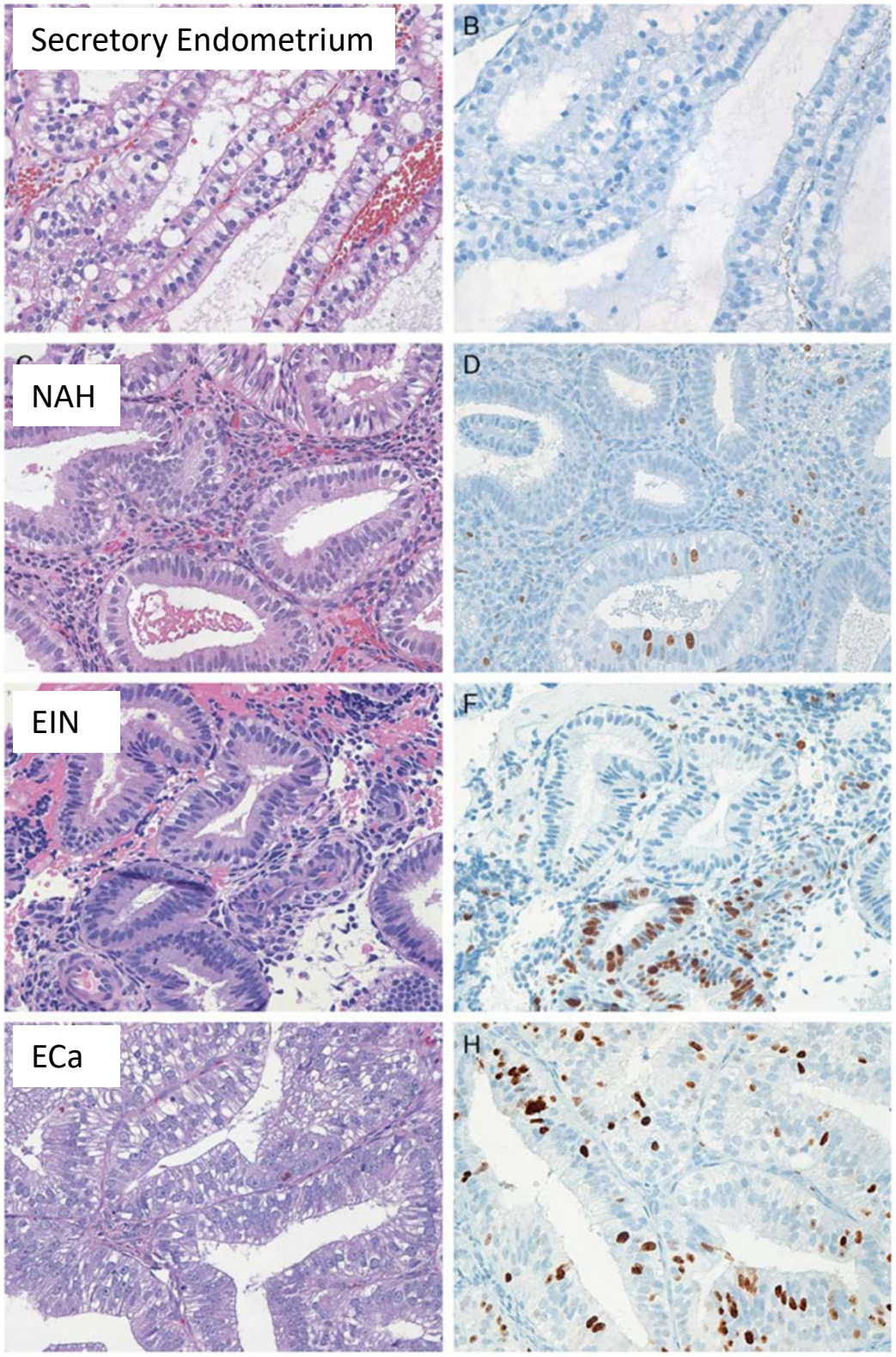
# Architecture and Ki-67

| Diagnosis or diagnostic category | Ki67 index (range) |
|---|---|
| Controls (secretory and gestational endometria) | 4.6 (0–9) |
| Non-neoplastic lesions | 5.4 (3–10) |
| Complex hyperplasia without atypia | 9.3 (3–15) |
| Neoplastic lesions | 44.8 (12–84) |

**TABLE 2.** *Ki-67 positivity in assessment of endometrium with secretory change*

| Ki-67 positivity | Interval endometrium (+ control) | Secretory endometrium | Nonatypical hyperplasia | Atypical hyperplasia | Endometrial carcinoma |
|---|---|---|---|---|---|
| Manual count (gold standard) (%) | 56 ± 22 | 2.6 ± 3.8 | 17 ± 8.0** | 42 ± 20** | 60 ± 21** |
| Estimate (preselected) (%) | 64 ± 31 | 1.3 ± 2.3 | 13 ± 16** | 47 ± 28** | 72 ± 32** |
| Estimate (whole slides) (%) | 54 ± 27 | 0.8 ± 0.8 | 11 ± 12** | 33 ± 27** | 73 ± 32** |
| # cases (n) (total = 74) | 11 | 19 | 22 | 11 | 11 |

**$P \leq 0.01$ (within each row, relative to secretory endometrium).


Secretory Endometrium
B
NAH
D
EIN
F
ECa
H

# Take Home Messages

1. EIN with secretory change can be identified by its unique architecture, and clear cytologic demarcation.
2. Ki-67 appears to be a useful adjunct.

# Biomarkers in EIN

Biomarkers *assist* morphologic evaluation.

In other words: You cannot diagnose EIN if the morphology is not diagnostic.

Biomarkers: PAX2, B-catenin and PTEN

ORIGINAL ARTICLE

OPEN

# Reliable Identification of Endometrial Precancers Through Combined Pax2, β-Catenin, and Pten Immunohistochemistry

*Mitzi Aguilar, BS,* Hao Chen, MD, PhD,* Glorimar Rivera-Colon, MD,* Shuang Niu, MD,* Kelley Carrick, MD,* Katja Gwin, MD,* Ileana C. Cuevas, PhD,* Subhransu S. Sahoo, PhD,* Hao-Dong Li, PhD,* Song Zhang, PhD,†‡ Wenxin Zheng, MD,*‡ Elena Lucas, MD,*‡ and Diego H. Castrillon, MD, PhD*‡*

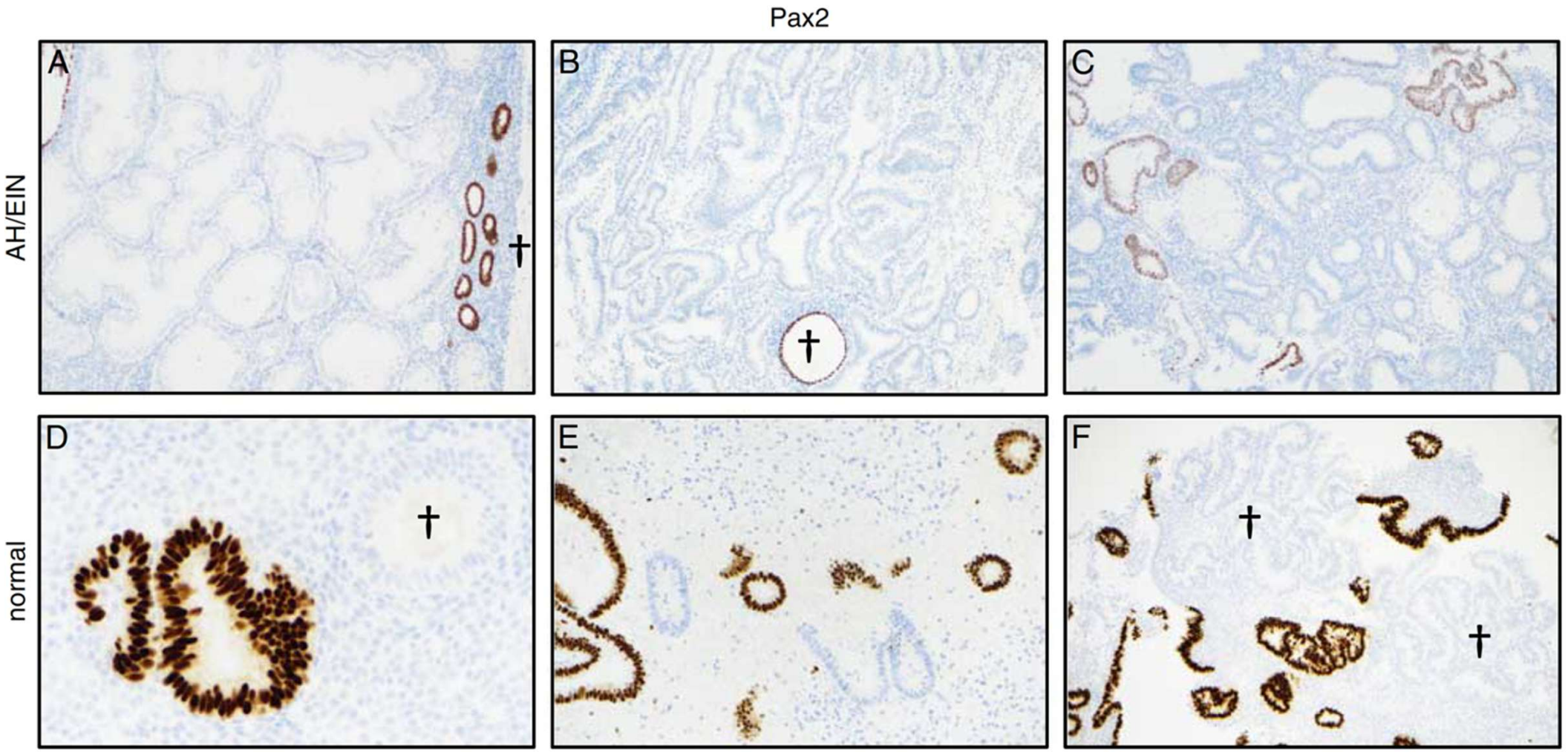
111 EIN cases

79 controls (65 proliferative, 11 secretory, 3 interval phase)

| Protein | EIN | Normal |
|---|---|---|
| PAX2 | Aberrant: Loss or reduced expression over broad areas | Occasional loss in individual glands or focal areas <5% |
| PTEN | Aberrant: Complete absence, sometimes heterogeneous<br><br>Other patterns: Weak staining is NOT aberrant | Occasional loss in individual glands or focal areas <5% |
| B-catenin | Aberrant: Nuclear staining as strong or stronger than cytoplasmic | Membranous with some cytoplasmic |

Aguilar M, Chen H, Rivera-Colon G, Niu S, Carrick K, Gwin K, Cuevas IC, Sahoo SS, Li HD, Zhang S, Zheng W, Lucas E, Castrillon DH. Reliable Identification of Endometrial Precancers Through Combined Pax2, β-Catenin, and Pten Immunohistochemistry. Am J Surg Pathol. 2022 Mar 1;46(3):404-414. doi: 10.1097/PAS.0000000000001810. PMID: 34545858; PMCID: PMC8860214.

# PAX2

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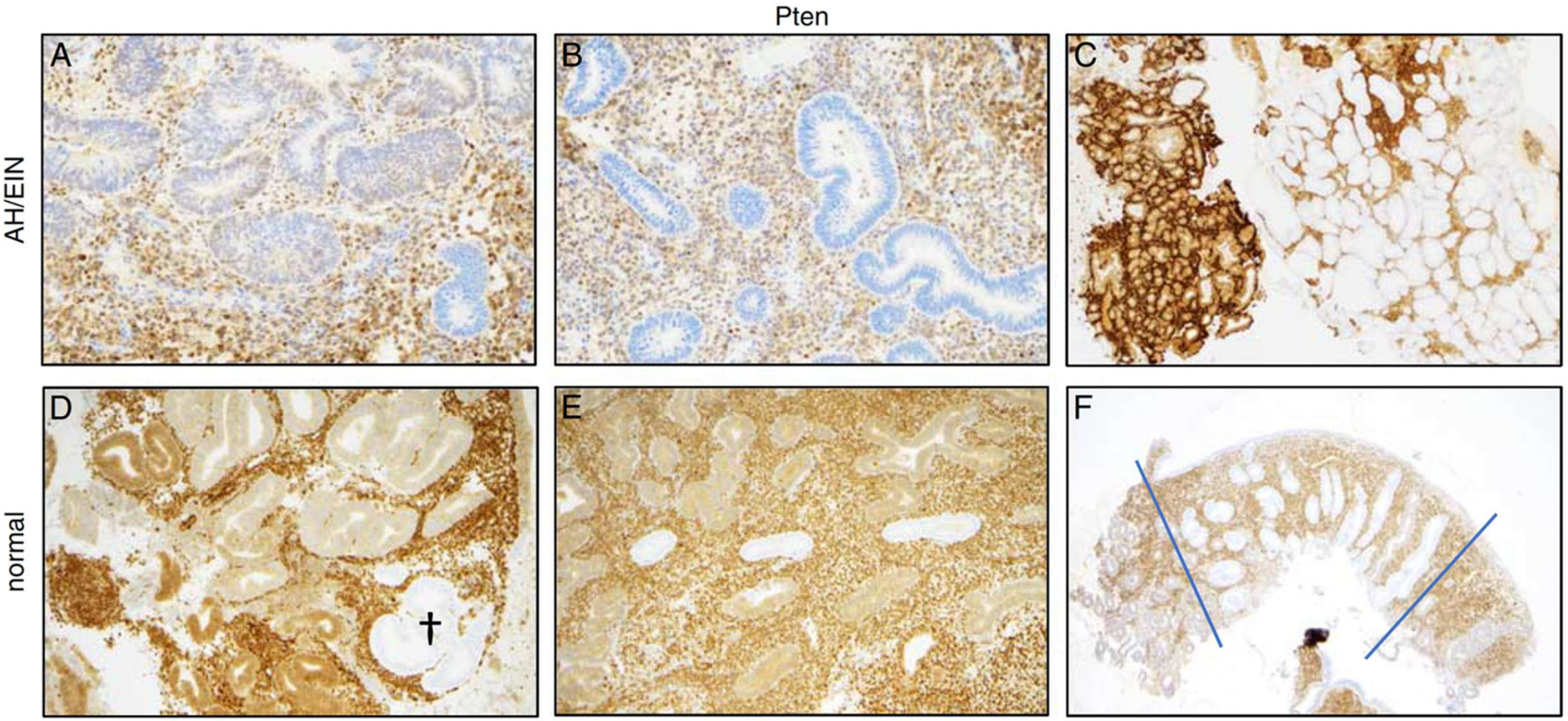
# PTEN

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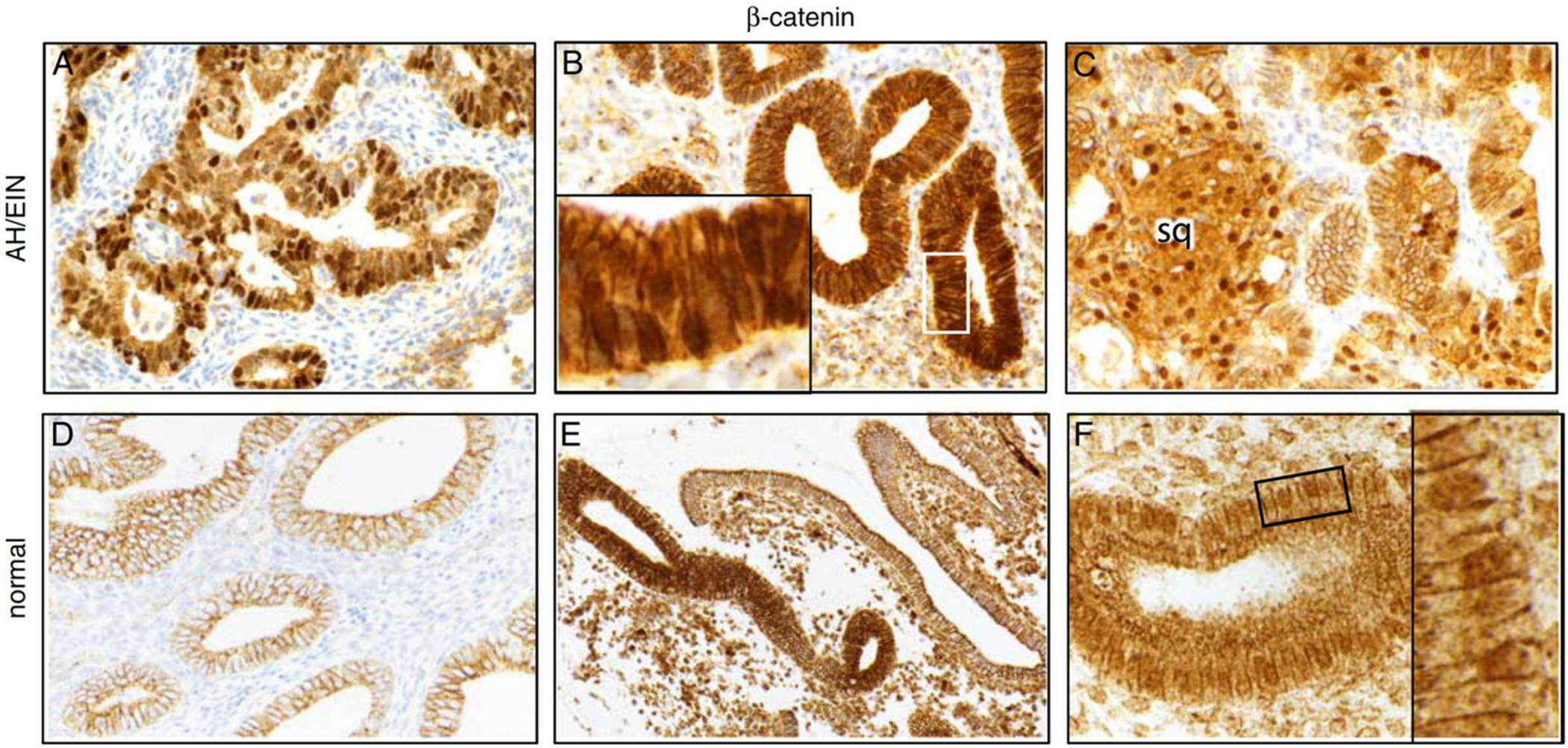
# B-catenin

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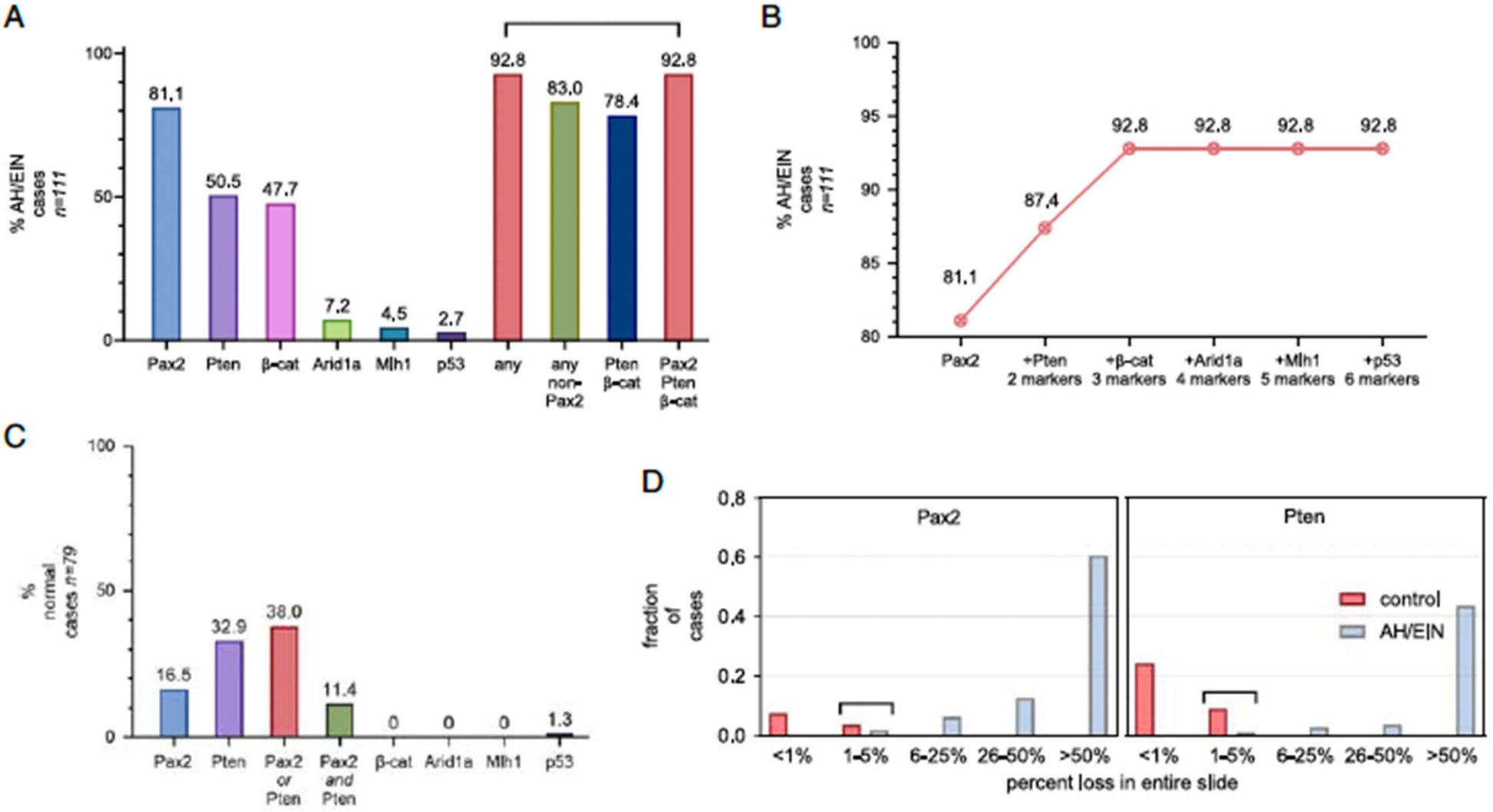
# A panel consisting of only Pax2, Pten, and β-catenin identified 92.8% of cases.




Monte NM, Webster KA, Neuberg D, Dressler GR, Mutter GL. Joint loss of PAX2 and PTEN expression in endometrial precancers and cancer. Cancer Res. 2010 Aug 1;70(15):6225-32. doi: 10.1158/0008-5472.CAN-10-0149. Epub 2010 Jul 14. PMID: 20631067; PMCID: PMC2912978.

- In order of number of cases detected, the most frequently aberrant markers in AH/EIN were Pax2 (81.1% of cases), Pten (50.5%), β-catenin (47.7%), Arid1a (7.2%), Mlh1 (4.5%), and p53 (2.7%).
- The majority of cases showed aberrant expression of ≥ 2 markers. All 6 markers together identified 92.8% of cases.
- Arid1a, Mlh1, and p53 were robust and readily scored markers, but all cases showing aberrant expression of these 3 markers were also detected by Pax2, Pten, or β-catenin.
- A focused panel of only 3 markers (Pax2, Pten, and β-catenin) showed optimal performance characteristics as a diagnostic adjunct in the histopathologic diagnosis of AH/EIN. Use of this panel is practicable and robust, with at least 1 of the 3 markers being aberrant in 92.8% of AH/EIN.

# What about following EIN during progestin therapy?

ORIGINAL ARTICLE

## Specific Biomarker Expression Patterns in the Diagnosis of Residual and Recurrent Endometrial Precancers After Progestin Treatment

*A Longitudinal Study*

*Hao Chen, MD, PhD,* Elena Lucas, MD,* Amanda L. Strickland, MD,* Kelley Carrick, MD,* Katja Gwin, MD, PhD,* Diego H. Castrillon, MD, PhD,*†‡ Glorimar Rivera-Colon, MD,* Shuang Niu, MD,* Kyle H. Molberg, MD,* and Wenxin Zheng, MD*†‡*

54 patients

254 endometrial biopsies

Index biopsy for all patients with EIN

Subsequent progestin therapy with interval biopsies

Morphologic review and PAX2/PTEN on all biopsies

Divided into (1) persistent or residual disease; (2) recurrent disease; (3) complete response.

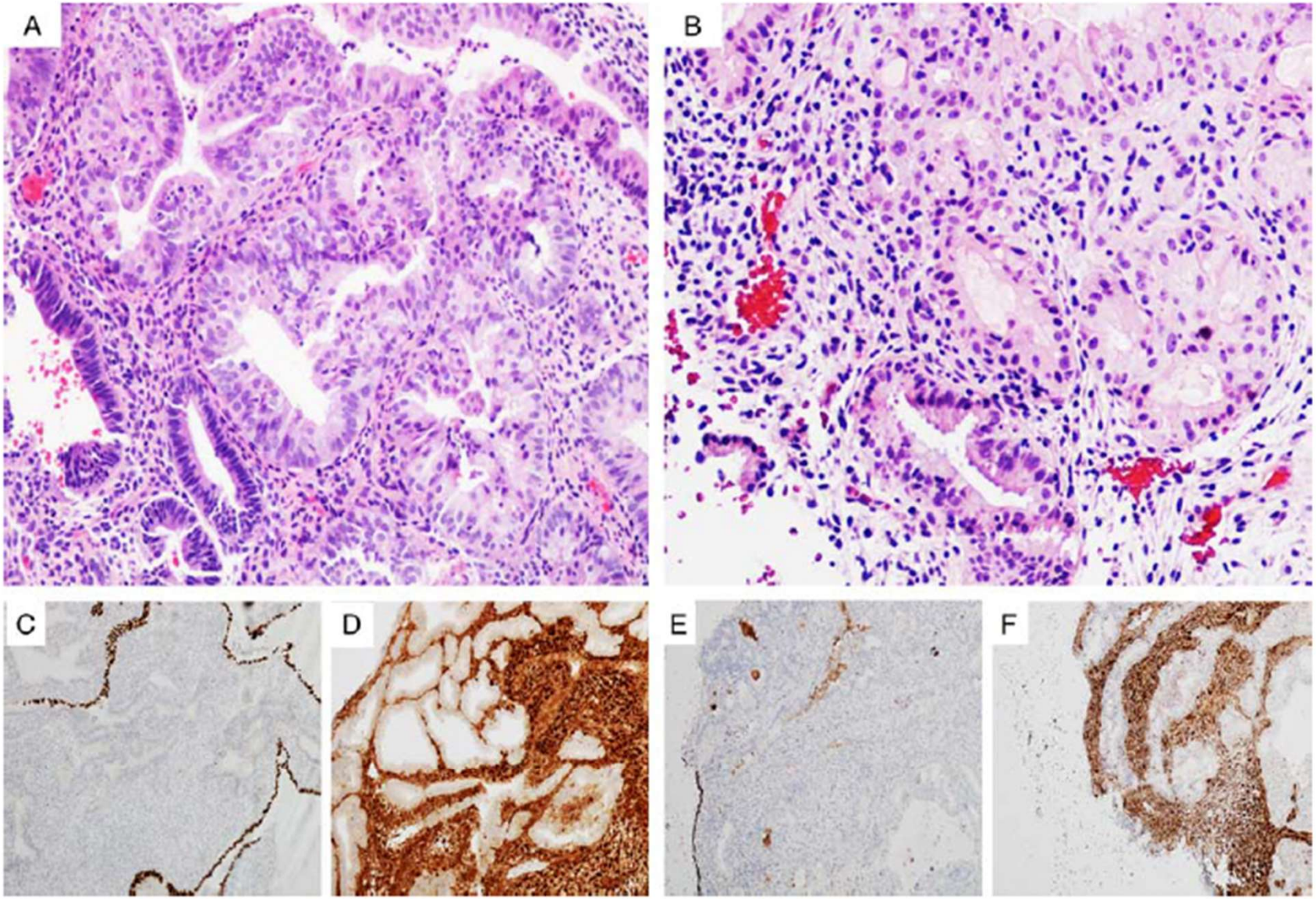
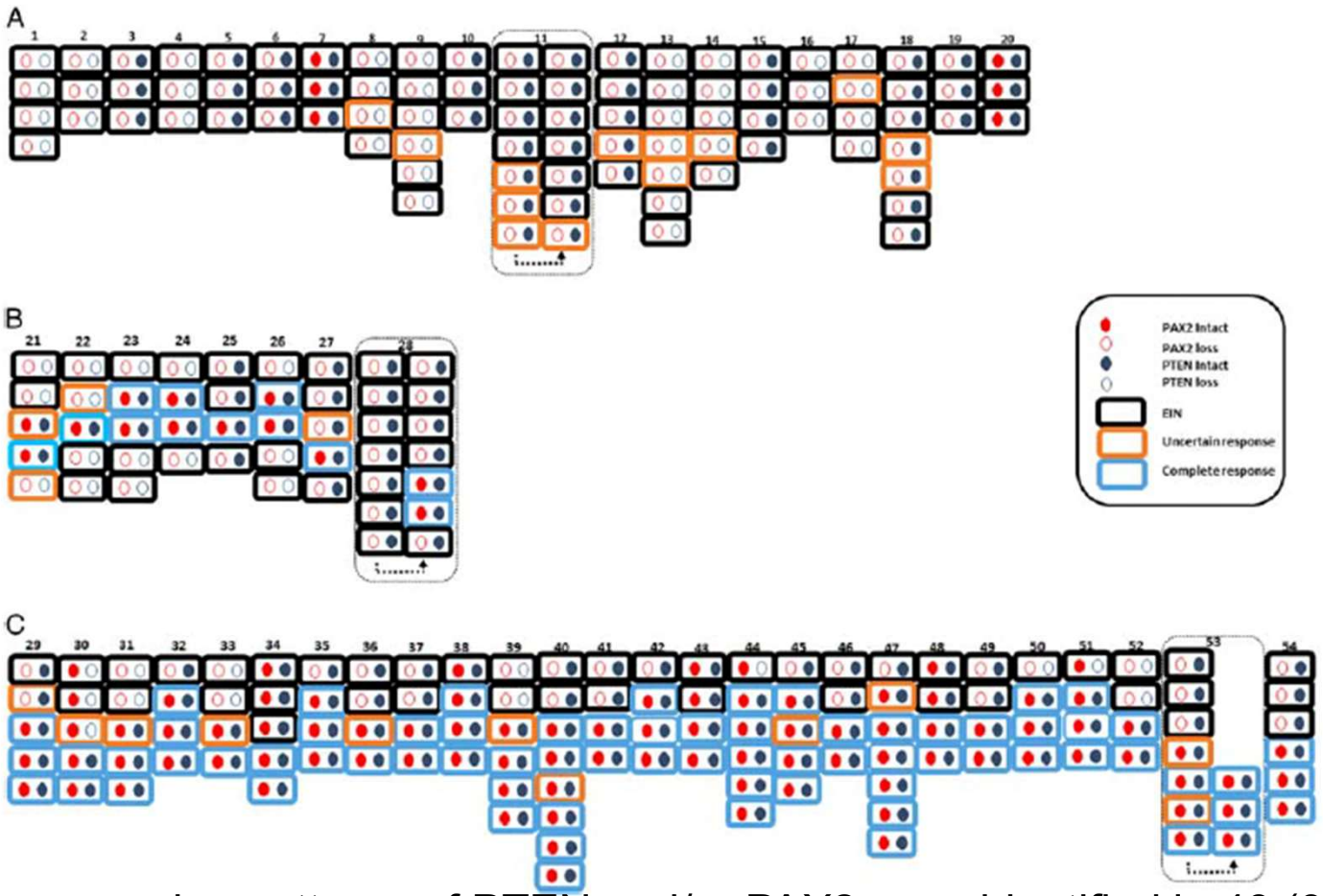



**FIGURE 3.** An example of persistent PTEN and PAX2 expression pattern in initial and follow-up biopsies (patient #4). H&E (A) and corresponding PAX2 (C) and PTEN (D) from biopsy #1. H&E (B) with persistent AH/EIN showing gland crowding and nuclear atypia. Corresponding PAX2 (E) and PTEN (F) from biopsy #3. Both initial and follow-up biopsies show loss of PAX2 and PTEN staining. Retained expression of PAX2 and PTEN is focally seen in adjacent normal epithelium.




- Aberrant expression patterns of PTEN and/or PAX2 were identified in 48 (88.9%) of the 54 primary biopsies and persisted in persistent/recurrent AH across serial endometrial biopsies (n= 99, P<0.00001)
- Normal PTEN and PAX2 expressions were consistently observed in optimally treated cases (n= 84, P<0.00001).
- Follow-up biopsies that showed a morphologically uncertain response but a PTEN/PAX2 expression pattern identical to the initial biopsy were significantly correlated with persistent or recurrent disease (n =18, P=0.000182), as evidenced by areas with morphologic features diagnostic of AH on subsequent biopsy.

# Biomarkers in EIN

Biomarkers *assist* morphologic evaluation.

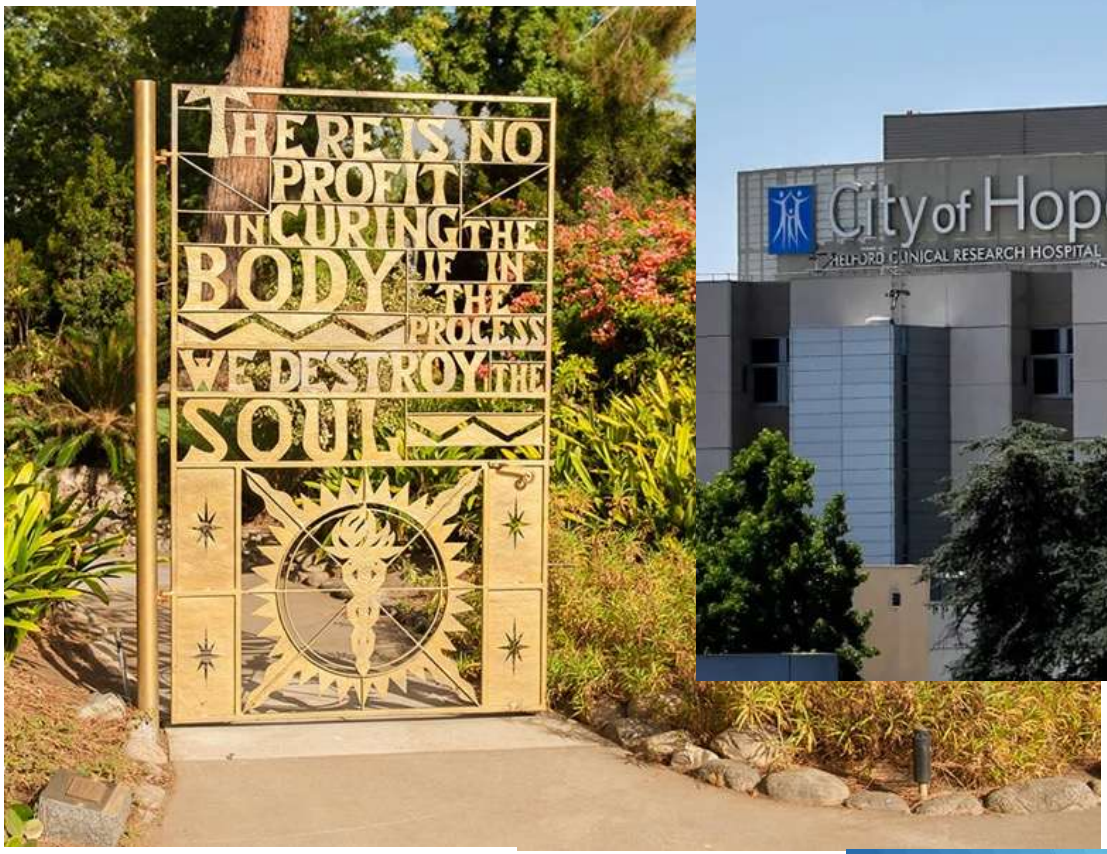
Most useful: Subtle difference between background and EIN morphology

These biomarkers can highlight rare, non-neoplastic, background glands that can then be evaluated in the H&E

# Take Home Messages

1. Biomarker studies with PAX2, PTEN and B-catenin appear to be very useful in EIN diagnosis
2. They can assist with primary diagnosis
3. They can assist with identifying residual disease.
4. They may have a role in teasing out patients at risk from the DPE/NAH group! More data is needed here, especially prospective studies.

# Thank you for your attention!





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