CURRENT UPDATES ON PD-L1 AND HER2 TESTING IN GASTROESOPHAGEAL CANCER: A PRACTICAL APPROACH

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February 10th, 2022

DISCLOSURES

- I do not have any conflicts of interest or disclosures for this presentation

OBJECTIVES

- Learn the indications for PD-L1 testing in gastroesophageal cancers
- Understand the components within the Combined Positive Score (CPS) equation
- Participate in practical examples for CPS scoring and identify common pitfalls
- Identify the clinical utility for HER2 testing in gastroesophageal cancers
- Learn the HER2 scoring system for gastroesophageal cancers and recognize the differences from the scoring system used in breast cancers

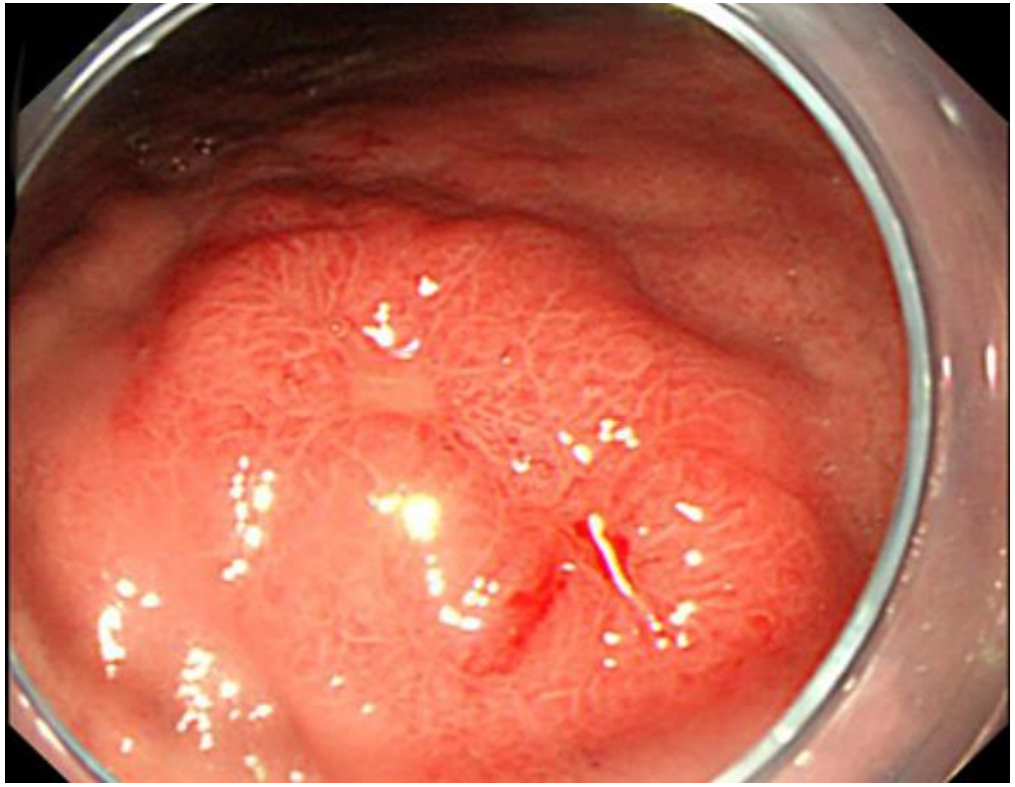
GASTROESOPHAGEAL CANCER

- Epidemiology:
  - Esophageal squamous cell carcinoma (SCC) is more common worldwide
  - GEJ adenocarcinoma is more common in Western countries and is increasing in prevalence
- Etiology:
  - SCC – alcohol, tobacco, HPV
  - Adenocarcinoma – GERD/Barrett's esophagus, obesity, Helicobacter pylori
- 5-year survival rates from 2011 to 2017 SEER Database:

	Esophageal	Gastric
Localized	46.4%	69.9%
Regional	25.6%	32.4%
Distant	5.2%	5.5%
All Stages	19.9%	32.4%

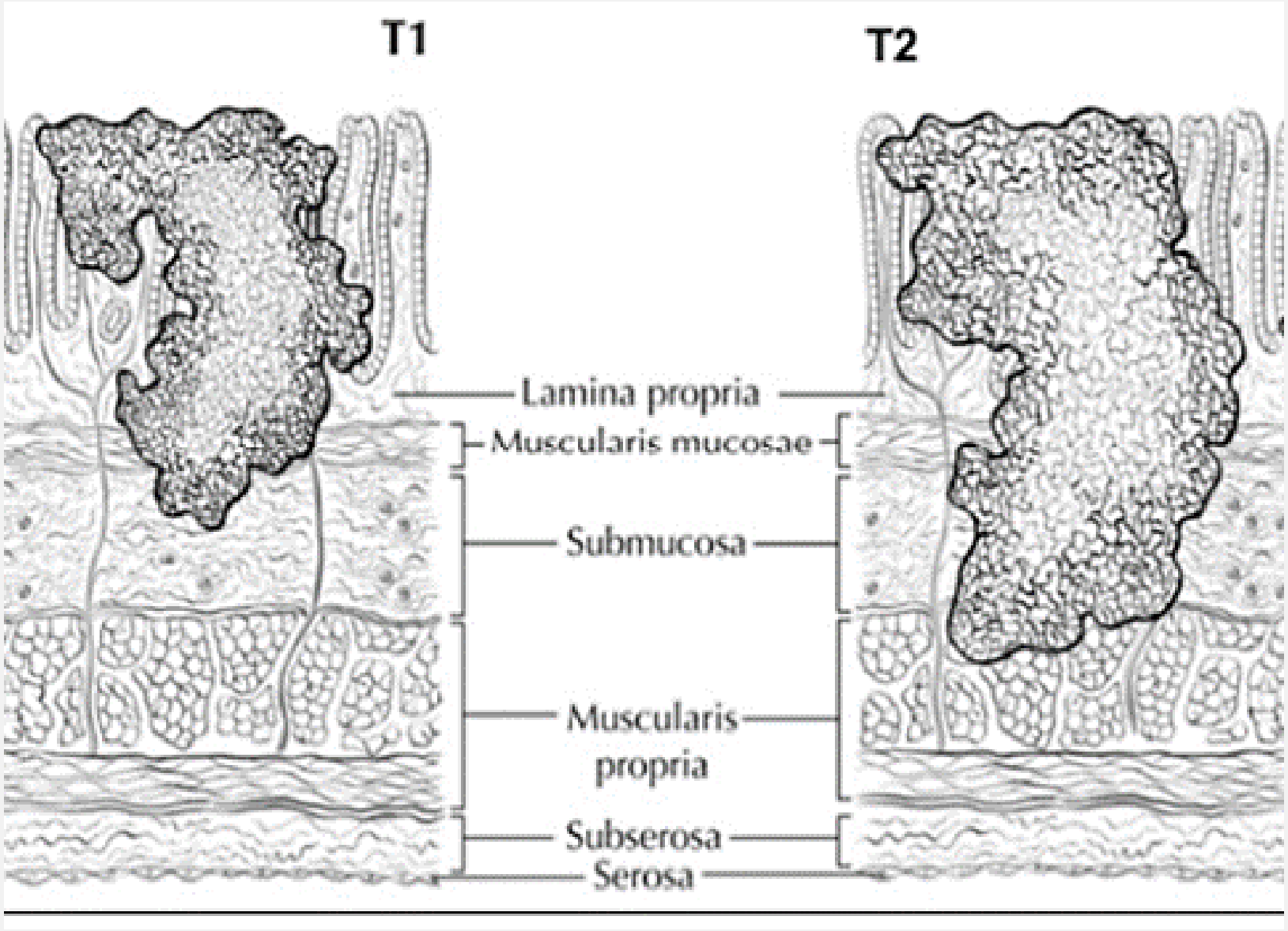
GASTROESOPHAGEAL CANCER

- Workup up:
  - Confirm diagnosis through biopsy
  - PET/CT
  - Endoscopic ultrasound - depth of invasion and locoregional lymph nodes
  - Possible diagnostic laparoscopy

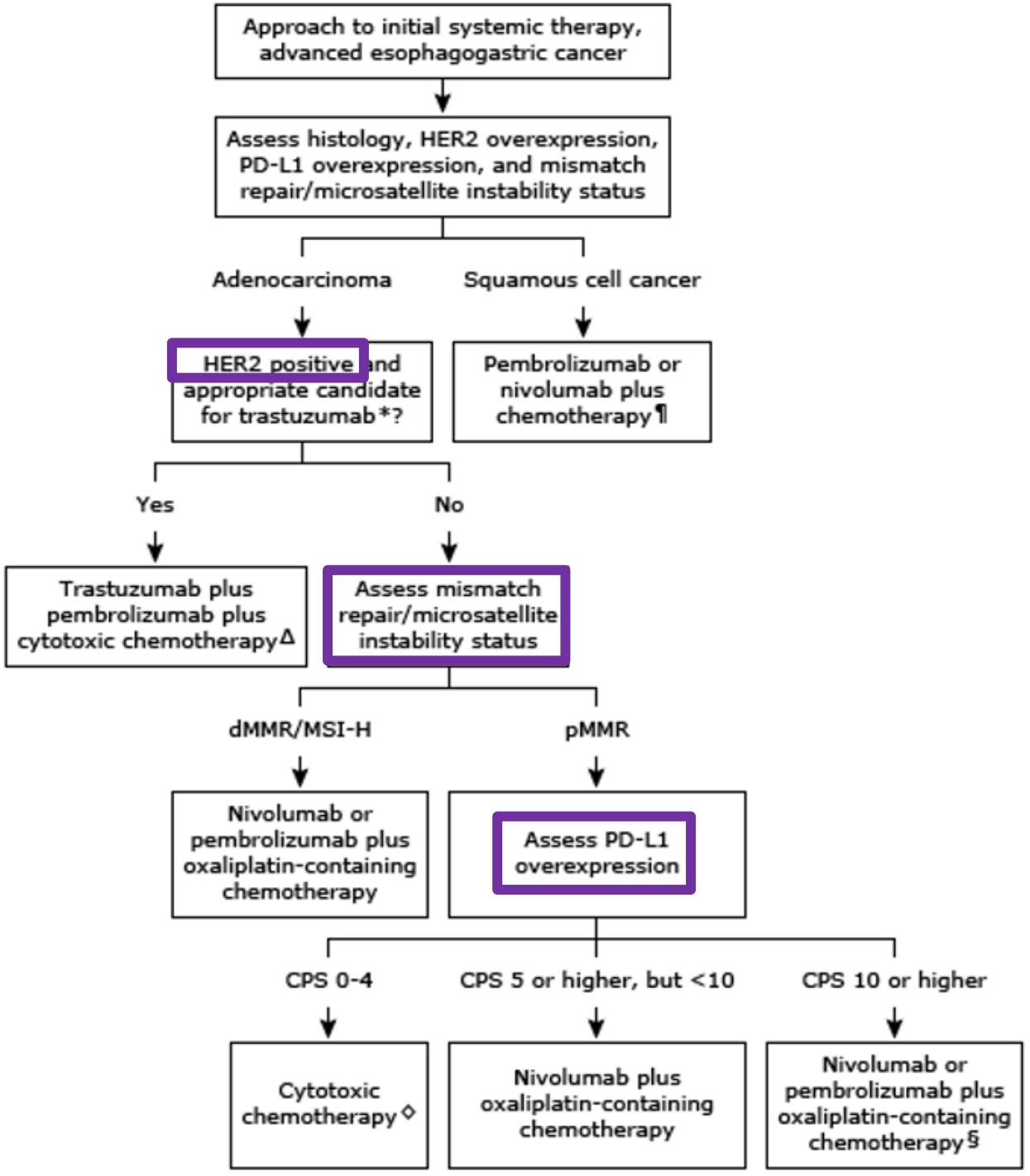


https://www.endoscopy-campus.com/en/classifications/paris-classification-early-gastric-cancer/

- Treatment for clinical T1-T2, N0:
  - Surgical resection
  - Neoadjuvant chemoradiation, followed by surgical resection
- **Unresectable disease:**
  - T4 – involving pericardium, pleura, diaphragm, aorta, or other organs
  - Peritoneal, lung, bone, adrenal, brain or liver metastases
  - Extra regional lymph node spread – para-aortic or retroperitoneal



https://documents.cap.org/protocols/Stomach_4.2.1.0.REL_CAPCP.pdf



PD-L1

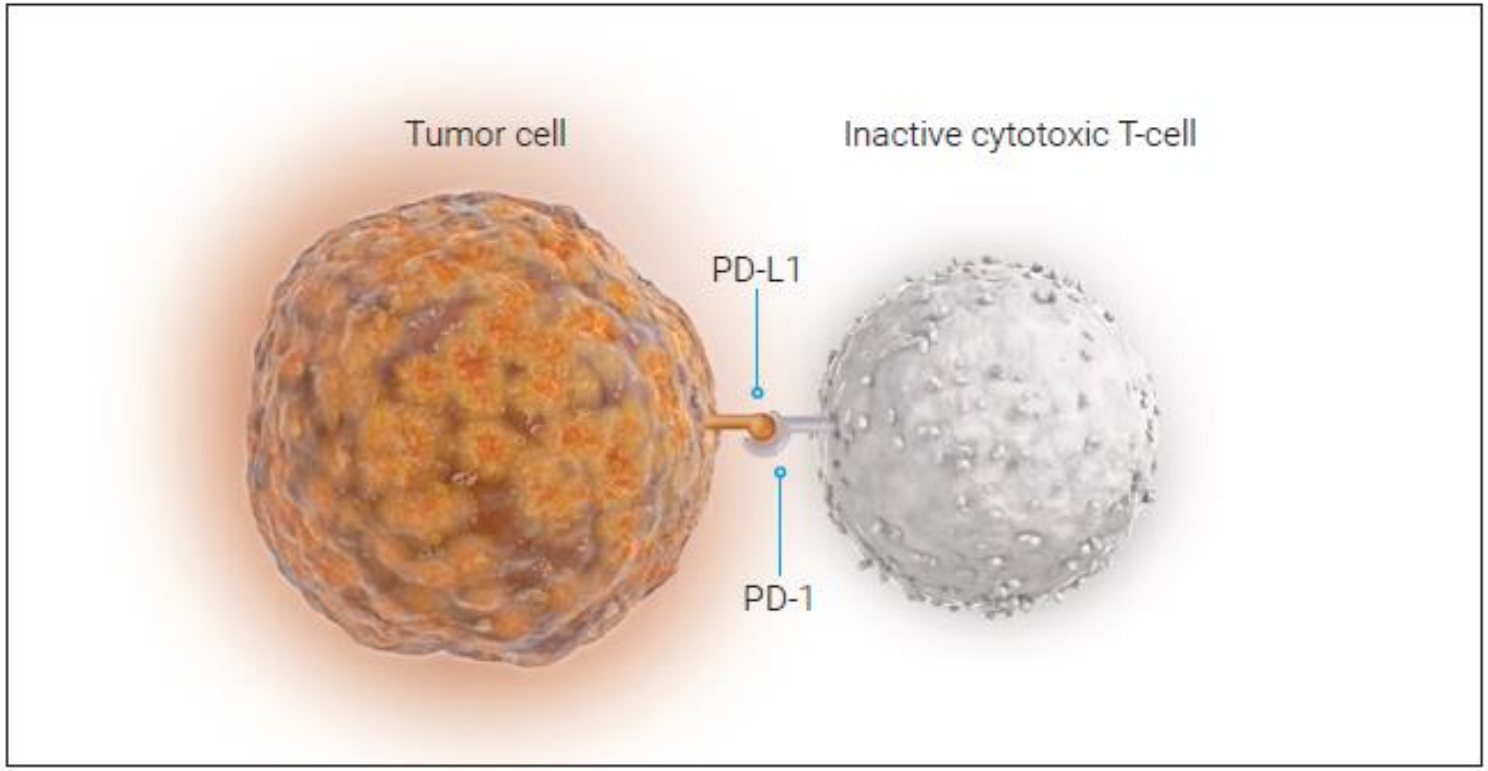


Figure 2: Inactivation of T-cells reduces tumor cell death and elimination.

- Cytotoxic T-cells detect and eliminate abnormal cells in the body to prevent autoimmunity
- **PD-L1 – programmed cell death ligand 1**
  - Ligand expressed on normal antigen-presenting cells, T-cells, B-cells, monocytes, and epithelial cells
- **PD-1 – programmed cell death 1**
  - Transmembrane protein (receptor) expressed on antigen-experienced memory T-cells in peripheral tissues
  - Also on B-cells, activated monocytes, dendritic cells, and natural killer cells
- Binding inactivates cytotoxic T-cells, downregulates immune response, inhibits proliferation and cytokine generation, and ultimately leads to programmed death of the T-cells

https://www.agilent.com/cs/library/usermanuals/public/D54358%20rev01%20KN181%20ESCC%20Interpretation%20Manual.pdf

PD-L1

- When tumor cells express PD-L1, they mimic normal cells and escape detection and elimination by cytotoxic T-cells
- Anti-PD-1 therapy blocks the receptor interaction so that the immune system can remain active
- Many solid tumors (NSCLC, melanoma, urothelial) use the strategy
- Tumors can express PDL1 through different biological processes

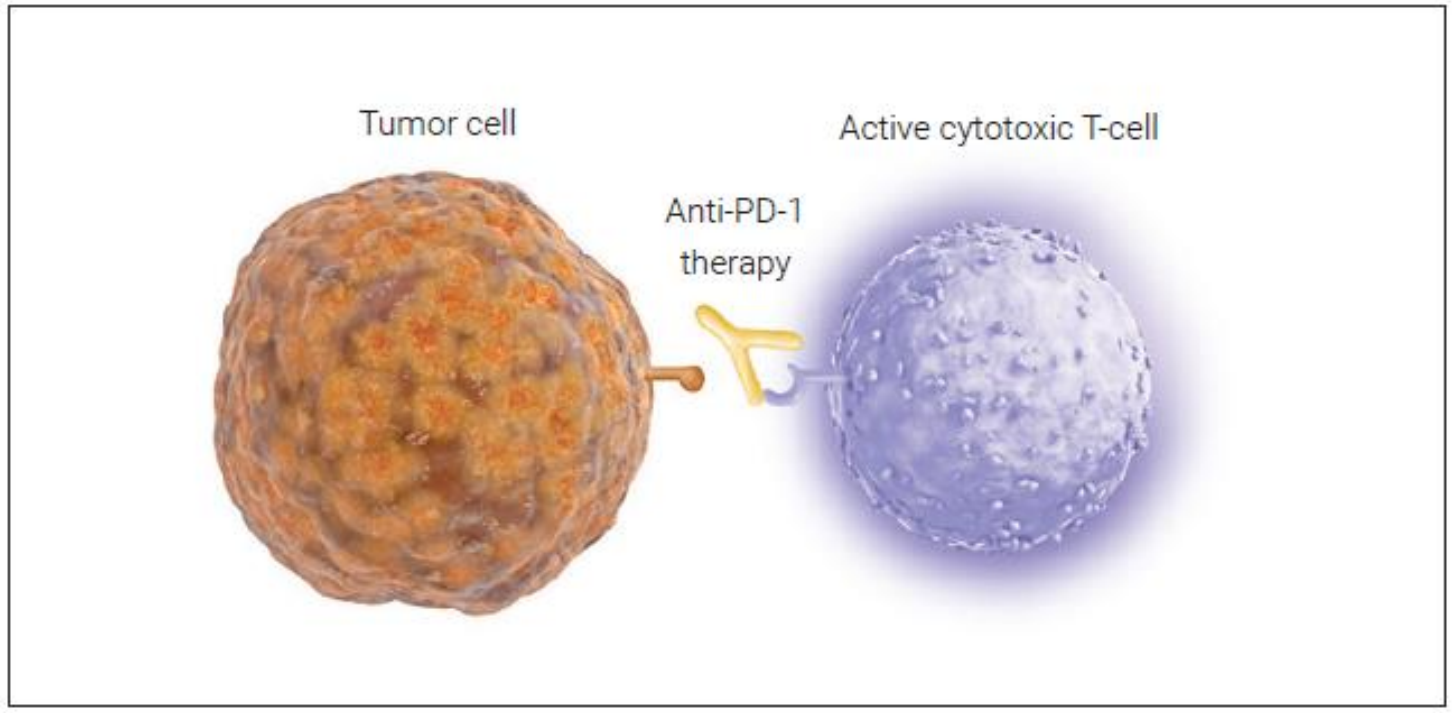


Figure 3: Blocking the PD-1/PD-L1 interaction helps to enable active T-cells and tumor cell death and elimination.

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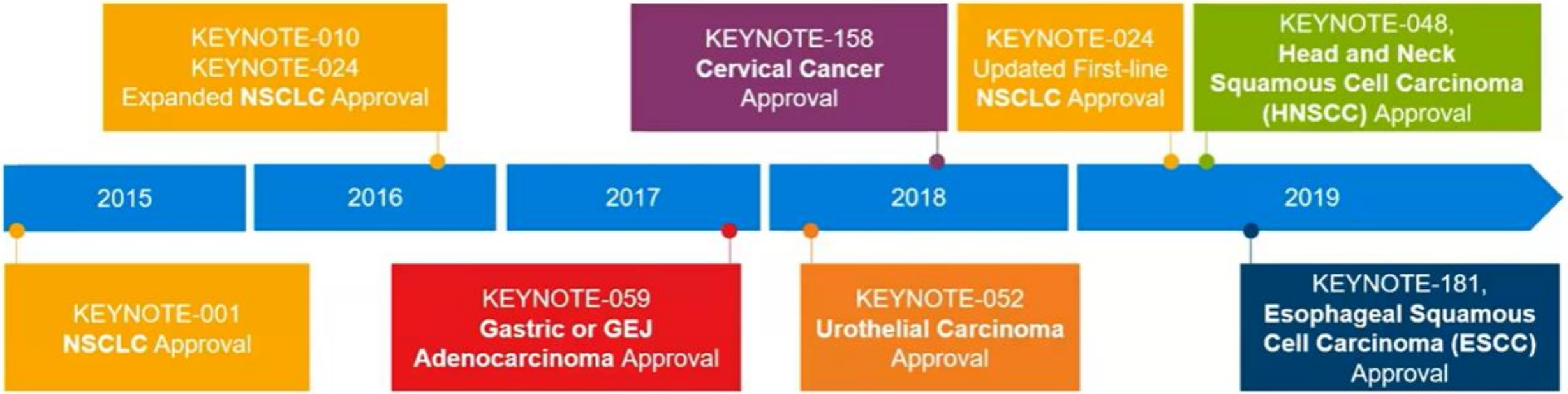
BRIEF HISTORY OF IMMUNE CHECK POINT INHIBITORS

- Anti-PD-1
  - **Pembrolizumab**
    - FDA-approved drug as a third line treatment in PD-L1 expressing gastroesophageal adenocarcinomas (CPS ≥ 1*)
    - FDA-approved drug as a second line for esophageal squamous cell carcinoma (CPS ≥ 10)
  - Nivolumab, cemiplimab
- Anti-PD-L1
  - Atezolizumab, avelumab, durvalumab


KEYNOTE-010
KEYNOTE-024
Expanded **NSCLC** Approval
KEYNOTE-158
Cervical Cancer
Approval
KEYNOTE-024
Updated First-line
NSCLC Approval
KEYNOTE-048,
Head and Neck Squamous Cell Carcinoma (HNSCC) Approval
2015
2016
2017
2018
2019
KEYNOTE-001
NSCLC Approval
KEYNOTE-059
Gastric or GEJ Adenocarcinoma Approval
KEYNOTE-052
Urothelial Carcinoma
Approval
KEYNOTE-181,
Esophageal Squamous Cell Carcinoma (ESCC)
Approval

BRIEF HISTORY OF IMMUNE CHECK POINT INHIBITORS

- NSCLC clinical trial used **Tumor Proportion Score (TPS)**

$$TPS = \frac{\text{\# PD-L1 positive tumor cells}}{\text{Total \# of PD-L1 positive + PD-L1 negative tumor cells}}$$

- NSCLC tend to have high positivity rates on tumor cells
- Did not find presence of positive immune cells to be predictive of response to therapy

KEYNOTE-012 STUDY

- Evaluated pembrolizumab in recurrent or metastatic gastric or GEJ adenocarcinoma
- 8/39 patients **(22%) had a partial response**
- 5/39 (13%) with adverse effects: pemphigoid, hypothyroidism, peripheral sensory neuropathy, and pneumonitis
- Justified trial of pembrolizumab monotherapy for phase II KEYNOTE-059

KEYNOTE-059 STUDY

- Evaluated PD-L1 expression in 257 patients with at least 2 prior systemic treatments for advanced gastric/gastroesophageal adenocarcinoma

Table 4. Objective Response Rate (ORR) From KEYNOTE-059 by Combined Positive Score (CPS) and Tumor Proportion Score (TPS; N = 257)

	Total (N = 257), No. (%)	Response	No Response	ORR, %	Odds Ratio
CPS ≥1	148 (57.6)	24	124	16.2	2.8
CPS <1	109 (42.4)	7	102	6.4	
TPS ≥1	32 (12.5)	5	27	15.6	1.4
TPS <1	225 (87.5)	26	199	11.6	

KEYNOTE-061 STUDY

- Evaluated monotherapy pembrolizumab vs standard chemotherapy in patients that progressed following first line therapy with combined fluoropyrimidine and platinum-based agents
- Pembrolizumab median OS 9.1 months vs 8.3 months paclitaxel
- Median PFS 1.5 months vs 4.1 months
- Grade 3-5 adverse events 14% vs 35%
- **Did not significantly improve OS** but had better safety profile

KEYNOTE-062 STUDY

- 763 patients with untreated, locally advanced/unresectable or metastatic gastric or GEJ adenocarcinoma with CPS ≥ 1; assigned pembrolizumab alone, chemotherapy alone, or combination
  - Pembrolizumab was noninferior to chemotherapy, with fewer adverse events
  - **Pembrolizumab** or **pembrolizumab + chemotherapy** was **not superior** to chemotherapy for the OS and PFS tested

ODAC Votes Against Pembrolizumab for PD-L1+ Gastric/GEJ Cancer

April 29, 2021
Caroline Seymour

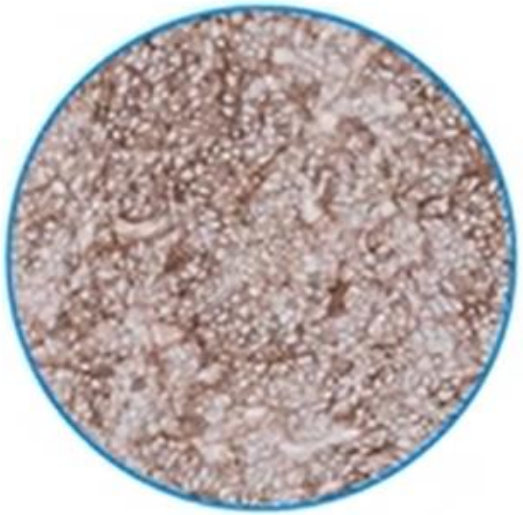
Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.[1] (1.9)

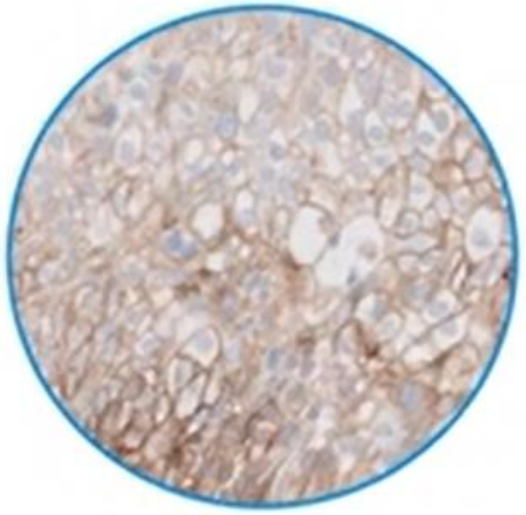
In a 6 to 2 vote, the FDA's Oncologic Drugs Advisory Committee voted against maintaining the accelerated approval of pembrolizumab for the treatment of patients with PD-L1–positive recurrent or advanced gastric or gastroesophageal junction adenocarcinoma who have received 2 or more lines of therapy.

In a 6 to 2 vote, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted against maintaining the accelerated approval of pembrolizumab (Keytruda) for the treatment of patients with PD-L1–positive (combined positive score [CPS] ≥1) recurrent or advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received 2 or more lines of therapy.

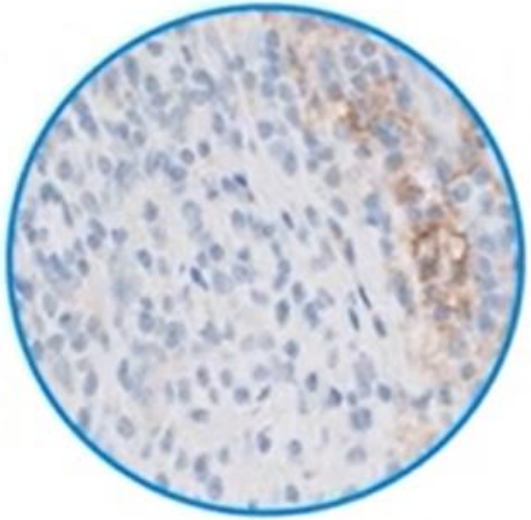
https://www.onclive.com/view/odac-votes-against-pembrolizumab-for-pd-l1-gastric-gej-cancer



Triple-Negative Breast Cancer

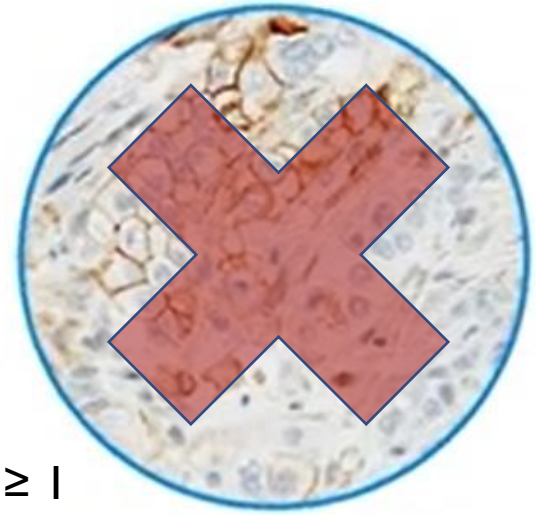


Head and Neck Squamous Cell Carcinoma



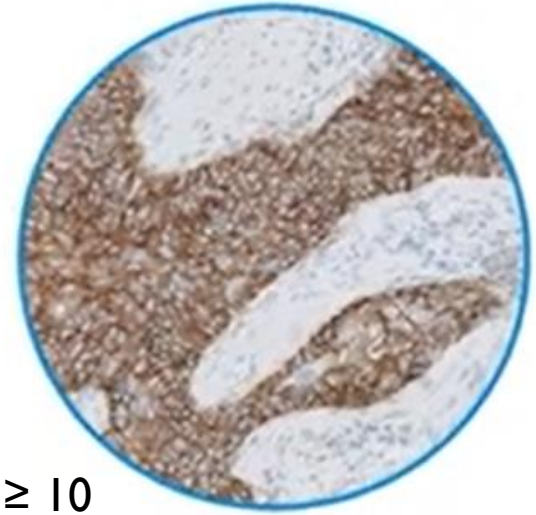
Cervical Cancer

Urothelial Carcinoma



CPS ≥ 1

Gastric or Gastroesophageal Junction Adenocarcinoma



CPS ≥ 10

Esophageal Squamous Cell Carcinoma

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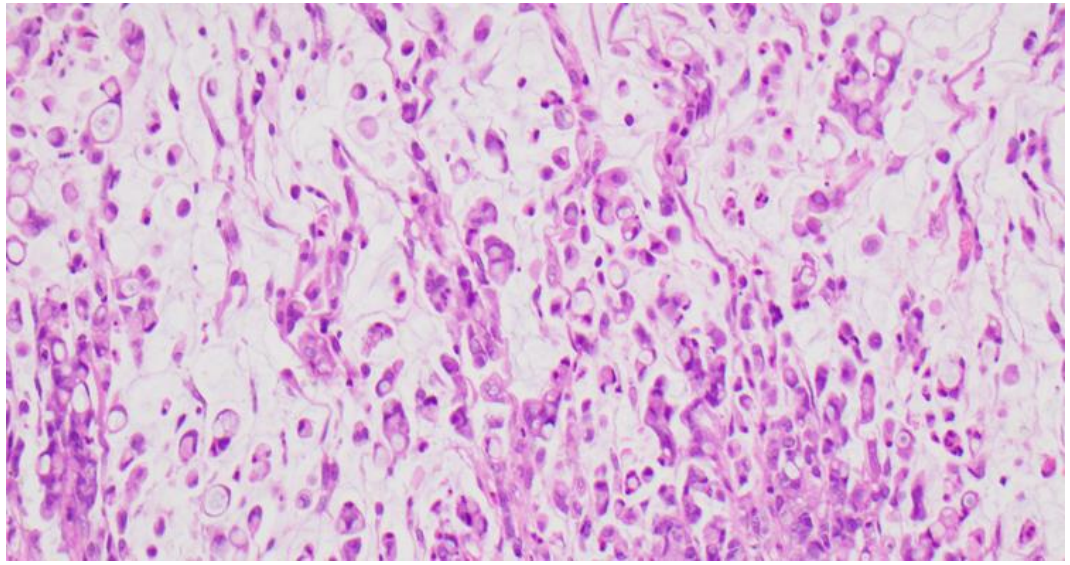
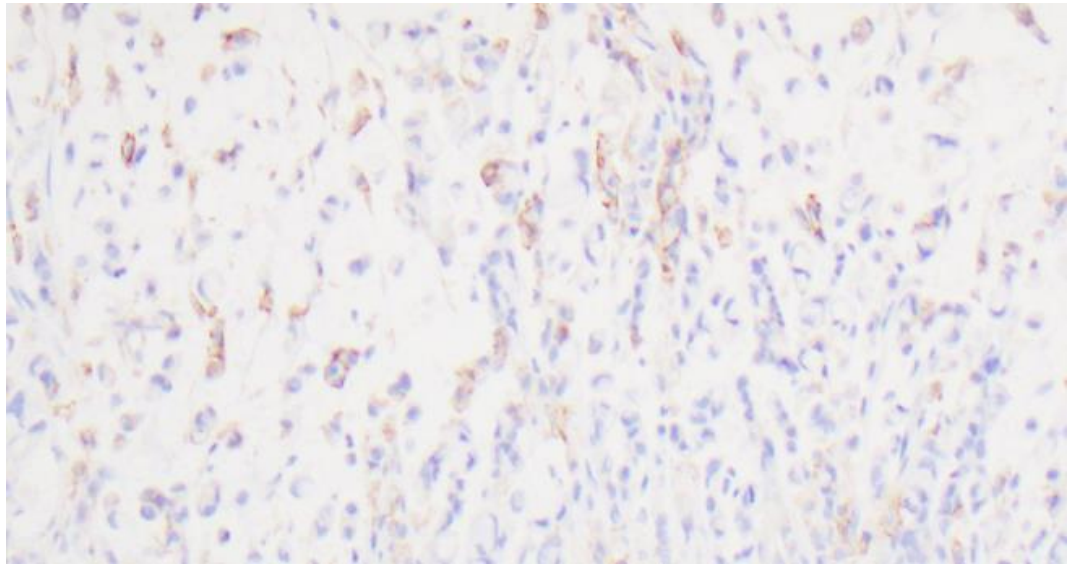
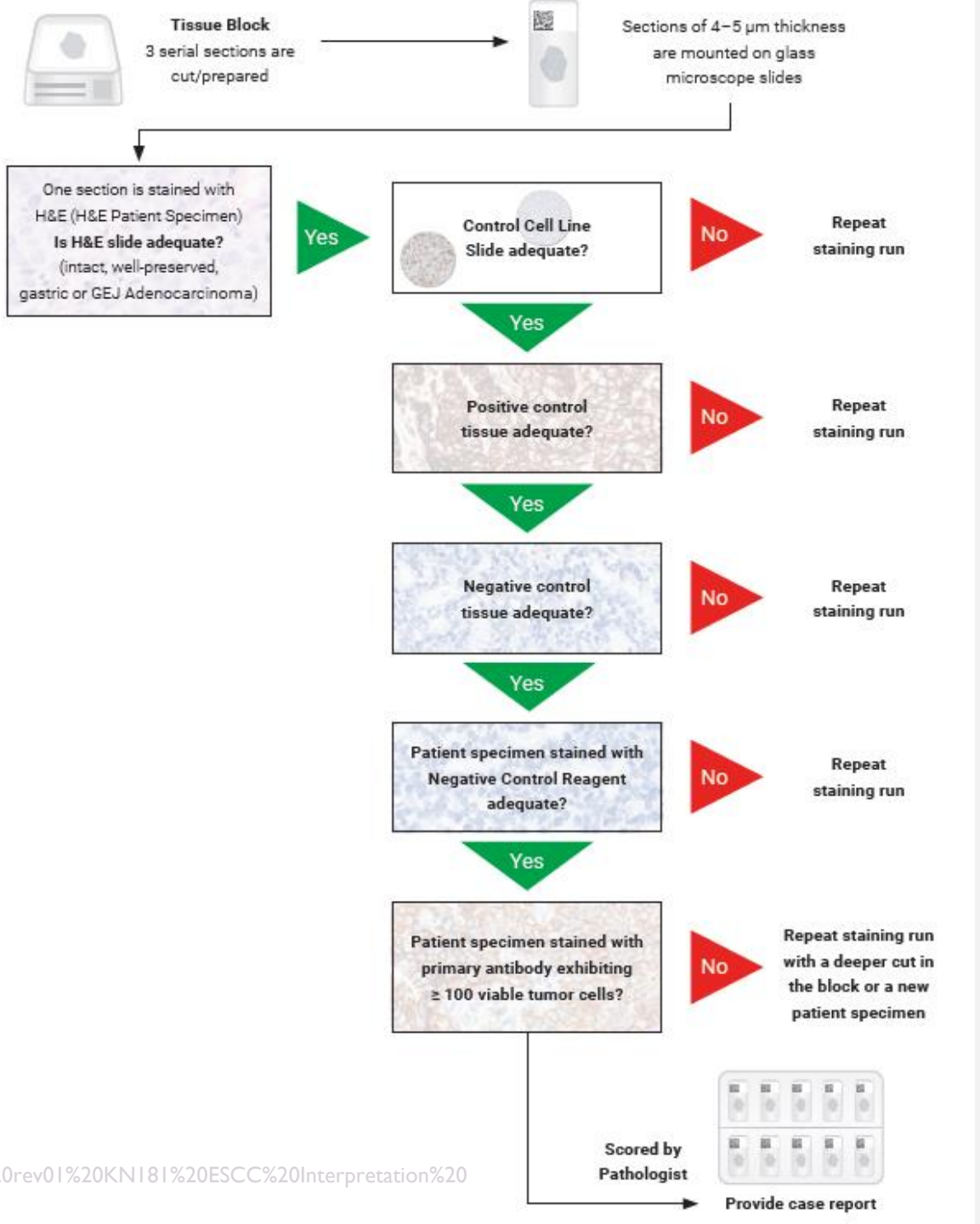




PD-L1 IMMUNOHISTOCHEMISTRY TESTING

Required: 100 viable tumor cells



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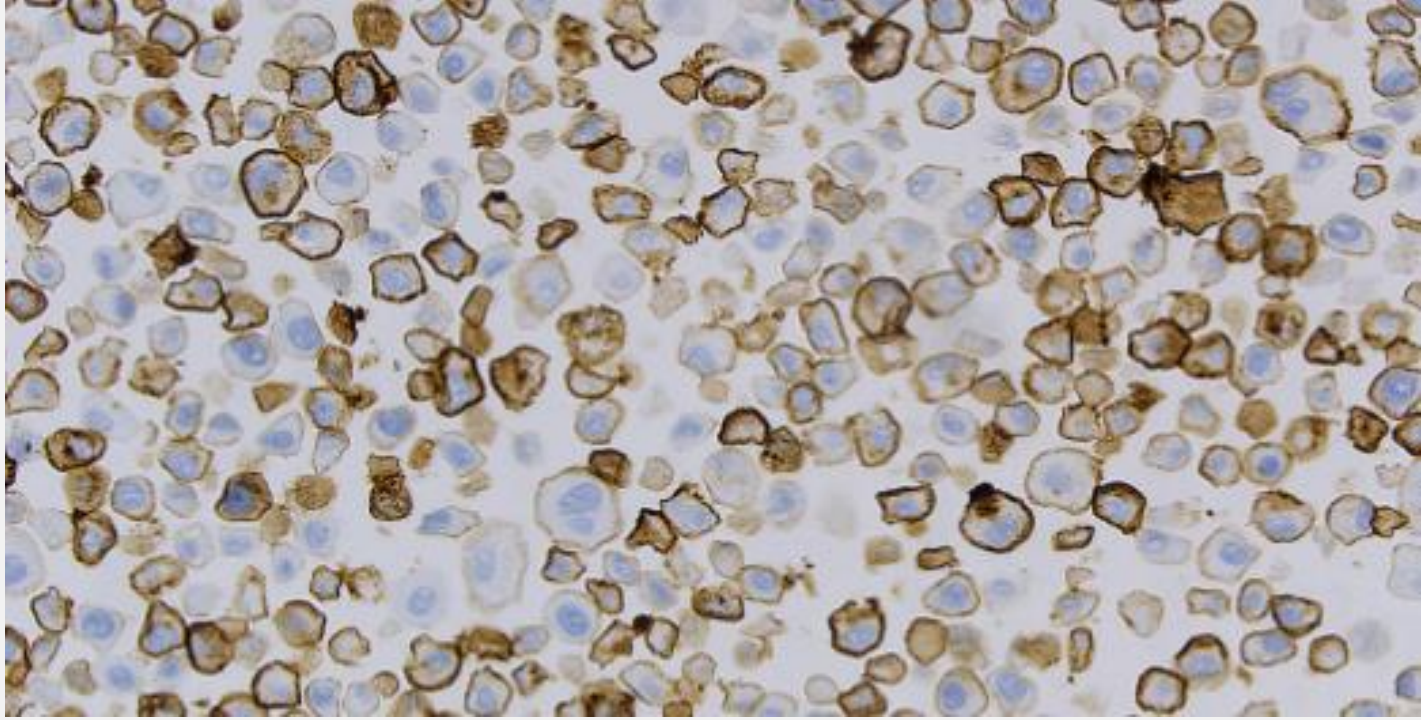
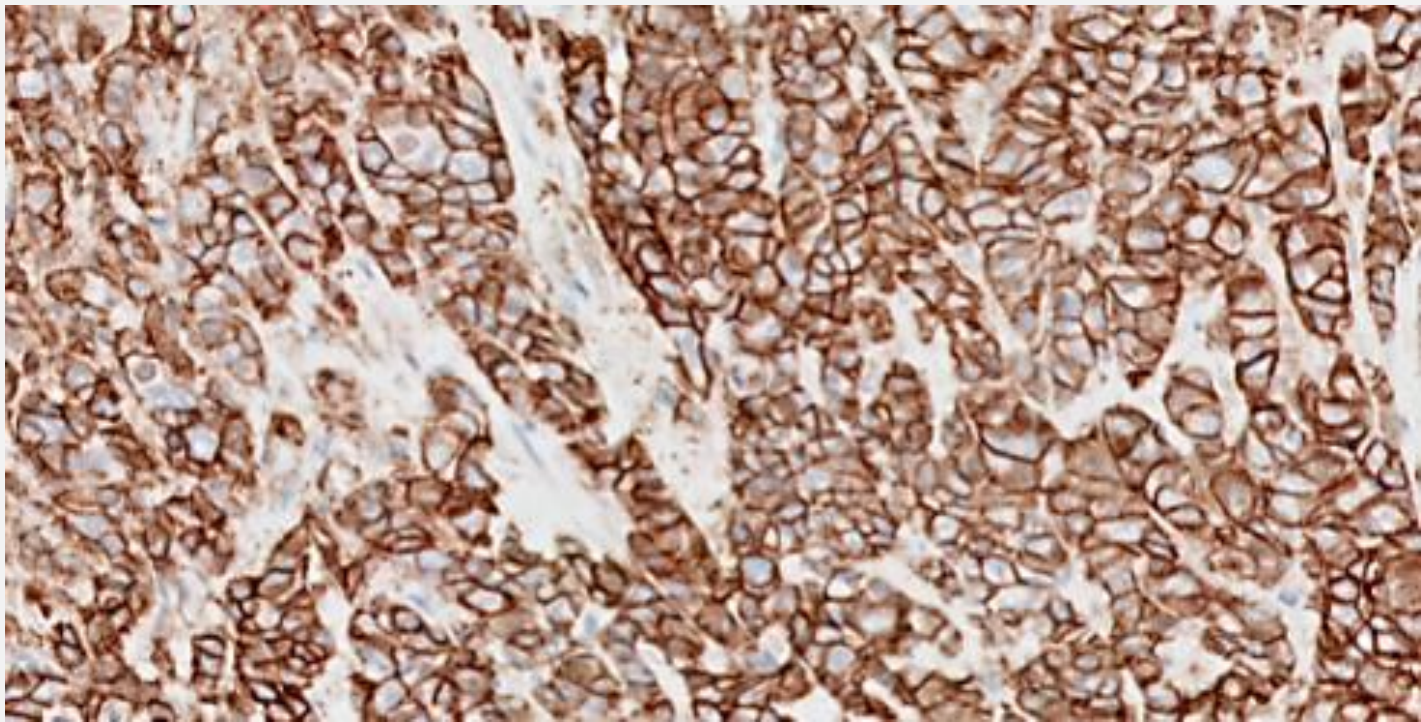
CONTROLS

- Positive controls
  - At least 70% cells with membranous staining of at least 2+ intensity
  - Background staining less than 1+ intensity





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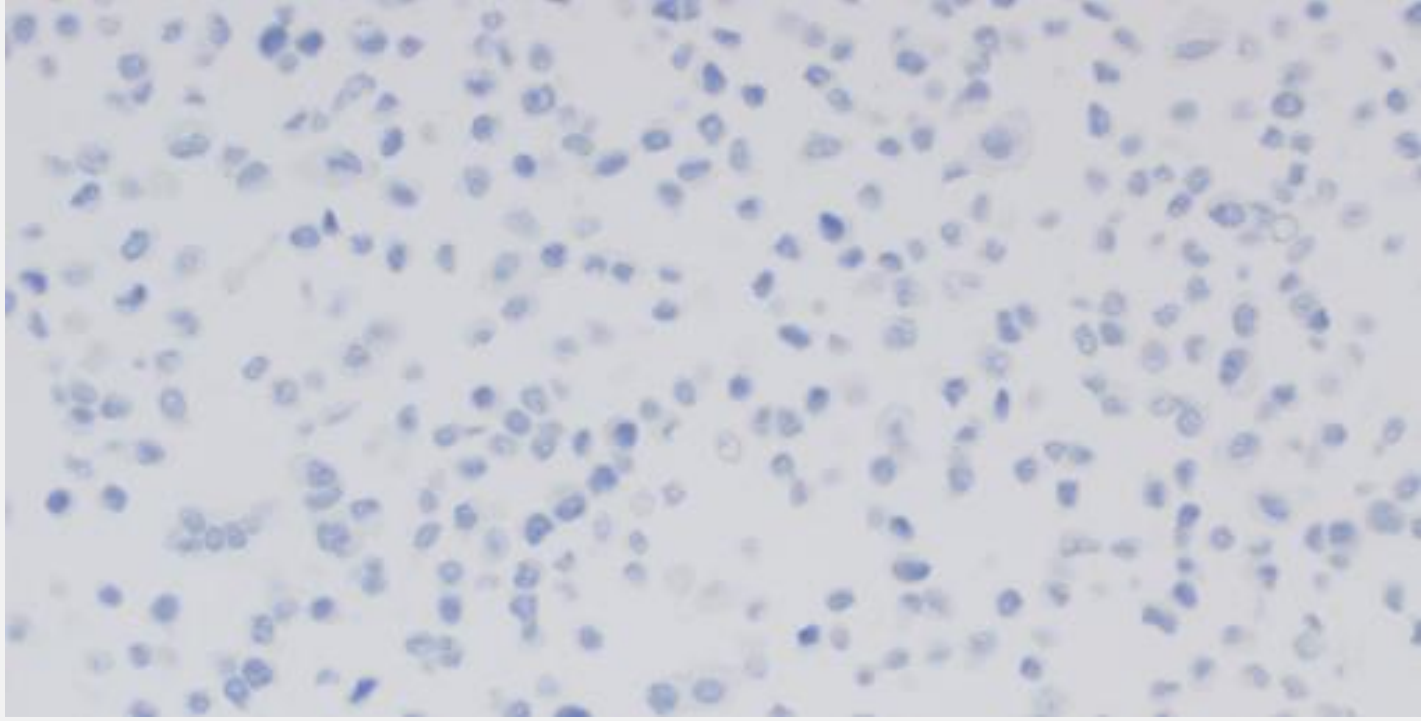
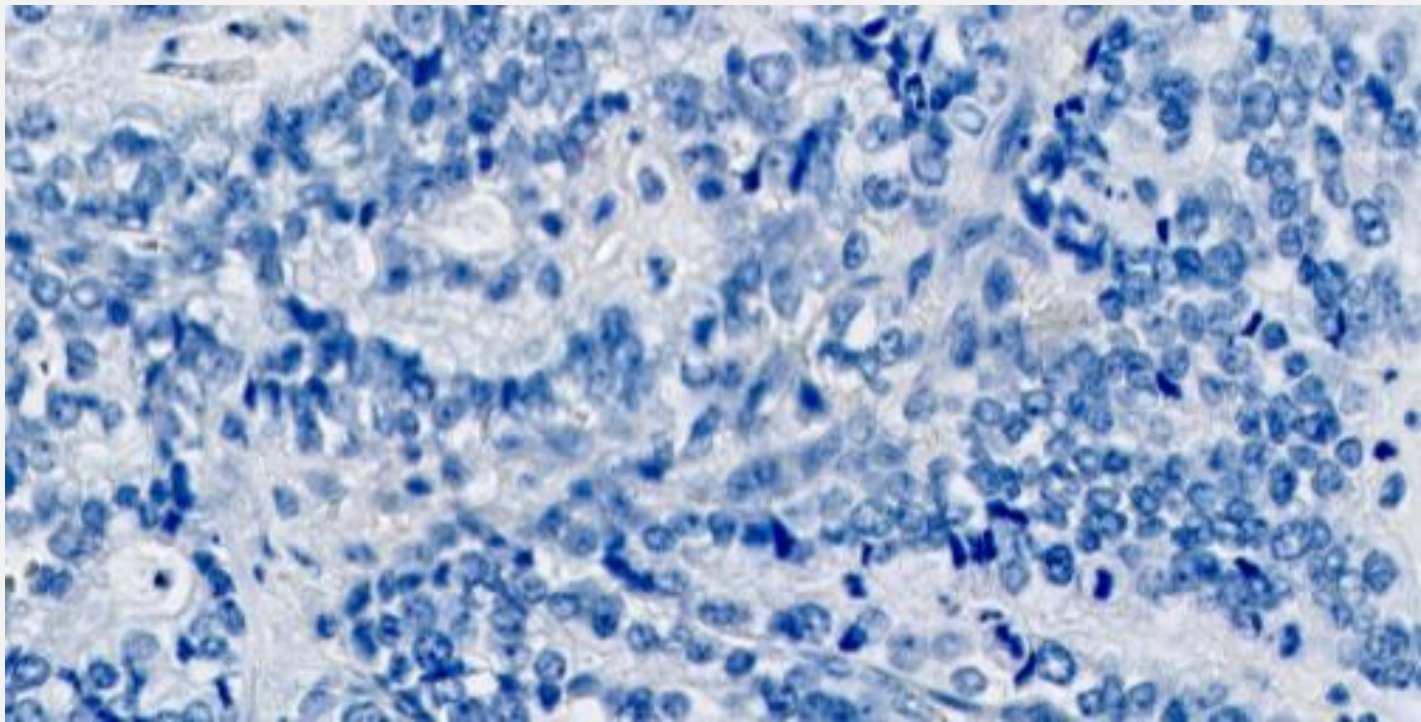
CONTROLS

- Negative controls
  - No significant tumor cell staining
  - Background staining less than 1+ intensity
  - CPS < 1





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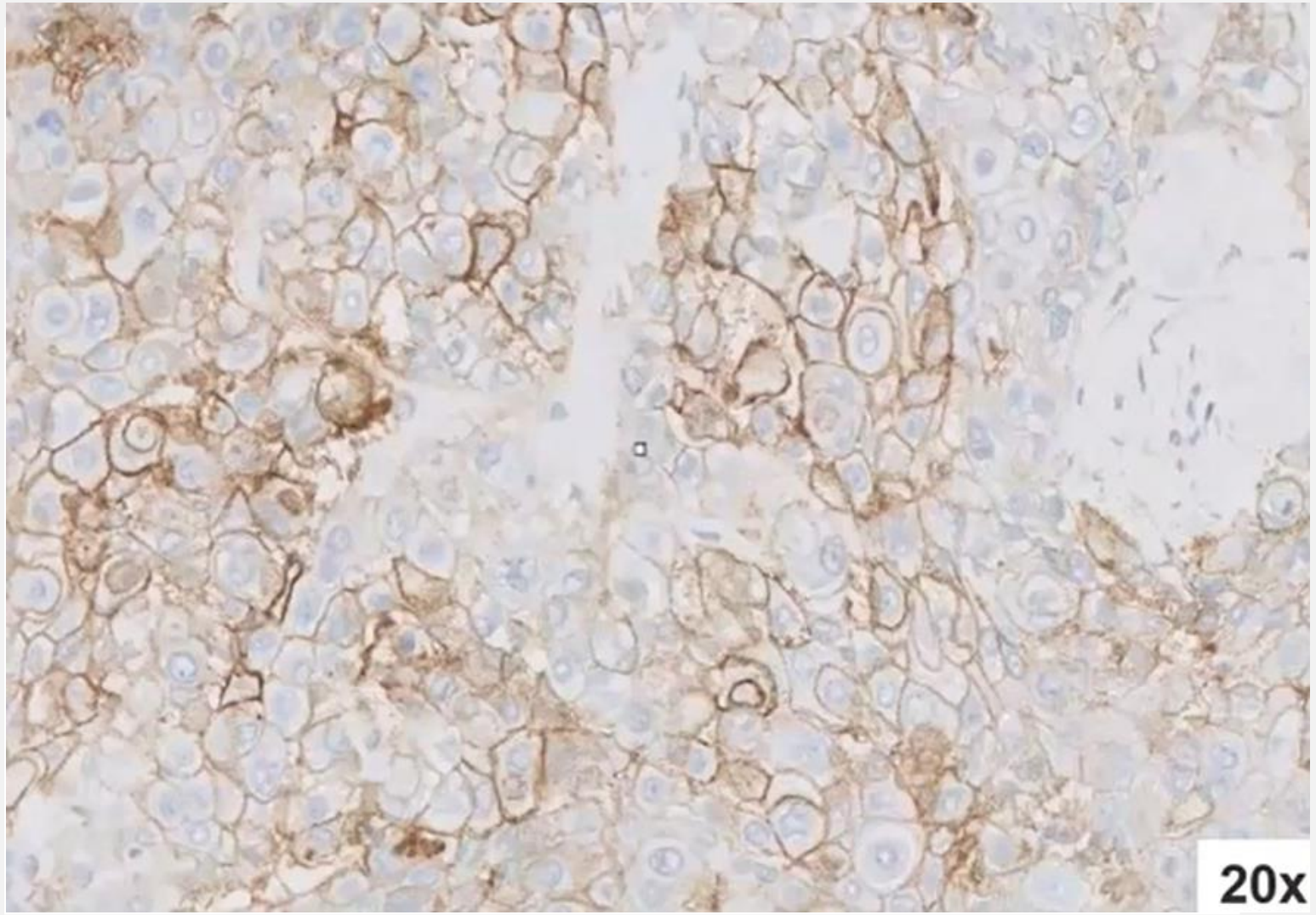
PRACTICE PRINCIPLES

$$\frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of viable tumor cells}} \times 100 = \text{Combined Positive Score (CPS)}$$

Table 1: CPS numerator inclusion/exclusion criteria

Tissue Elements	Included in the Numerator	Excluded from the Numerator
Tumor Cells	Convincing partial or complete linear membrane staining (at any intensity) of viable invasive gastric or GEJ adenocarcinoma tumor cells	– Non-staining tumor cells – Tumor cells with only cytoplasmic staining – Adenoma, dysplasia, and carcinoma in situ
Immune Cells	Membrane and/or cytoplasmic* staining (at any intensity) of mononuclear inflammatory cells (MICs) within tumor nests and adjacent supporting stroma†: – Lymphocytes (including lymphocyte aggregates) – Macrophages Only MICs directly associated with the response to the tumor are scored	– Non-staining MICs – MICs associated with adenoma, dysplasia, and carcinoma in situ – MICs (including lymphoid aggregates) associated with ulcers, chronic gastritis, and other processes not associated with the tumor – MICs associated with normal structures – Neutrophils, eosinophils, and plasma cells
Other Cells	Not included	– Normal cells – Stromal cells (including fibroblasts) – Necrotic cells and/or cellular debris



CPS

- Evaluate tissue at low magnification to assess all pieces
- Partial and 1+ staining may be difficult to see
- At 20x determine number of PD-L1 staining cells (tumor cells and MICs – numerator)
- H&E determine total number of viable tumor cells (denominator)

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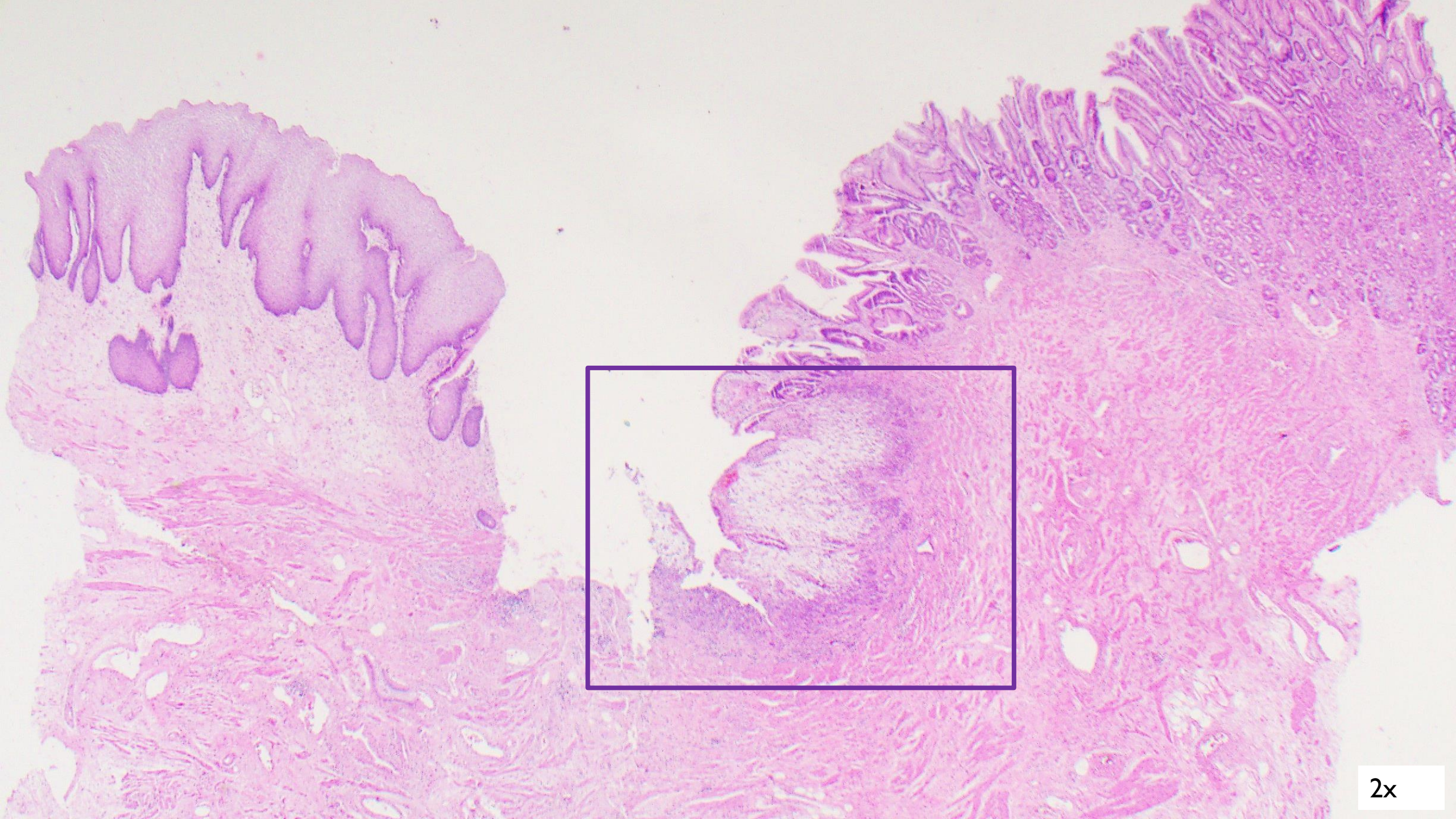
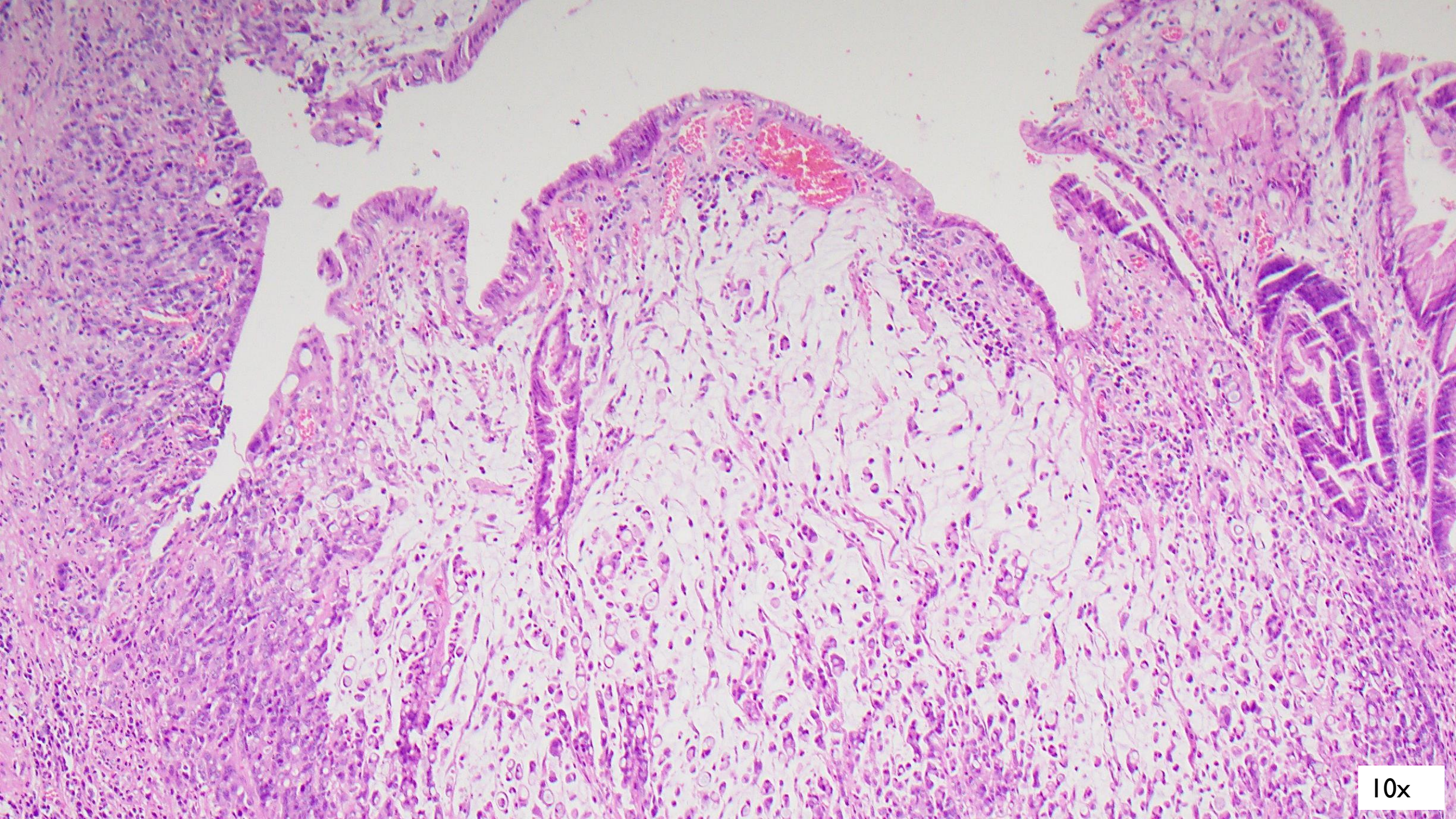
20 field number

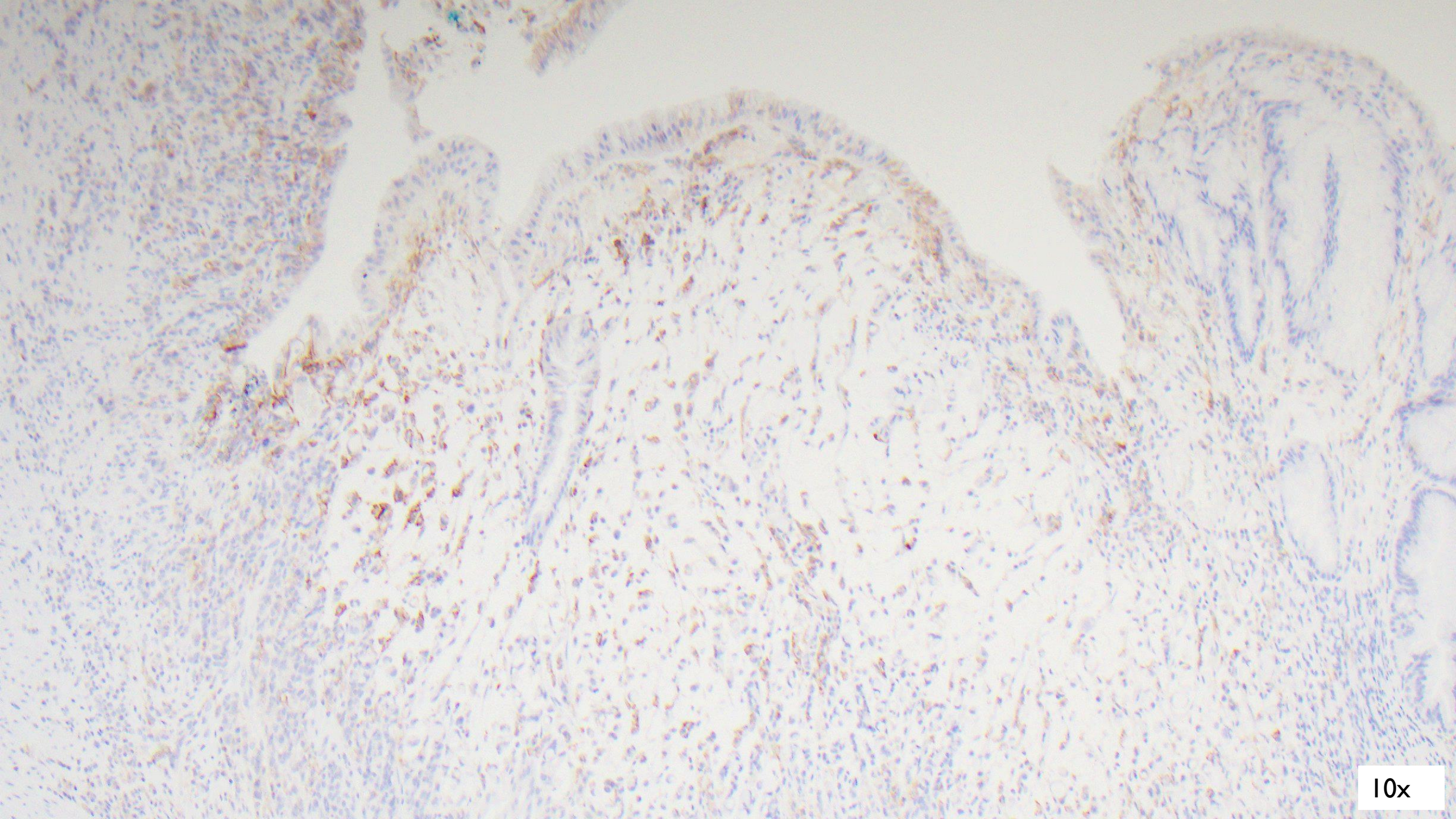
Magnification	Approximate # of Cells*
4×	60,000
10×	10,000
20×	2,500
40×†	-

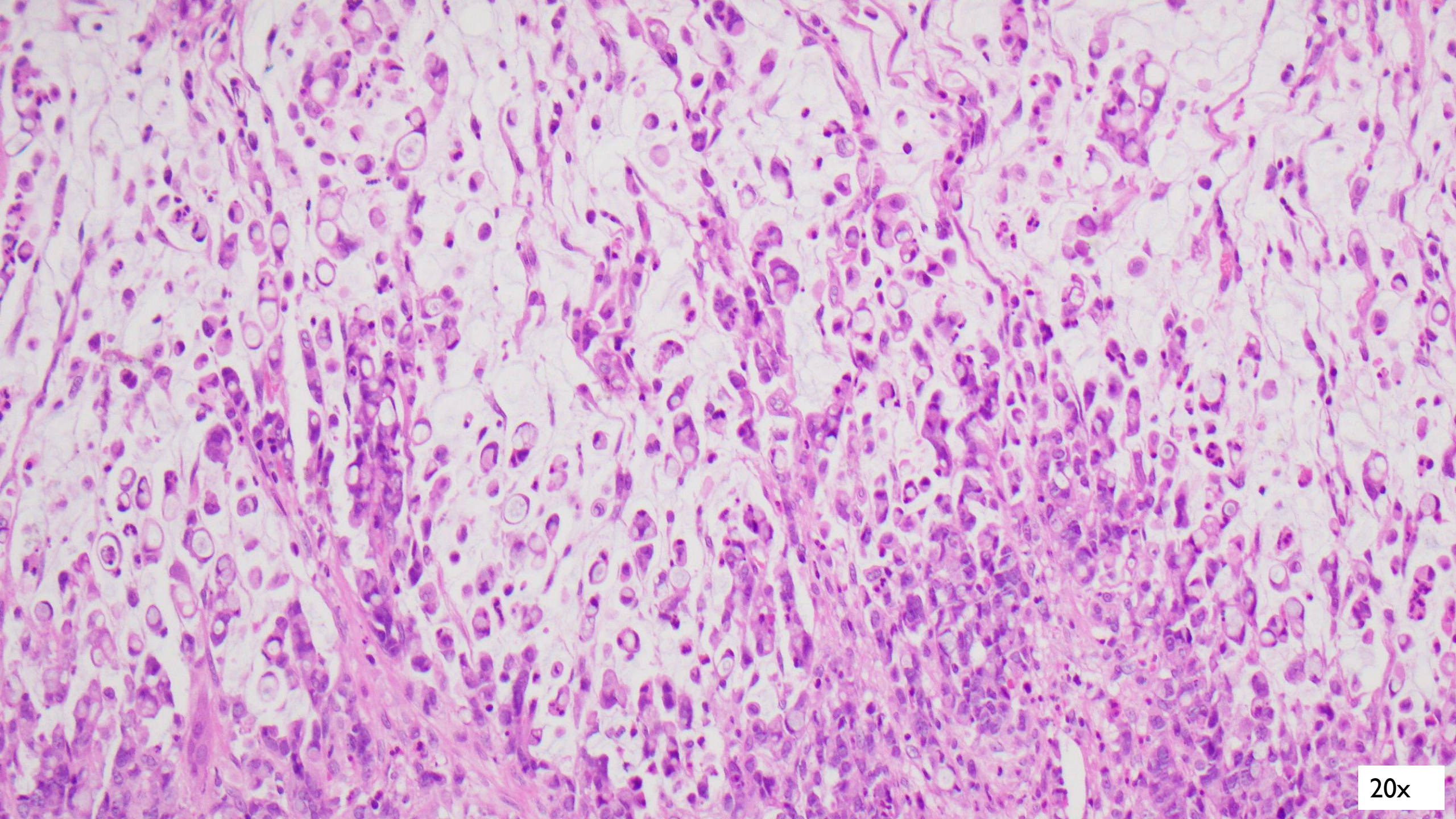
High-definition 24-inch monitor

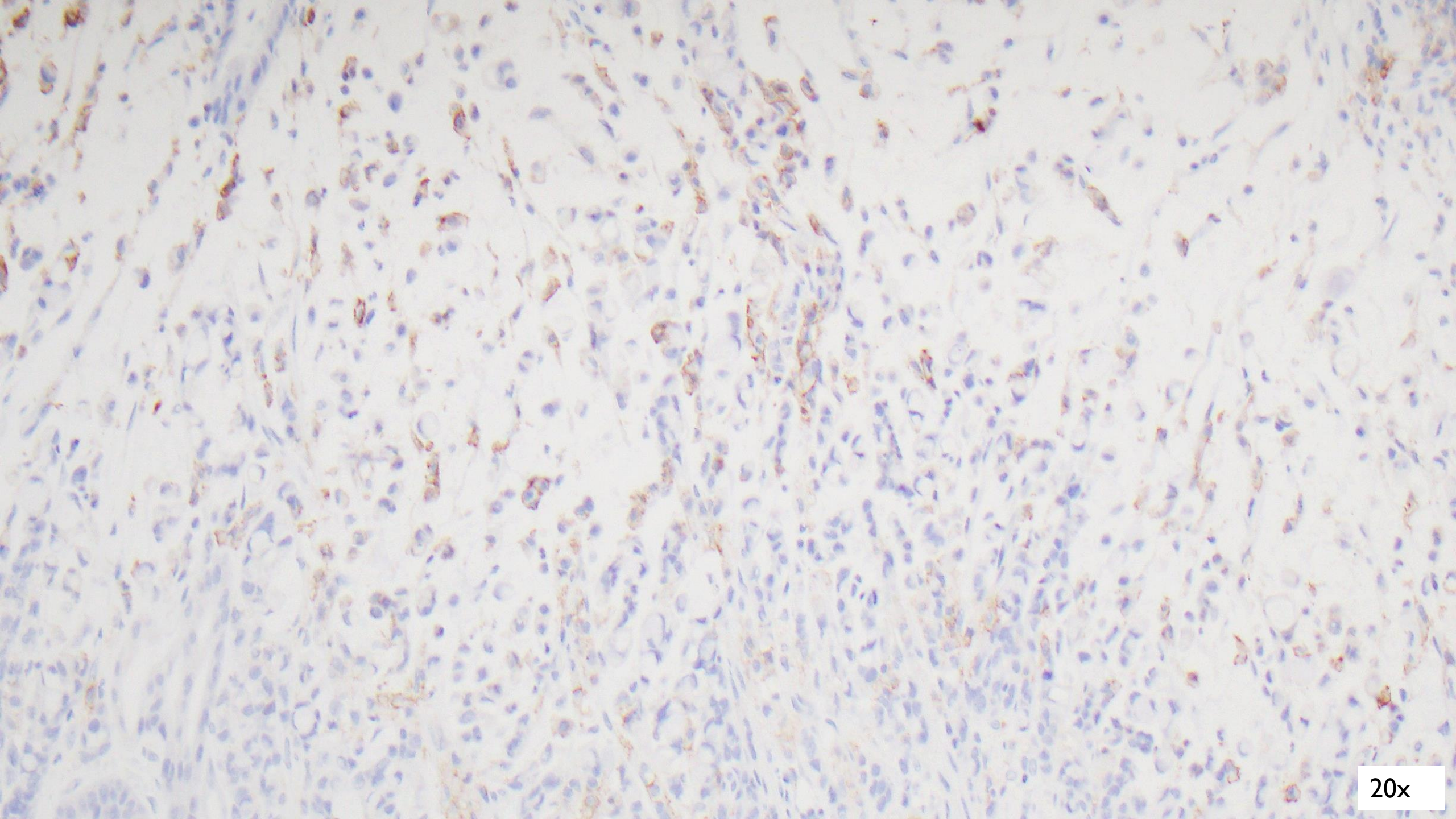
Magnification	Approximate # of Cells*
4×	39,300
10×	6,550
20×	1,750
40×†	-

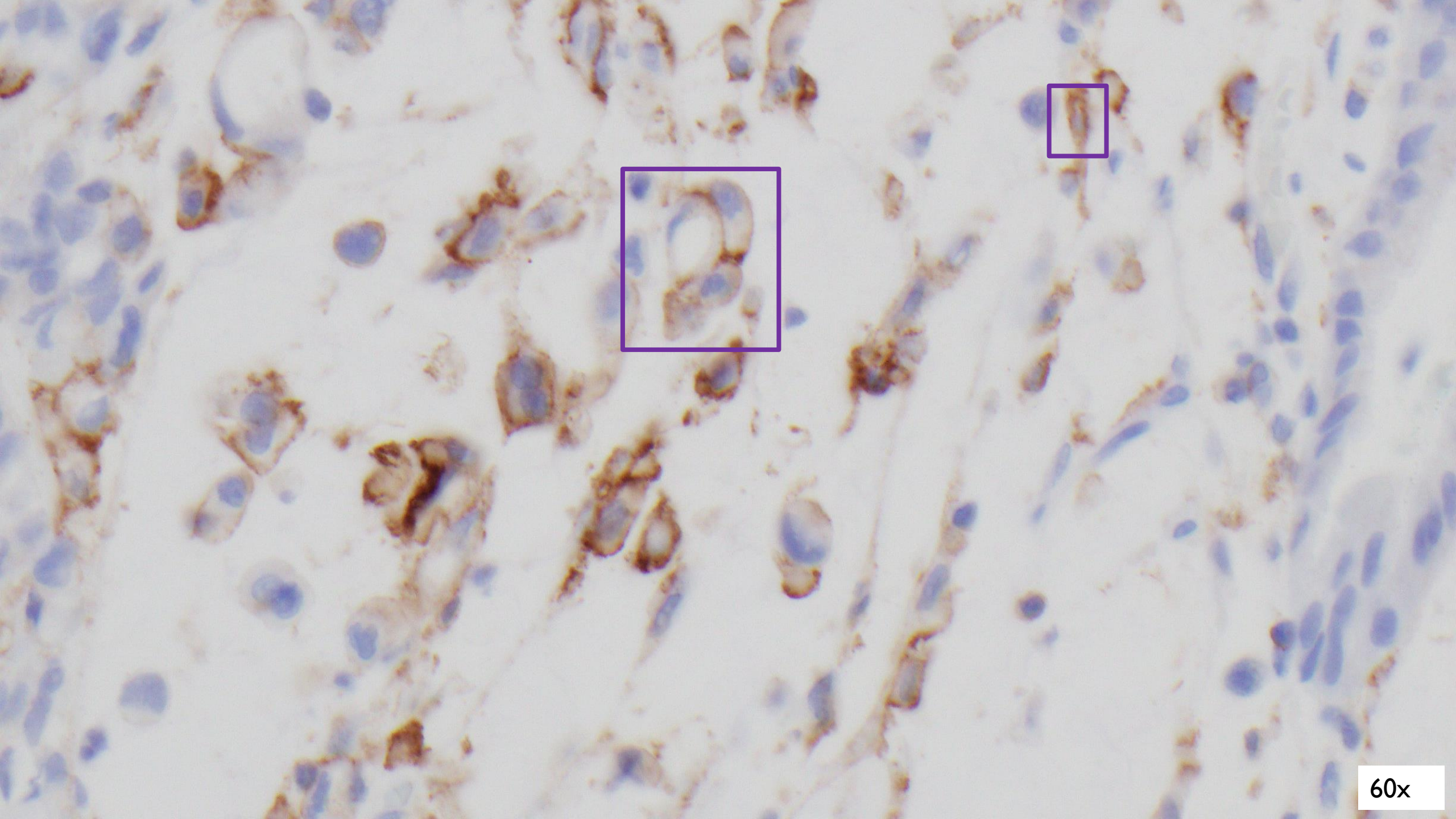

2x

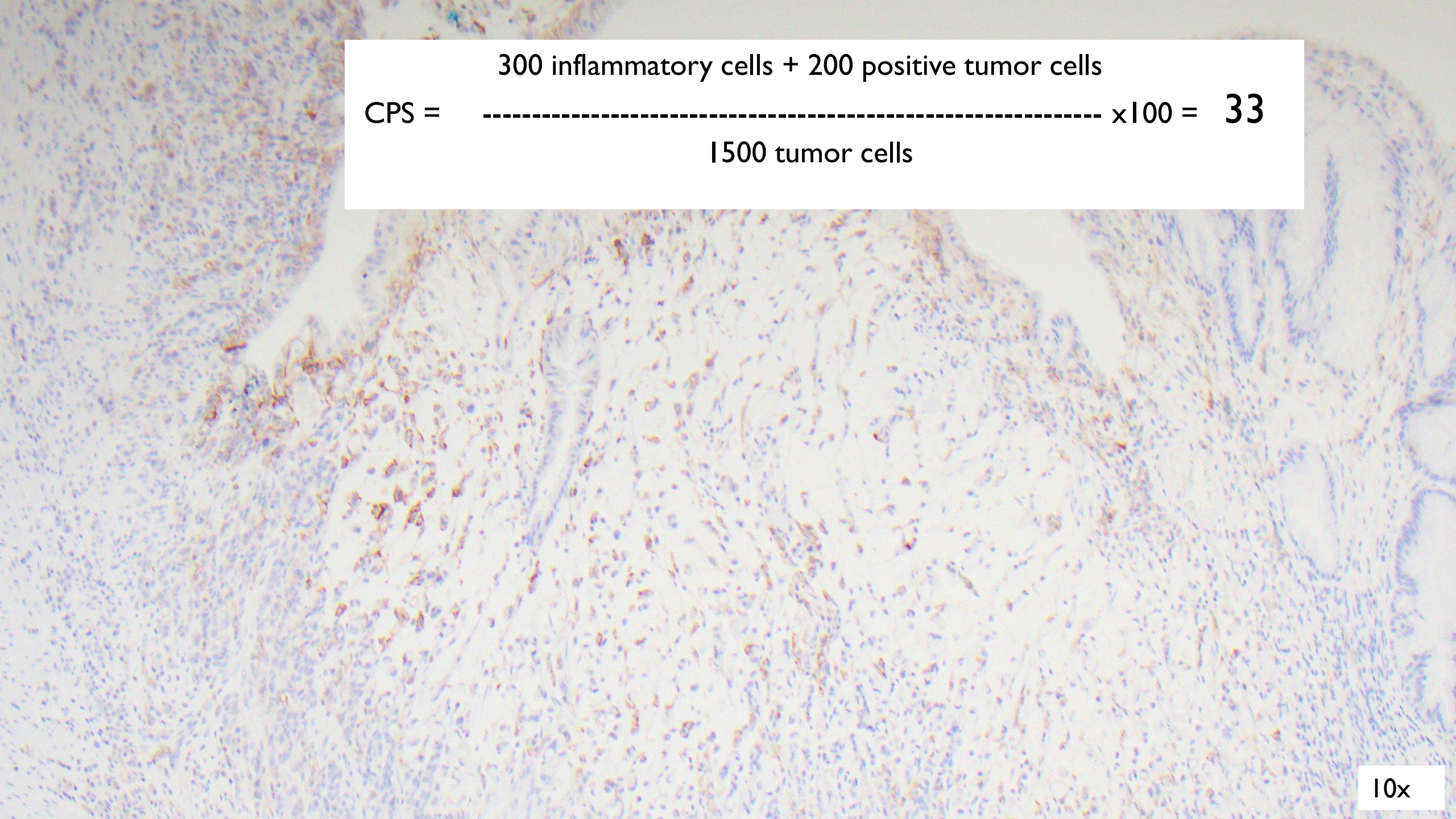

10x


10x


20x

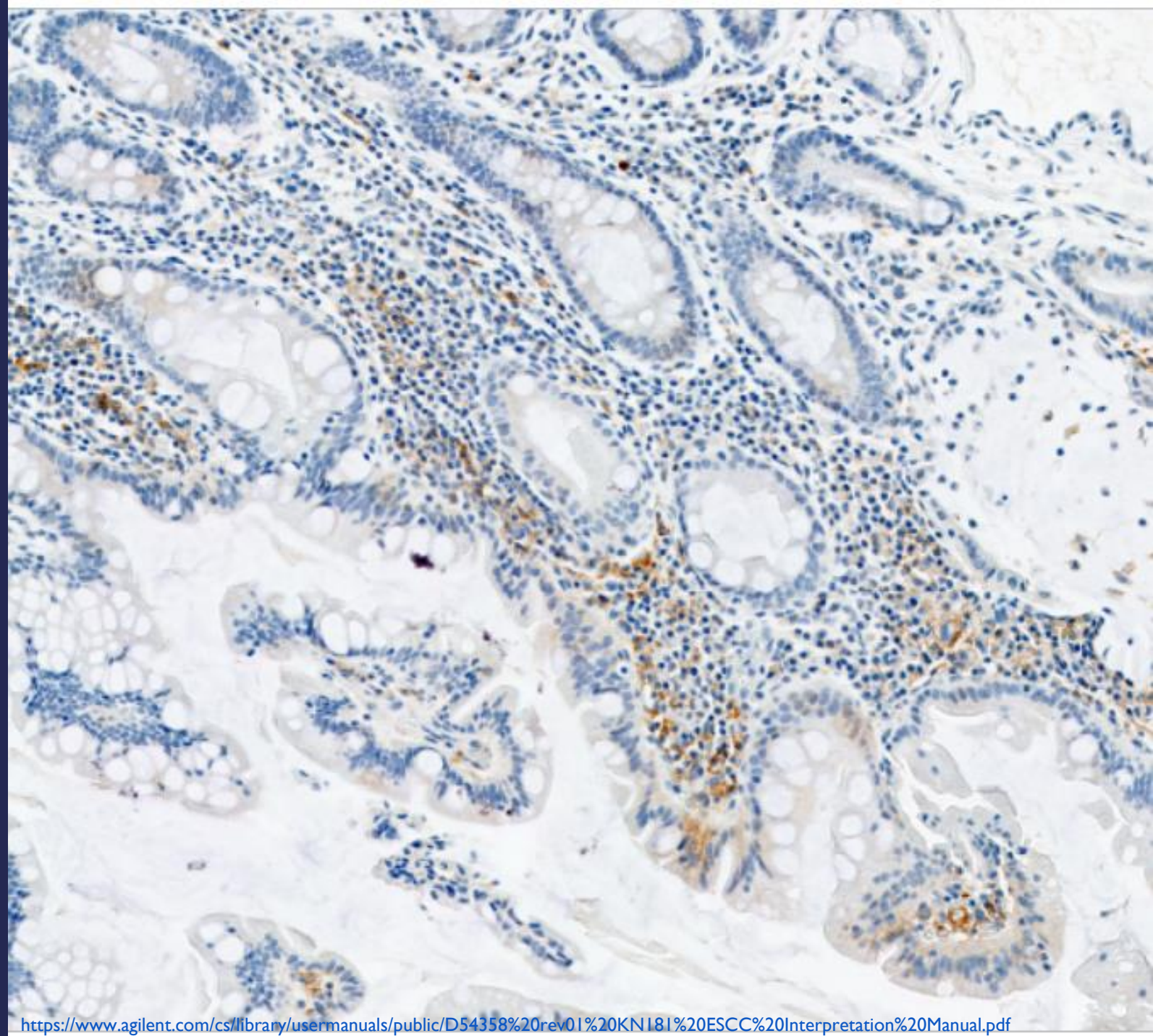

20x


60x


300 inflammatory cells + 200 positive tumor cells
CPS = ---------- x100 = 33
1500 tumor cells
10x

QUESTION

- True or false:
- The lymphocytes and macrophages in this photo should be included in the numerator for a CPS calculation.



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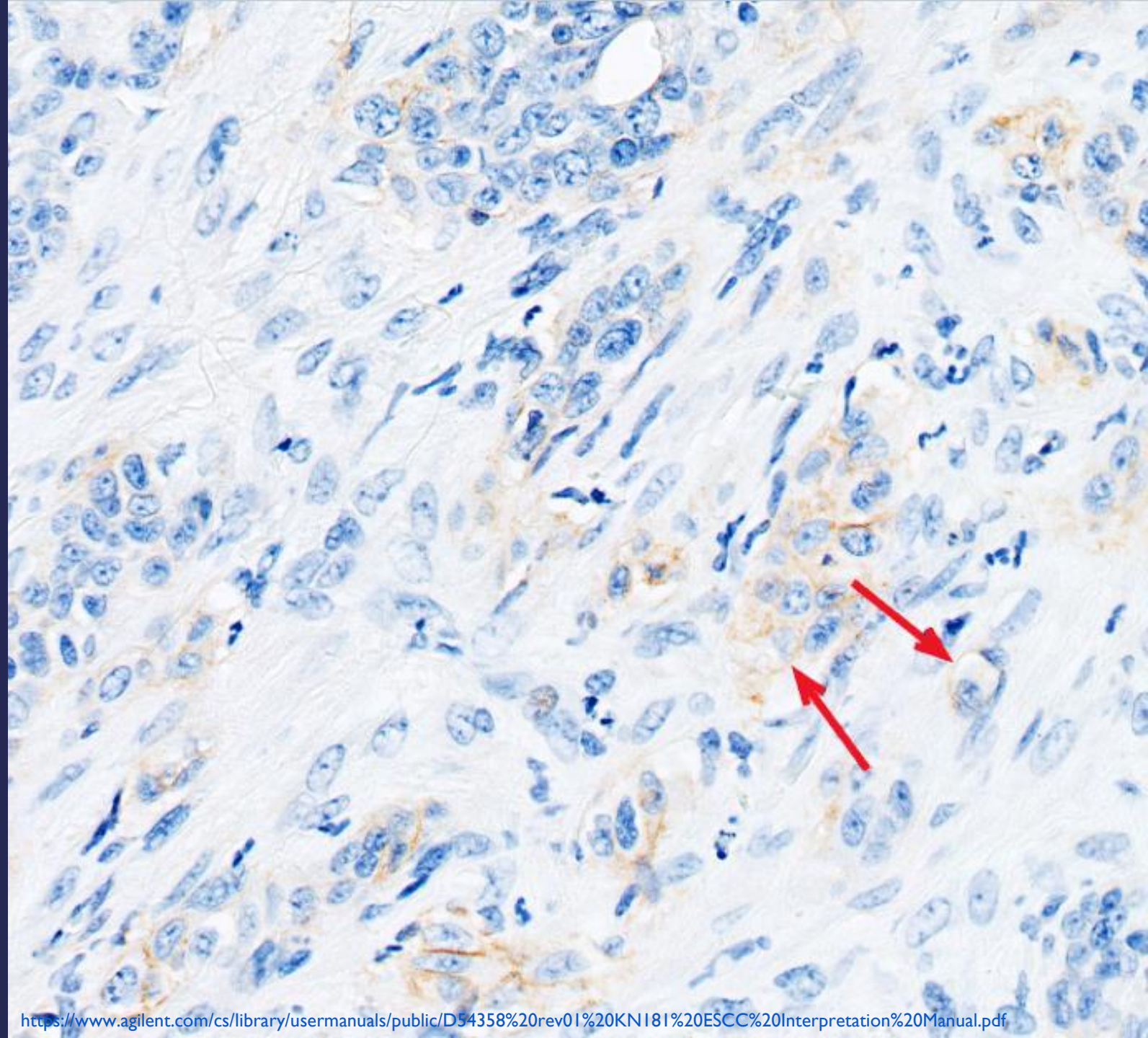
QUESTION

- True or false:
- Partial 1+ staining of tumor cells should be included in the numerator of a CPS calculation



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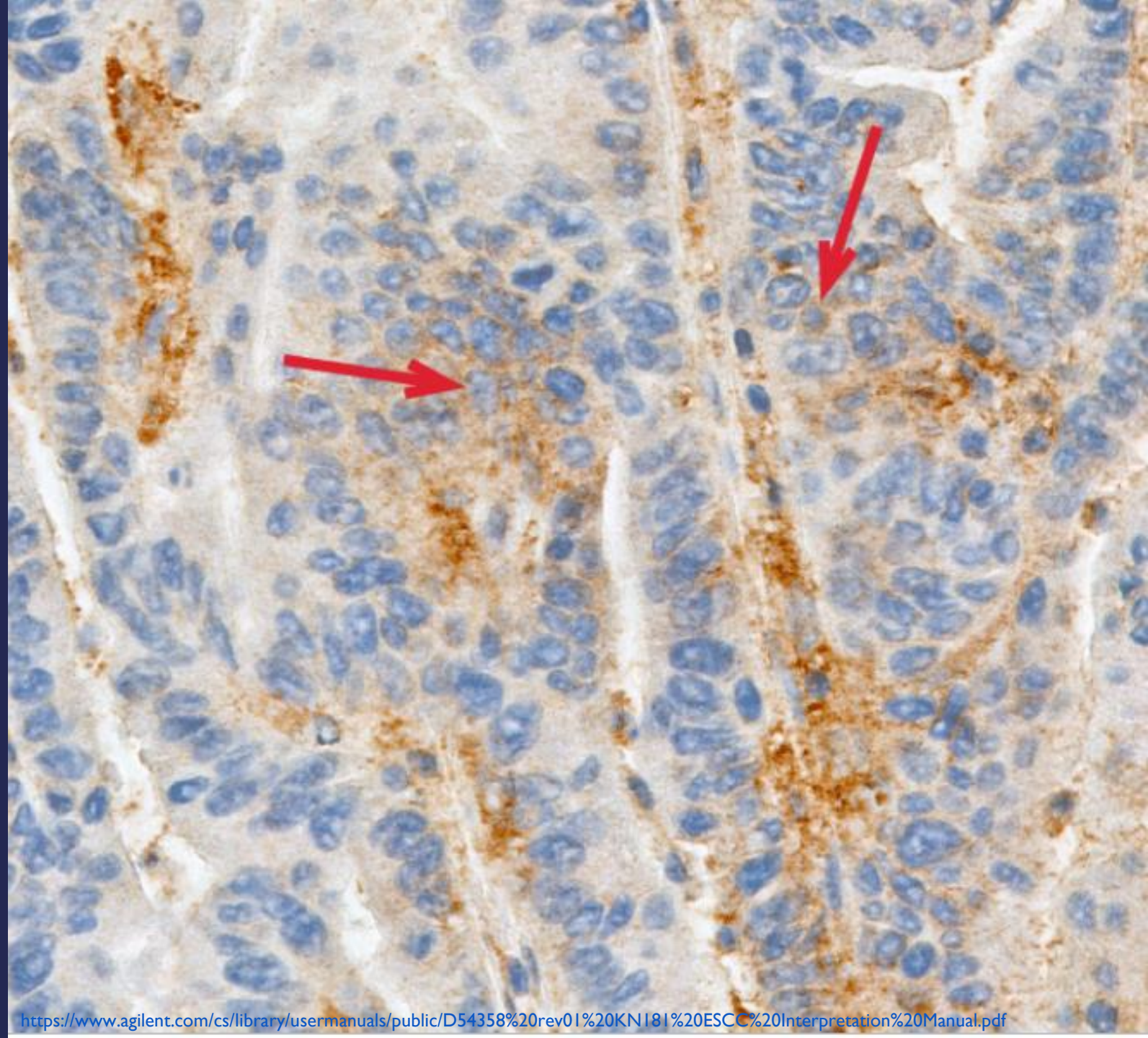
QUESTION

- How many tumor cells are staining with PDL1?
  - <1 %
  - 1-10%
  - 20-30%
  - 50-60%



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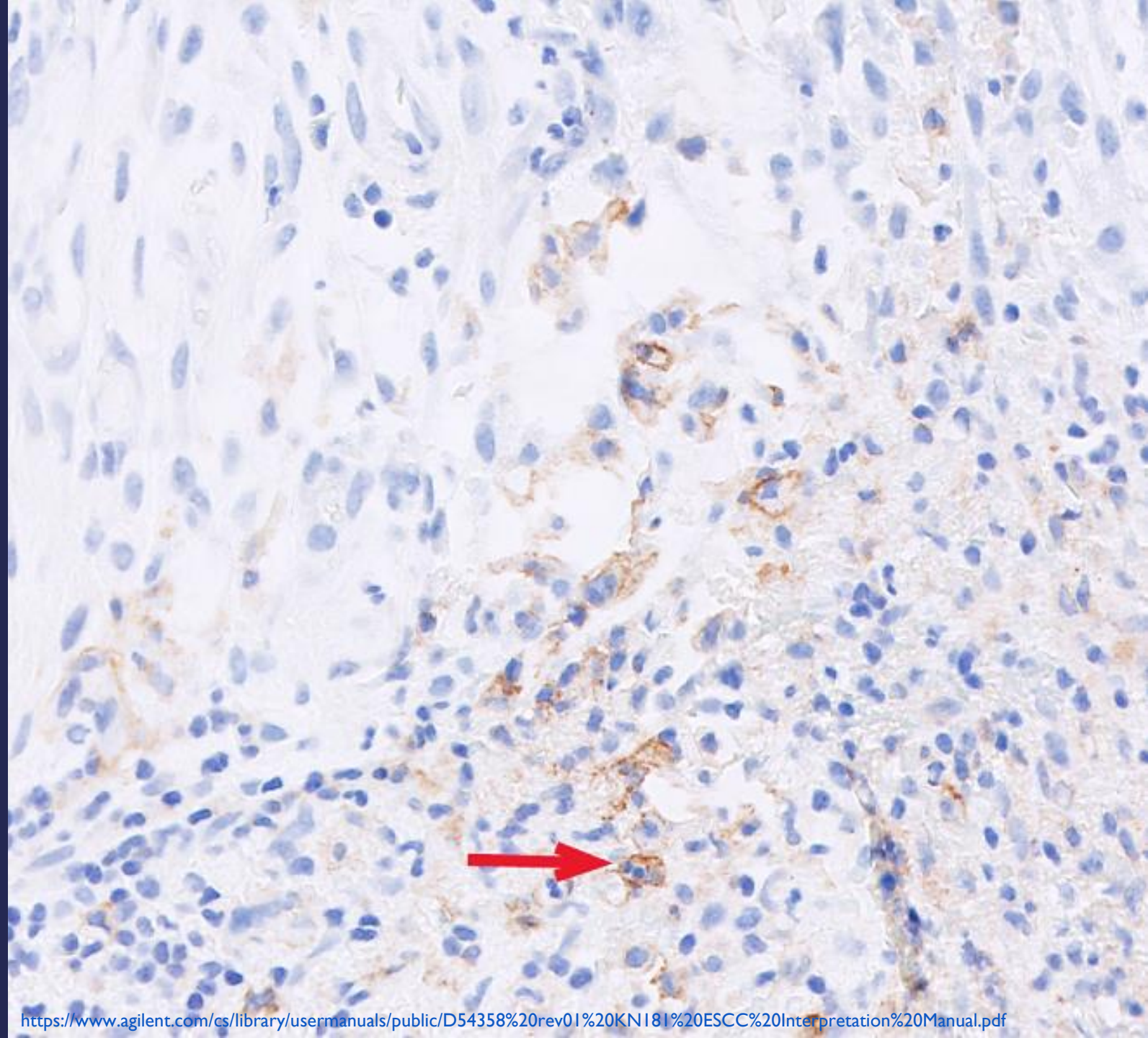
QUESTION

- In addition to lymphocytes, which other immune cells should be included in the CPS numerator?
  - Neutrophils
  - Eosinophils
  - Plasma cells
  - Macrophages



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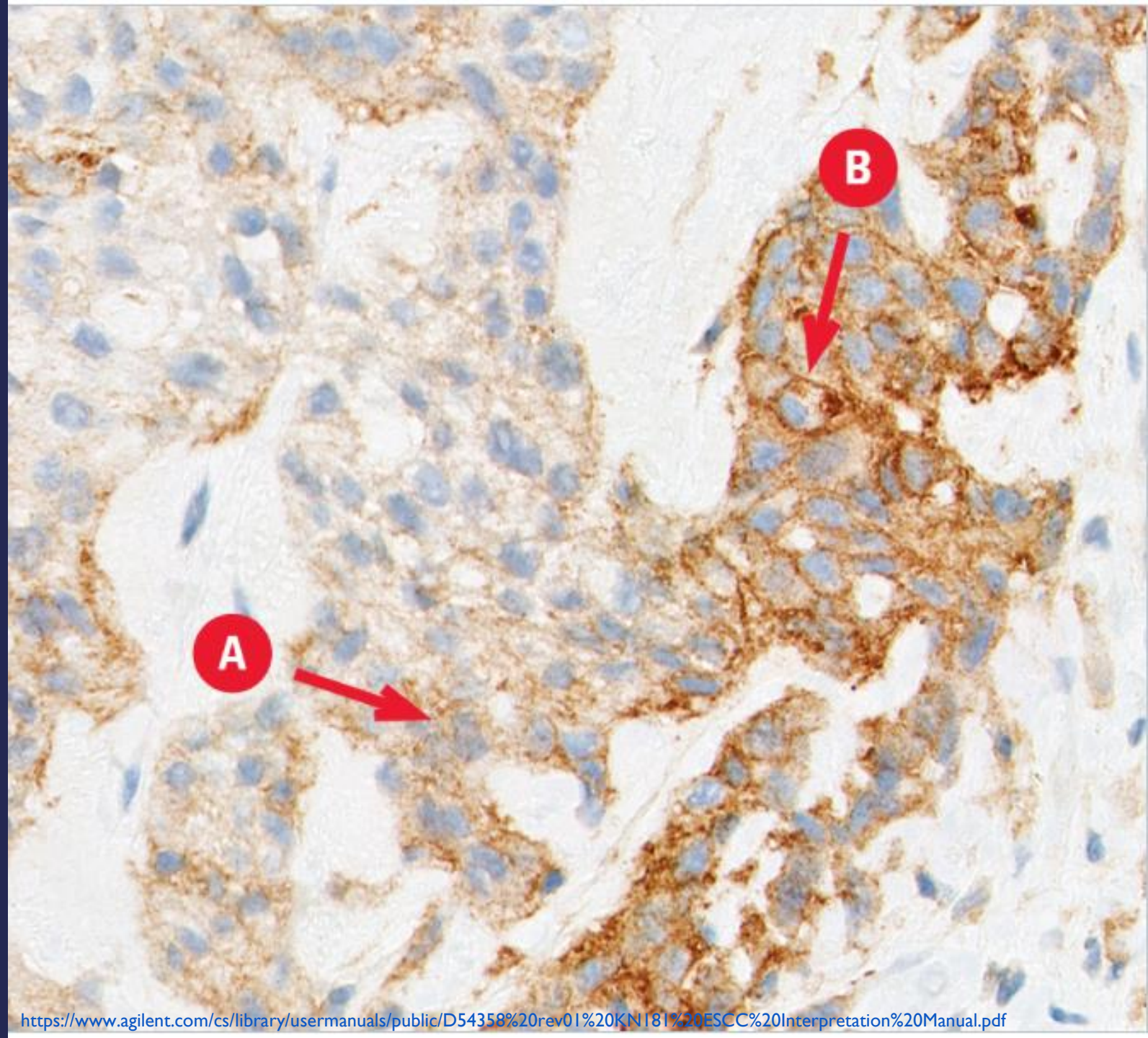
QUESTION

- Which tumor cells should be included in the CPS numerator?
- A
- B
- Both



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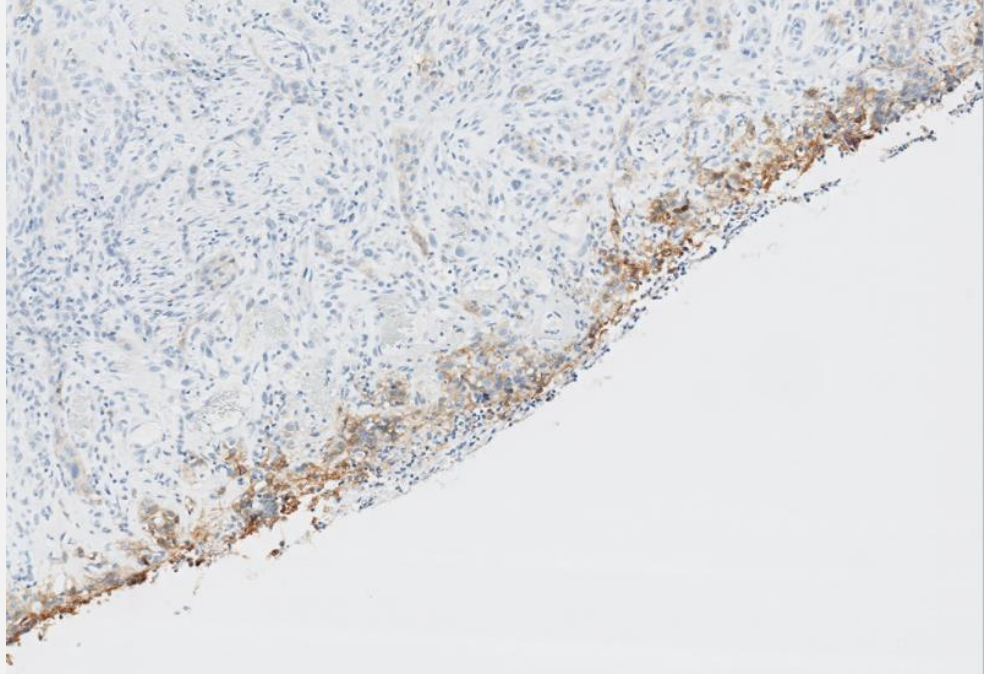
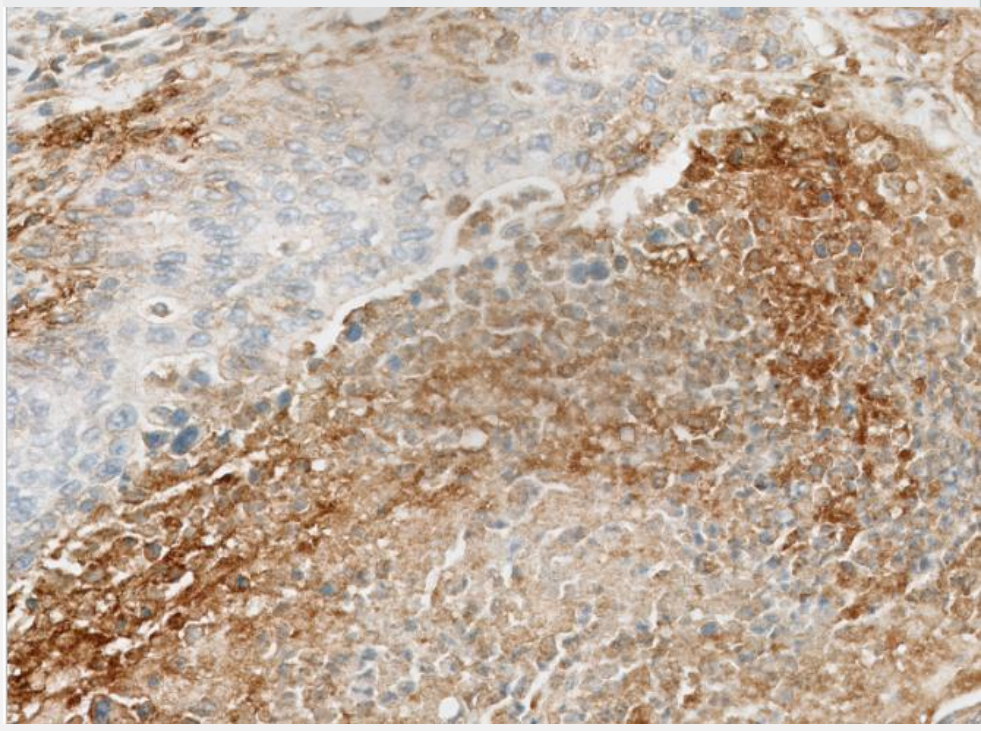
CHALLENGES

- Necrotic tissue will stain
- Edge artifact, crush
- Poor fixation





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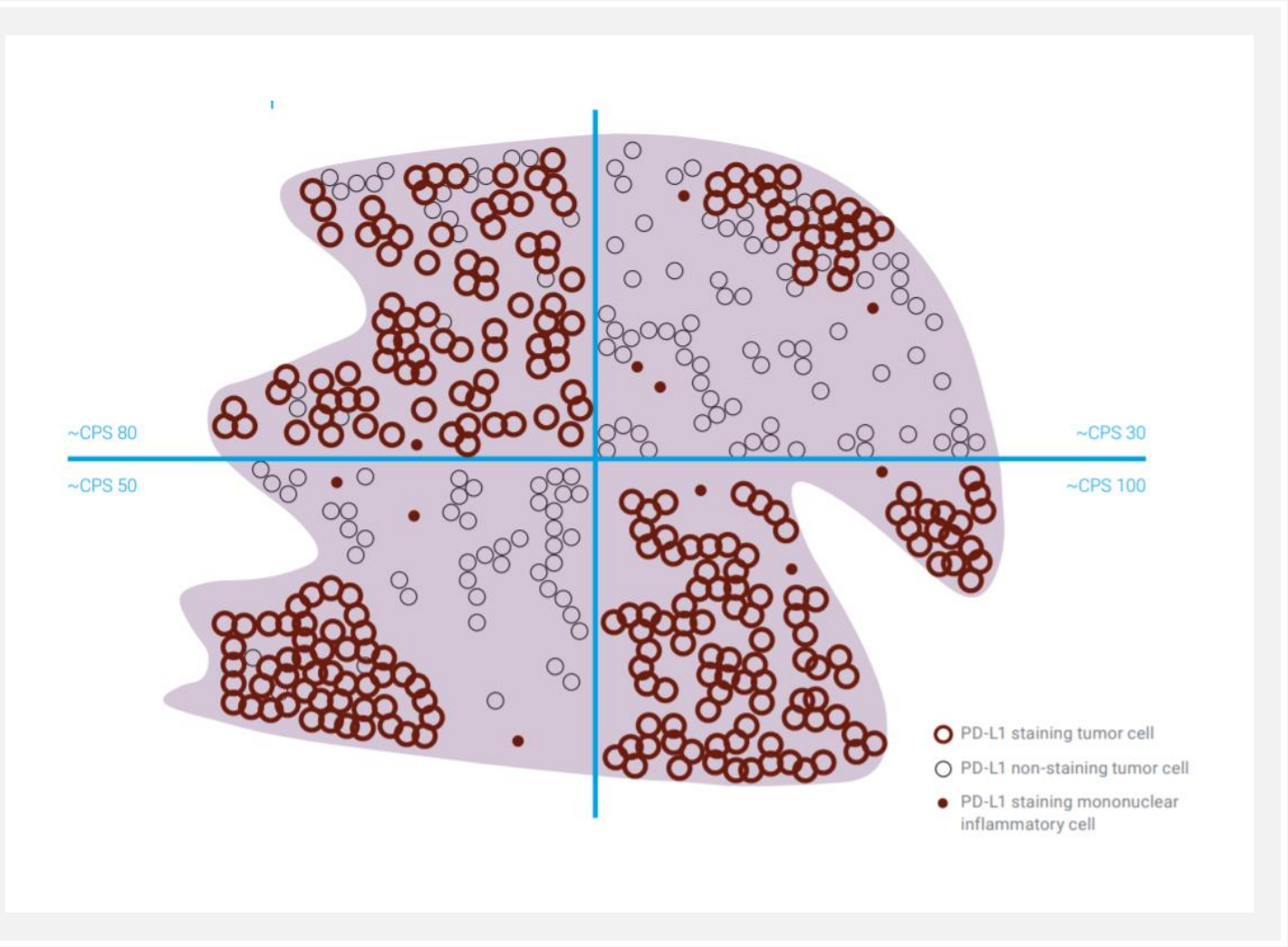
NUMERATOR TARGET METHOD

$$\frac{\text{X (positive tumor cells, lymphocytes, and macrophages)}}{\text{Total number of tumor cells (1000)}} \times 100 = \text{CPS 1}$$

- X = 10

HOT SPOT METHOD

- Good for heterogeneous samples with distinct foci of intense staining
- Estimate area percentage with "hot spots", then calculate the CPS of these areas
- Multiply the CPS of the hotspot by the percentage of the area that it makes up, assuming the background is a CPS of < 1



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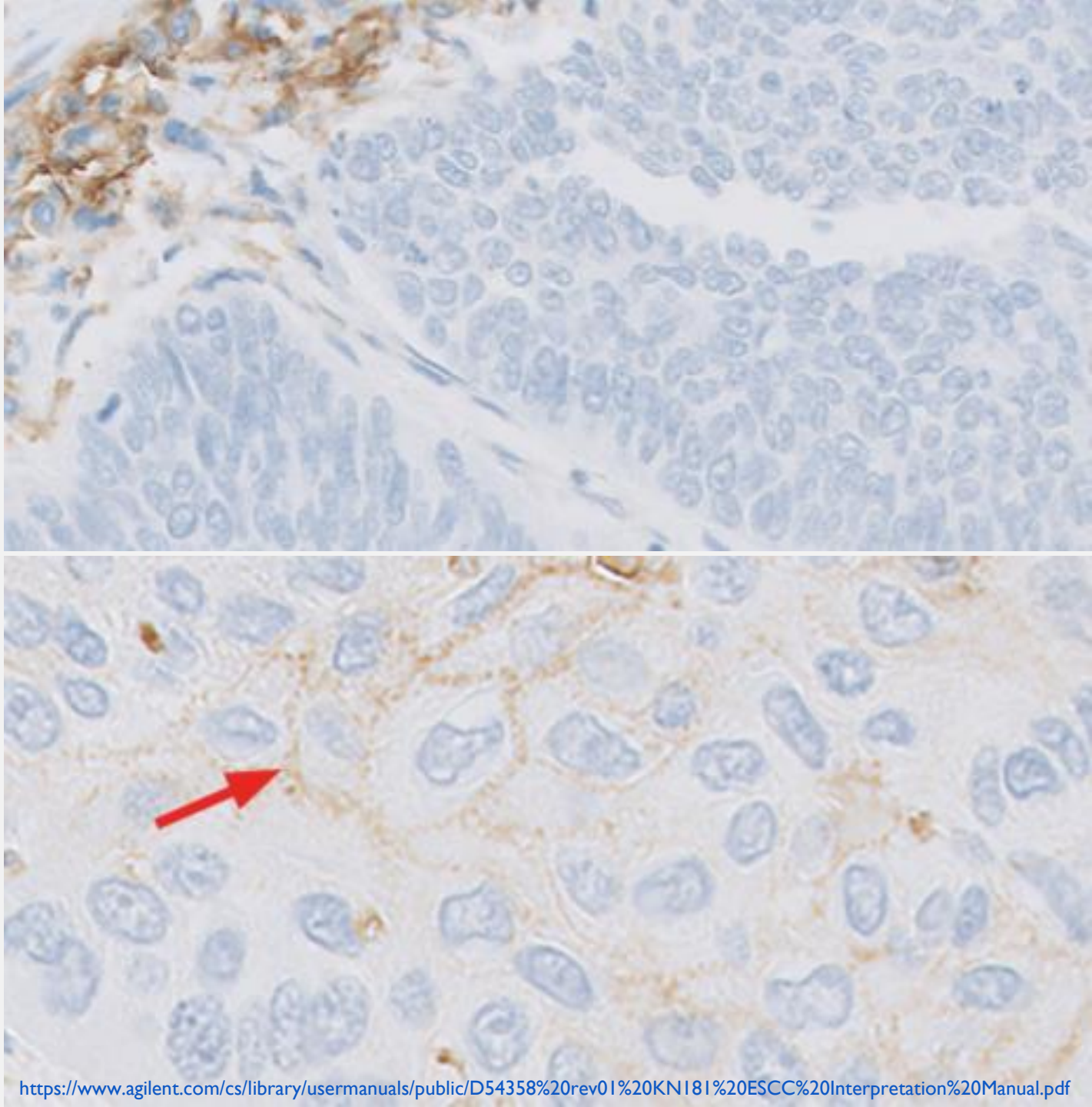
ESOPHAGEAL SQUAMOUS CELL CARCINOMA

CPS ≥ 10

- **KEYNOTE-180**
  - 121 patients with progressive disease after 2 or more therapies
  - ORR 13.8% (8/58) in PD-L1 positive tumors vs 6.3% (4/63) PD-L1 negative tumors
- **KEYNOTE-181**
  - 628 patients with advanced SCC or adenocarcinoma of GEJ or esophagus, second line
  - Pembrolizumab improved median OS (9.3 vs 6.7 months) and 12-month OS rates (43% vs 20%)
  - Improved OS compared with chemo alone with a more favorable safety profile

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

- Well differentiated SCC may have larger cells than basaloid variants
- Thus, lowering the number of tumor cells in the equation



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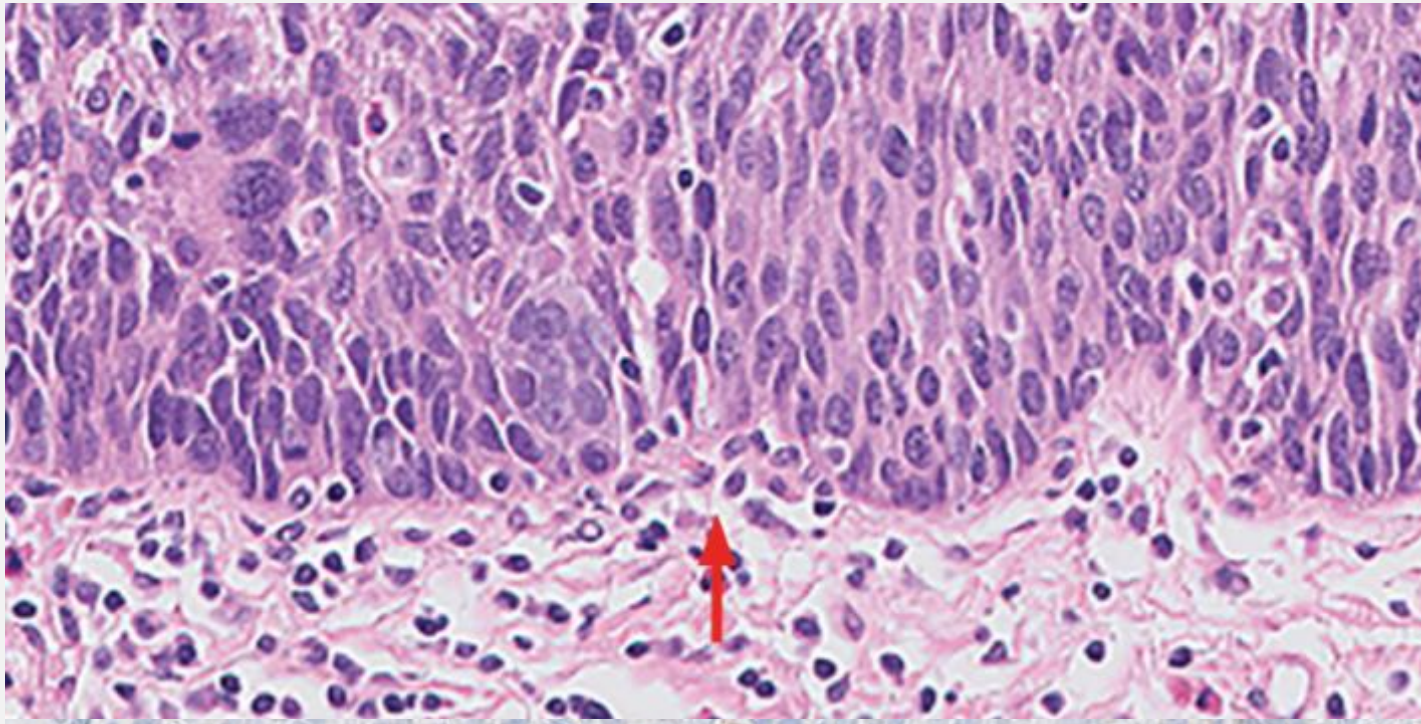
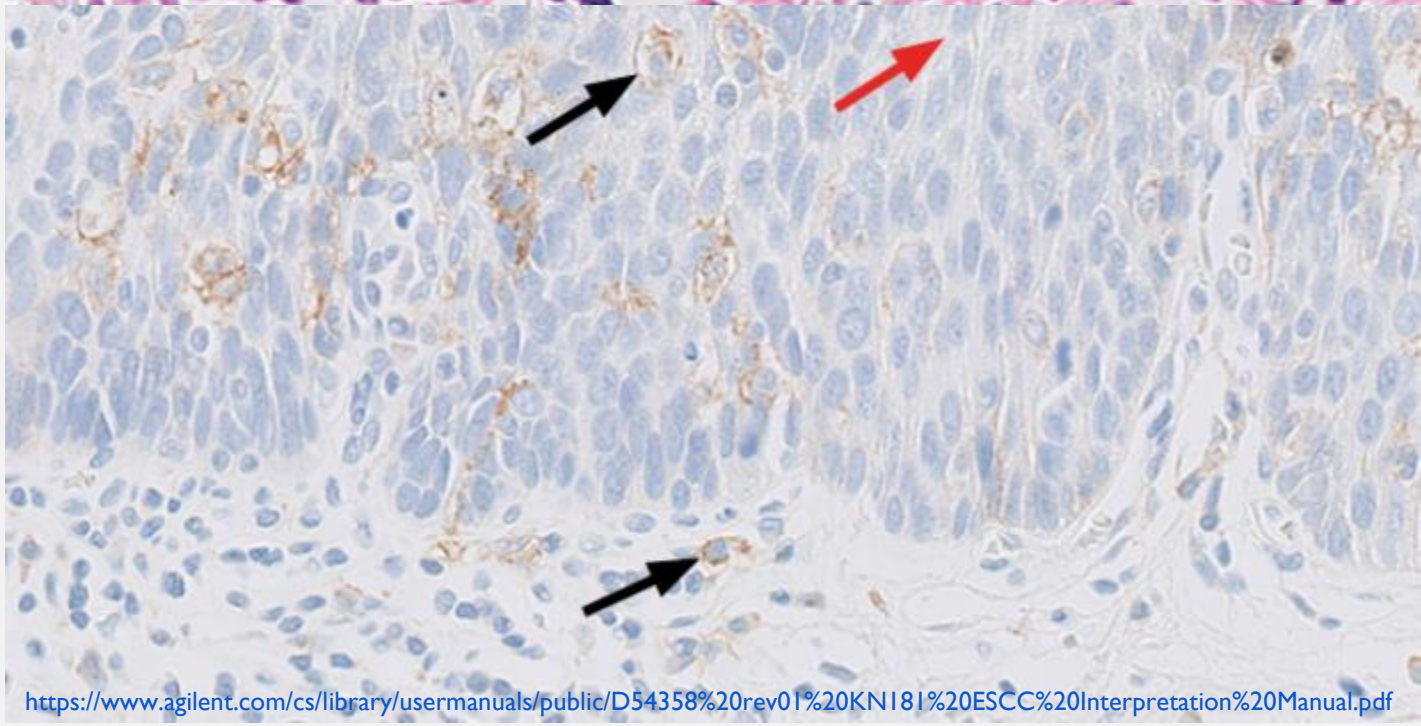
ESOPHAGEAL SQUAMOUS CELL CARCINOMA

- Carcinoma in situ/severe dysplasia is still excluded in the equation





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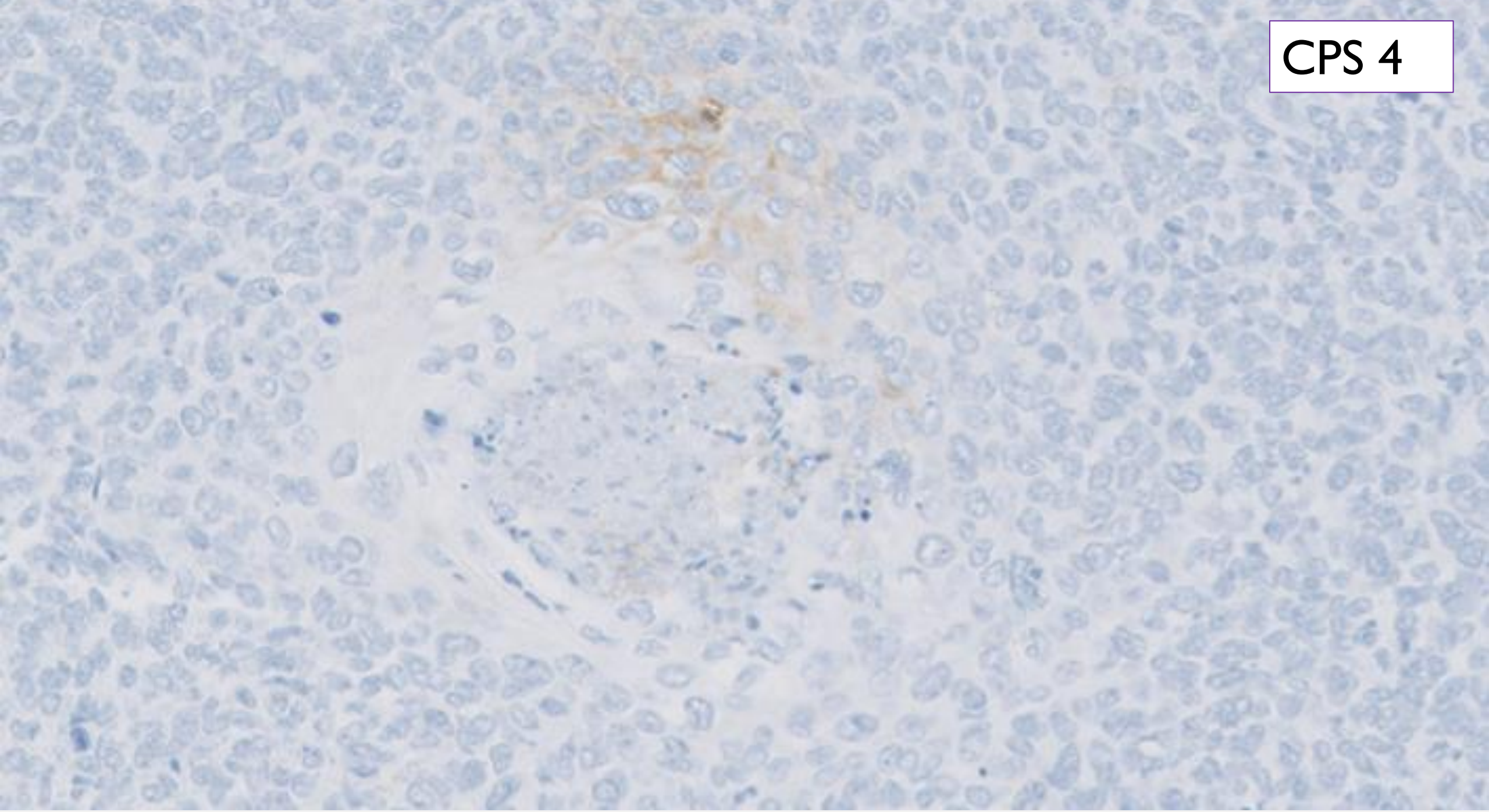

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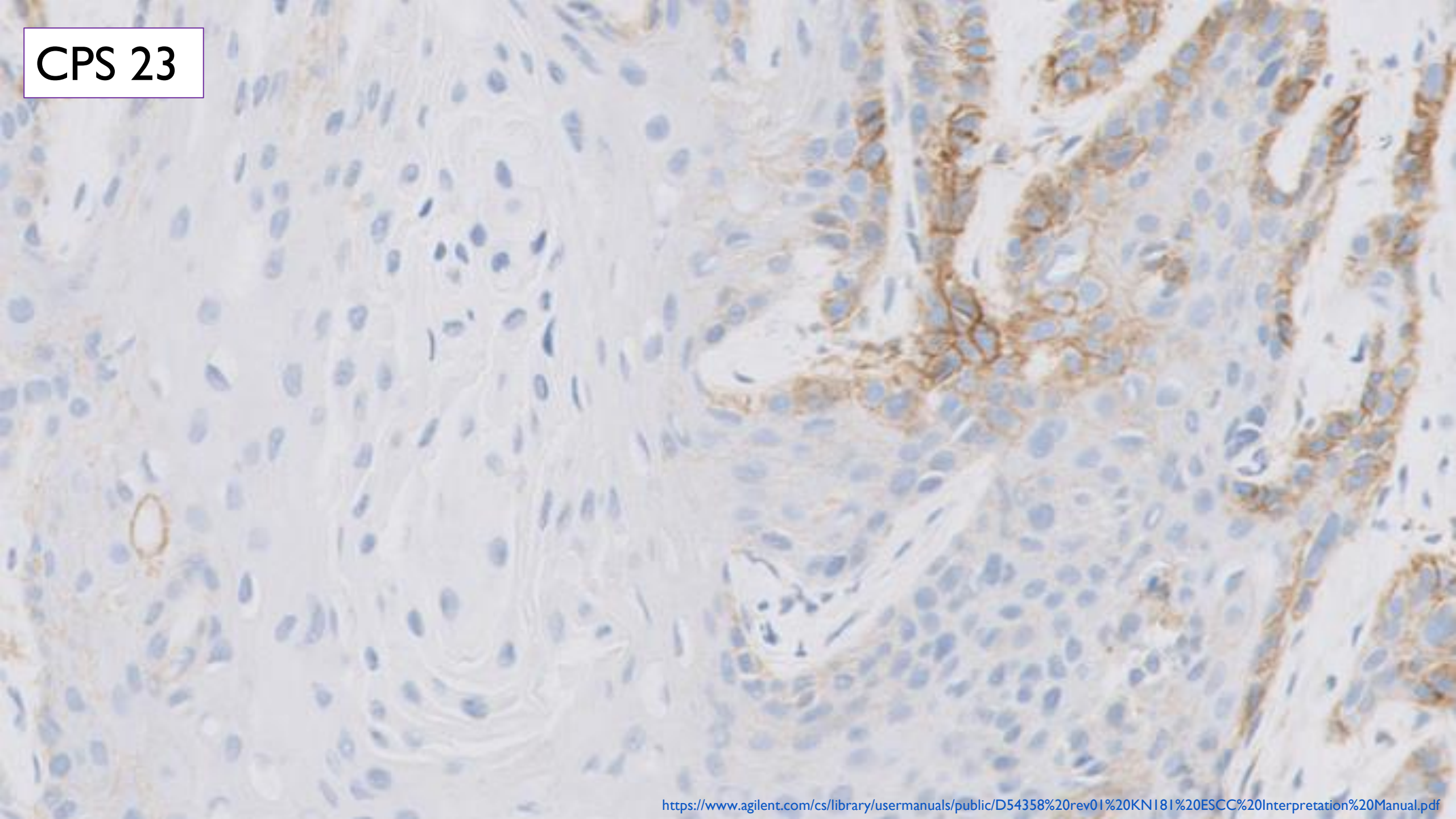

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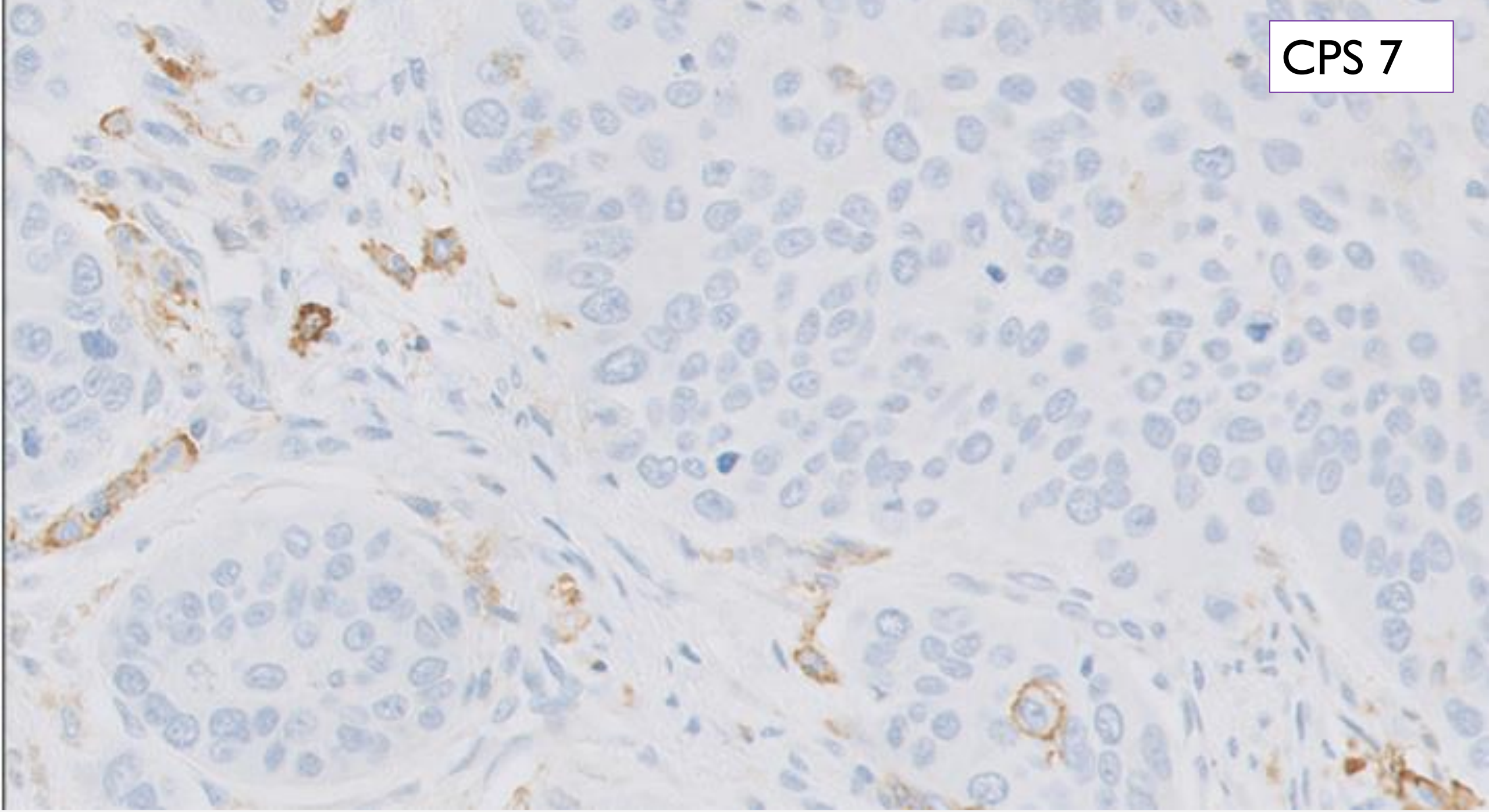

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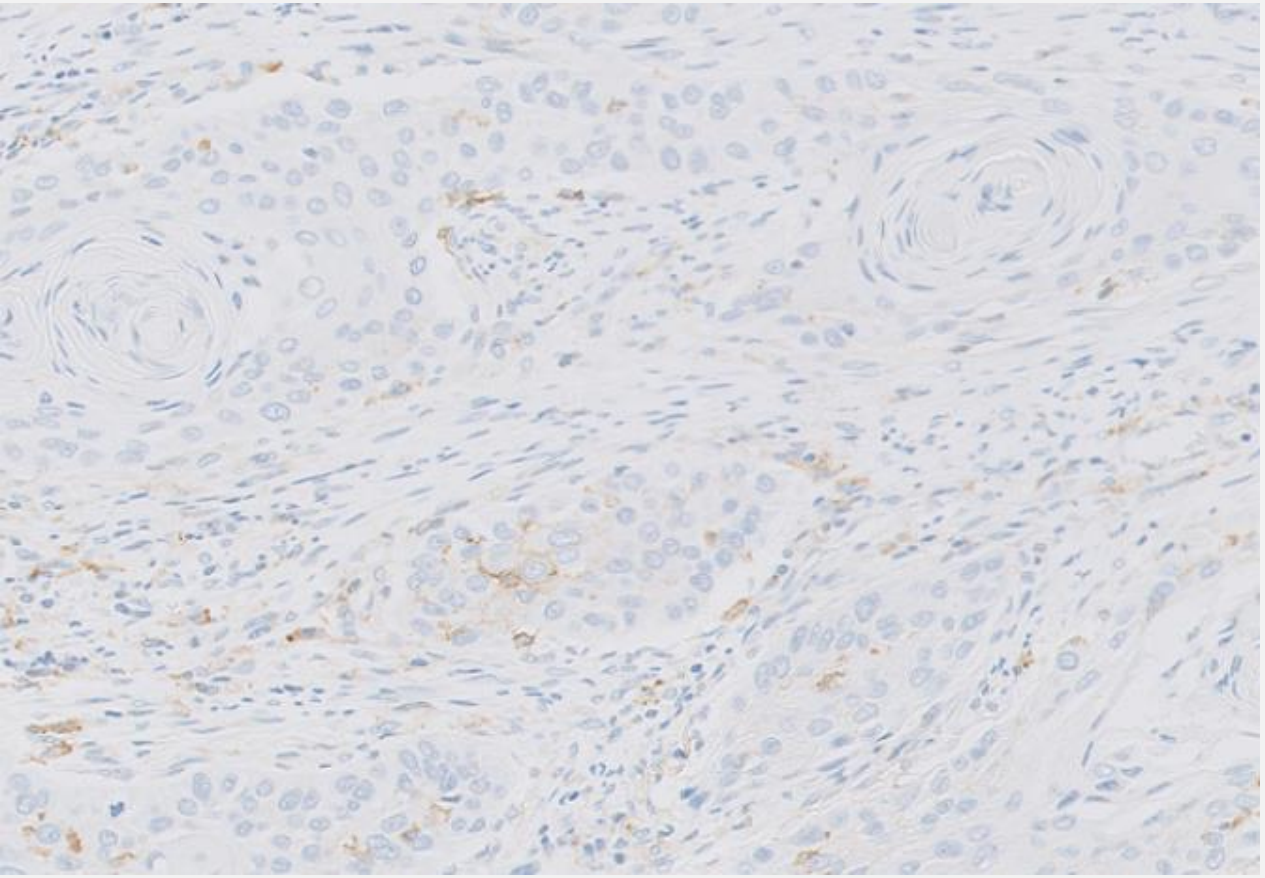
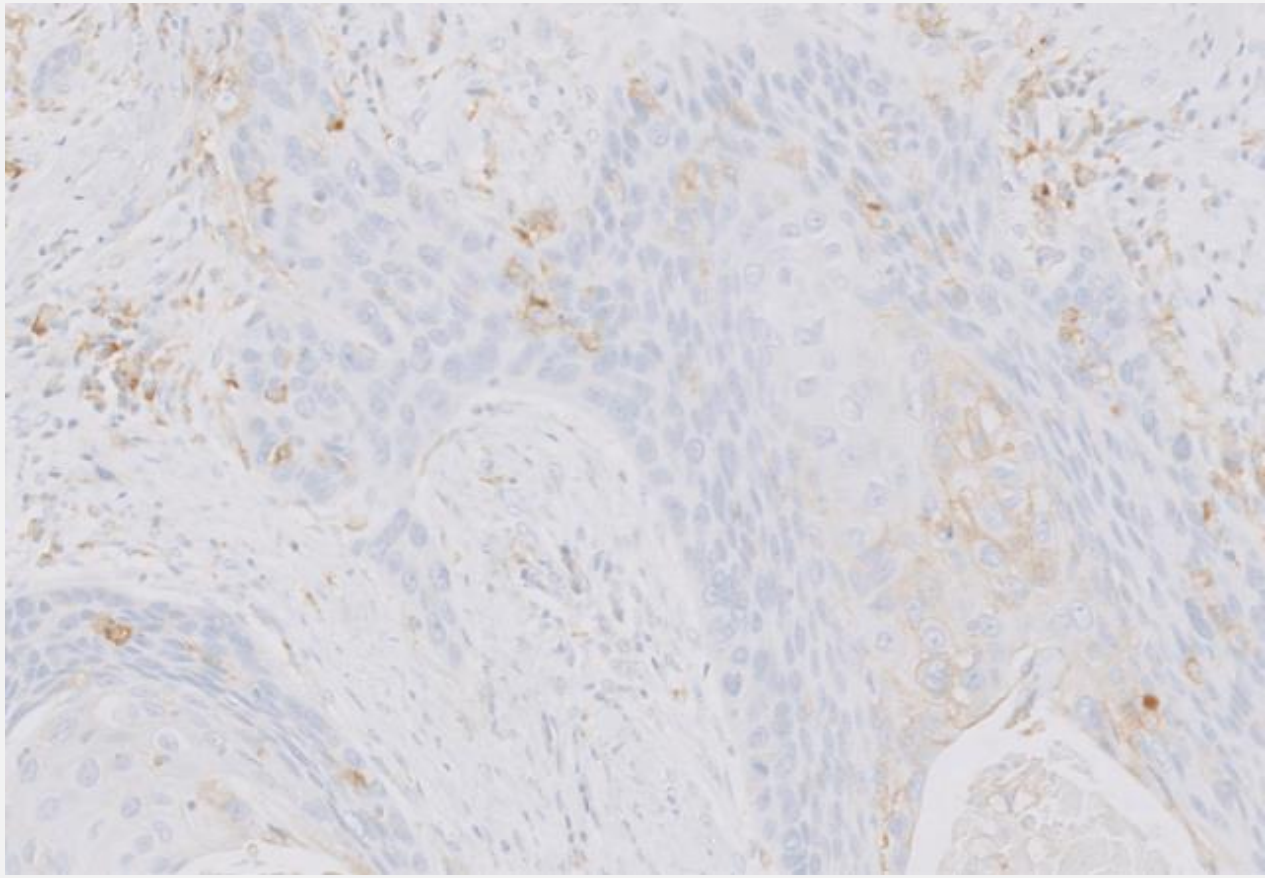
CPS 8



CPS 16



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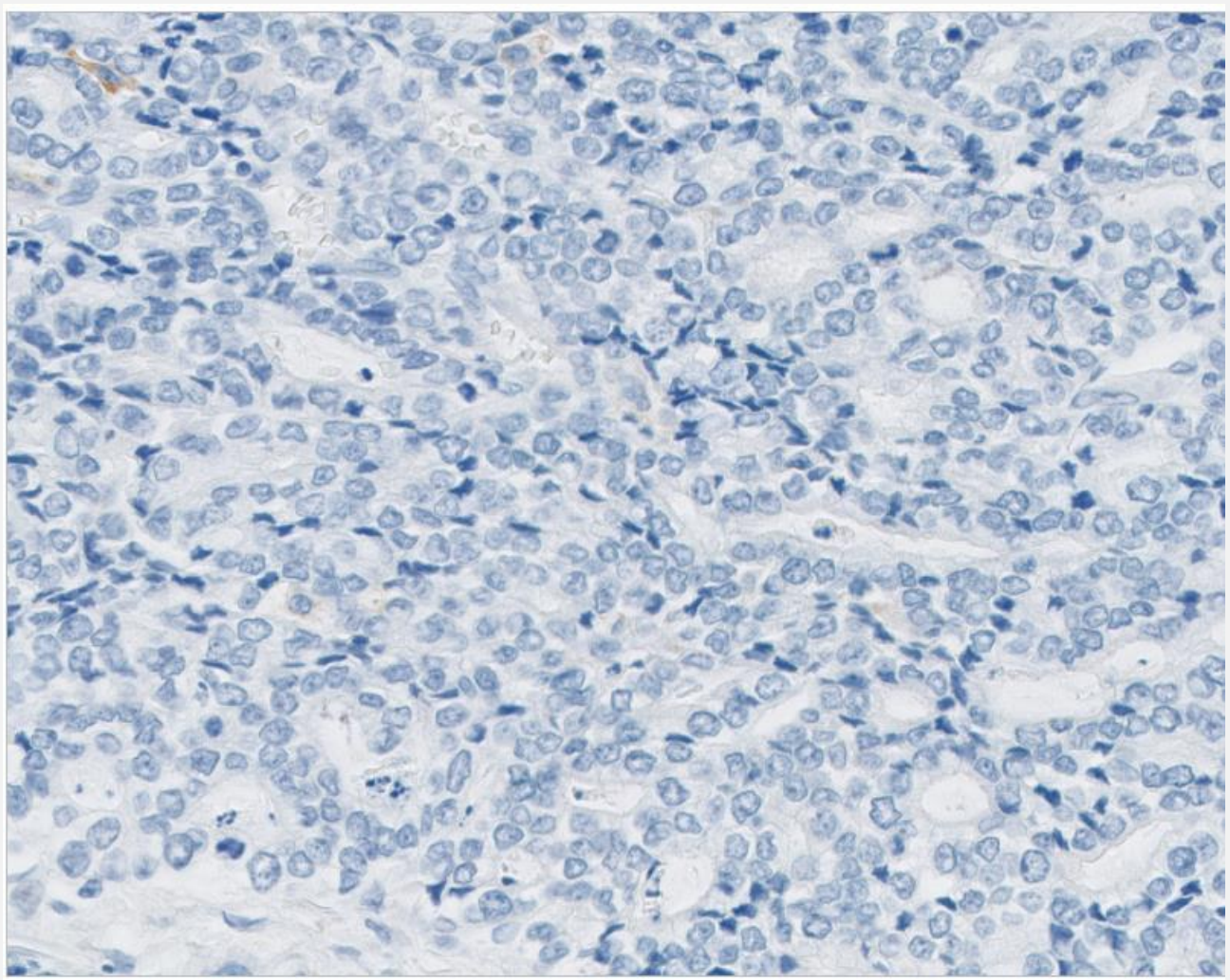
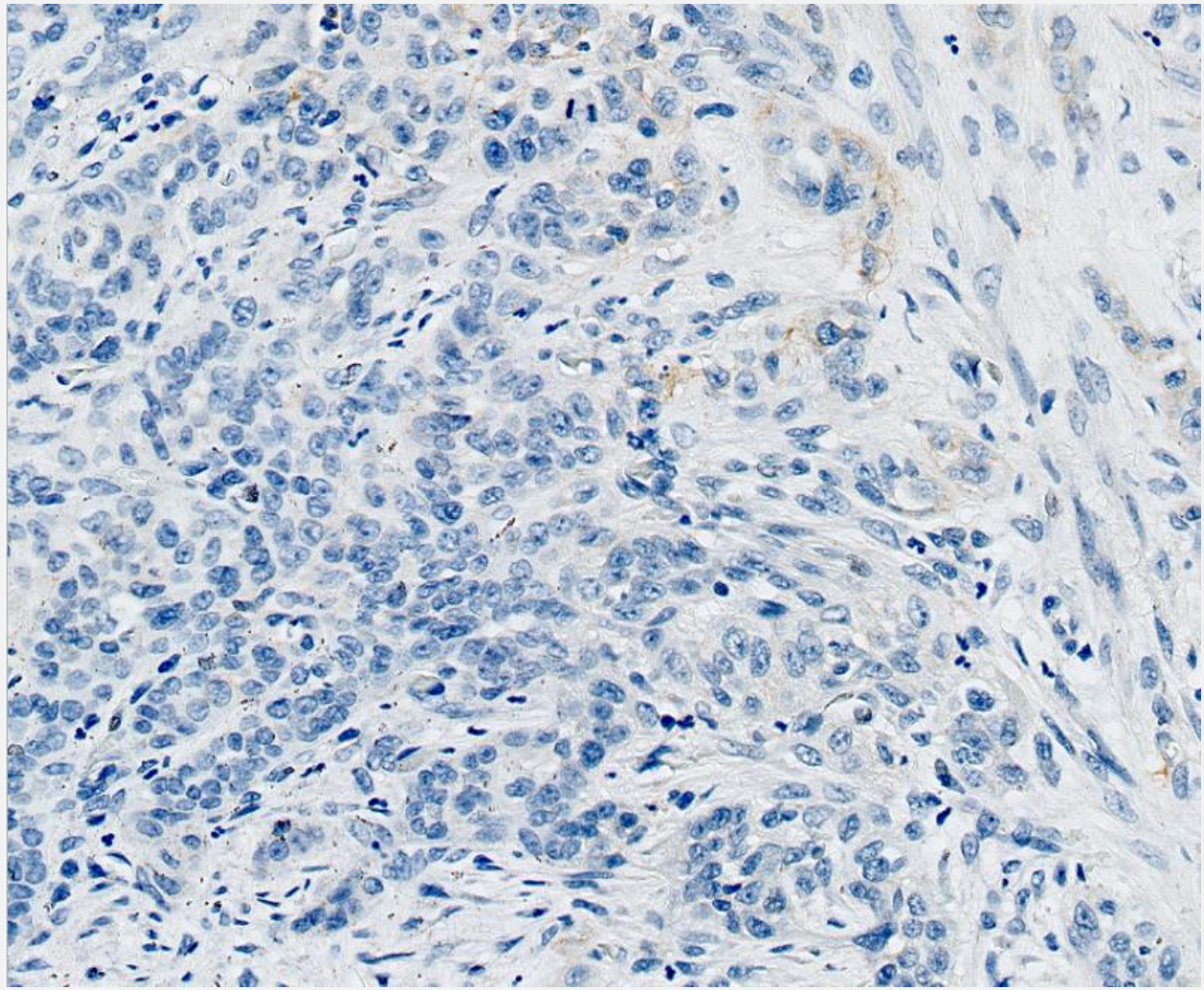
CPS < 1



CPS 2



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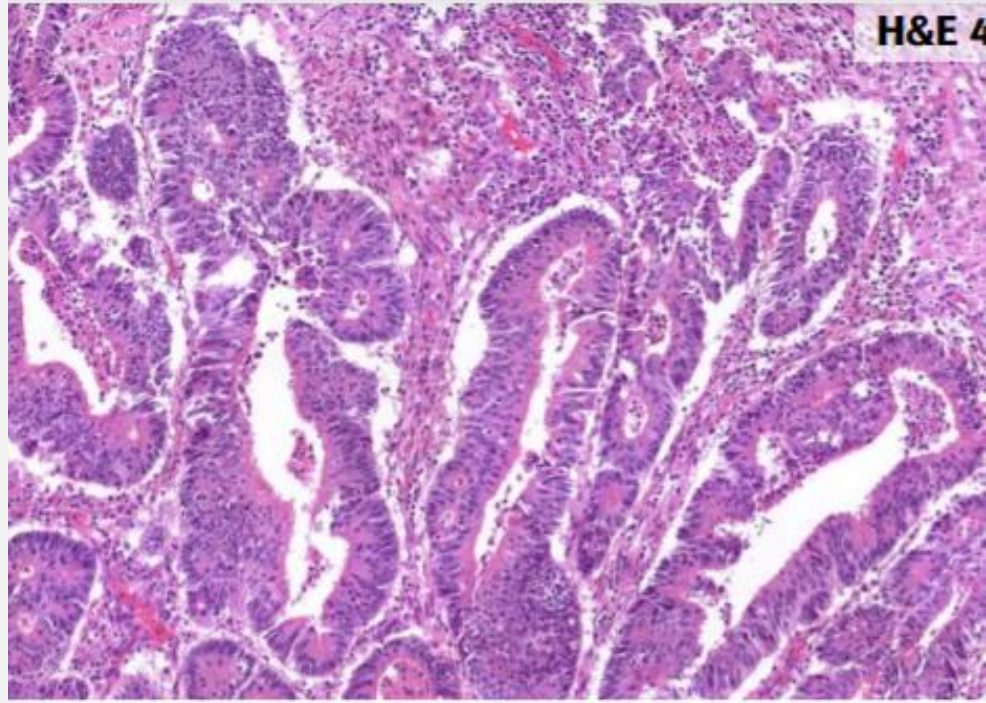
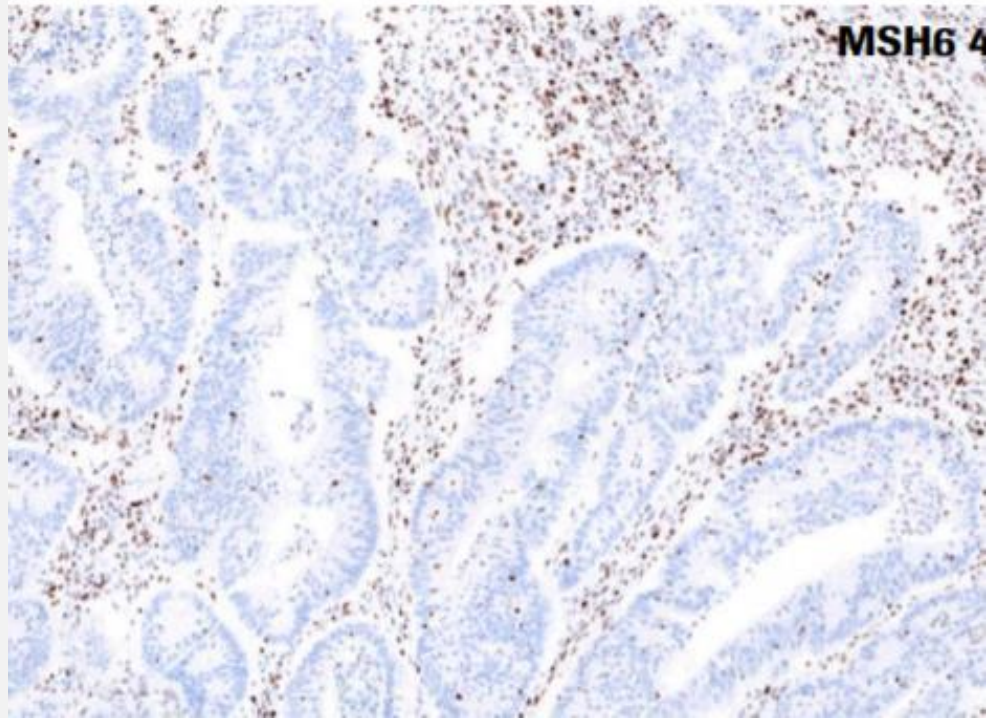
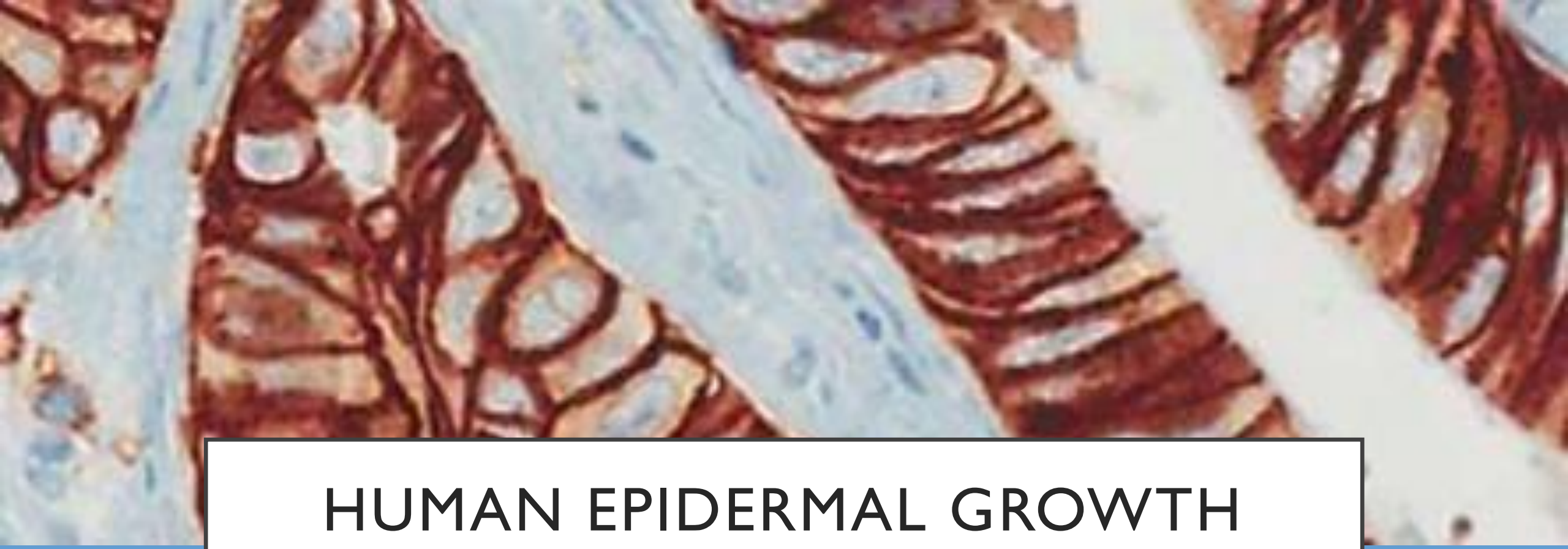
MICROSATELLITE INSTABILITY HIGH TUMORS

- Refractory cancers with deficient mismatch repair proteins/microsatellite instability-high may be susceptible to inhibition of PD-L1 pathway (**KEYNOTE-158**)
- May 2017 – FDA approved pembrolizumab for solid tumors, including gastric cancers, with MSI-H that had progressed on prior treatment and no alternative treatment options







HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2)

Rüschoff J, et al. HER2 testing in gastric cancer: a practical approach. Mod Pathol. 2012 May;25(5):637-50

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2)

- Also known as ERBB2 – proto-oncogene that encodes a tyrosine kinase receptor belonging to the epidermal growth factor receptor family
  - When phosphorylated, it initiates signaling pathways leading to cell division, proliferation, differentiation, and anti-apoptosis signaling
- **7-38%** of gastroesophageal adenocarcinomas will have **over-expression**
  - Slightly greater for GEJ adenocarcinomas than gastric
  - More frequent in intestinal type than diffuse type
  - Expressed in more well to moderately differentiated tumors than poorly differentiated

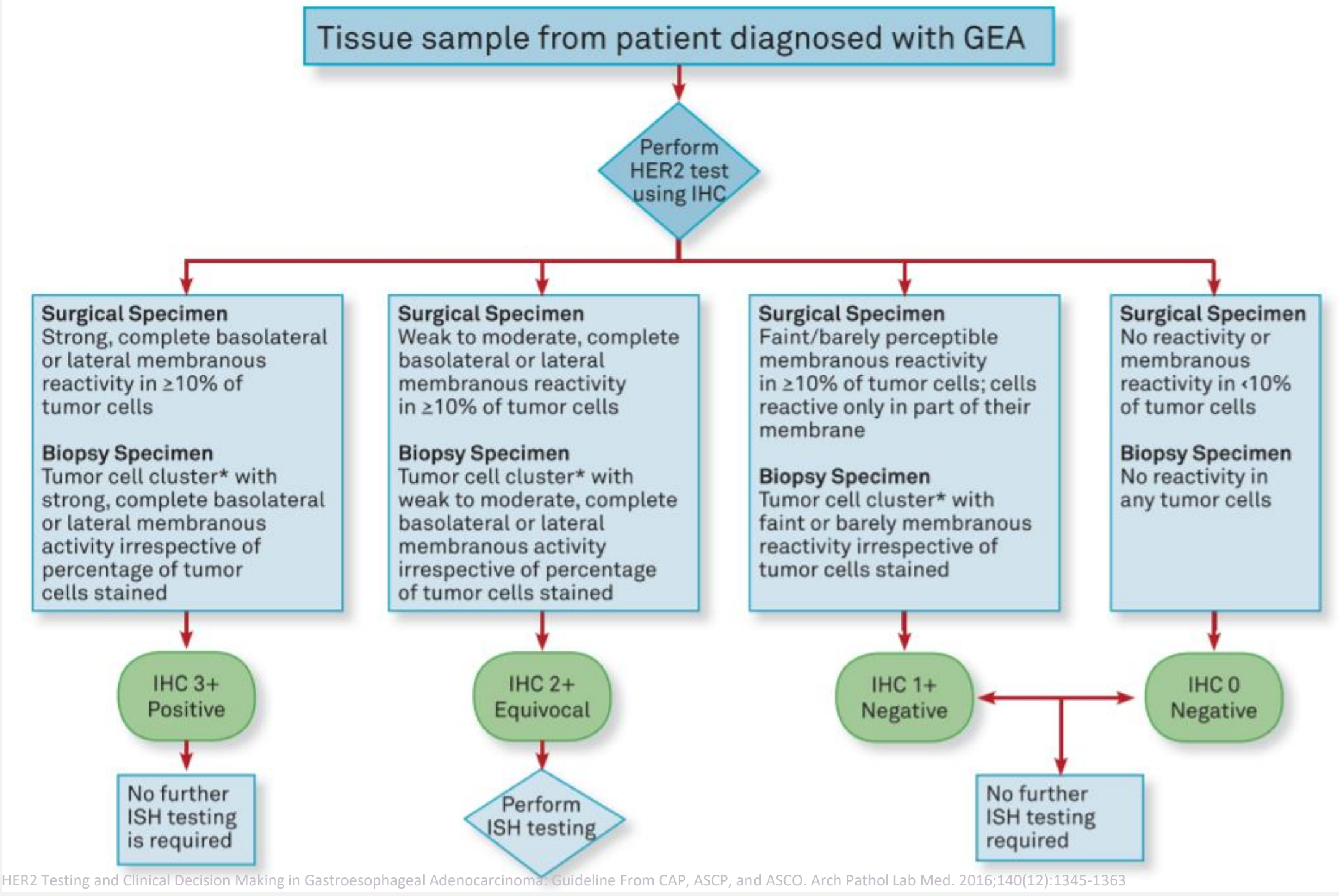
HER2

- **Trastuzumab**:
  - Humanized monoclonal antibody that targets extracellular domain of HER2 receptor
  - Stops signal activation
- 2010 clinical trial **Trastuzumab for Gastric Adenocarcinoma (ToGA)** showed prolonged survival with trastuzumab combined with chemotherapy rather than chemotherapy alone
- 2016 CAP provided comprehensive guidelines for HER2 testing
- Testing should be performed in unresectable, locally advanced, recurrent or metastatic tumors

		Esophagogastric	Breast
IHC	Extent	Biopsy ≥ 5 cells; resection ≥10%	≥ 30%
	Circumferential	Mostly missing	Required for IHC2+/3+
ISH	Cell number	20 cohesive tumor cells showing highest gene count	Same
	Amplification	*HER2*/CEP17 ≥ 2.0 is positive	*HER2*/CEP17 ≥ 2.2 is positive
HER2 +	Tumor type	~ 30% intestinal type, 15% mixed type, 5% diffuse type	15-25% G2/G3 ductal type; special types rarely +
	Tumor location	~ 30% of GEJ, 15% gastric	No correlation

COLLEGE of AMERICAN PATHOLOGISTS STRONGERTOGETHER ASCO American Society of Clinical Oncology

https://documents.cap.org/documents/gastroesophageal-adenocarcinoma-her2-teaching-presentation.pdf



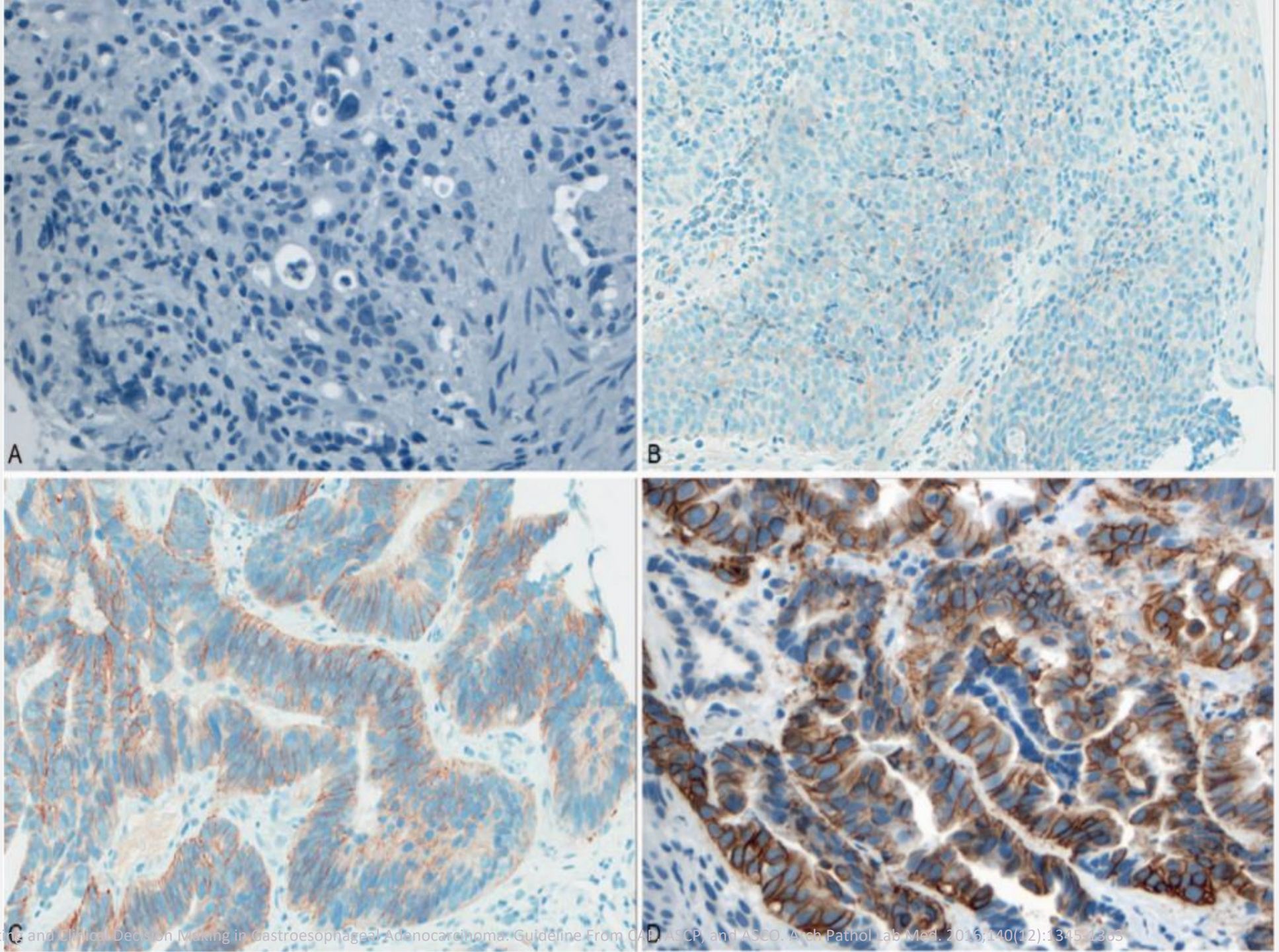
Bartley AN, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From CAP, ASCP, and ASCO. Arch Pathol Lab Med. 2016;140(12):1345-1363

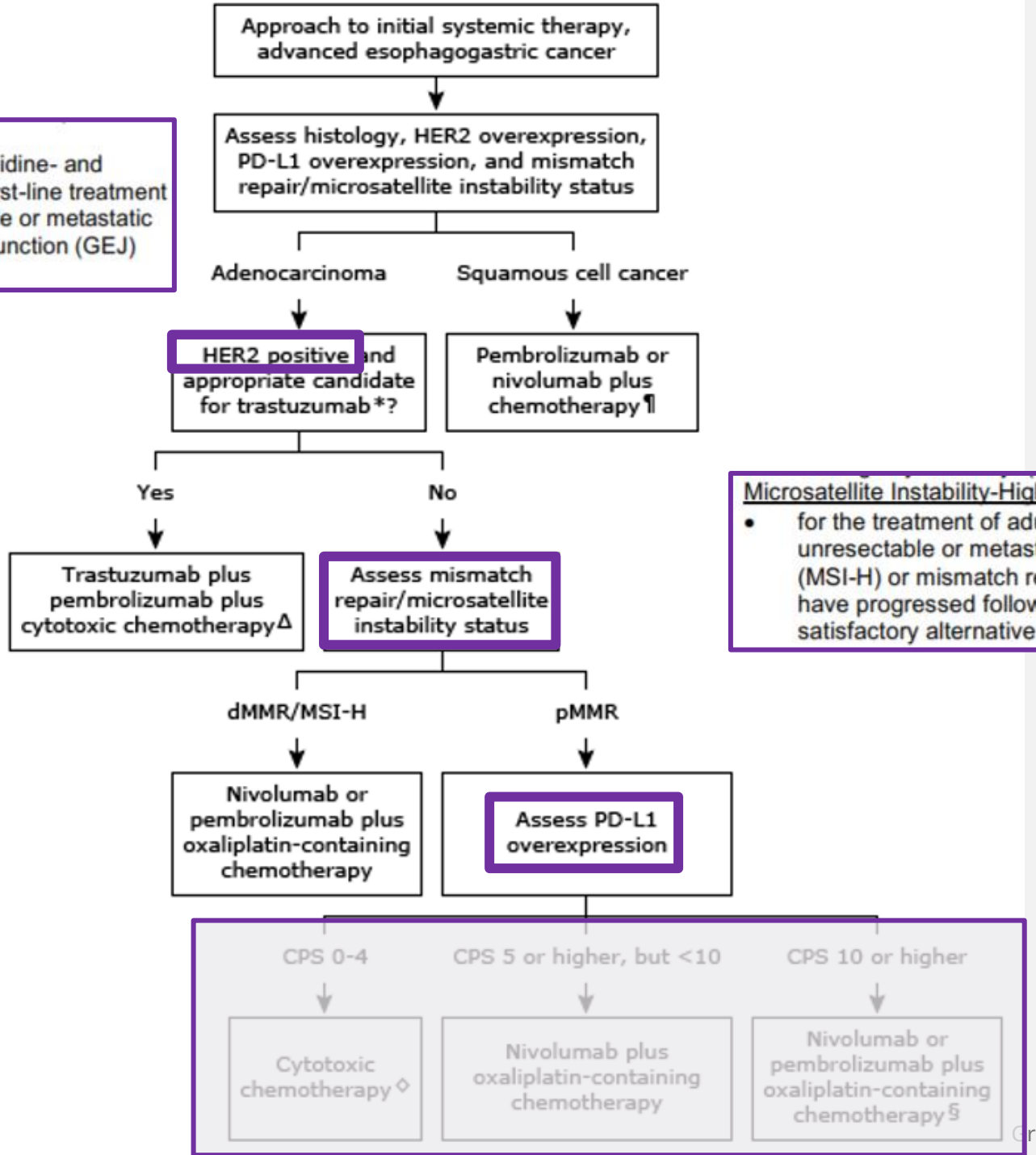
Table 4. Scoring Guidelines for Interpretation of HER2 IHC in Gastric Carcinoma[a]

Surgical Specimen–Staining Pattern	Biopsy Specimen–Staining Pattern	Score	HER2 Expression Assessment
No reactivity or membranous reactivity in <10% of tumor cells	No reactivity or no membranous reactivity in any tumor cell	0	Negative
Faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell cluster[b] with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	1+	Negative
Weak to moderate, complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster[b] with a weak to moderate, complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	2+	Equivocal
Strong, complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster[b] with a strong, complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	3+	Positive

RUSCHOFF/HOFMANN SCORING

Bartley AN, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From CAP, ASCP, and ASCO. Arch Pathol Lab Med. 2016;140(12):1345-1363


A
B
C
D



Gastric Cancer

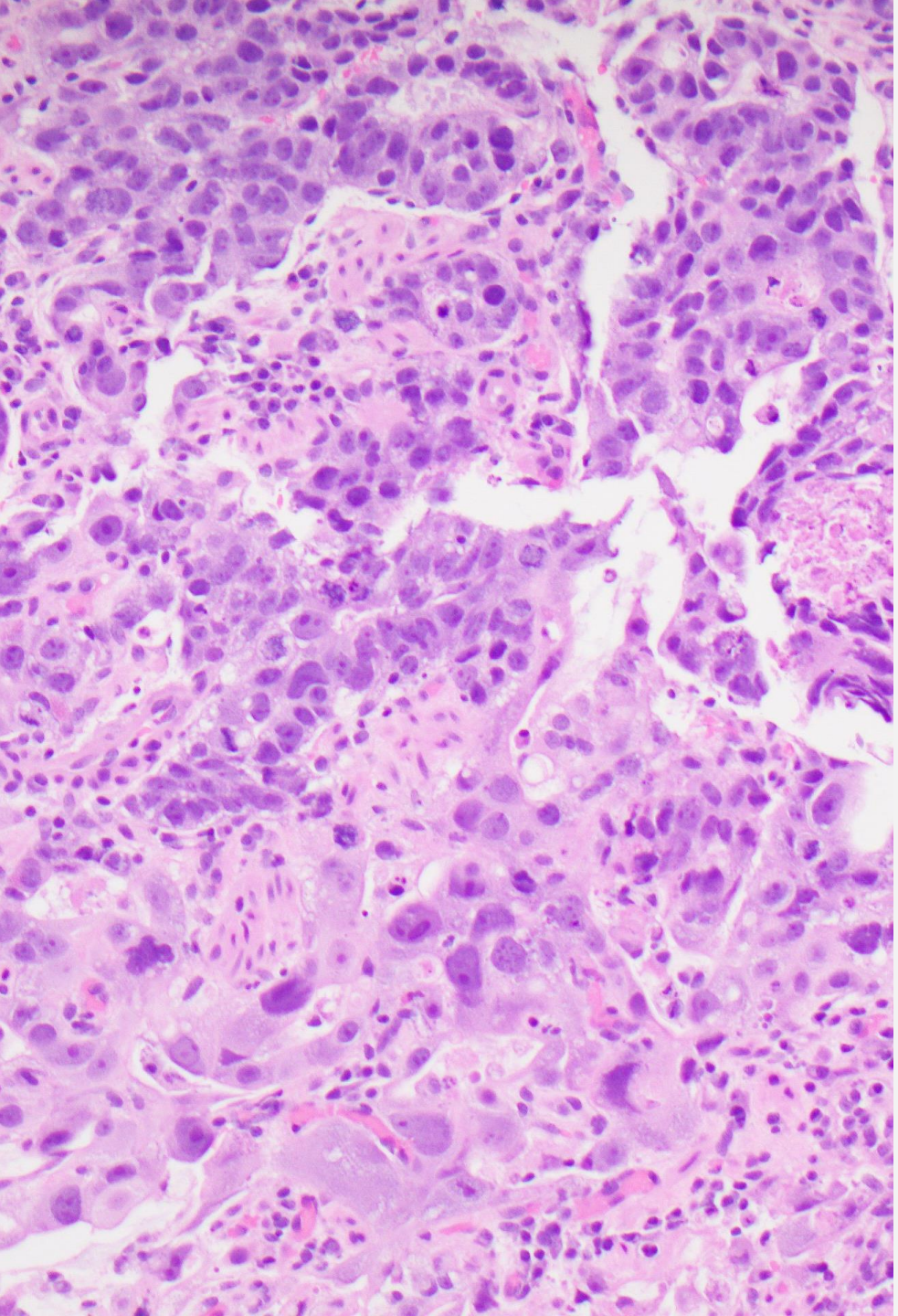
- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.[1] (1.9)

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1] (1.7, 2.1)

FUTURE STUDIES

- **Digital pathology and AI systems**
  - Different methods of AI (deep learning, random forest, some with feedback loops by pathologist/data evaluation) aid in quantitation and evaluation of IHC
  - Studies have trained algorithms to recognize membrane PD-L1 staining in tumor cells, unstained tumor cells, exclude inflammatory cells, and calculate TPS after manual annotation of tumor area by pathologist
- **Multiplex IHC**
  - Some patients with low PD-L1 respond to treatment and the reverse is true
  - CD8/PDL1 signature – some studies have begun to evaluate as a predictor of patient outcome
- **Clinical trials**
  - KEYNOTE-590 active, not recruiting for first line pembrolizumab in combo with chemo



SUMMARY

- Gastroesophageal cancers are commonly diagnosed at advanced stages, which portend **poor prognoses** and have limited available therapeutic options
- Biomarker testing for **PD-L1, HER2, and MSI** status have been studied and validated in advanced staged gastroesophageal cancers and have prognostic implications
- Continually evolving area of medicine!

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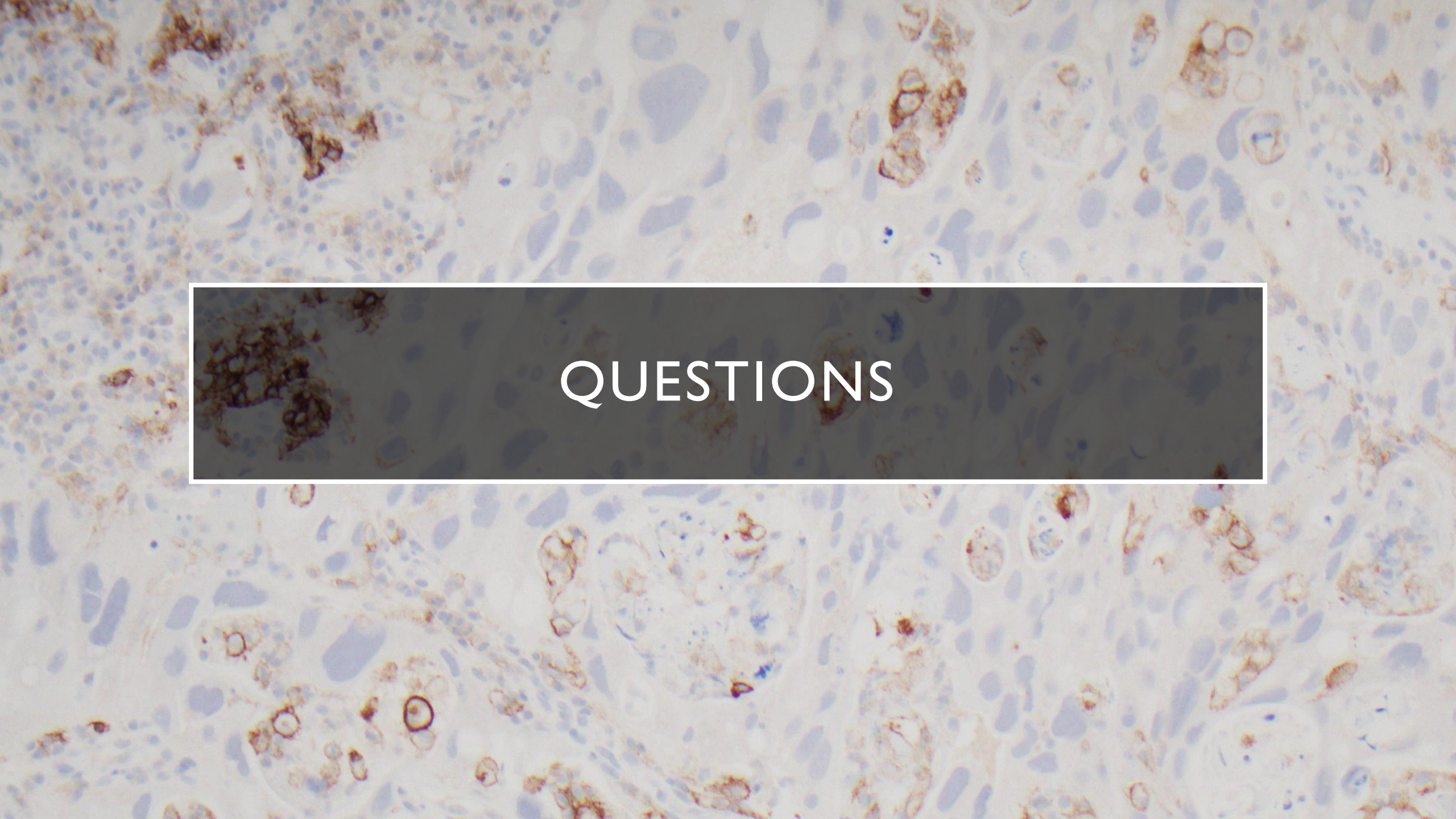
QUESTIONS