When Morphology Meets Molecular: The Evaluation of Small Biopsy Specimens of the Pancreas, Bile Duct, and Ampulla (Part 1)

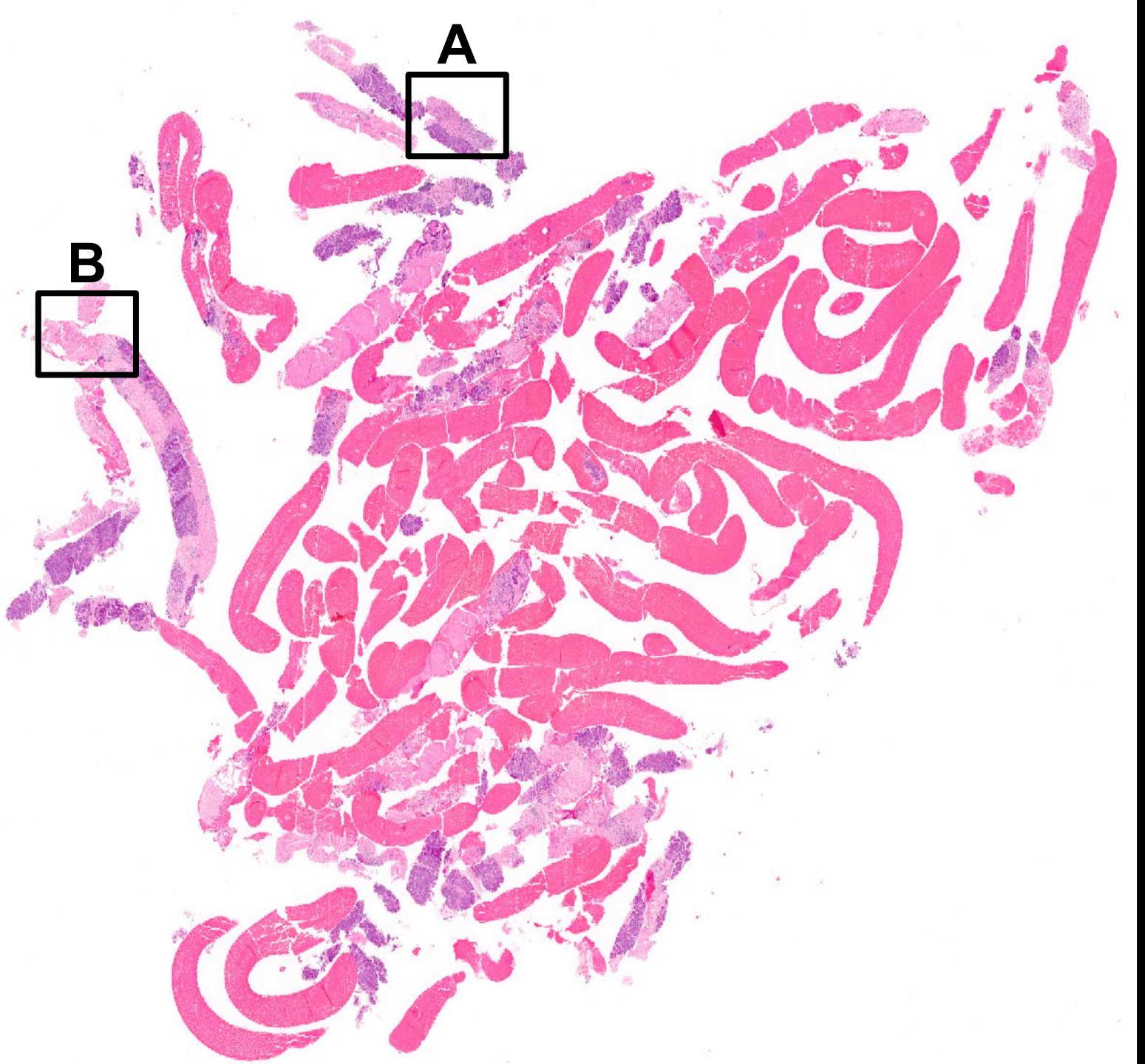
Aatur D. Singhi, MD PhD
University of Pittsburgh Medical Center
Gastrointestinal Pathology Center of Excellence
Division of Molecular and Genomic Pathology
singhiad@upmc.edu (@PancPathologist)

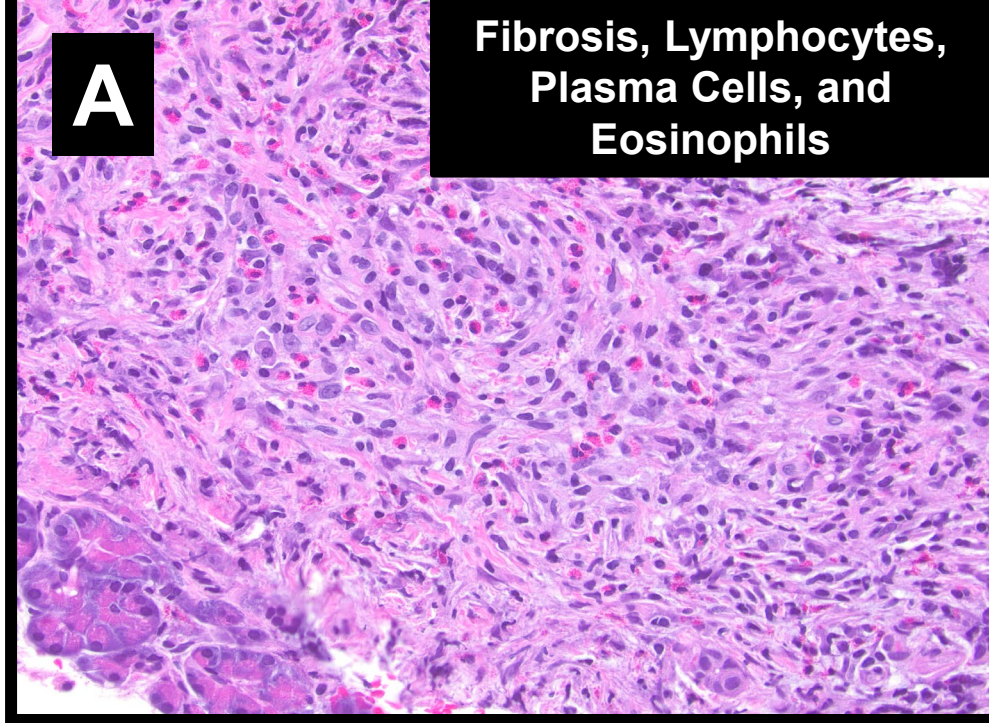
Objectives

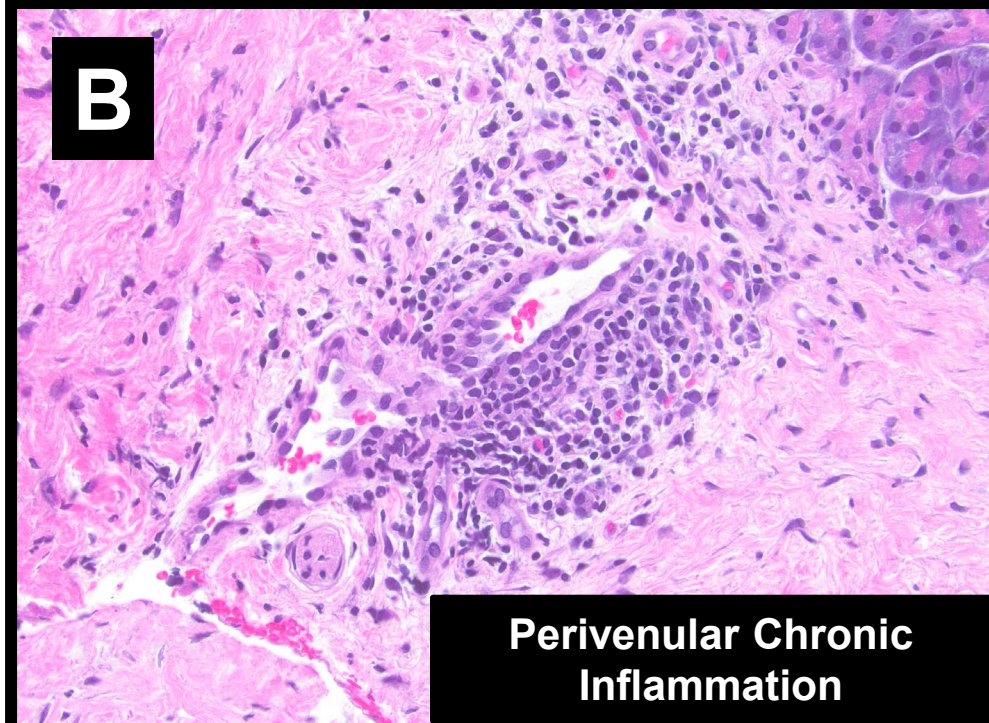
- Provide an algorithmic approach to the preoperative evaluation of pancreatobiliary lesions/neoplasms.
- Discuss next-generation needles for the evaluation of solid lesions of the pancreas.
- Review pancreatic cysts and the clinical utility of molecular testing.
- Present data on molecular testing of bile duct specimens for the assessment of associated strictures.

Case 1

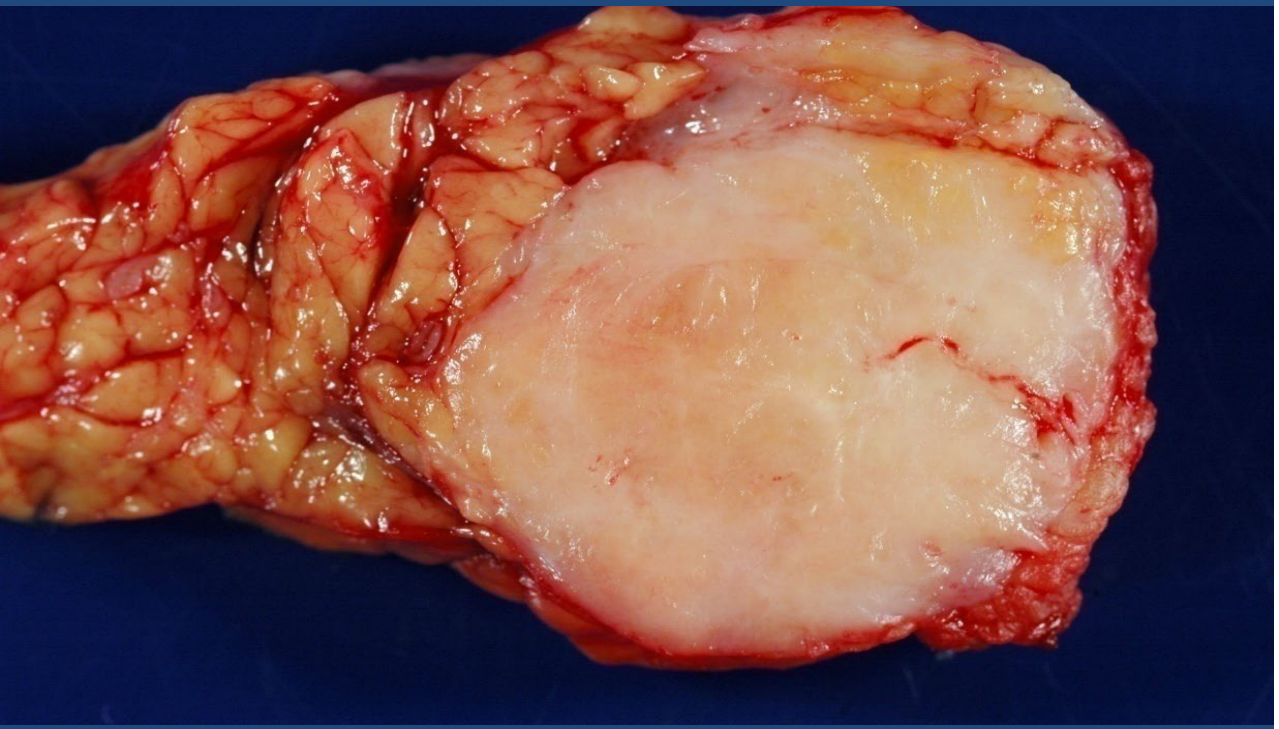
- A 69-year-old male with no known history but presenting with obstructive jaundice and imaging that identified a 3.0 cm mass in the pancreatic head.
- The pancreatic mass was poorly defined and abuts the superior mesenteric vein.
- Multiple peripancreatic lymph nodes were found to be enlarged and a SharkCore™ fine-needle biopsy (FNB) was performed.


A
B


A
Fibrosis, Lymphocytes, Plasma Cells, and Eosinophils

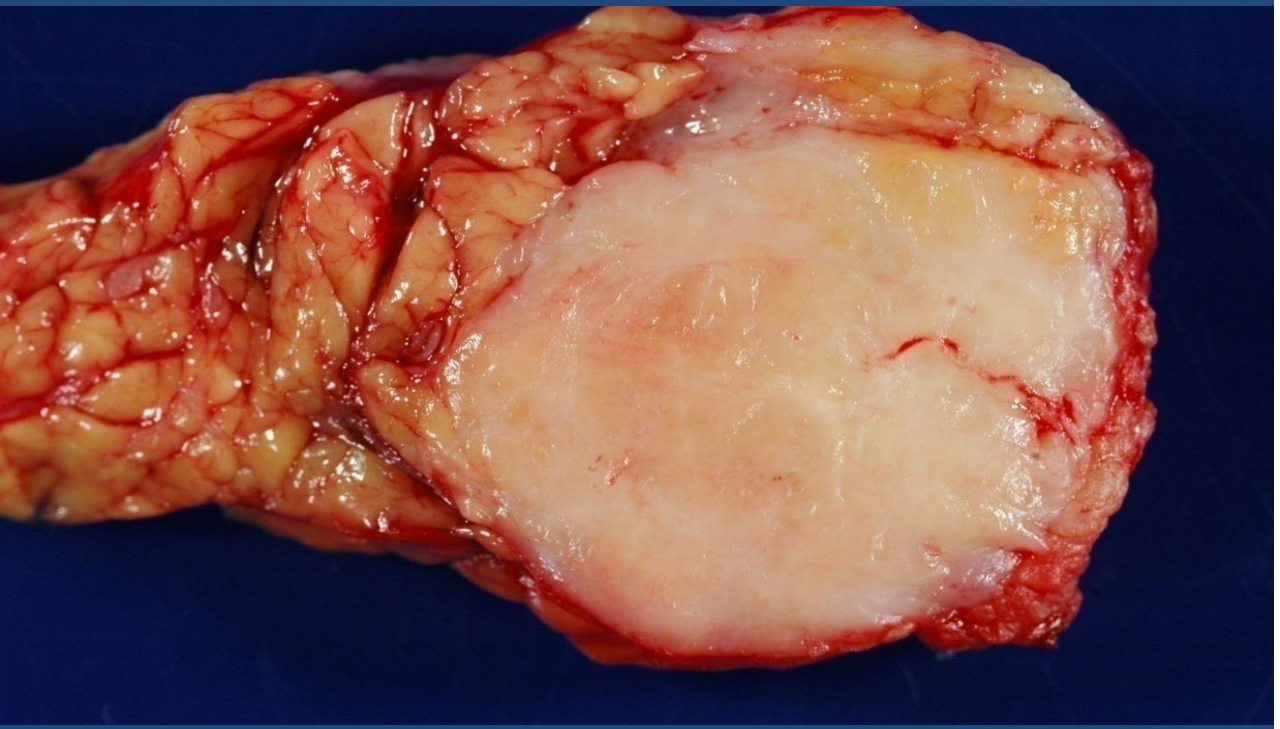

B
Perivenular Chronic Inflammation

Solid



Cystic

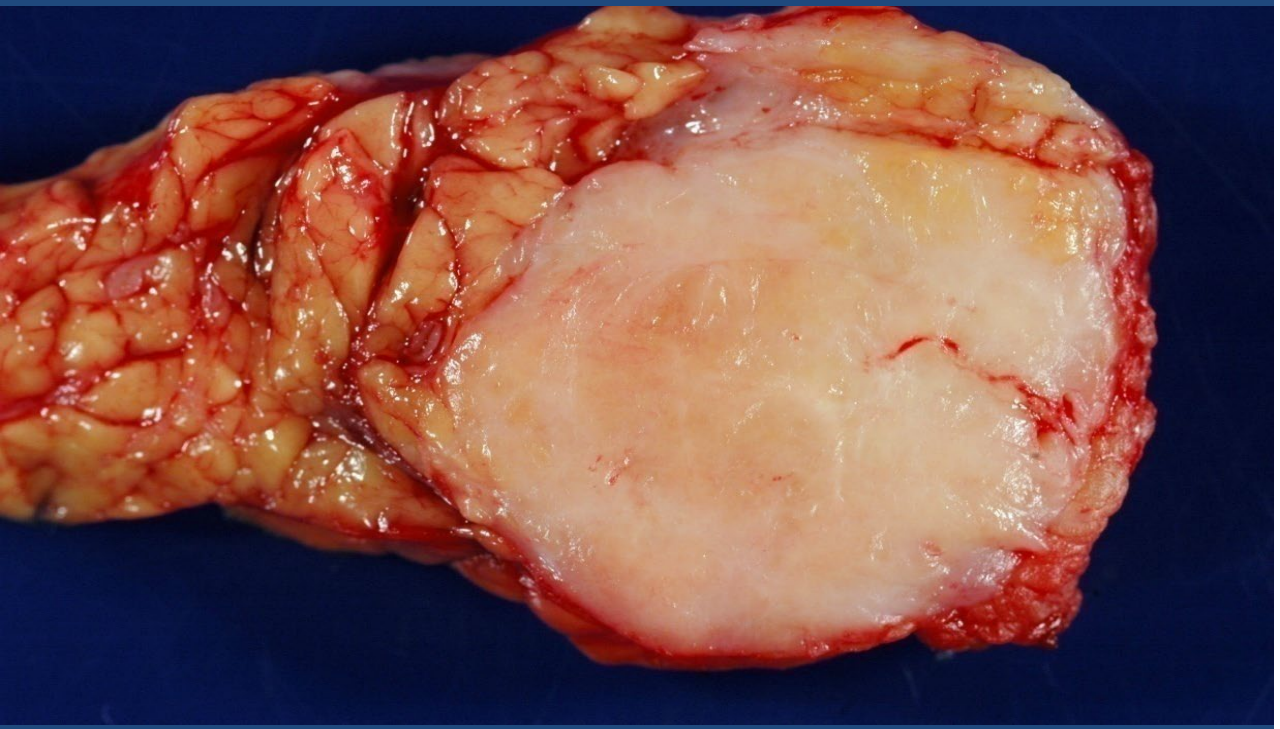
Solid



Differential Dx

- **Pancreatic Ductal Adenocarcinoma**
- Acinar Cell Carcinoma
- Pancreatoblastoma
- Well-Differentiated Neuroendocrine Tumor
- Poorly-Differentiated Neuroendocrine Carcinoma
- Solid-Pseudopapillary Neoplasm

Solid



Chronic Pancreatitis*

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Next-Generation Fine-Needle Biopsies

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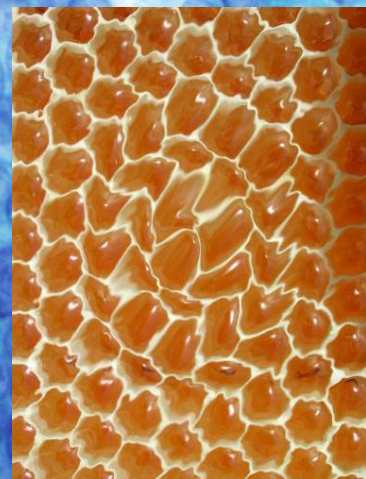
Benign Pancreatic Ductal Epithelium

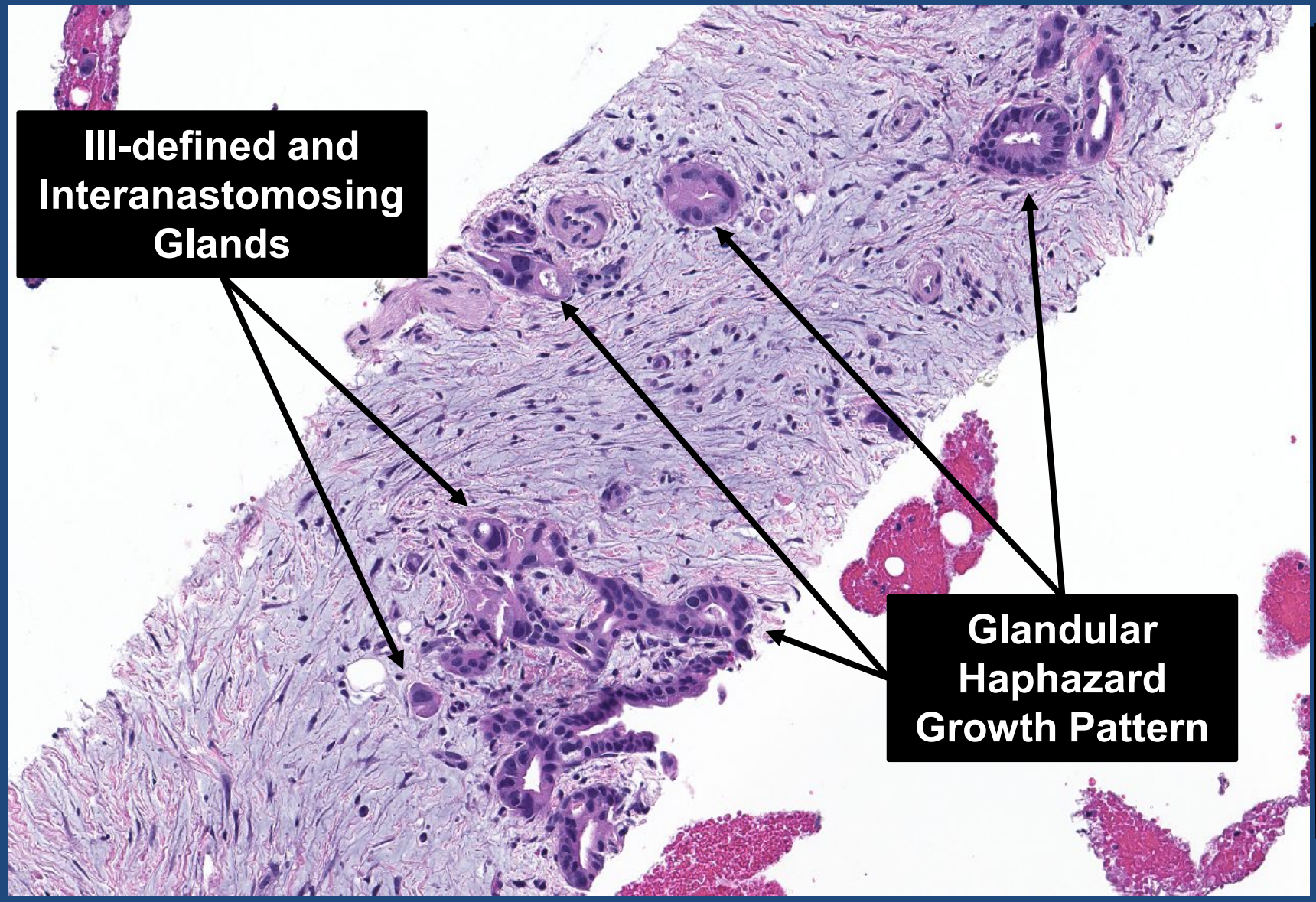
Pancreatic Ductal Adenocarcinoma



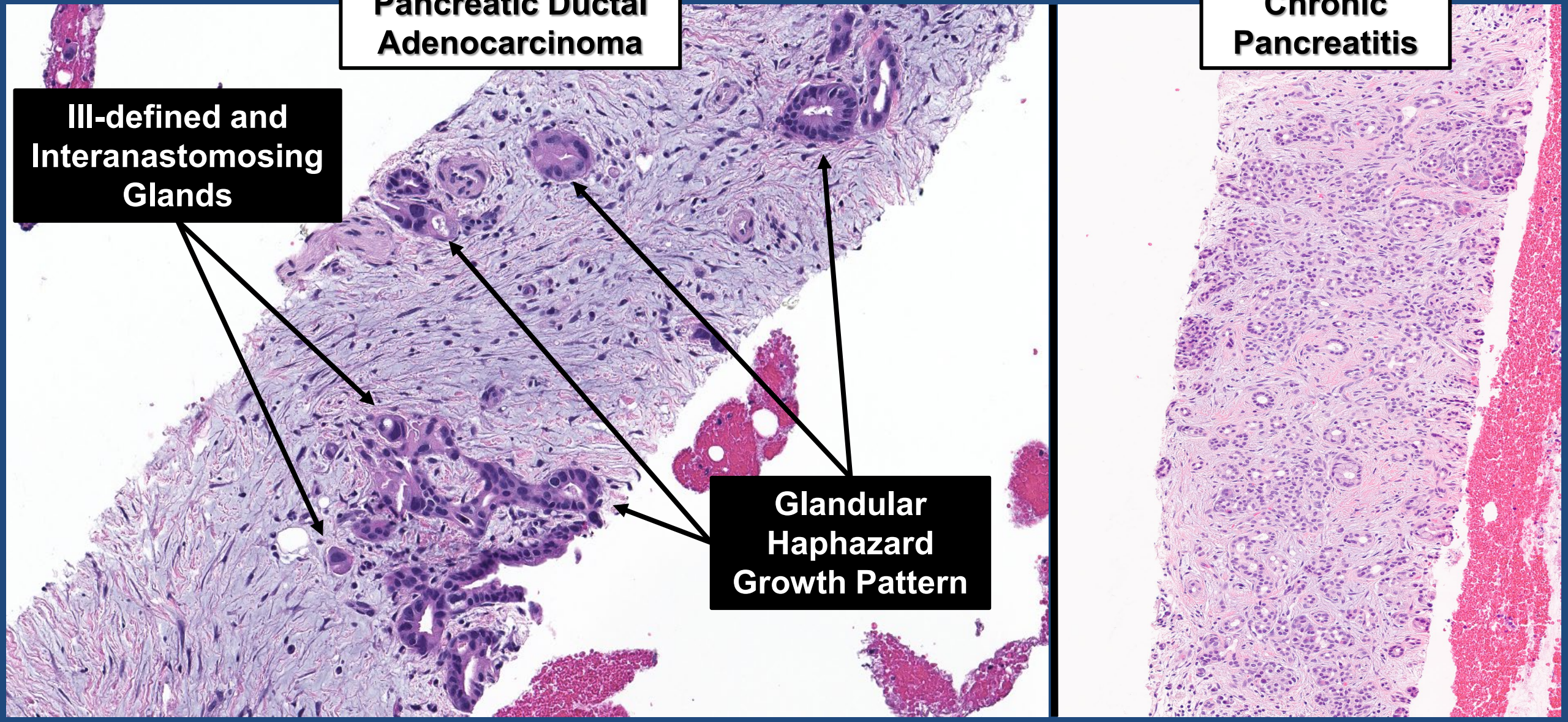
SharkCore Biopsy: Adenocarcinoma

Fragments of Tissue Amongst Cores of Blood are Frequently Present

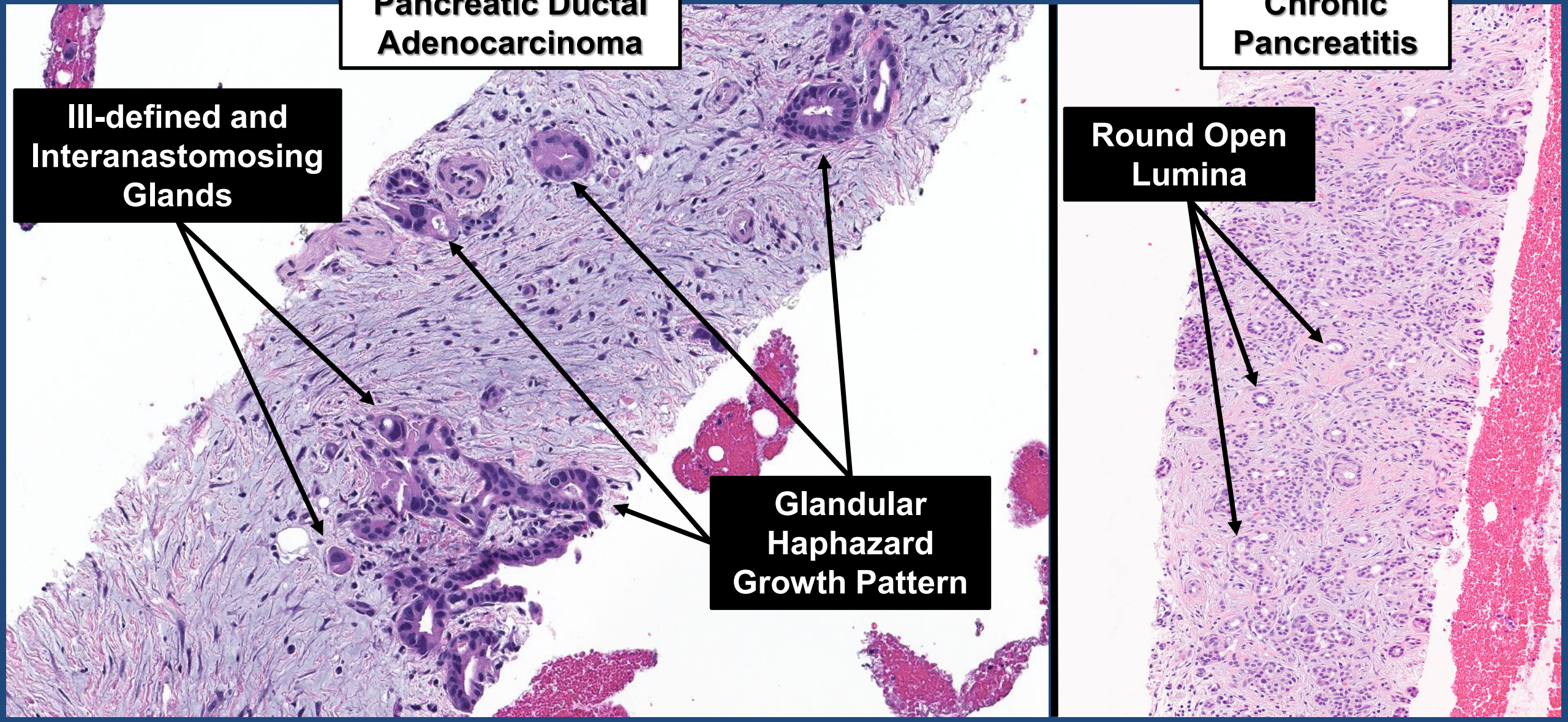
SharkCore Biopsy: Adenocarcinoma



SharkCore Biopsy: Adenocarcinoma



SharkCore Biopsy: Adenocarcinoma



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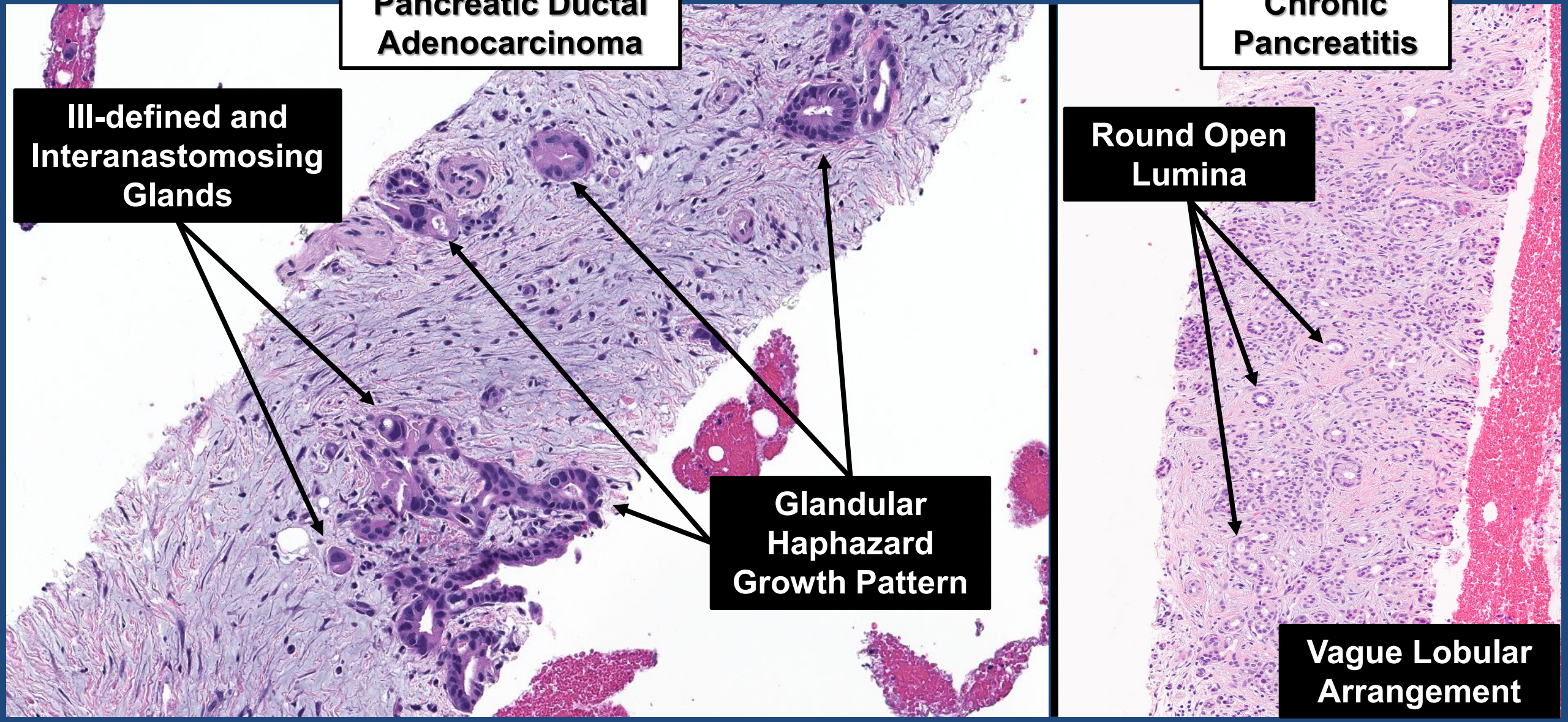
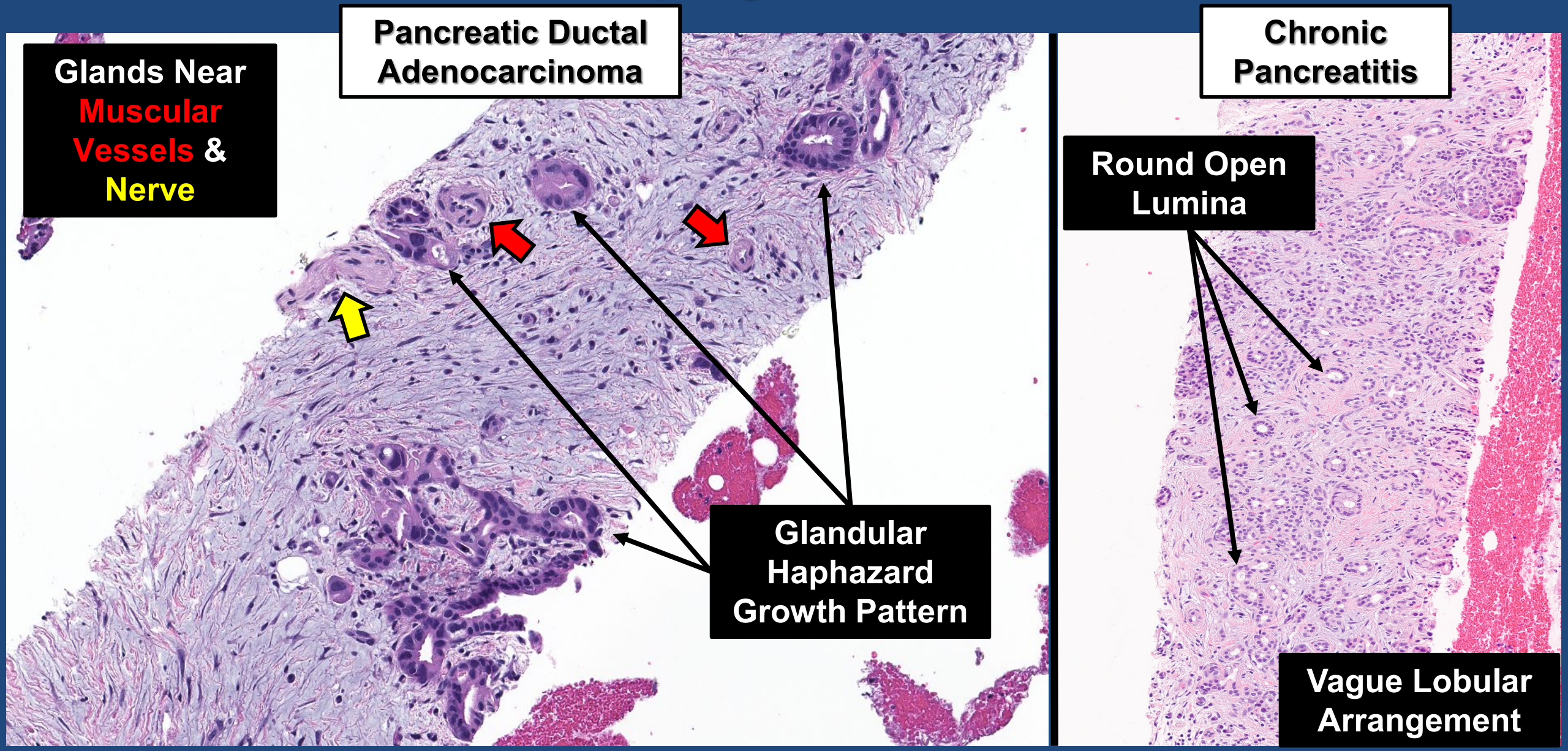


SharkCore Biopsy: Adenocarcinoma



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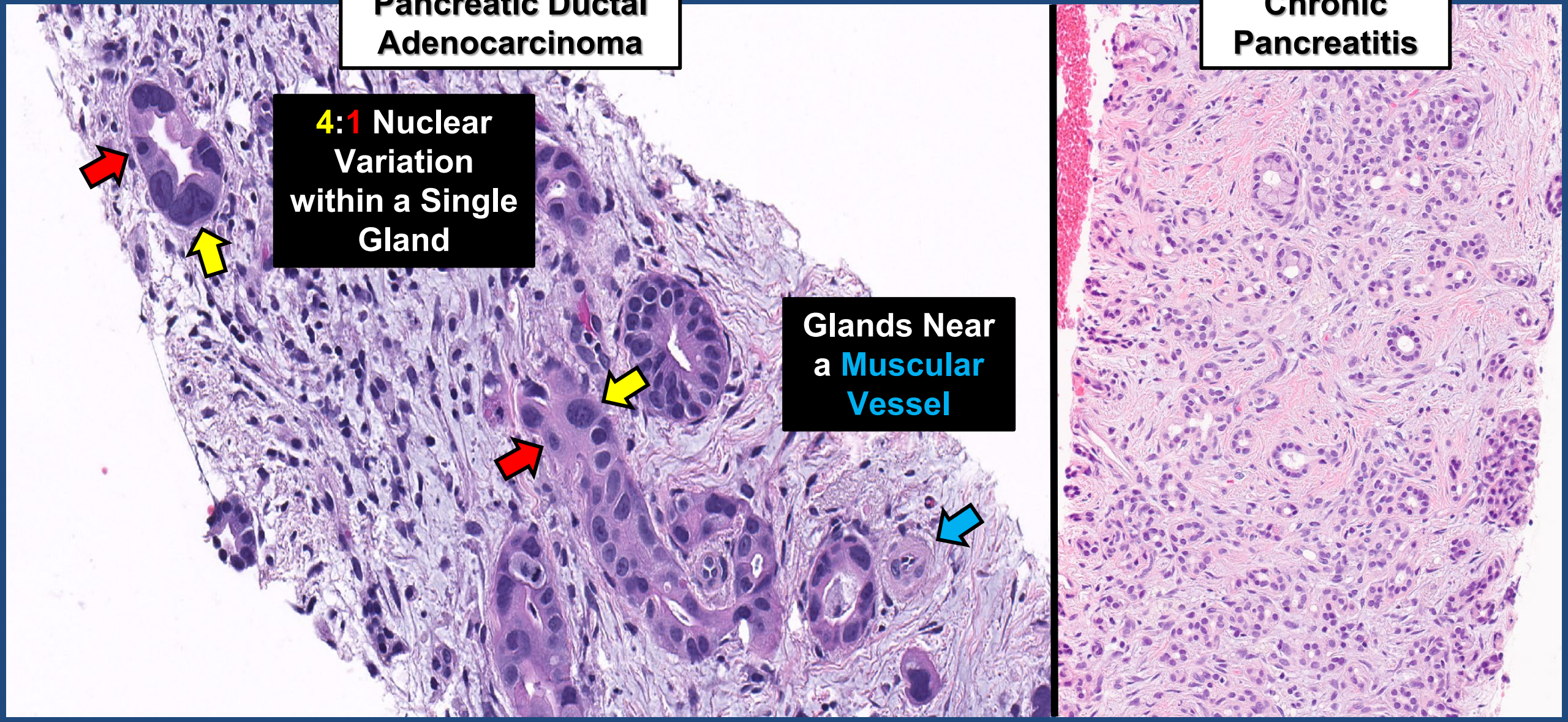
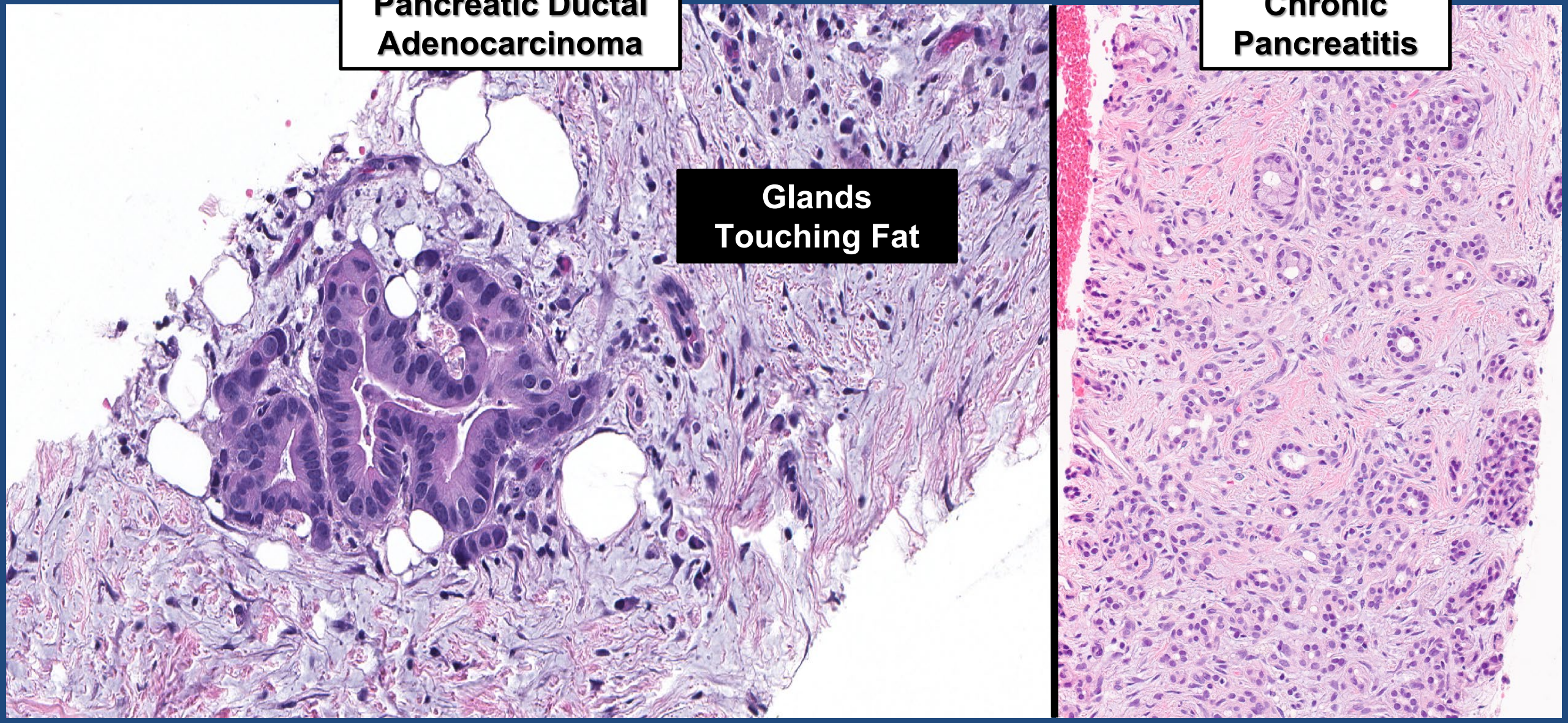
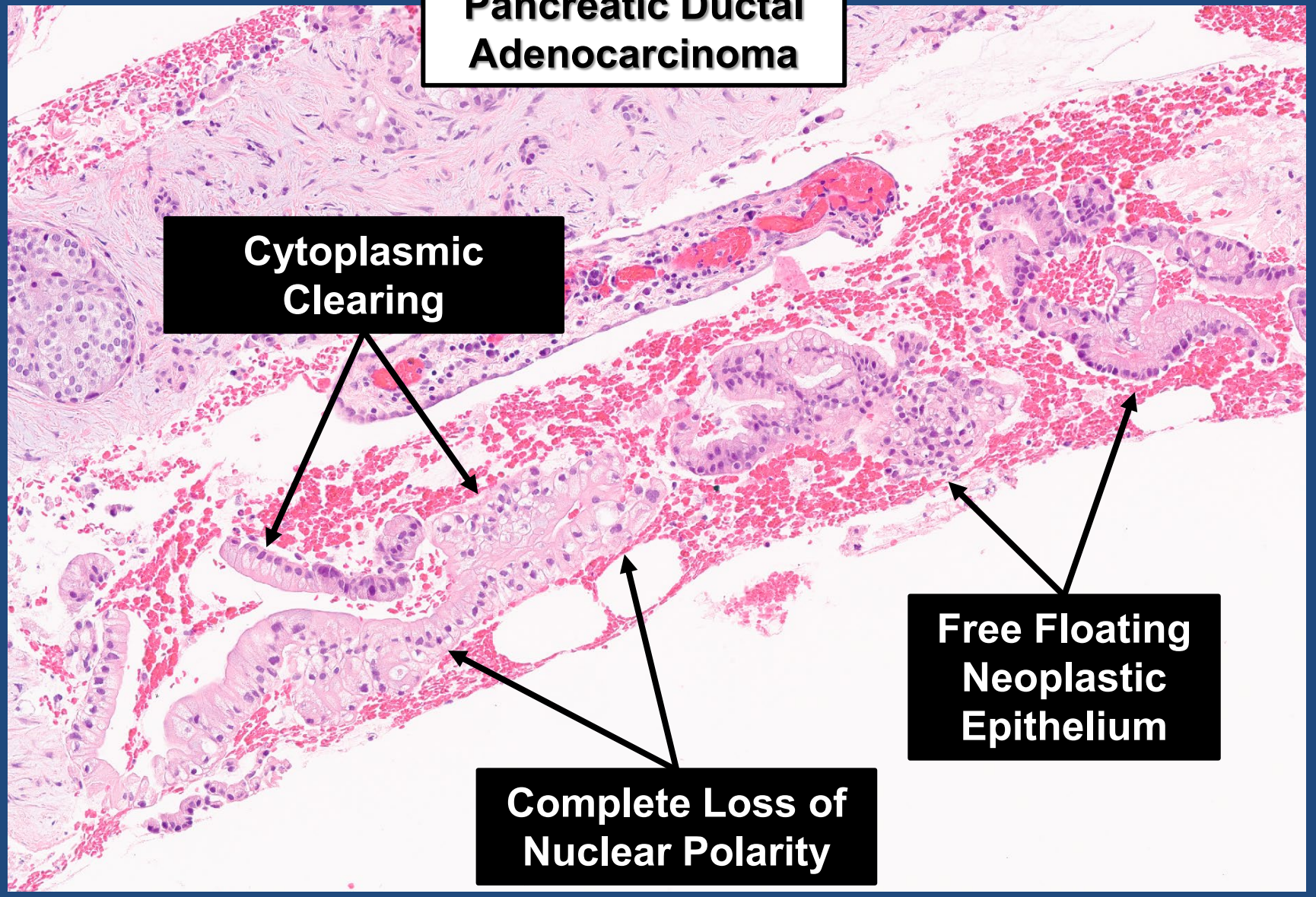


SharkCore Biopsy: Adenocarcinoma



SharkCore Biopsy: Adenocarcinoma

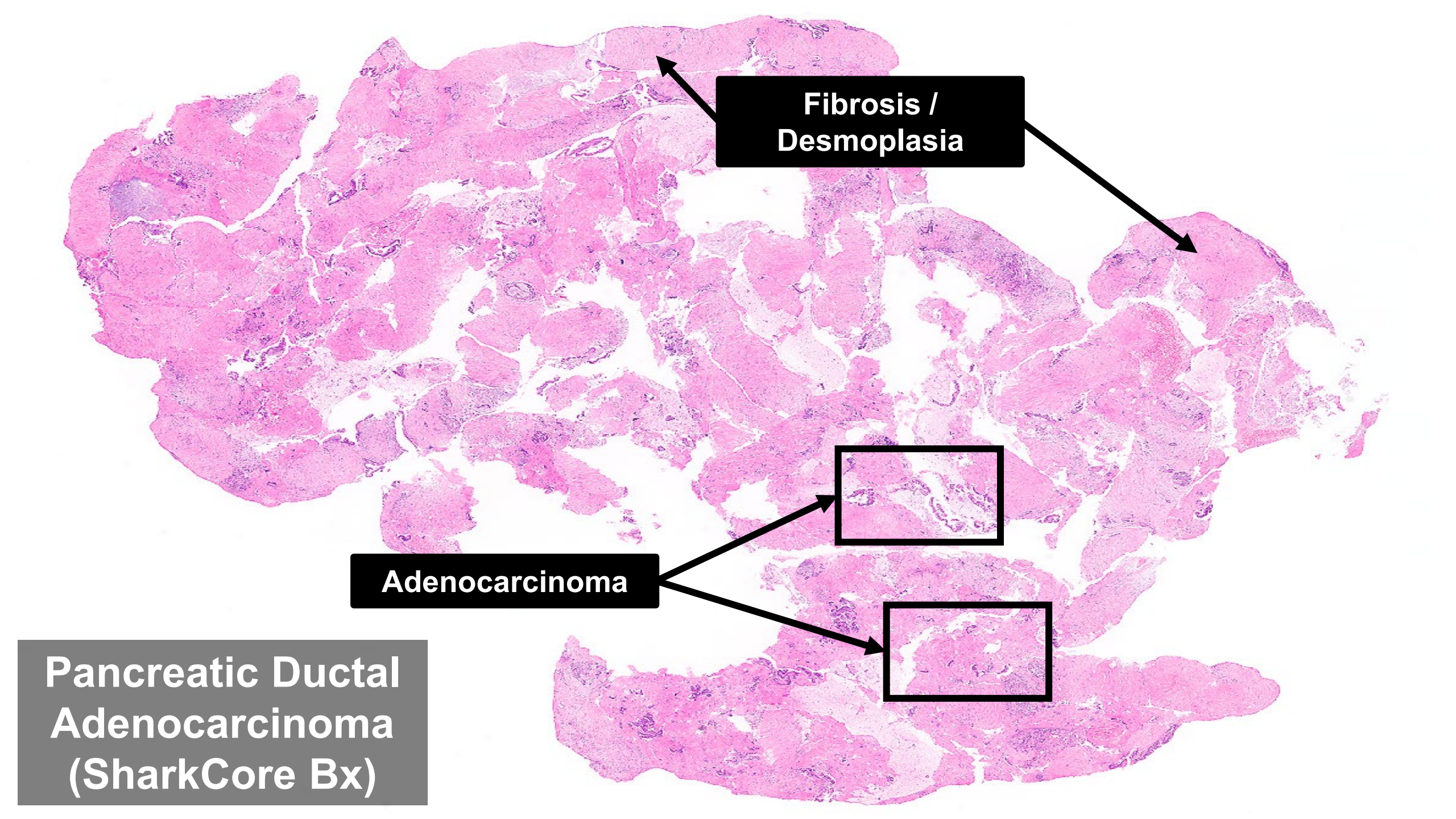


"In Tissue" Features Supporting a Diagnosis of Adenocarcinoma

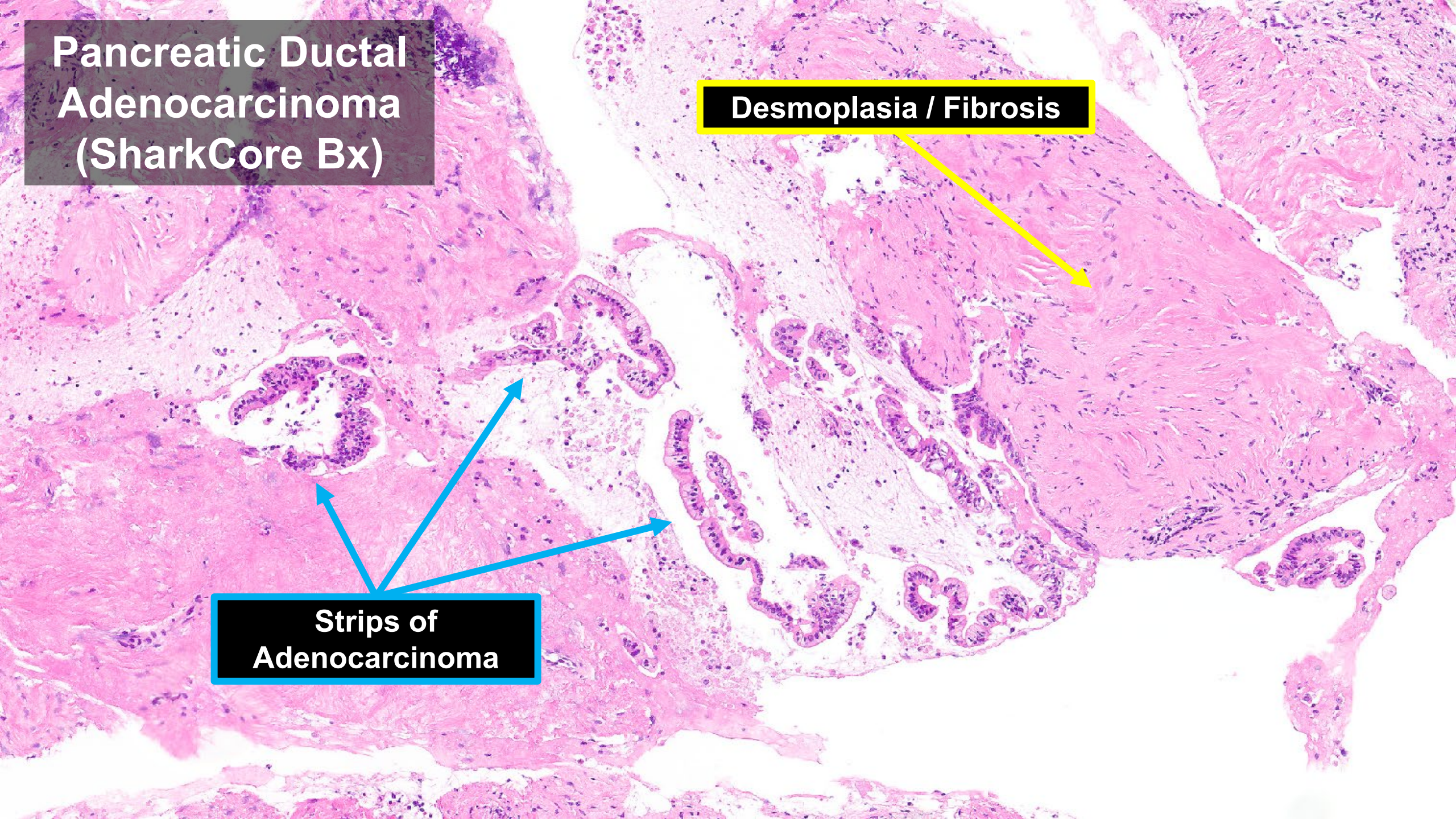
- Haphazard growth pattern
- Incomplete lumina
- Glands near muscular vessels
- Perineural/lymphovascular invasion
- 4:1 nuclear variation
- Glands touching fat
- Abnormal mitotic figures

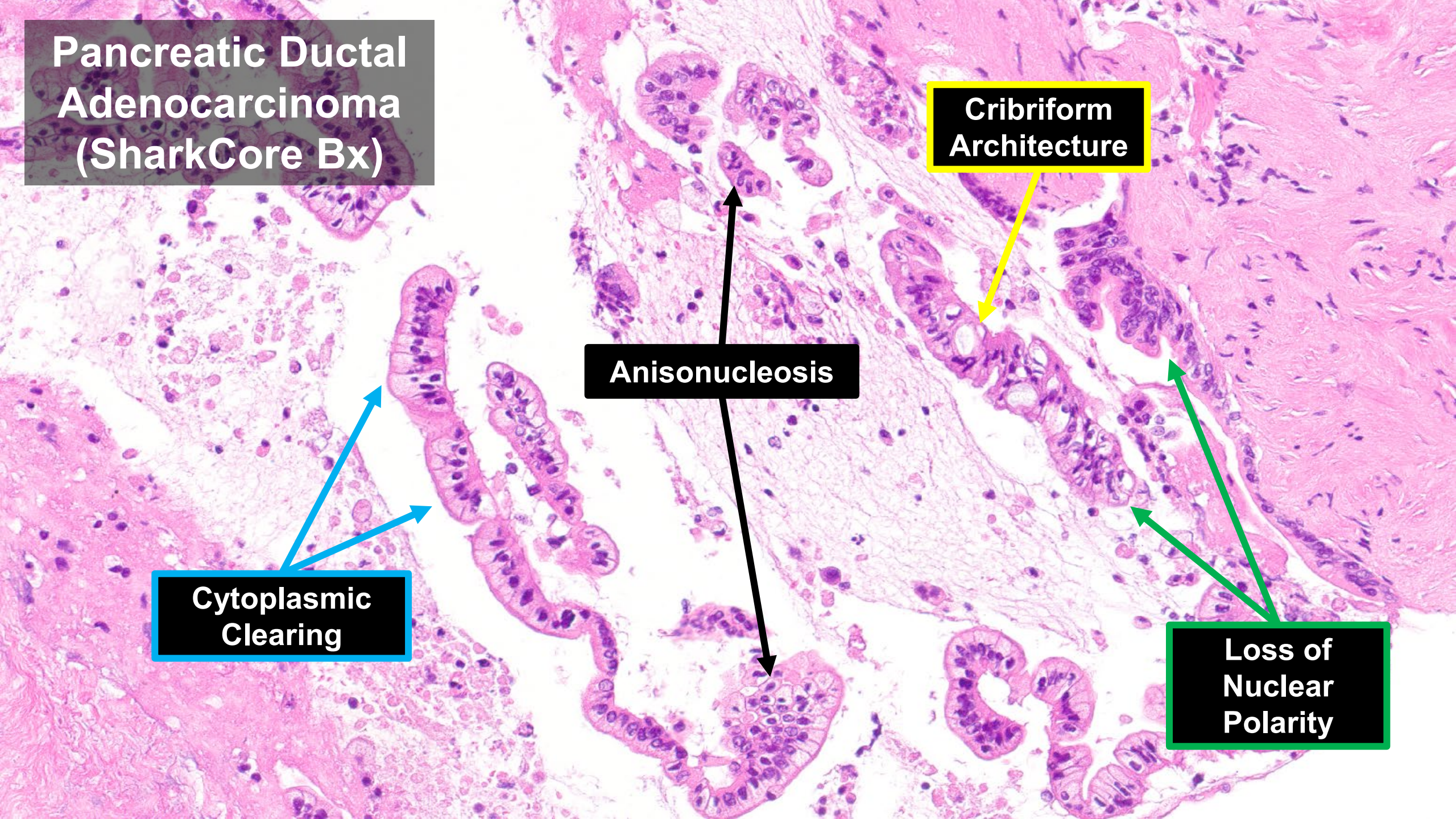
"Free Floating" Features Supporting a Diagnosis of Adenocarcinoma

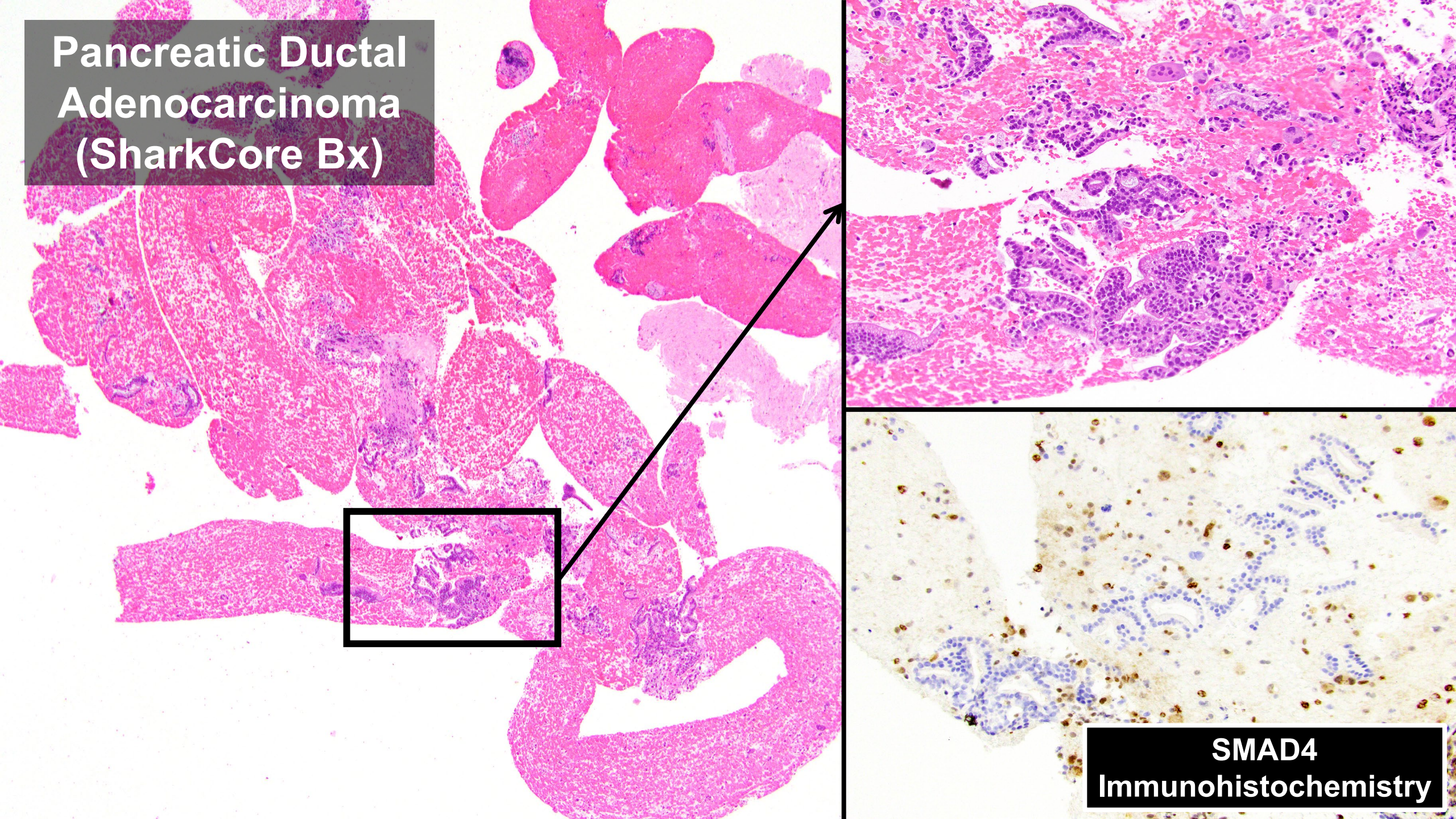
- Architecture, cytoplasmic and nuclear changes

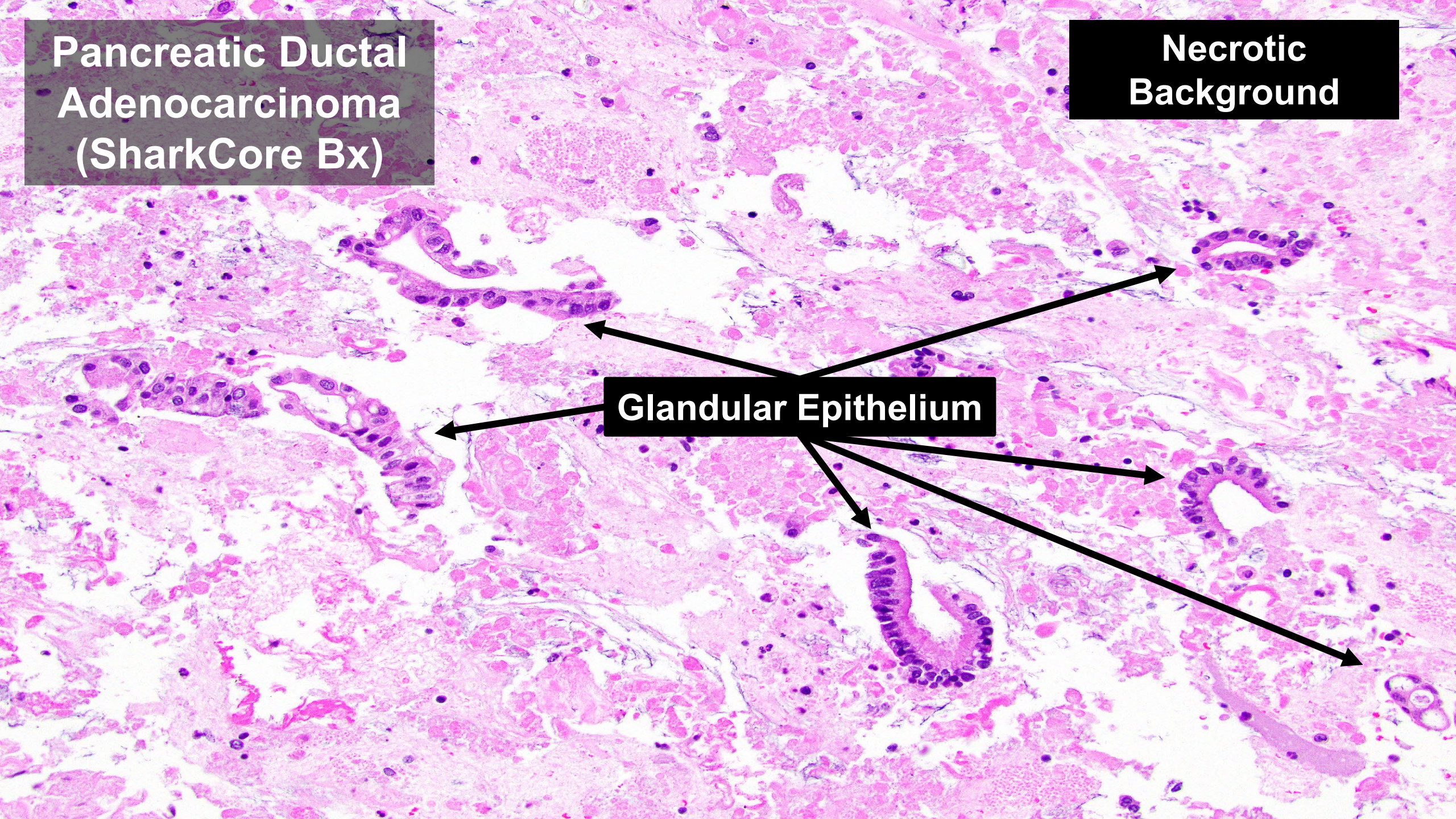


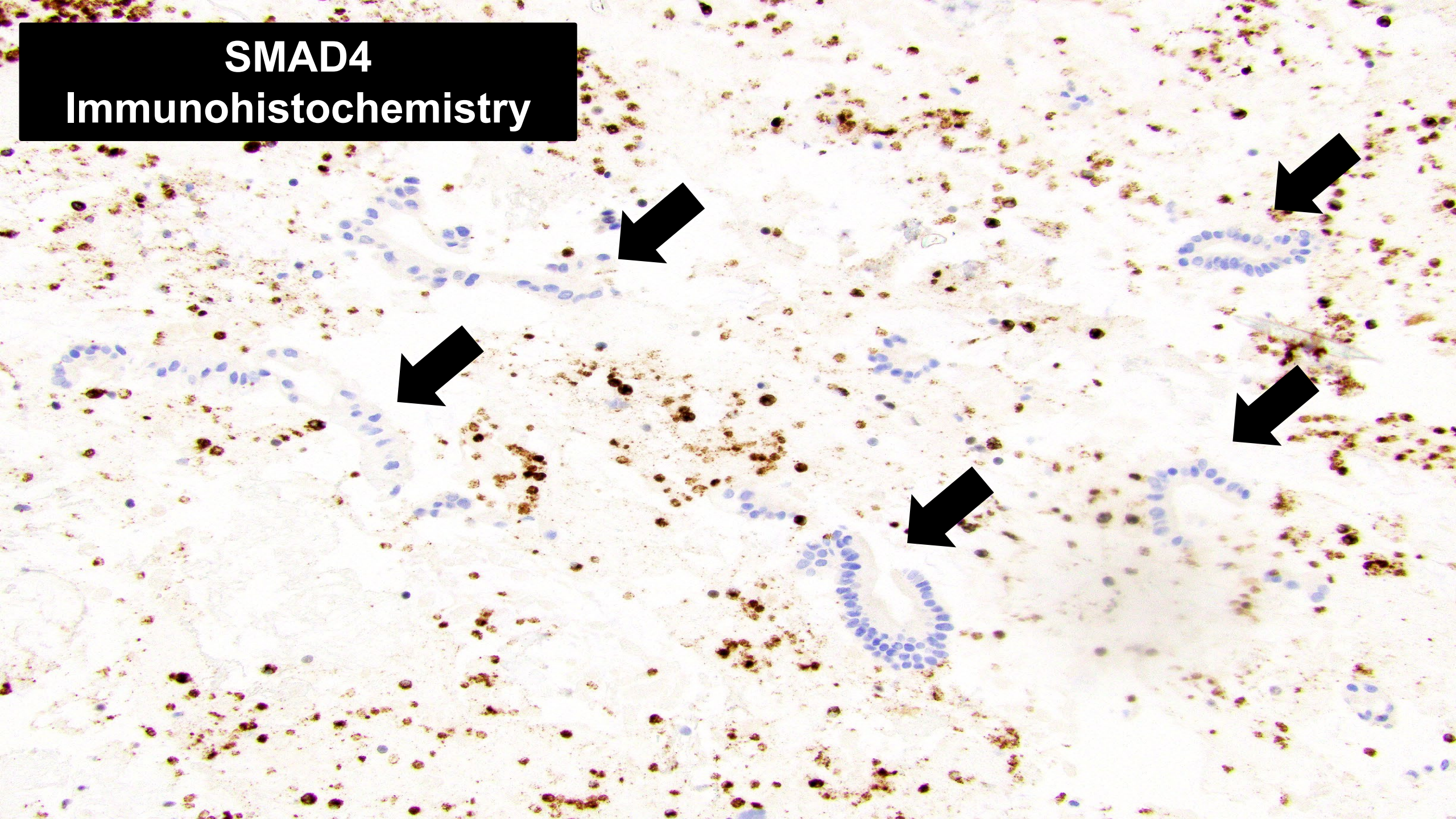
Pancreatic Ductal Adenocarcinoma (SharkCore Bx)


Pancreatic Ductal Adenocarcinoma (SharkCore Bx)
Desmoplasia / Fibrosis
Strips of Adenocarcinoma

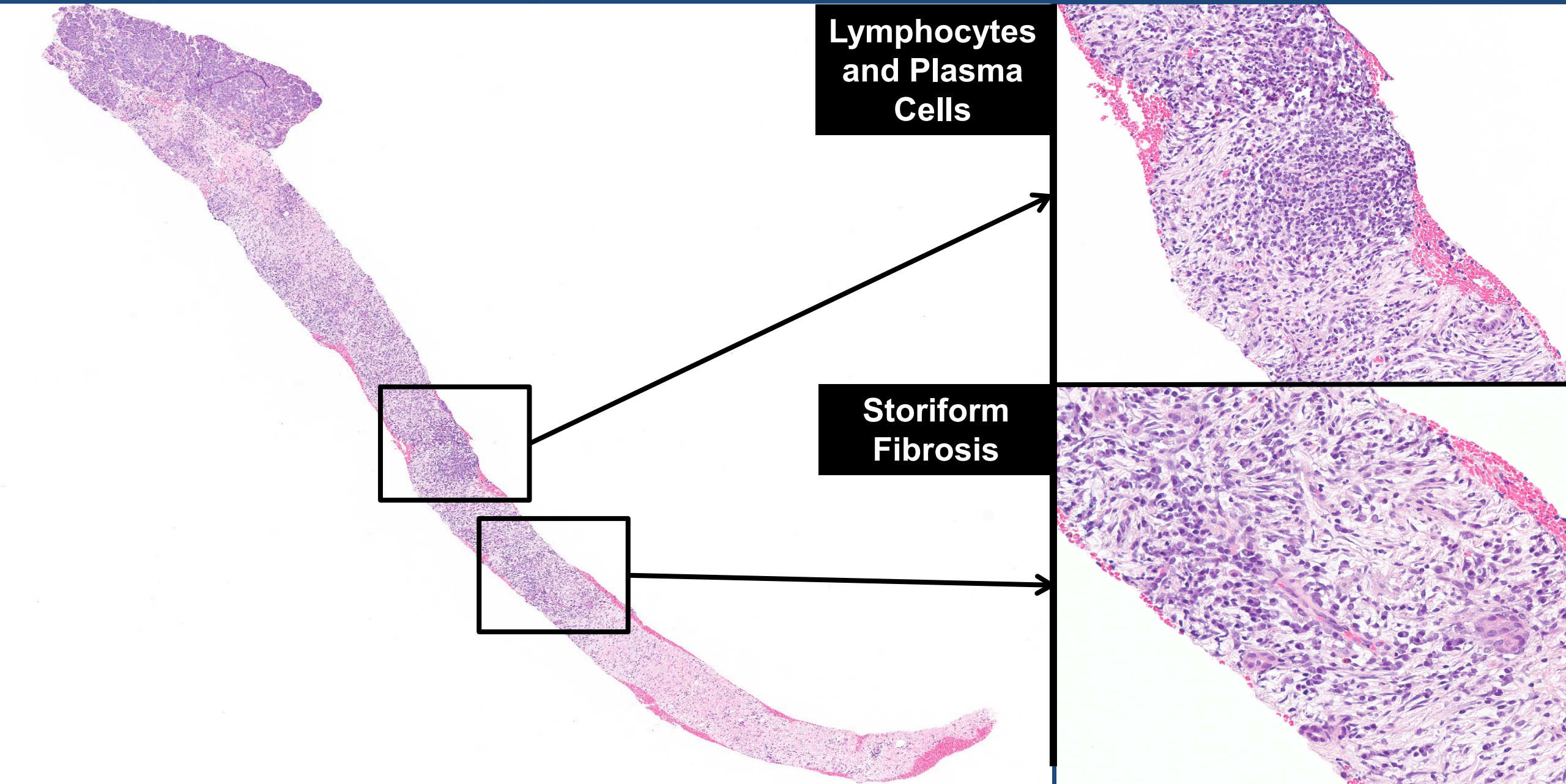

Pancreatic Ductal Adenocarcinoma (SharkCore Bx)
Cribriform Architecture
Anisonucleosis
Cytoplasmic Clearing
Loss of Nuclear Polarity

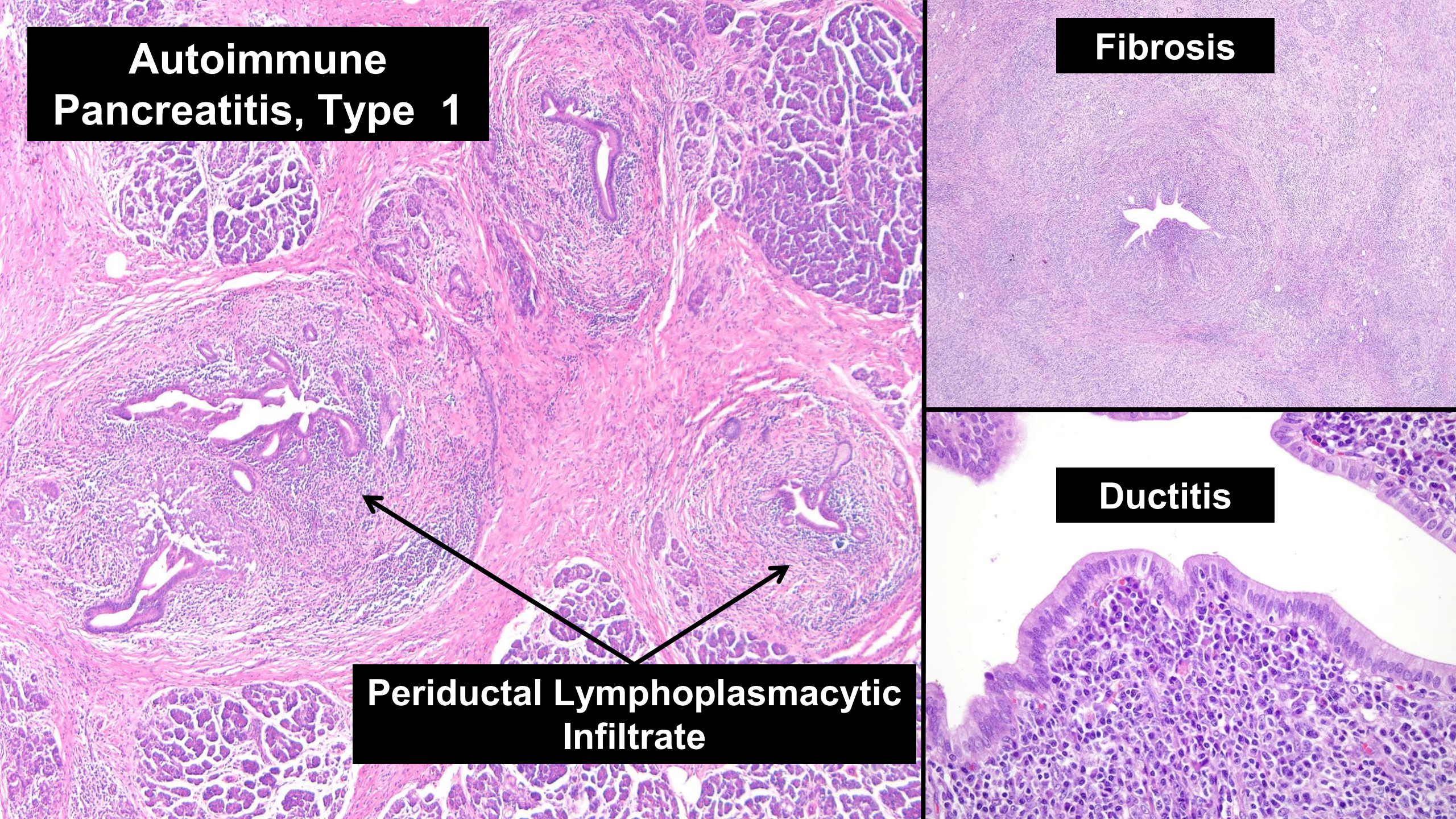

Pancreatic Ductal Adenocarcinoma (SharkCore Bx)
SMAD4 Immunohistochemistry

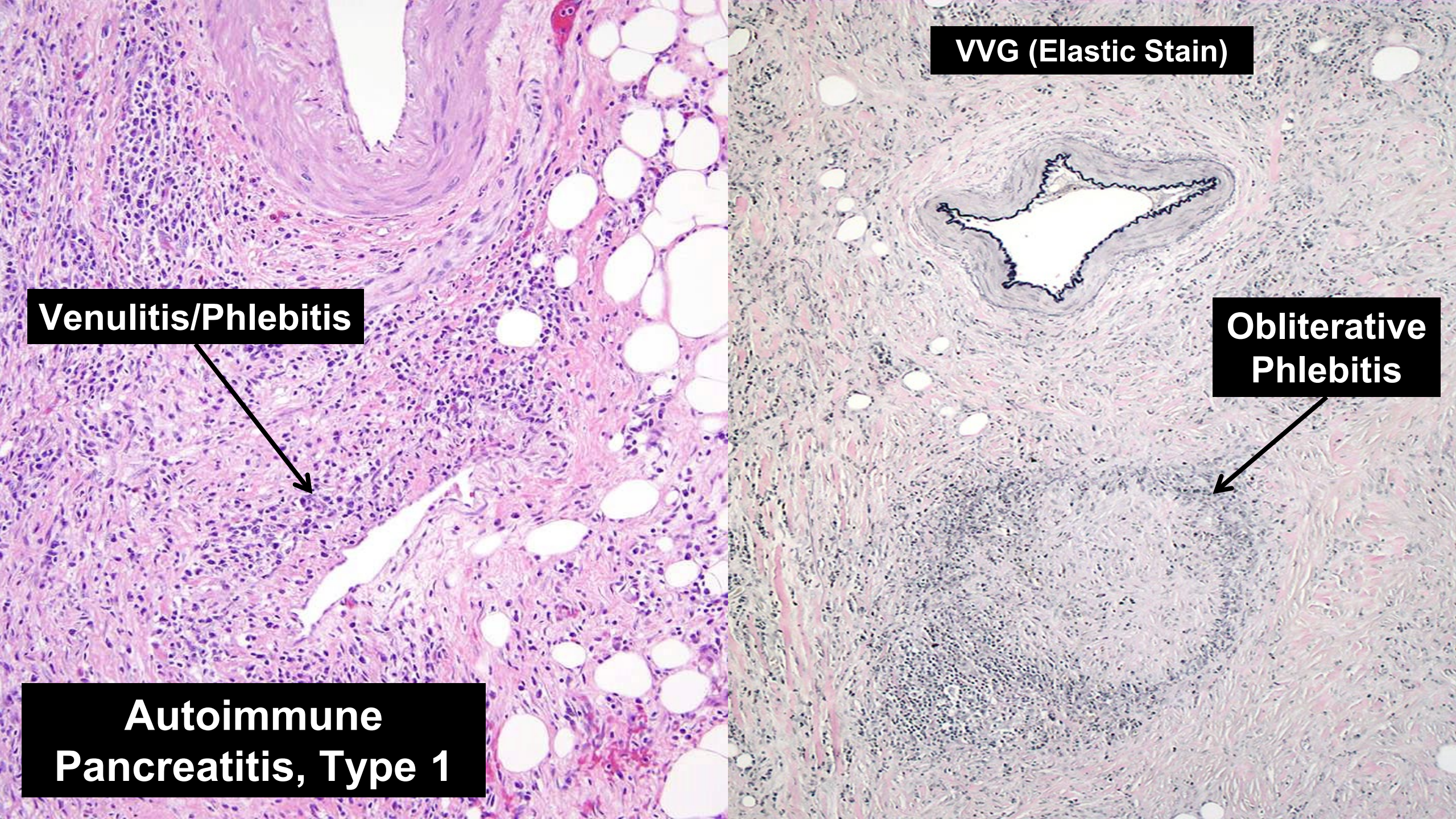

Pancreatic Ductal Adenocarcinoma (SharkCore Bx)
Necrotic Background
Glandular Epithelium

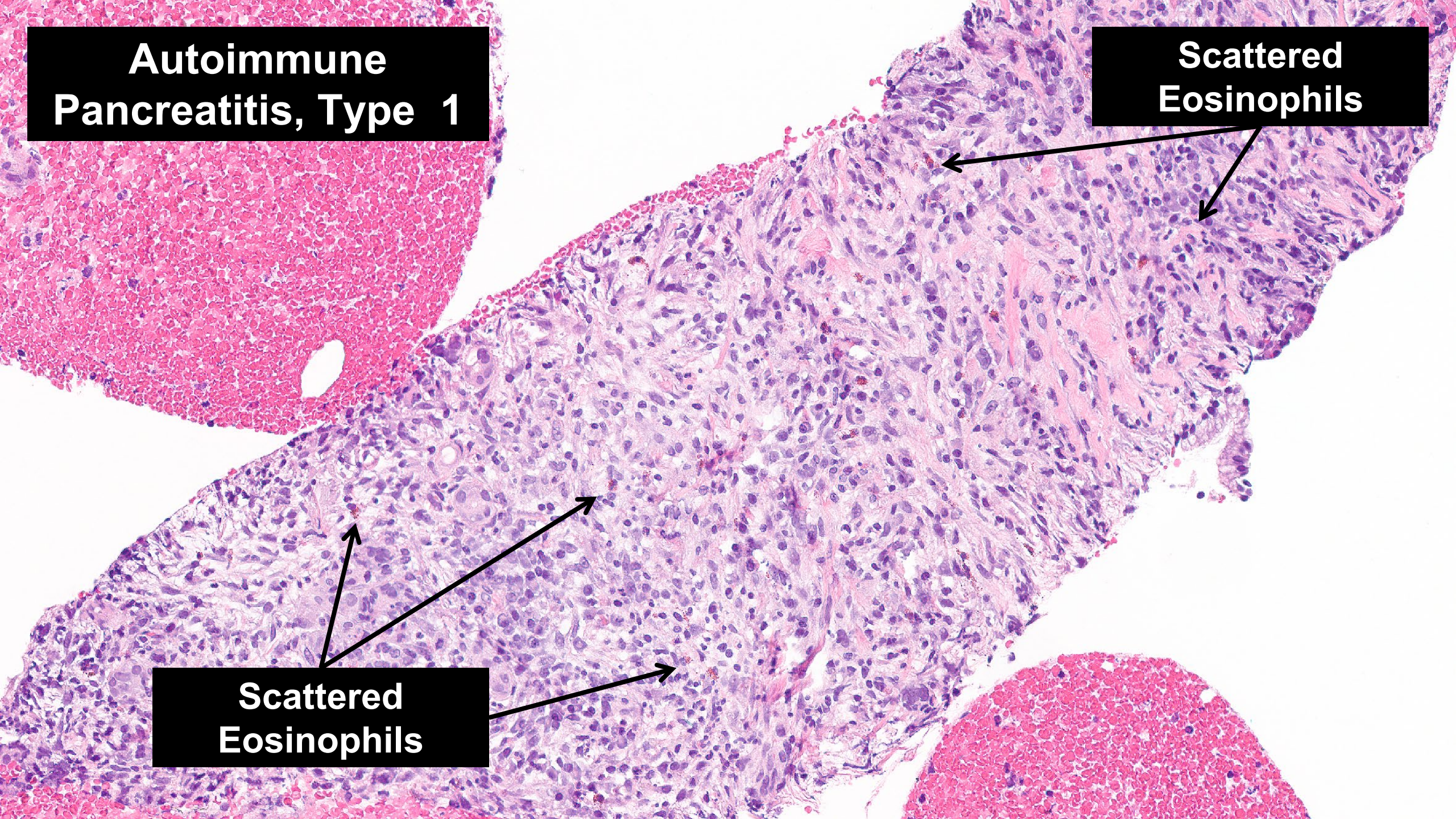

SMAD4
Immunohistochemistry

SharkCore Biopsy: Autoimmune Pancreatitis, Type 1




Autoimmune Pancreatitis, Type 1
Periductal Lymphoplasmacytic Infiltrate
Fibrosis
Ductitis


Venulitis/Phlebitis
Autoimmune Pancreatitis, Type 1
VVG (Elastic Stain)
Obliterative Phlebitis


Autoimmune Pancreatitis, Type 1
Scattered Eosinophils
Scattered Eosinophils

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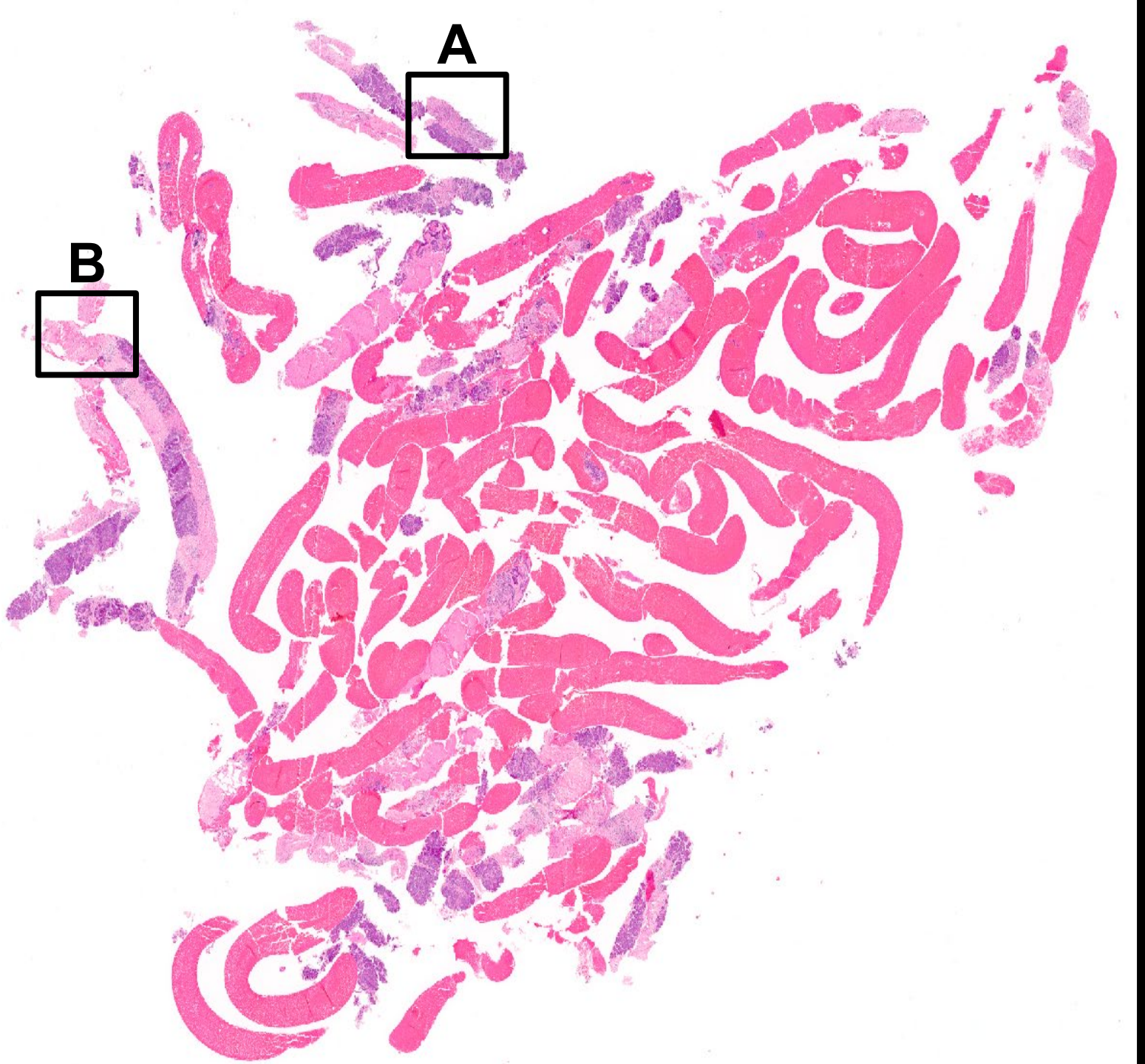
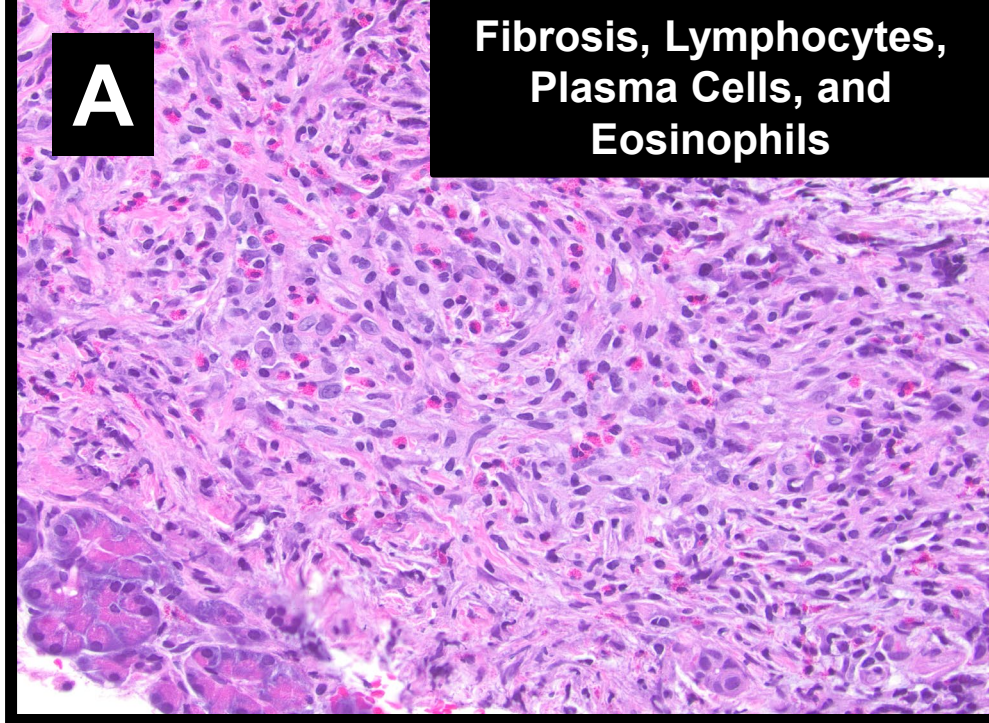

A
B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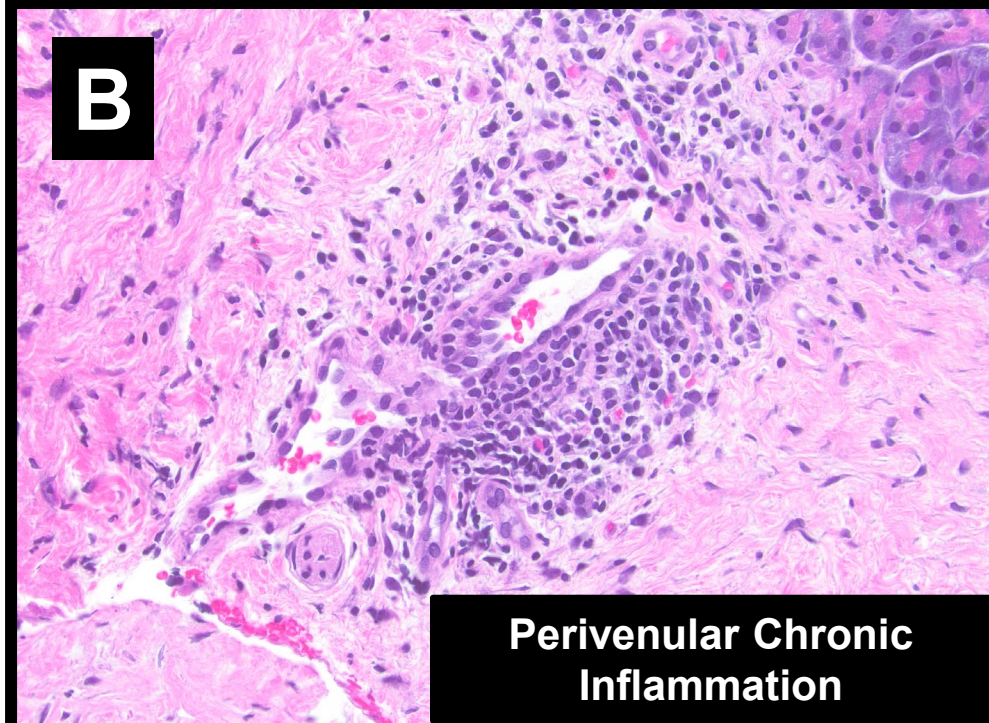
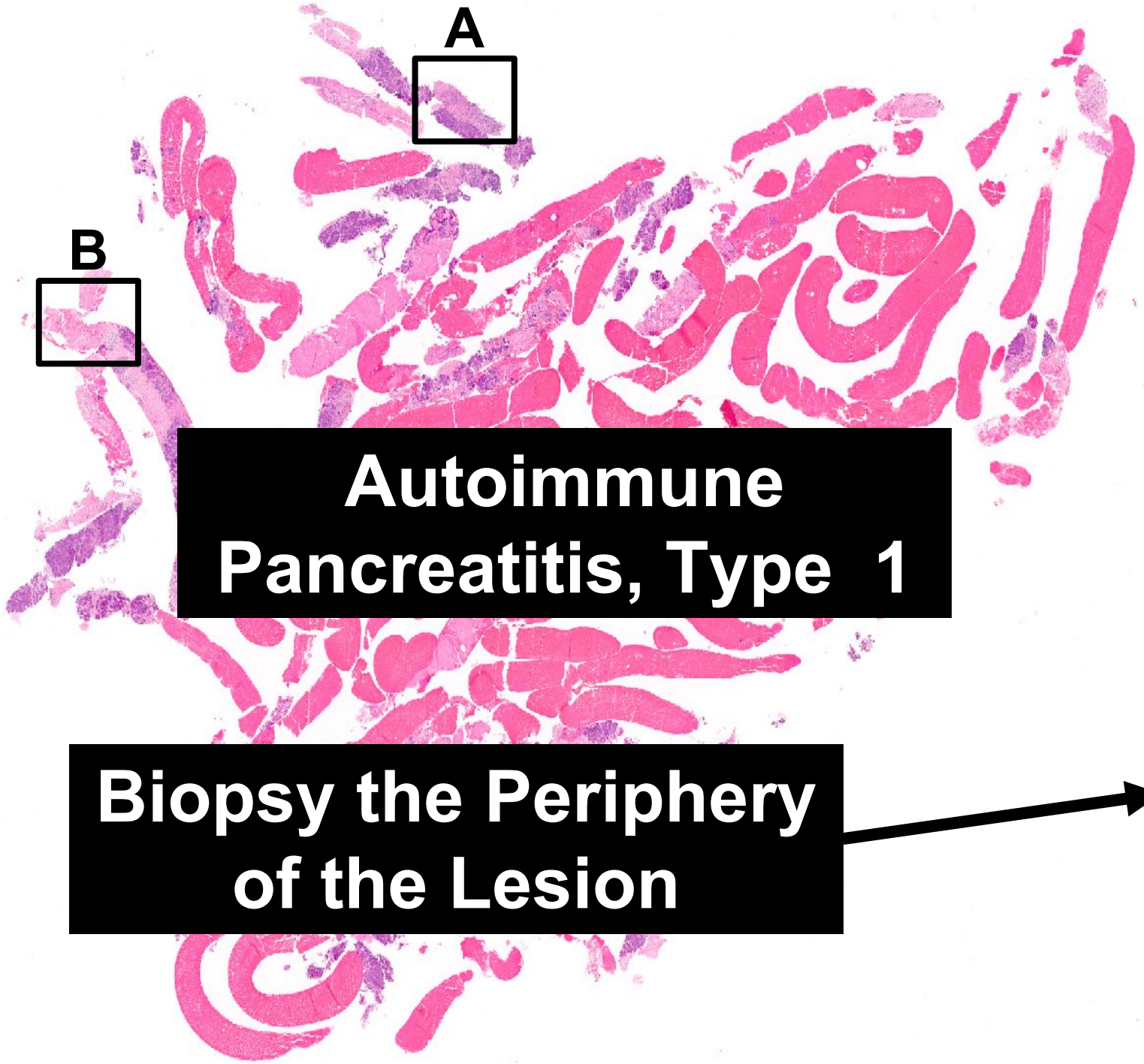
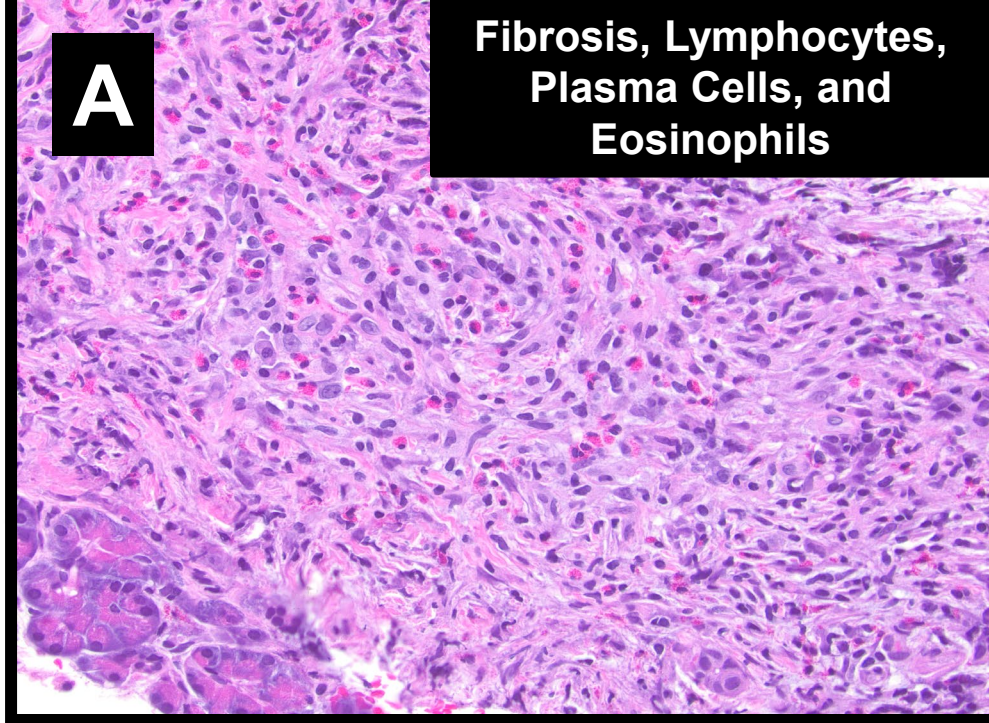
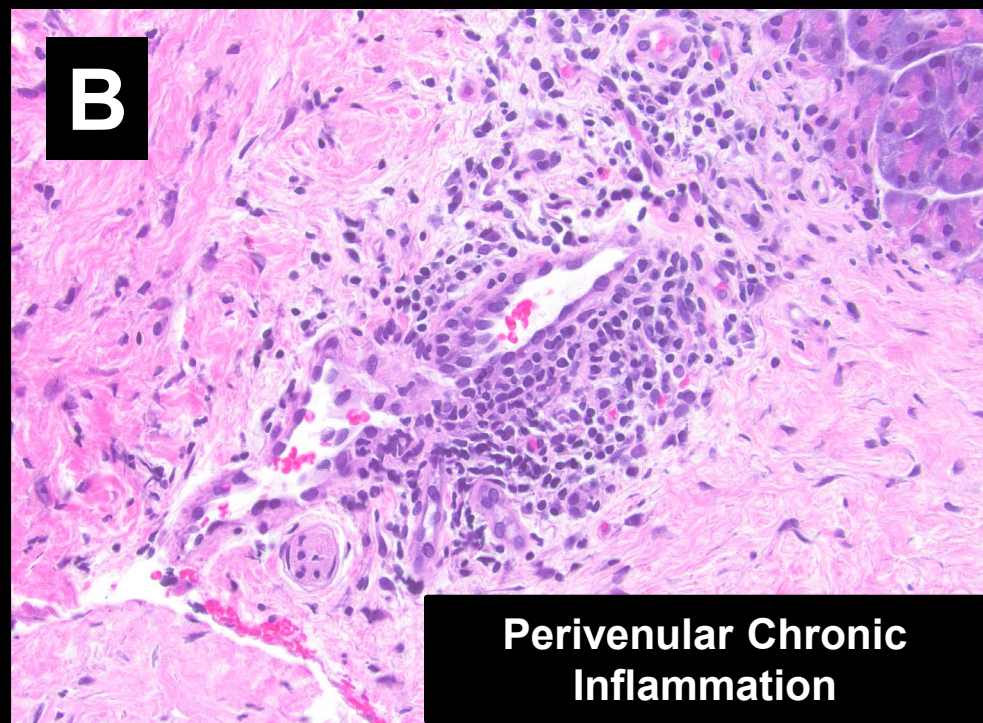

B
Perivenular Chronic Inflammation



Autoimmune Pancreatitis, Type 1

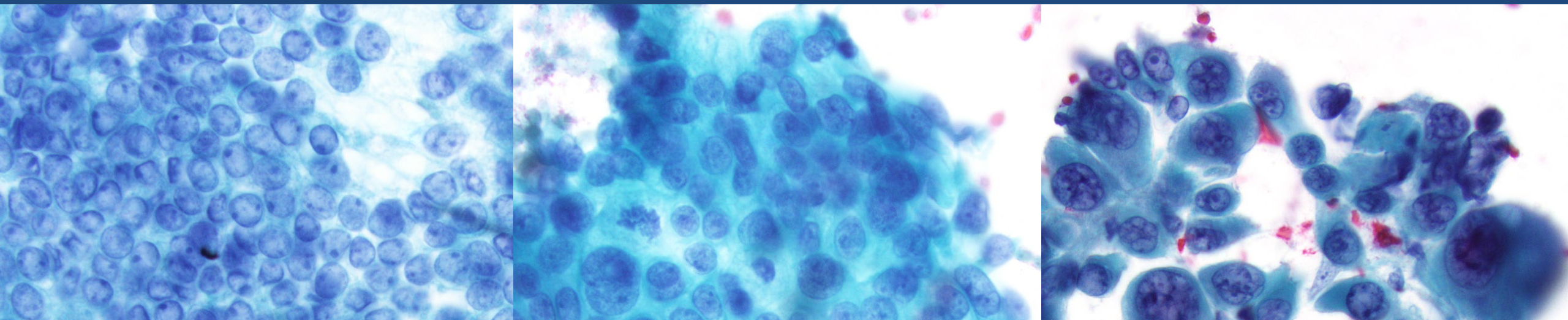
Biopsy the Periphery of the Lesion





Take Home Points: Case 1

- Traditional Cytopathology:
  - Crowded nuclei with uneven spacing (drunken honeycomb)
  - The nuclei often overlap at least focally with loss of polarity and loss of smoothness of the nuclear membranes



Take Home Points: Case 1

- Surgical Pathology:
  - Haphazard growth
  - Glands next to muscular vessels
  - Perineural/lymphovascular invasion
  - Nuclear variation, 4:1 rule
  - Incomplete lumina
  - Necrotic intraluminal debris
  - Glands touching fat
  - Abnormal mitotic figures

Take Home Points: Case 1

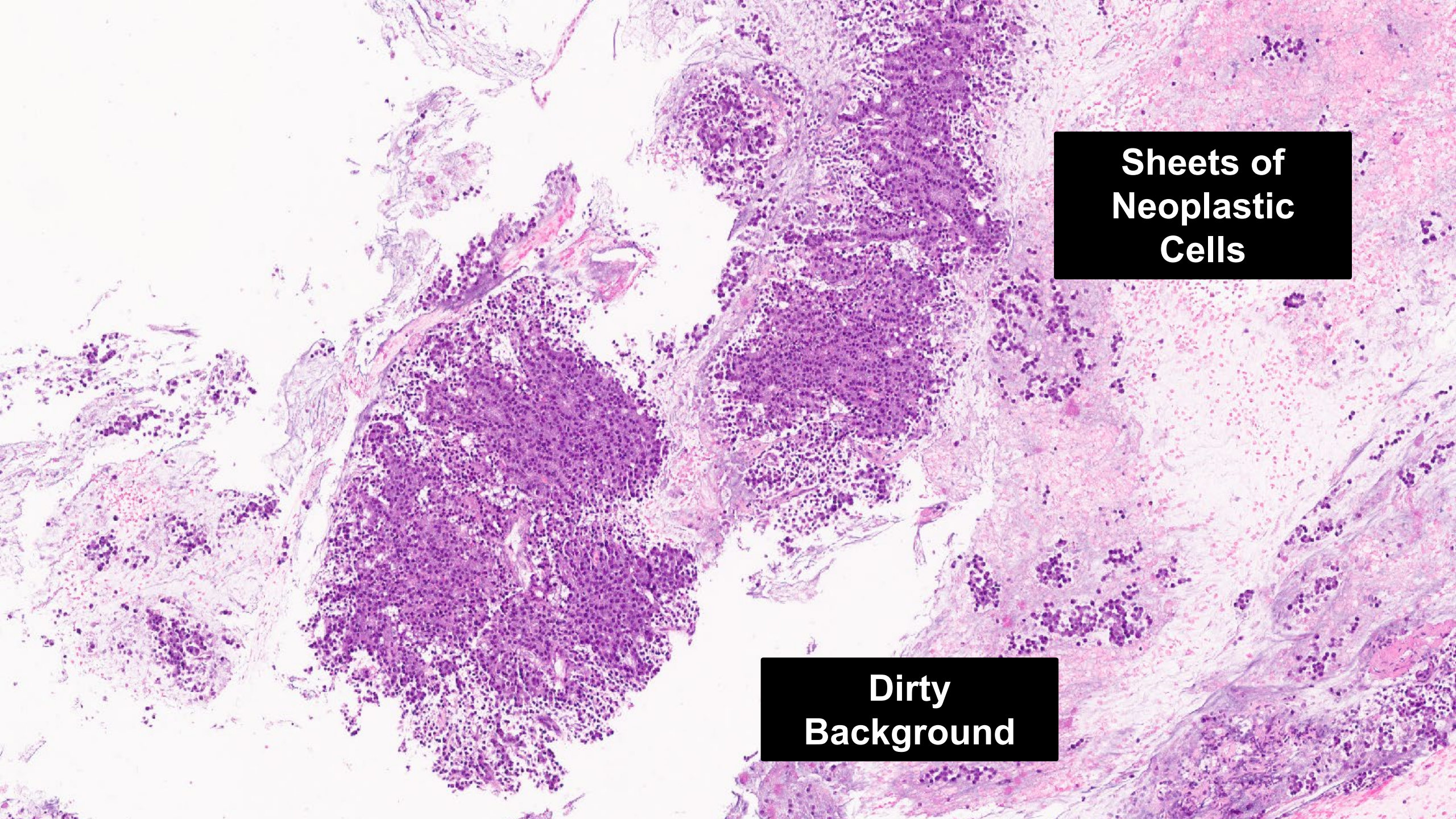
- Next-Generation Needle Pathology:
  - Combination of cytopathology and surgical pathology
  - Adenocarcinoma is often free-floating
  - Architectural complexity
  - Cytoplasmic clearing (bubbly/foamy)
  - Nuclear abnormalities (loss of polarity)
  - Immunohistochemical stains: p53 (strong/diffuse vs null), SMAD4 (loss), and ARID1A (loss)

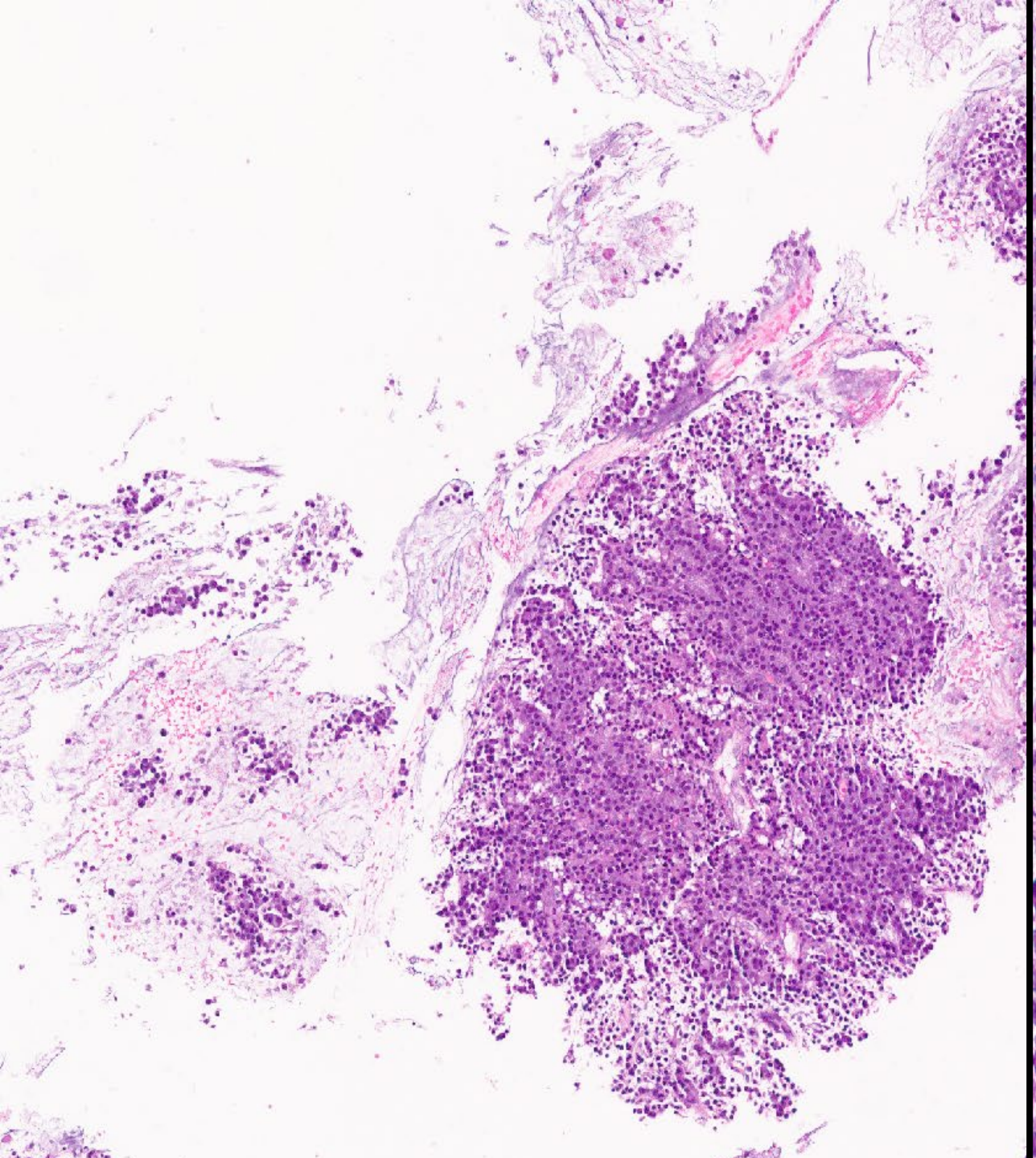
Take Home Points: Case 1

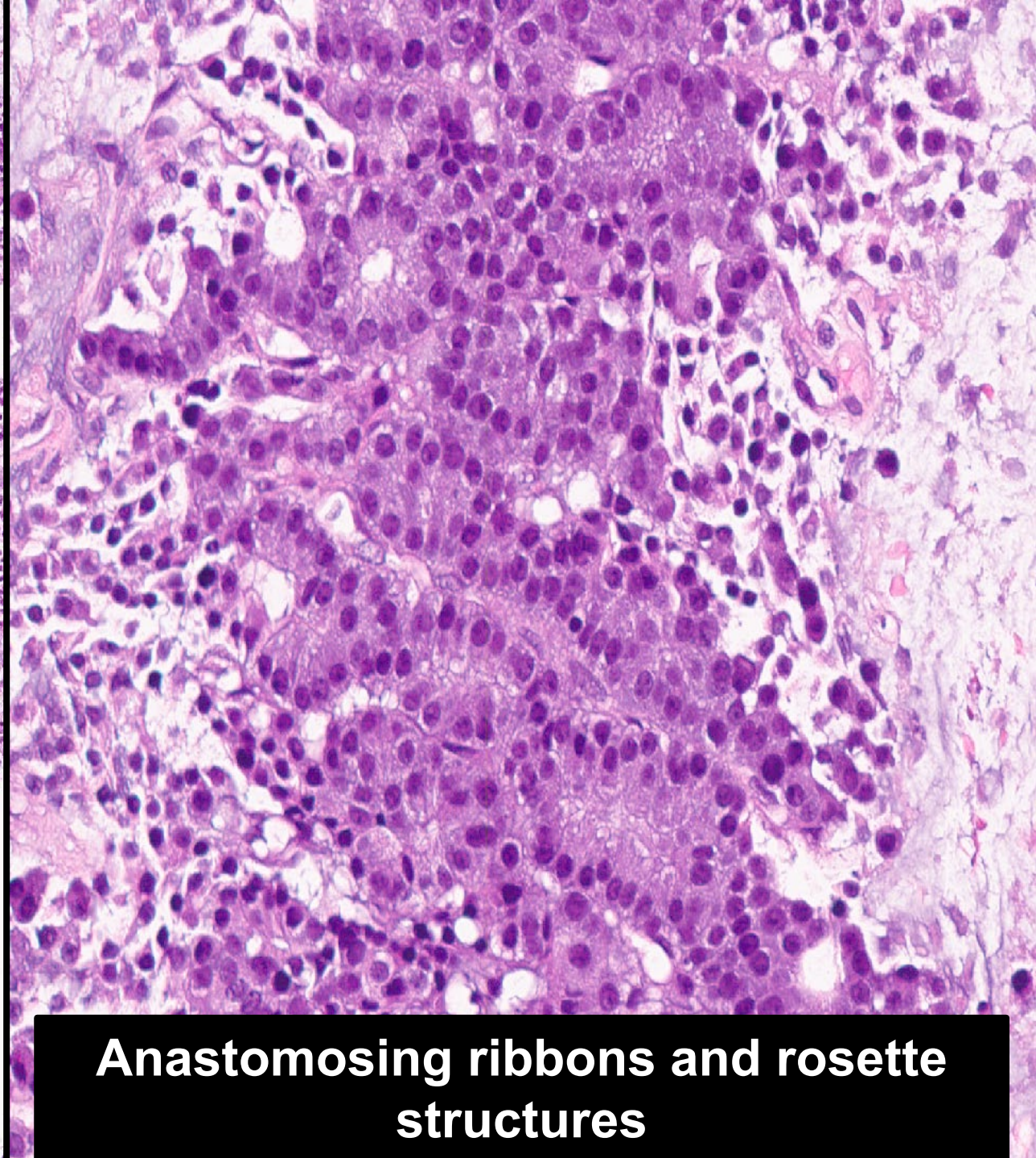
- Next-Generation Needle Pathology:
  - Chronic pancreatitis represents a spectrum of histologic/cytologic findings
  - Pancreatic parenchyma remains within a lobular pattern
  - Ducts demonstrate round, open lumina
  - Interlobular and intralobular fibrosis without glands
  - Autoimmune pancreatitis (type 1): lymphoplasmacytic infiltrate, ductitis and venulitis

Case 2

- A 65-ye ain, jaundic ne pancrea
- The pat ated at his extr
- Serum normal limits a FNB) was pe

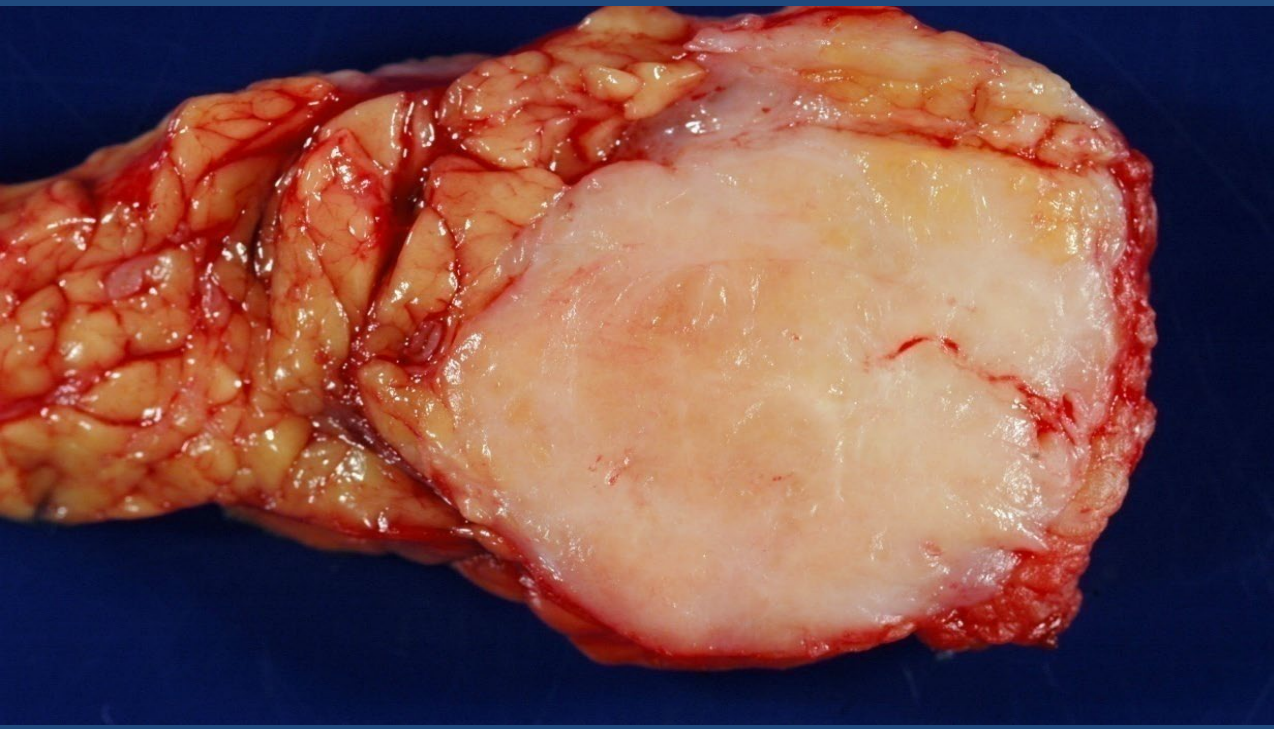

Sheets of Neoplastic Cells
Dirty Background





Anastomosing ribbons and rosette structures

Solid



Chronic Pancreatitis*

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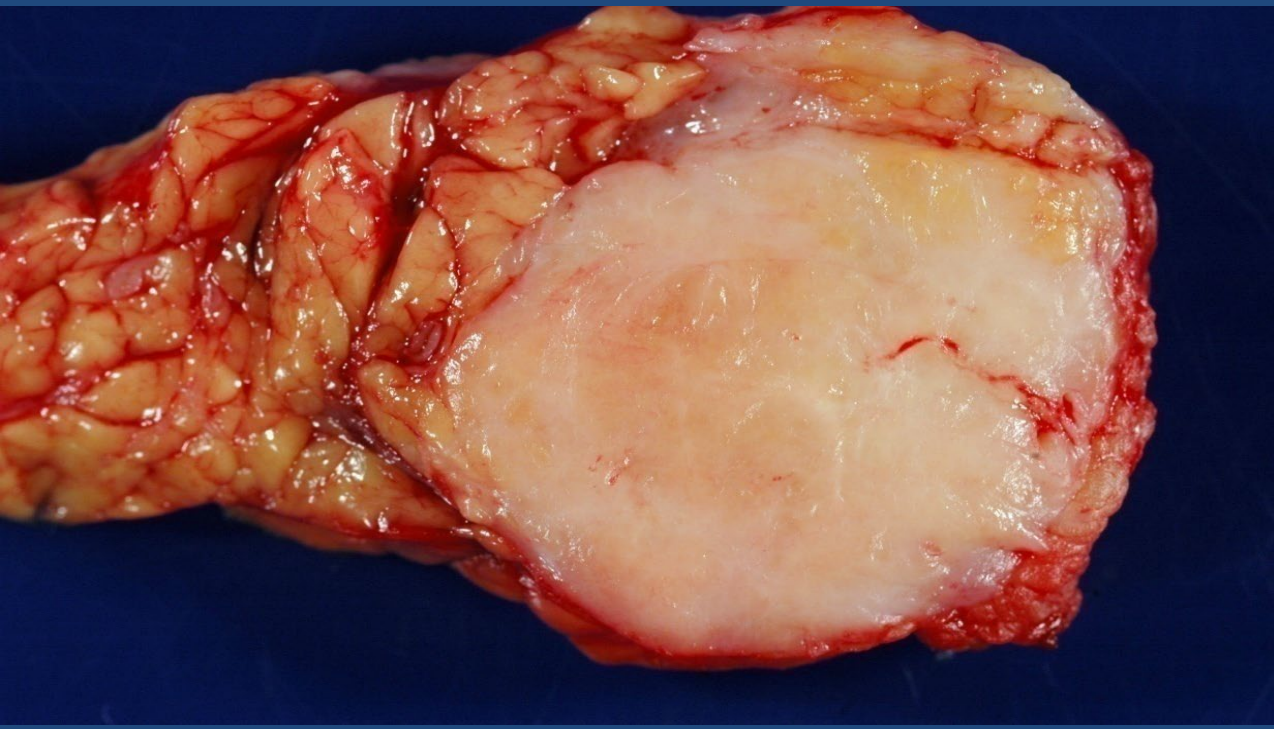

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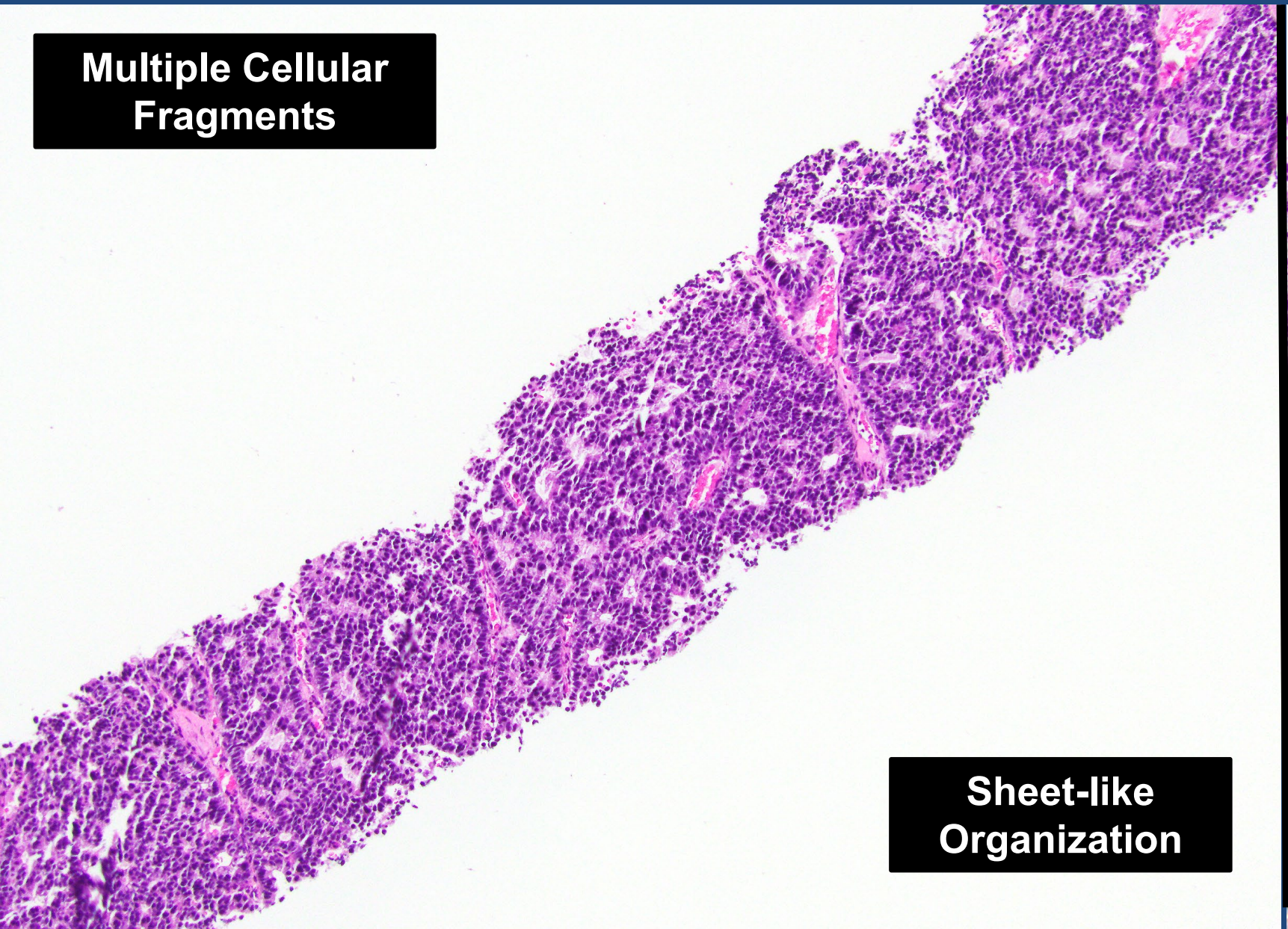
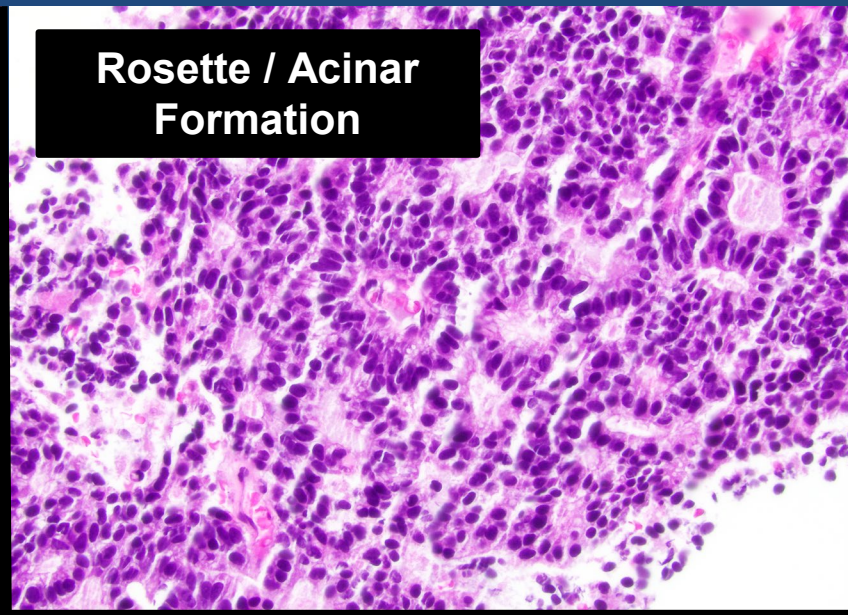
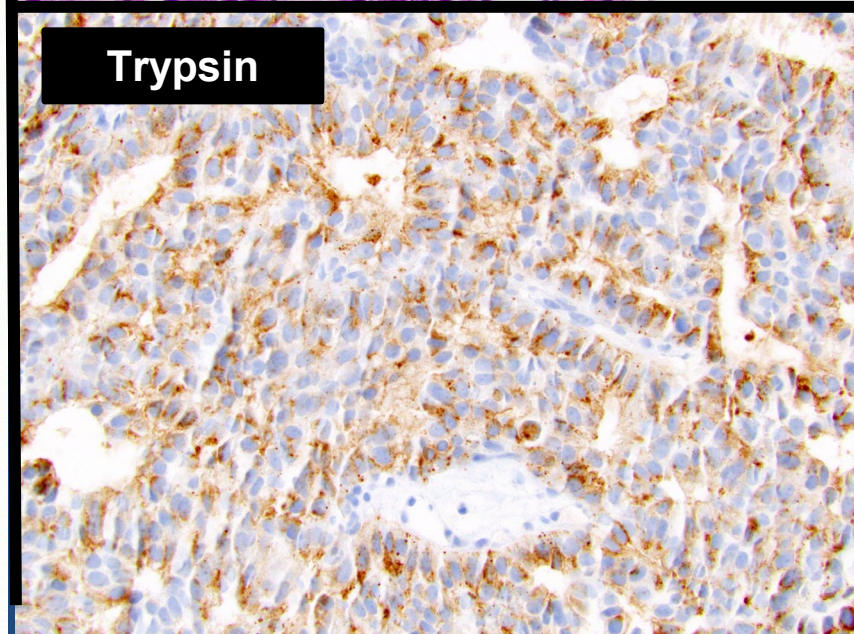
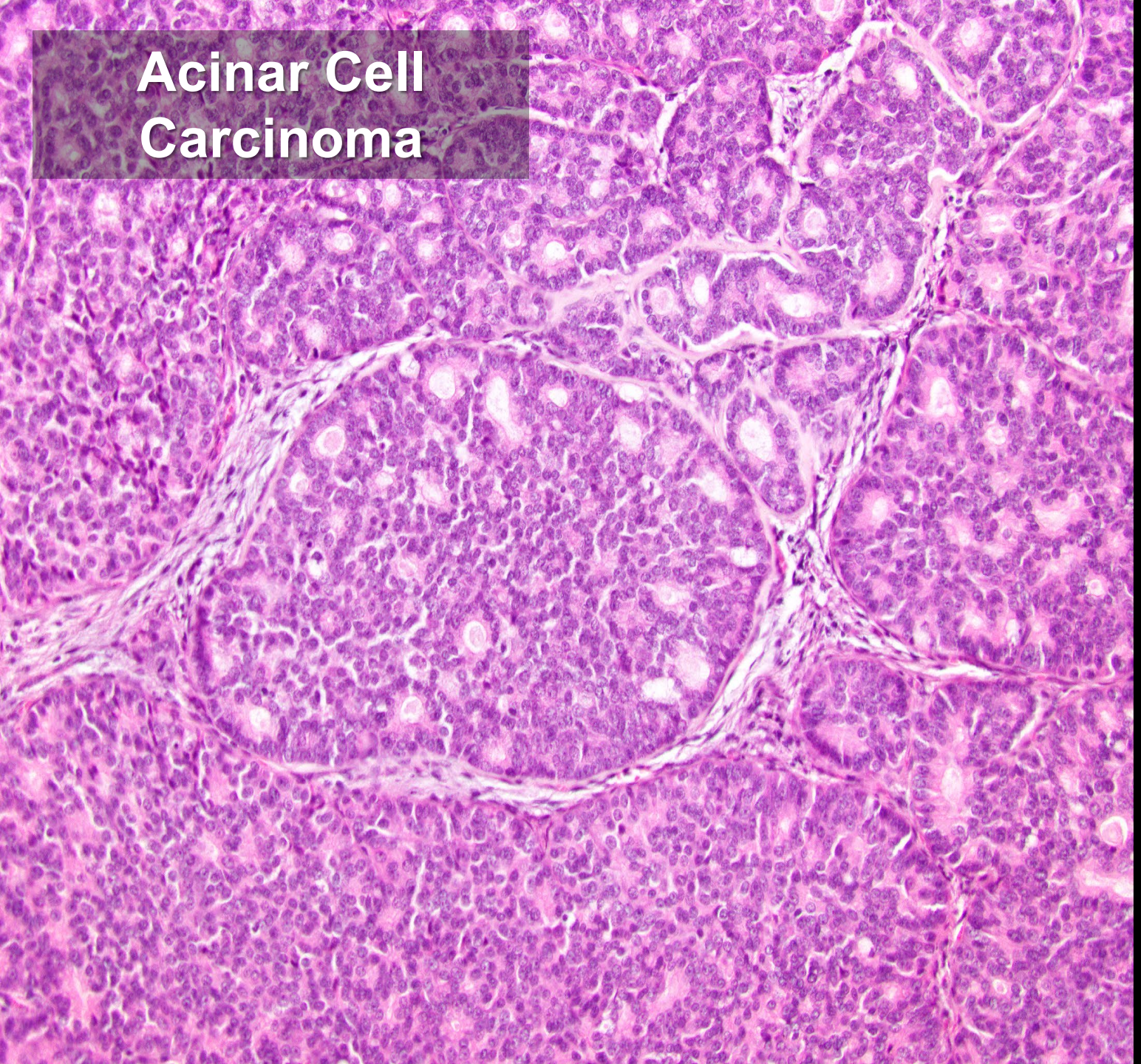
SharkCore Biopsy: Acinar Cell Carcinoma

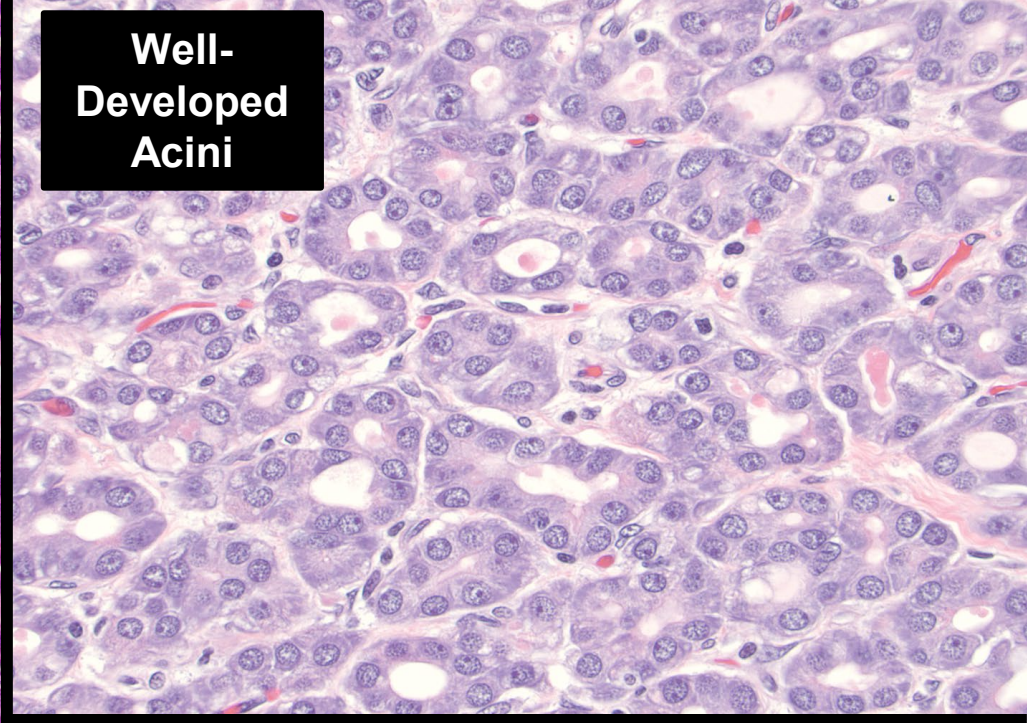


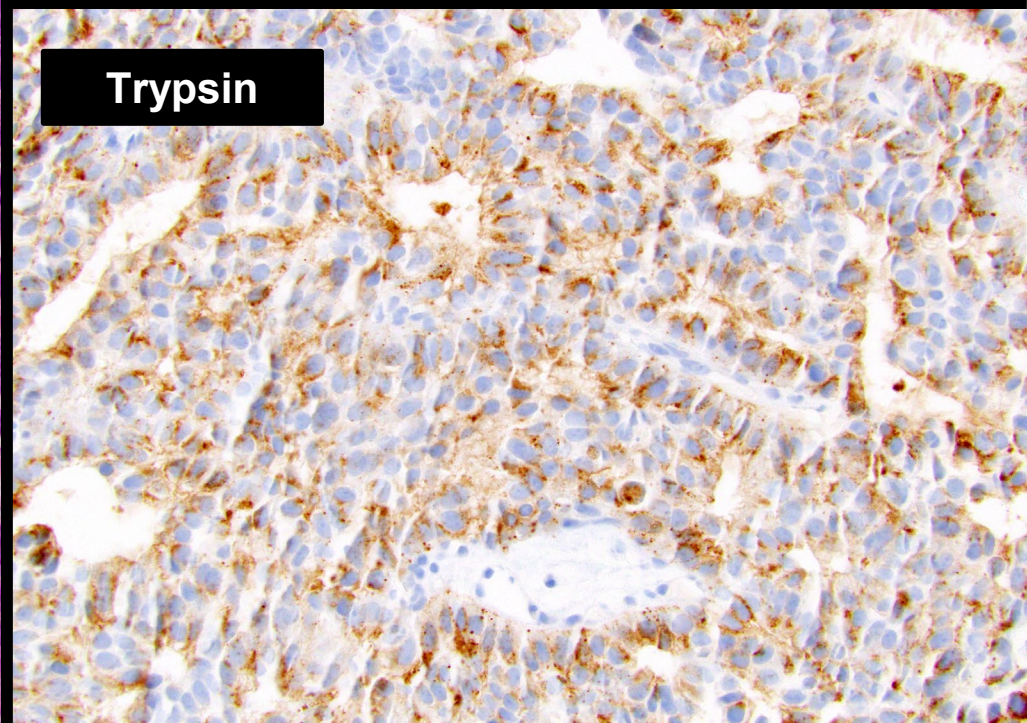




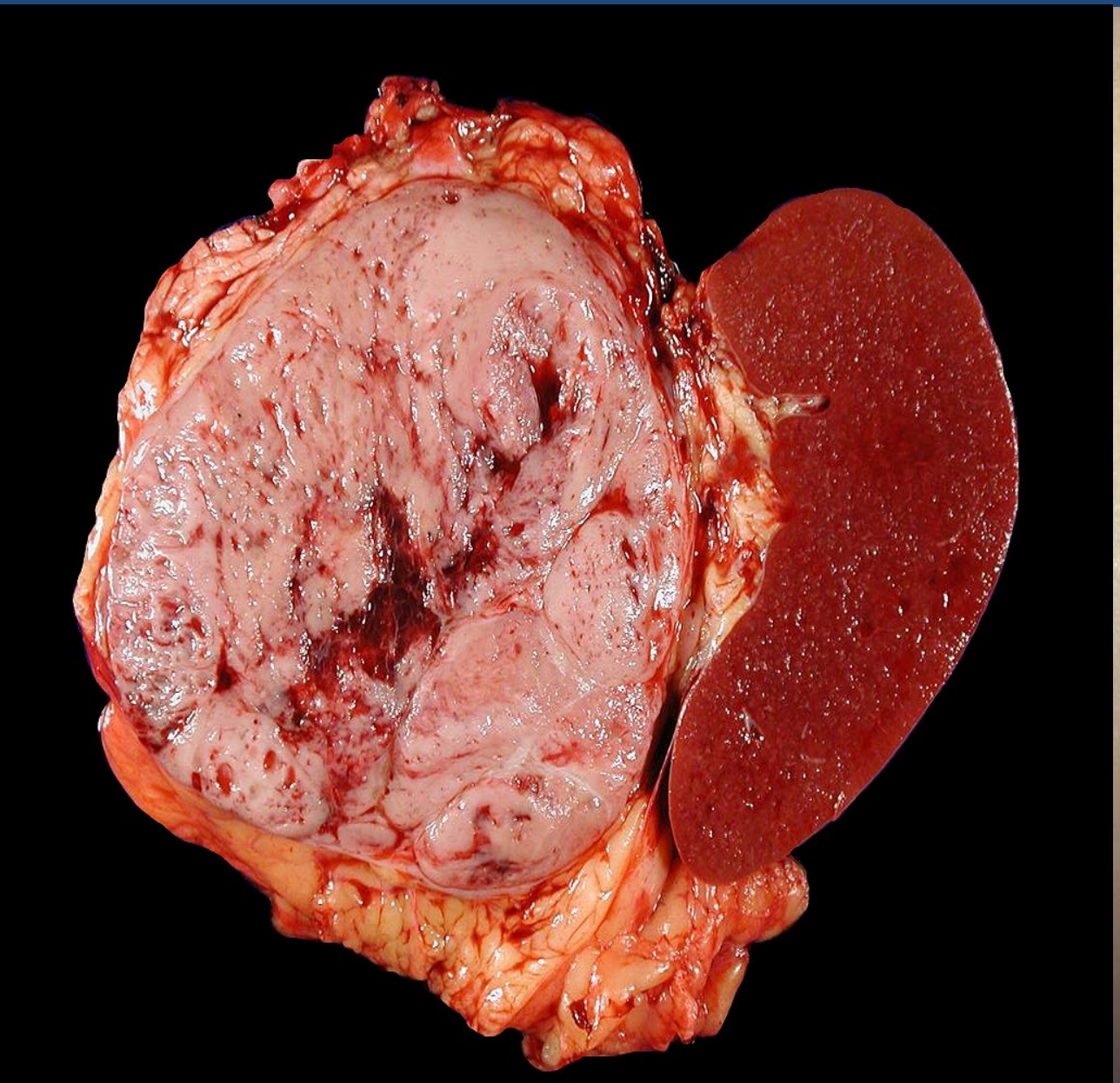
Acinar Cell Carcinoma

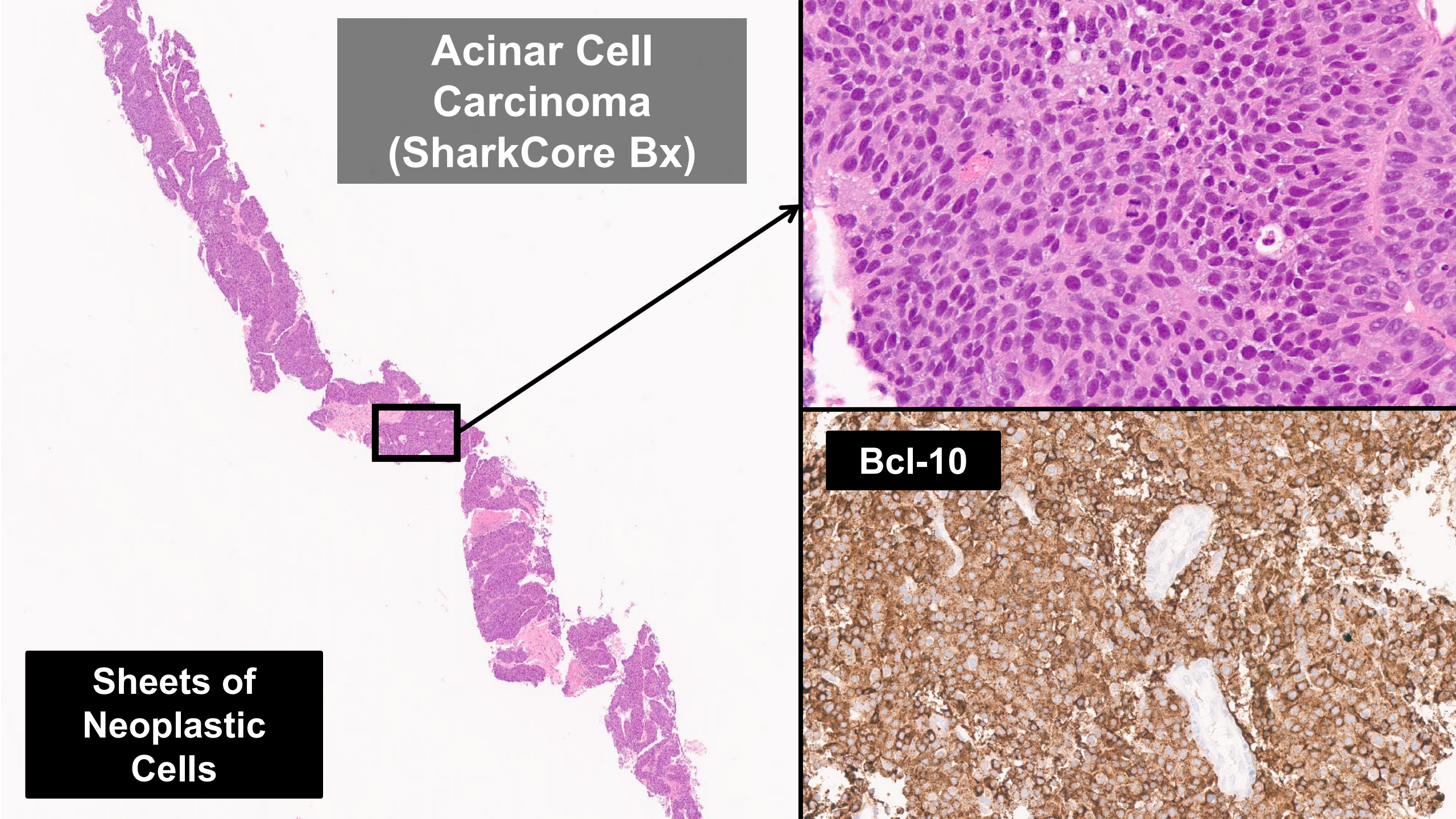


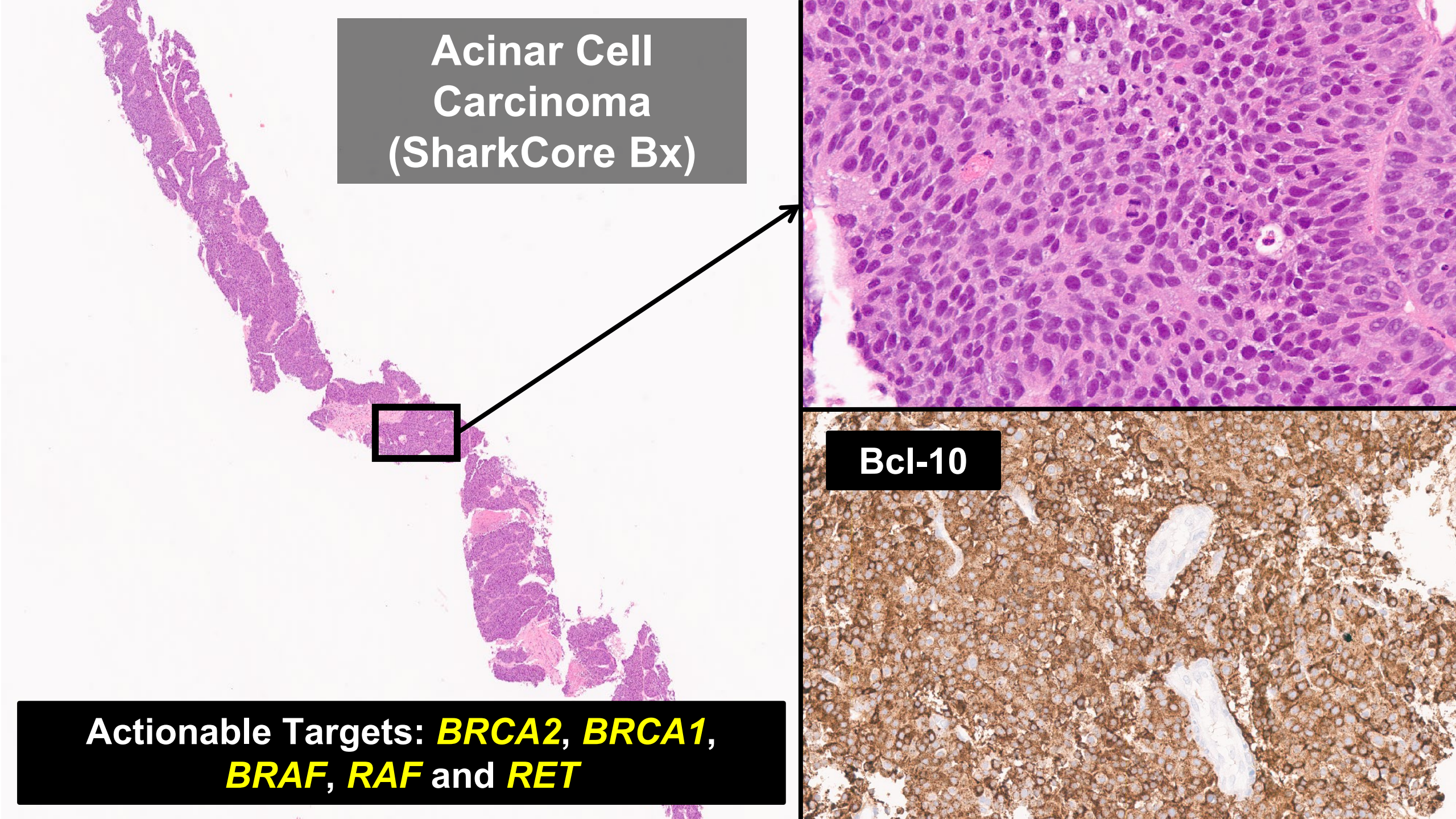


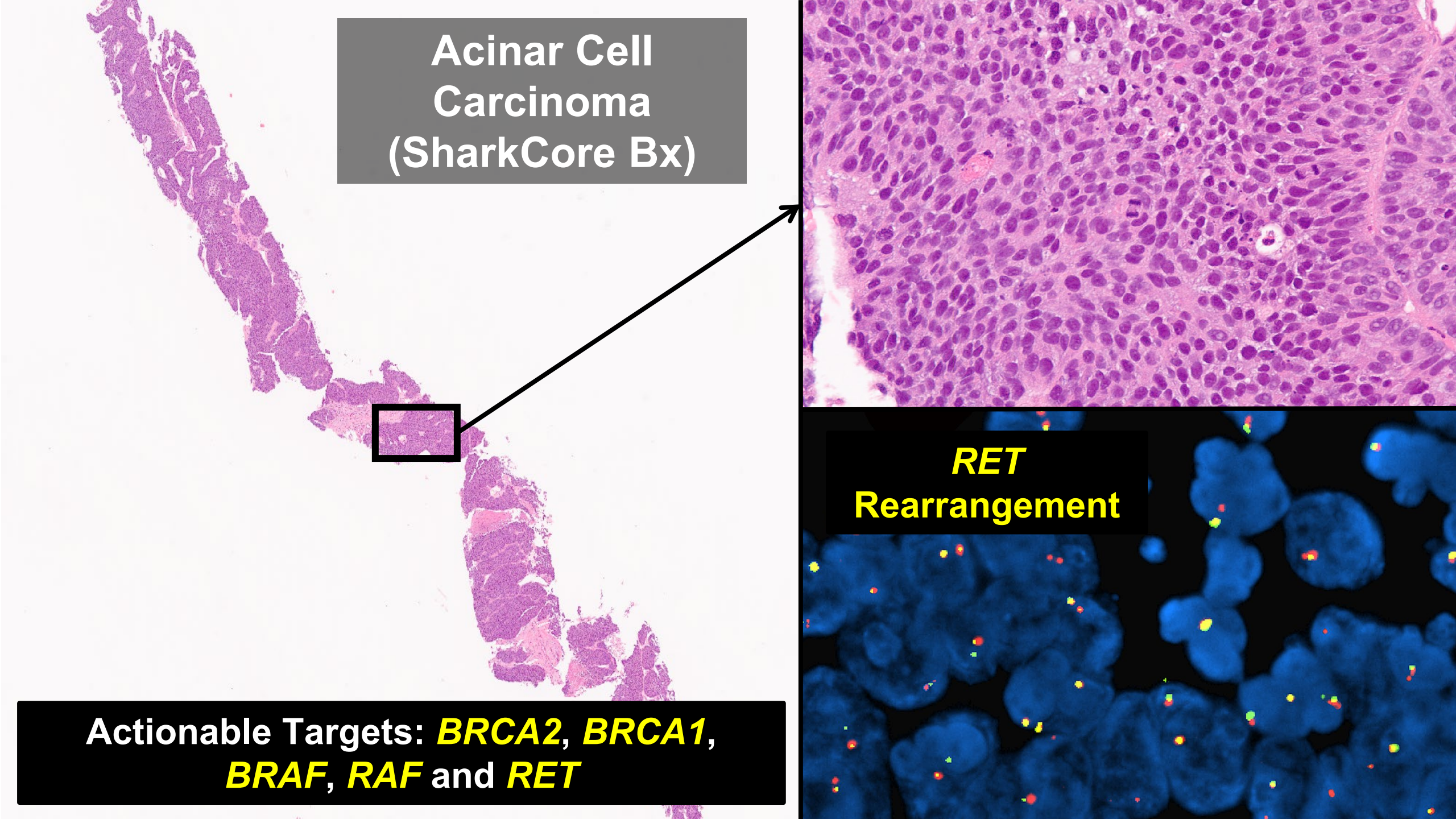


Acinar Cell Carcinoma

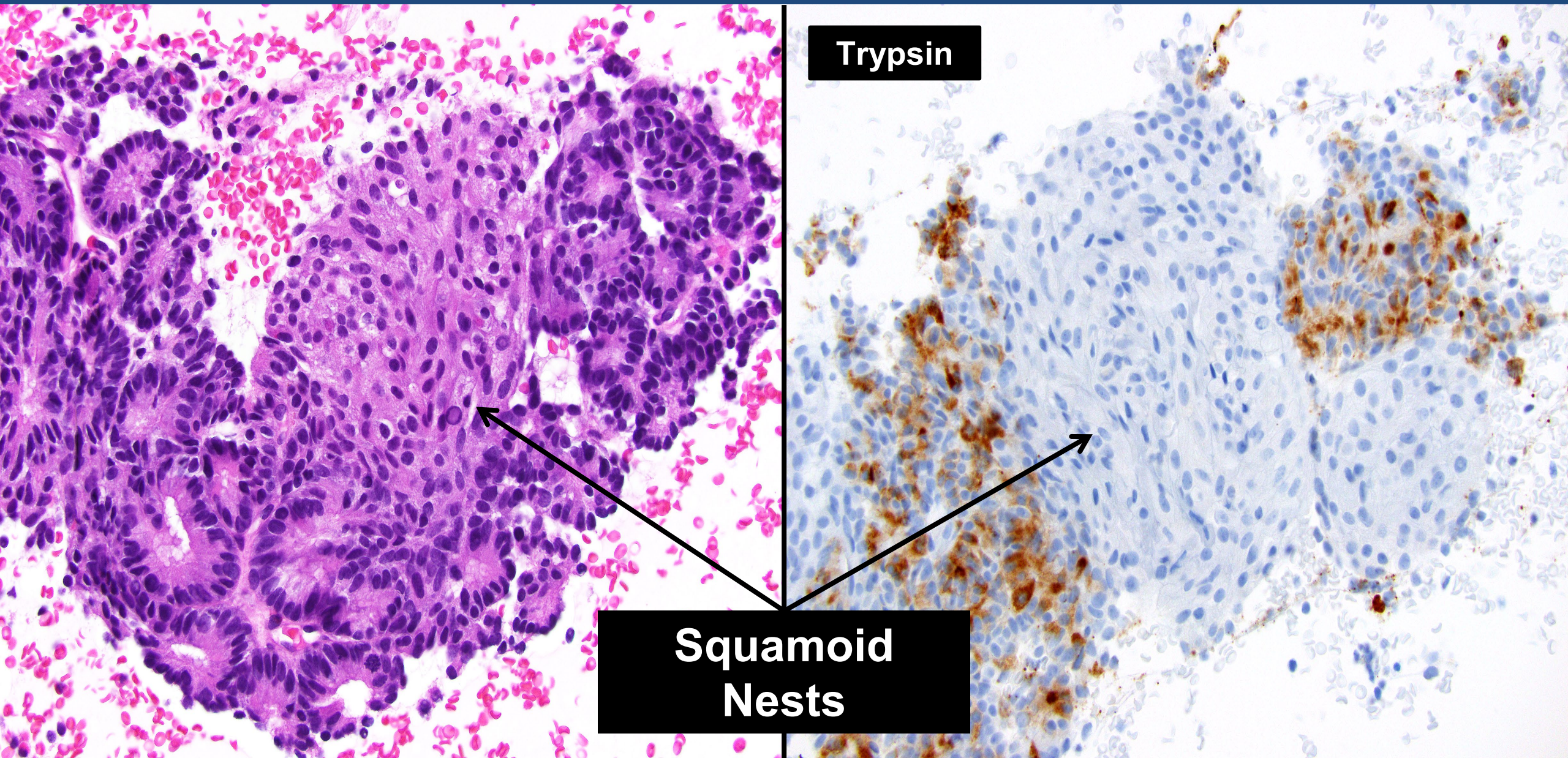


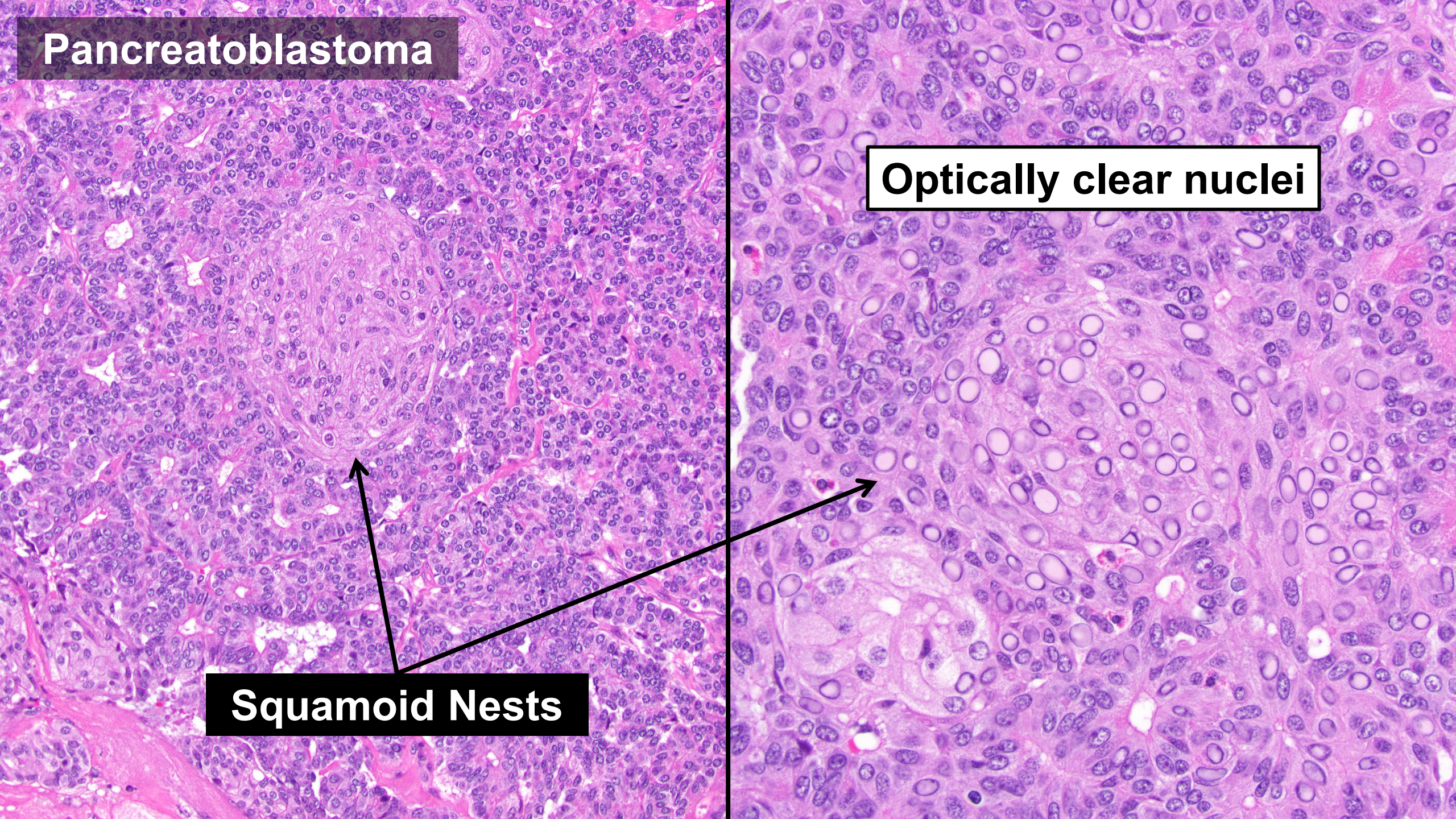

Acinar Cell Carcinoma (SharkCore Bx)
Bcl-10
Sheets of Neoplastic Cells


Acinar Cell Carcinoma (SharkCore Bx)
Bcl-10
Actionable Targets: BRCA2, BRCA1, BRAF, RAF and RET

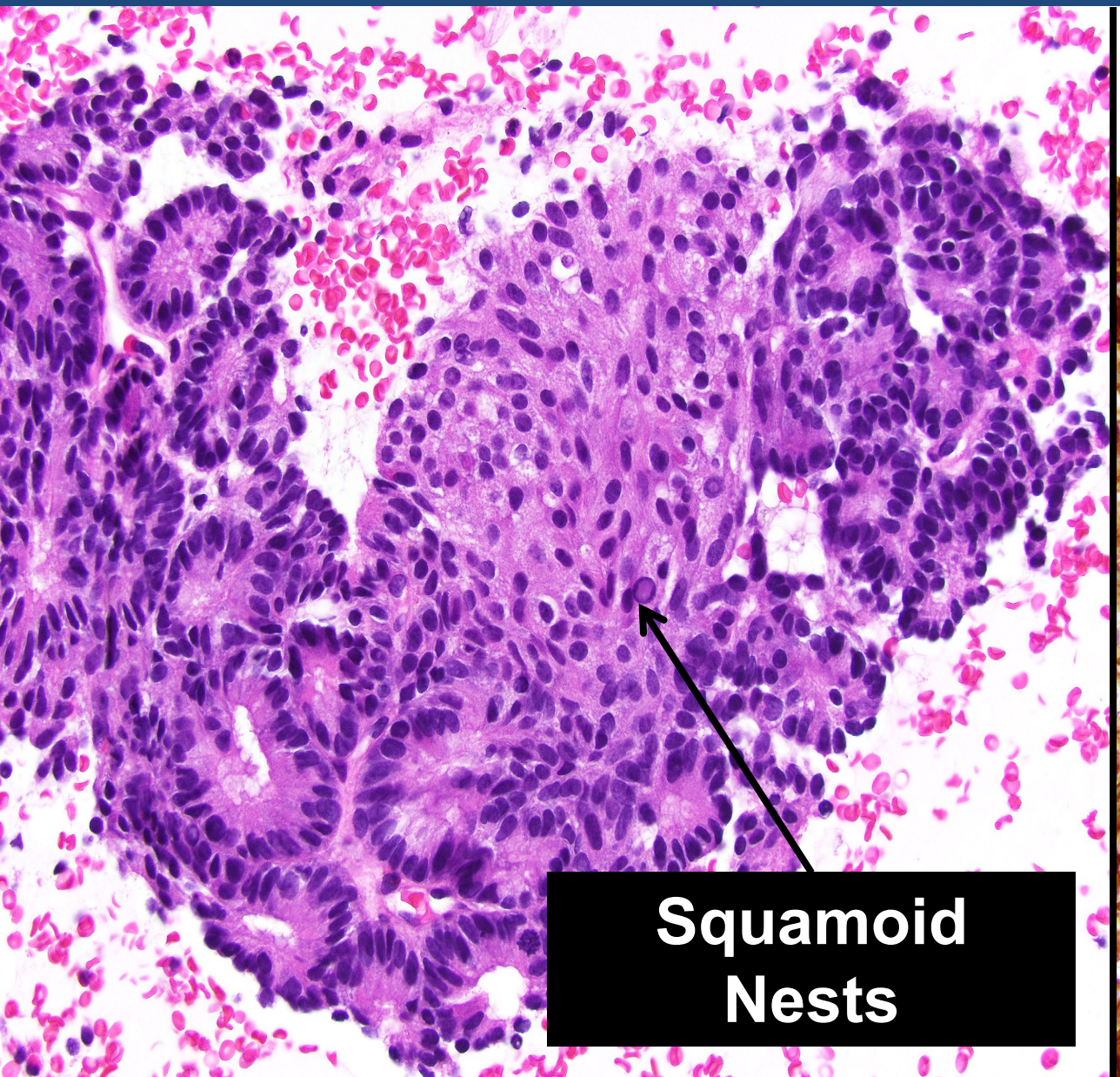

Acinar Cell Carcinoma (SharkCore Bx)
RET Rearrangement
Actionable Targets: BRCA2, BRCA1, BRAF, RAF and RET

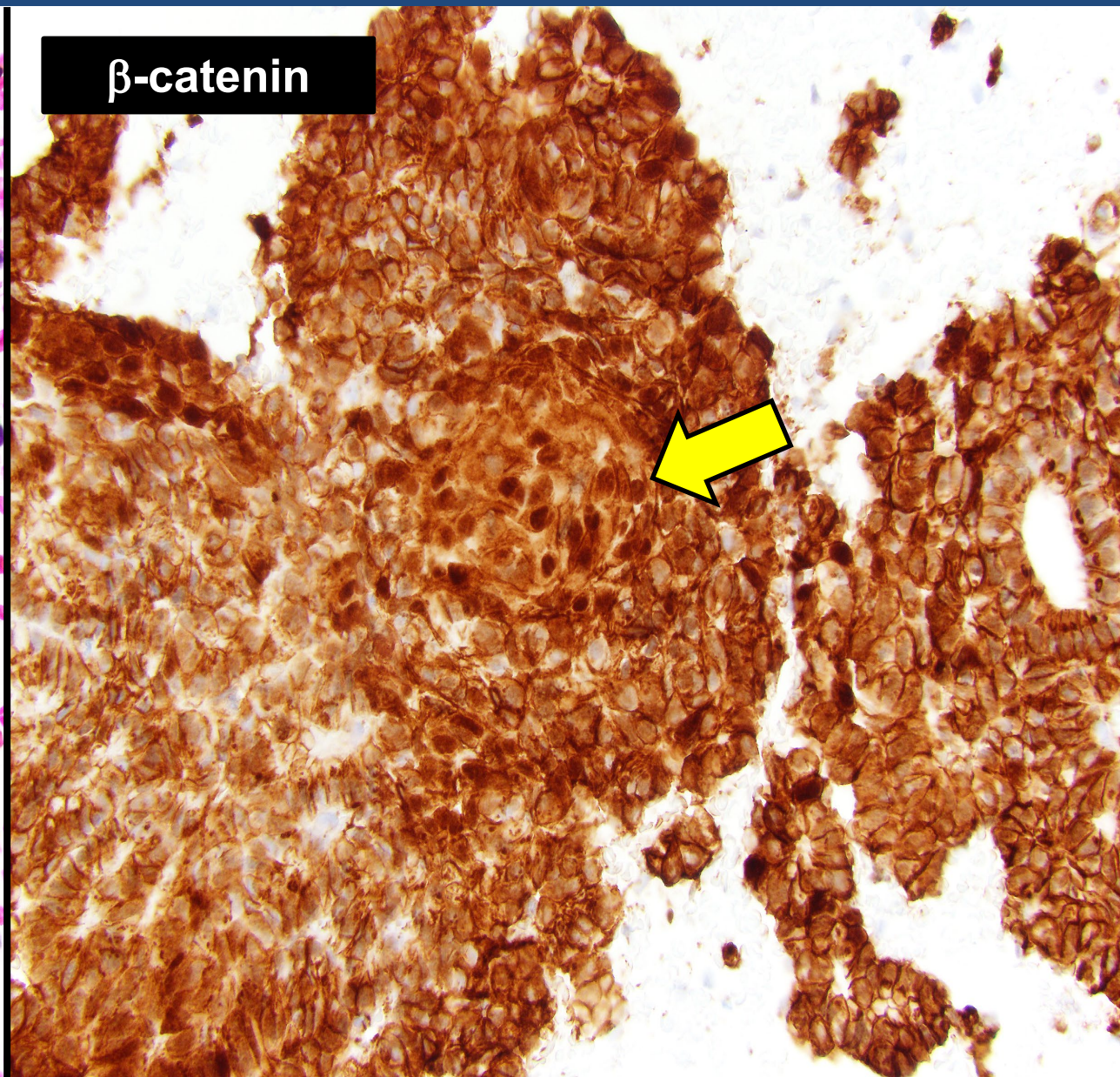
SharkCore Biopsy: Pancreatoblastoma



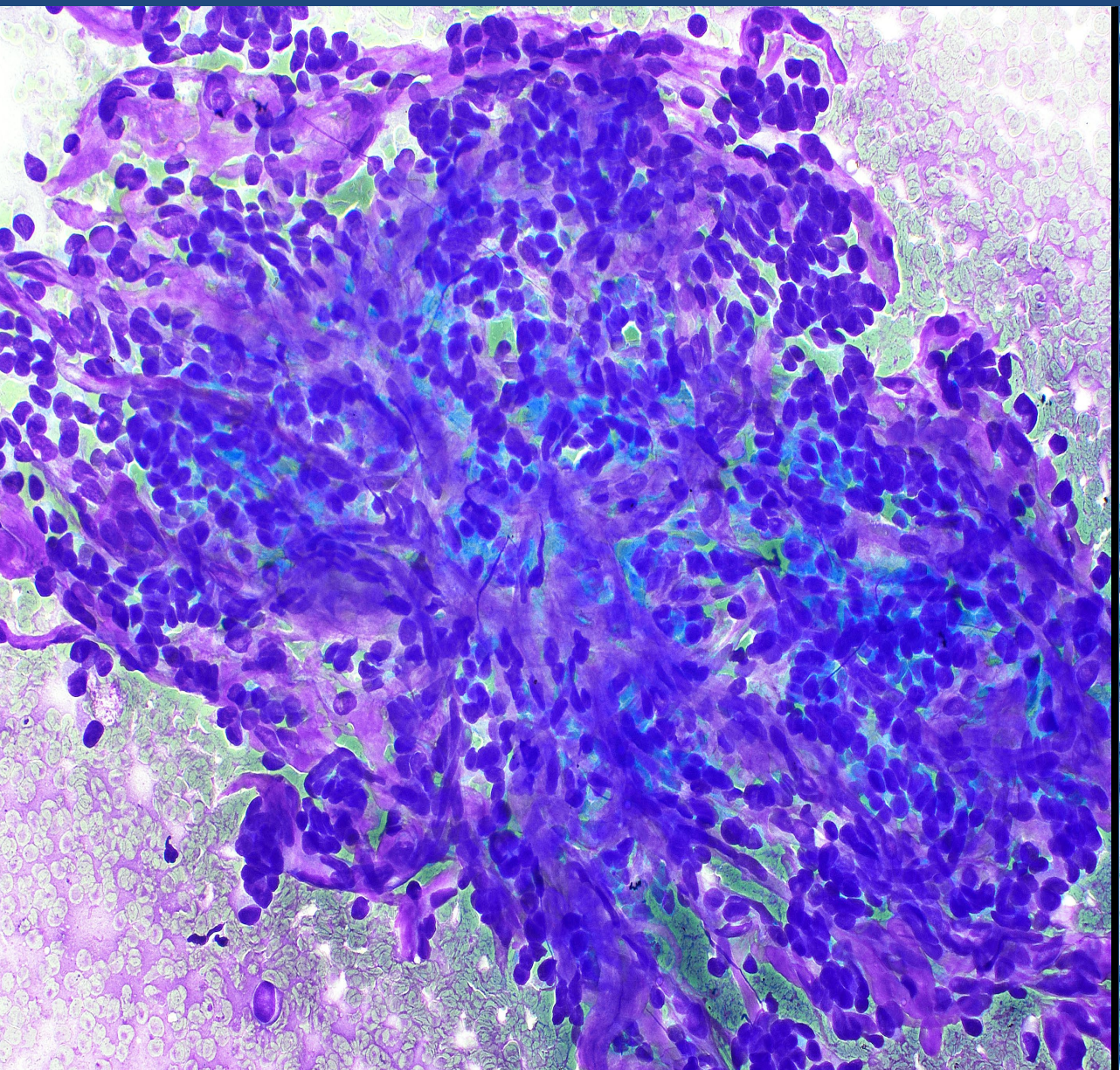

Pancreatoblastoma
Squamoid Nests
Optically clear nuclei

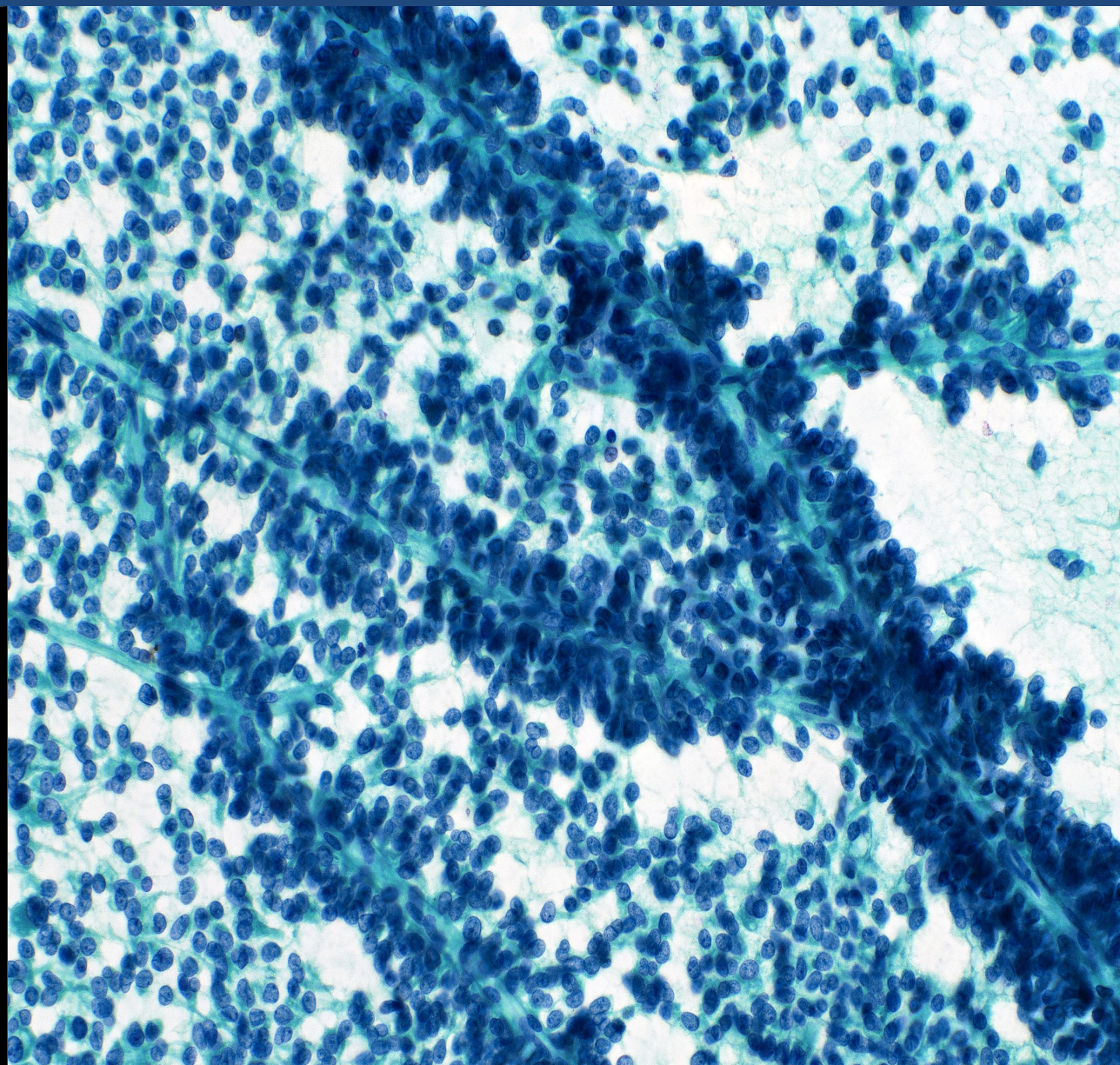
SharkCore Biopsy: Pancreatoblastoma

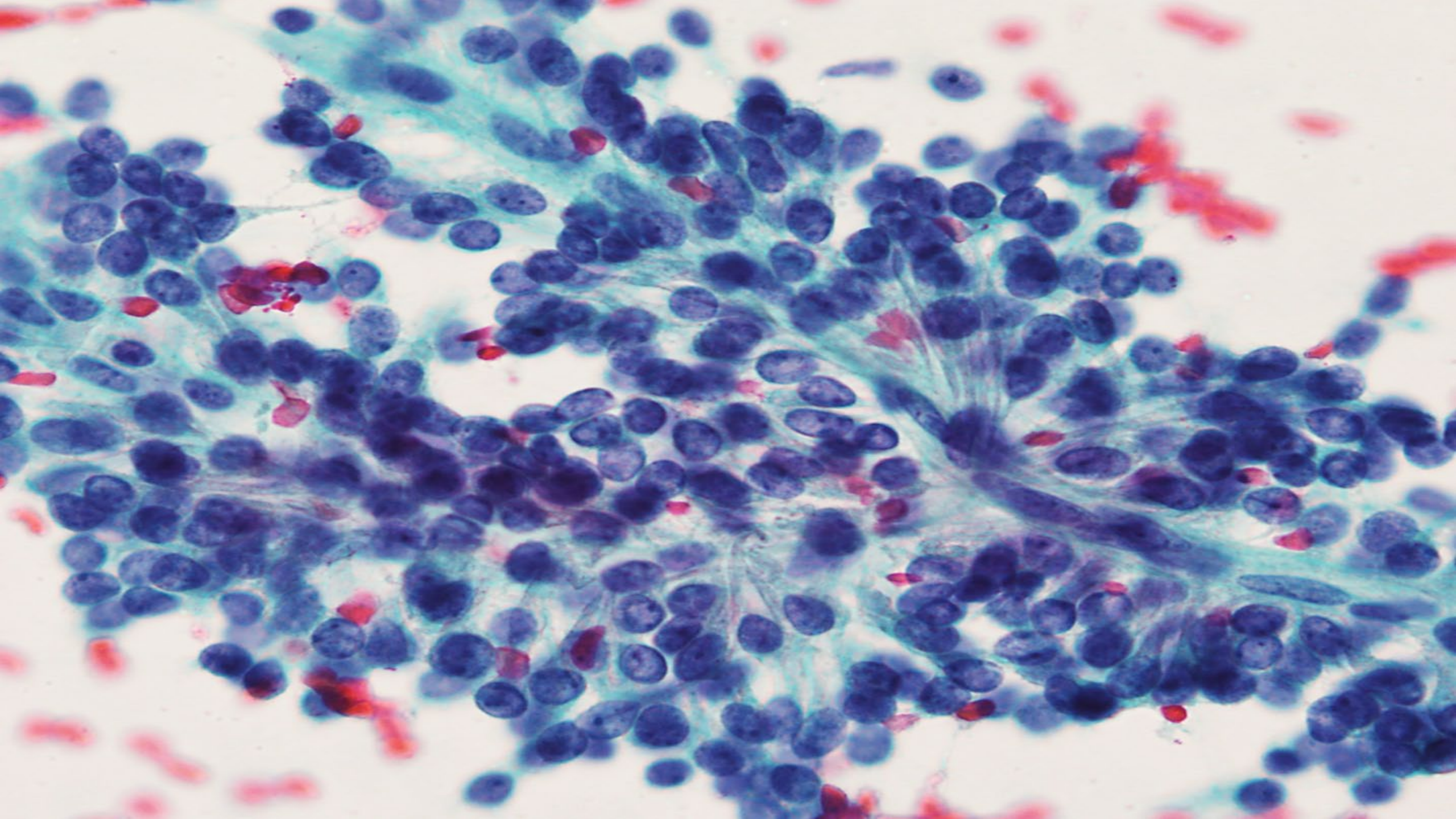




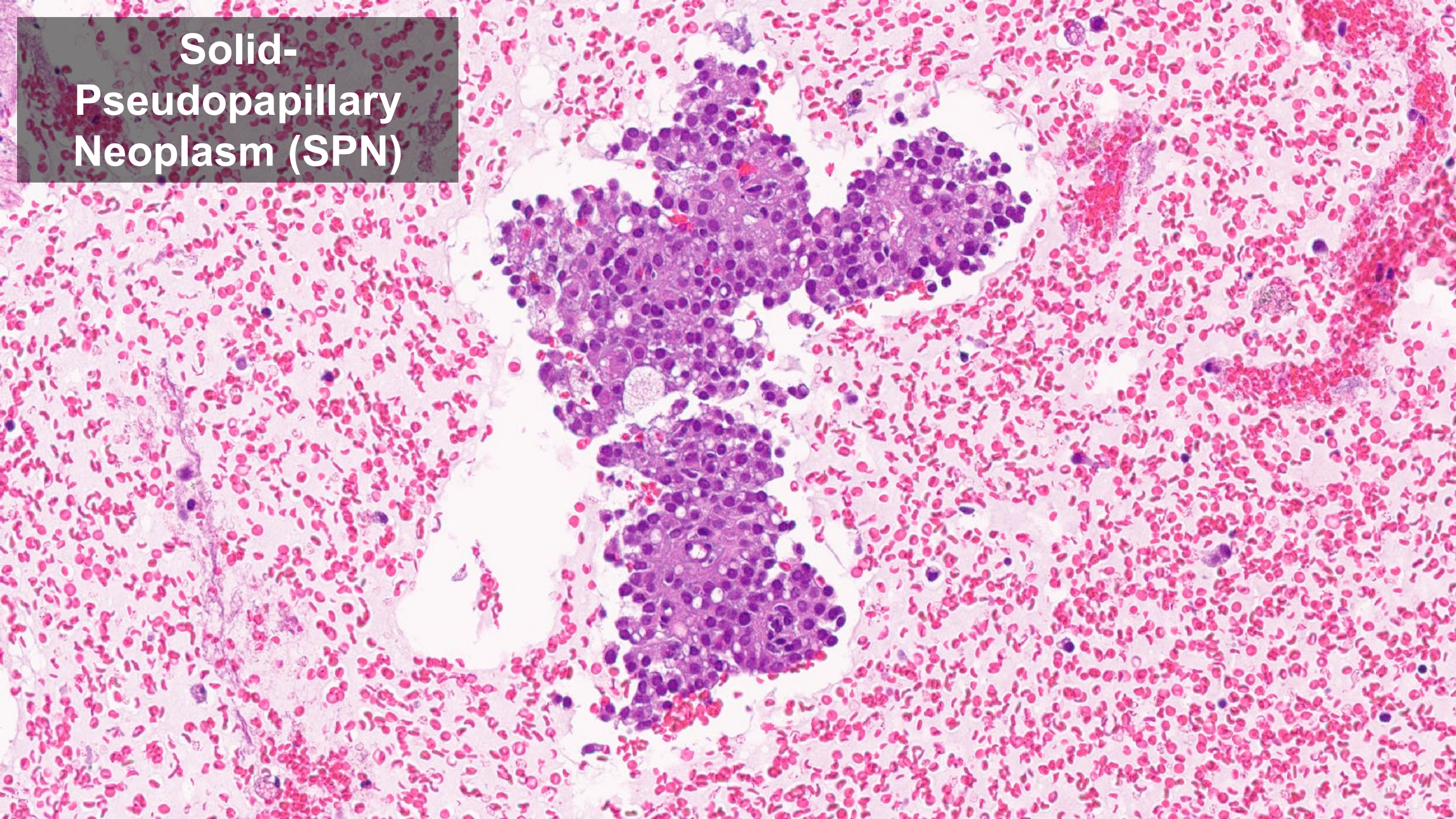
Solid-Pseudopapillary Neoplasm (SPN)



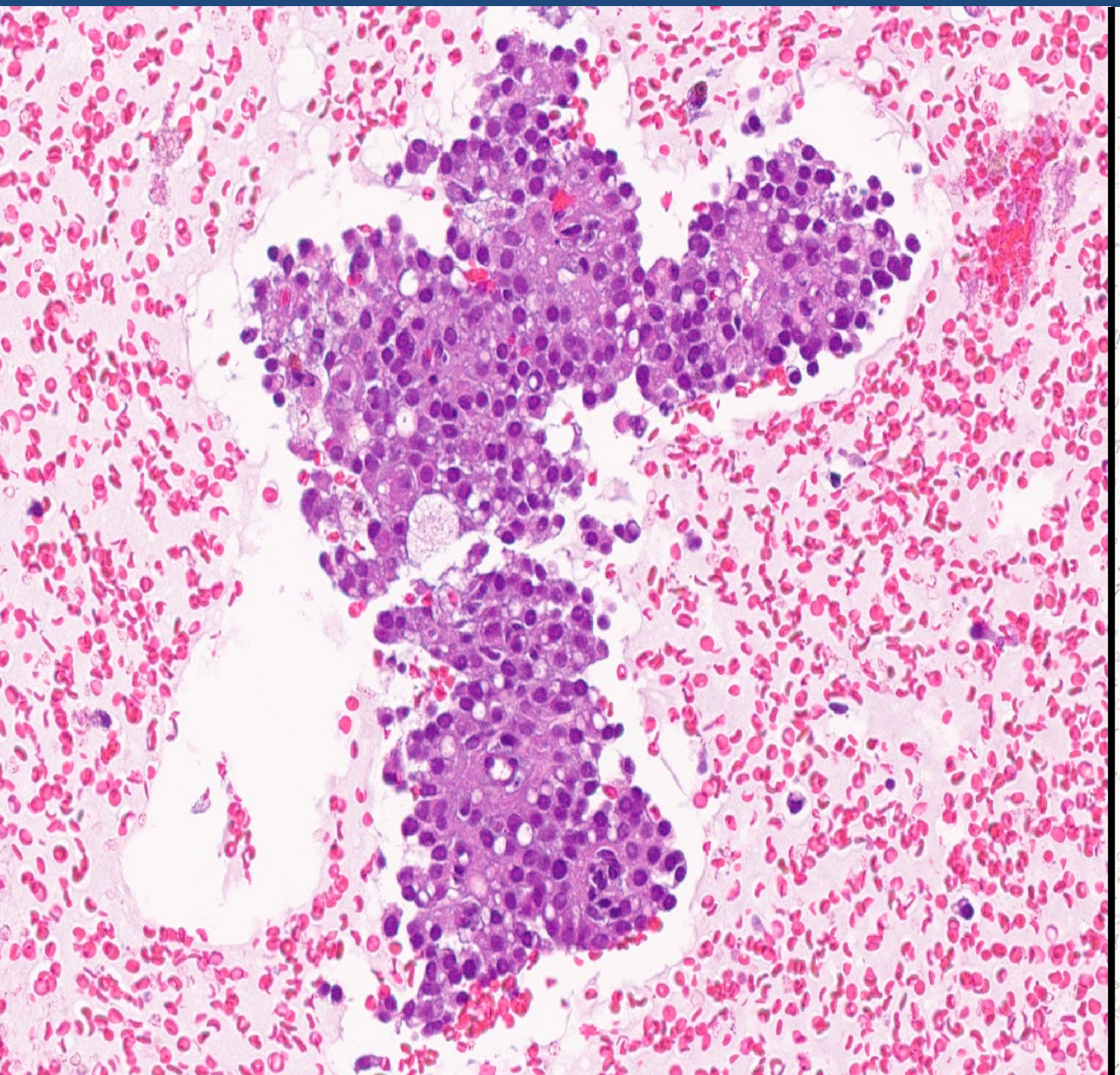


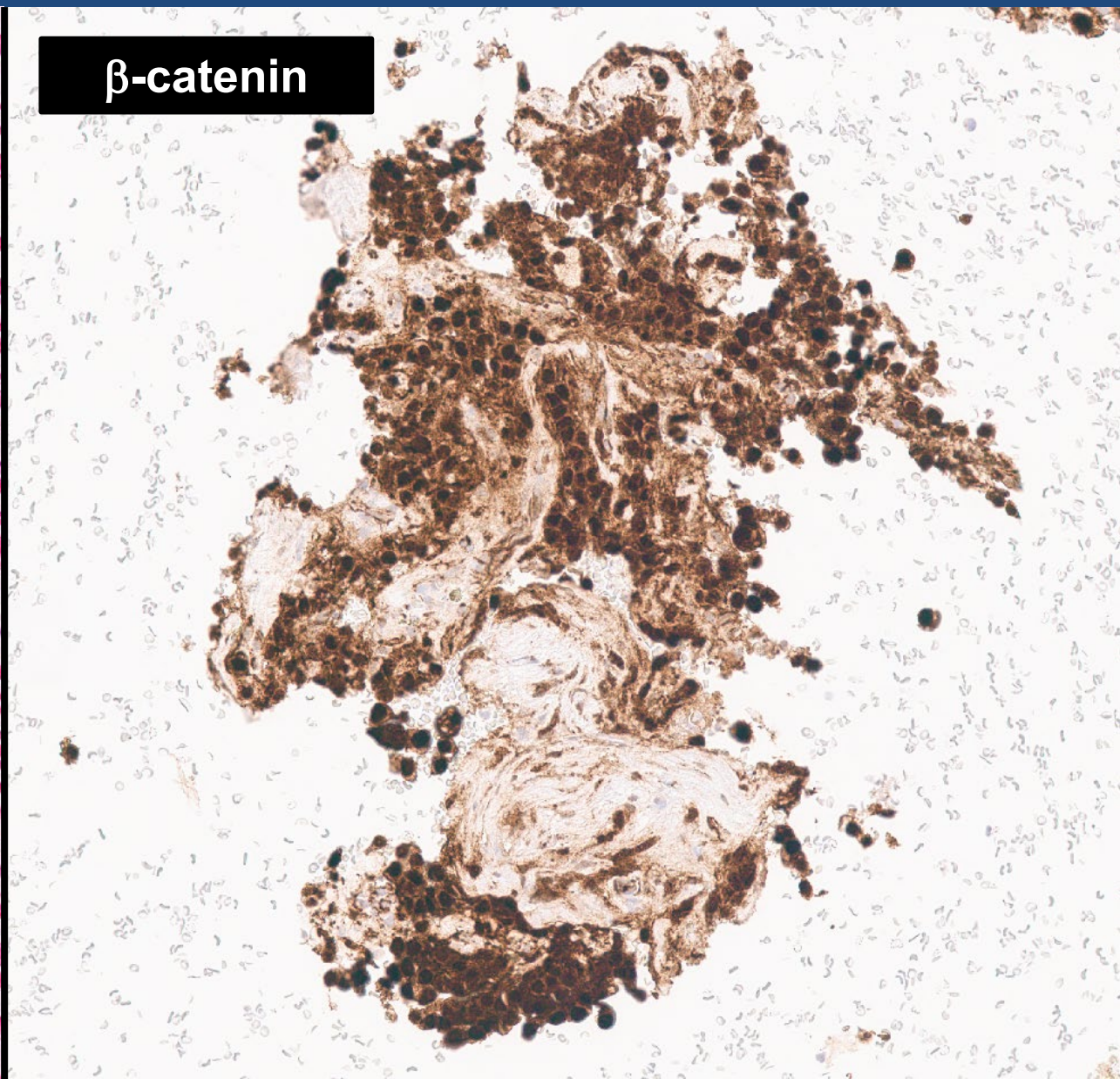


Solid-Pseudopapillary Neoplasm (SPN)

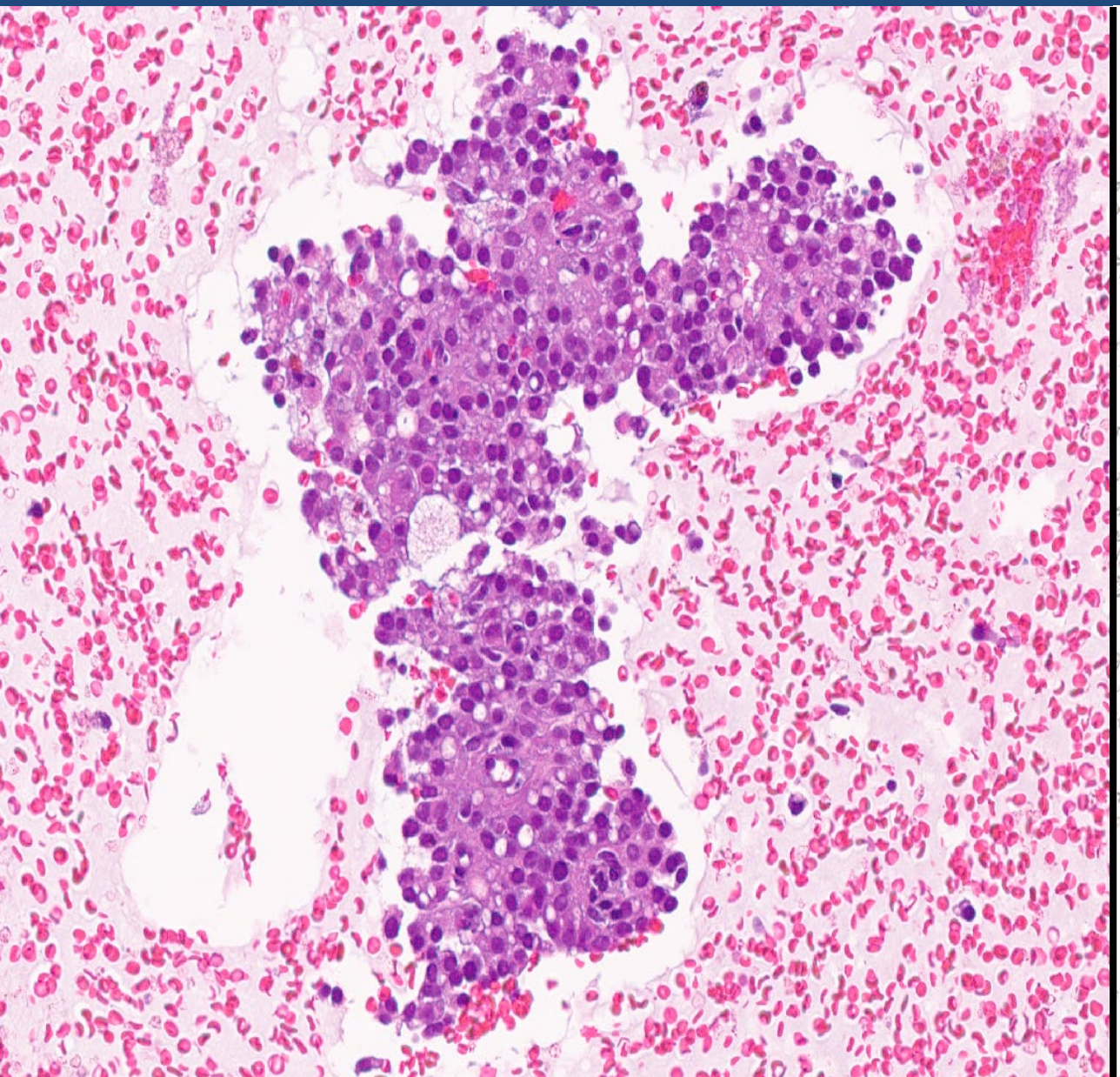


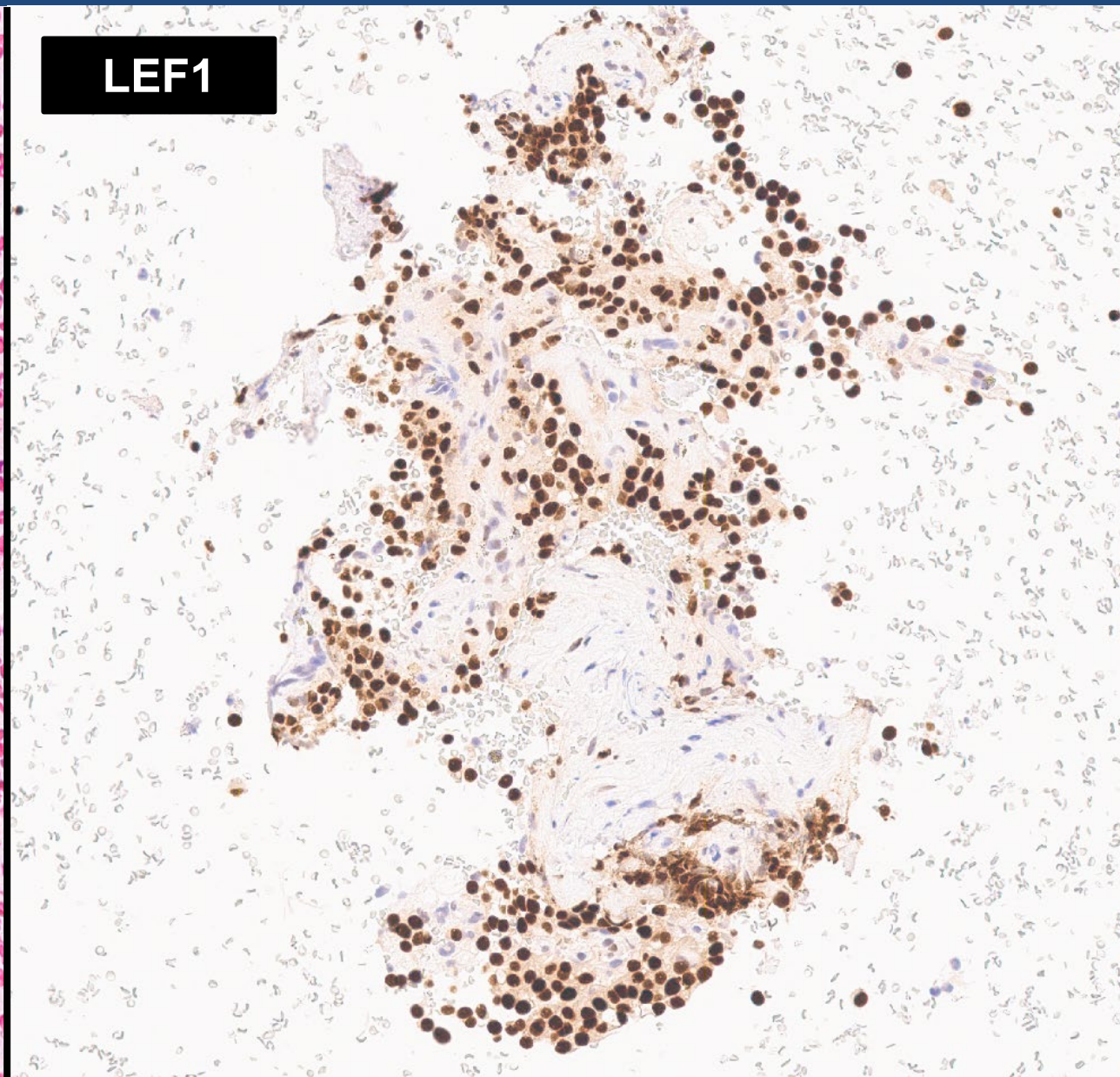
SharkCore Biopsy: SPN

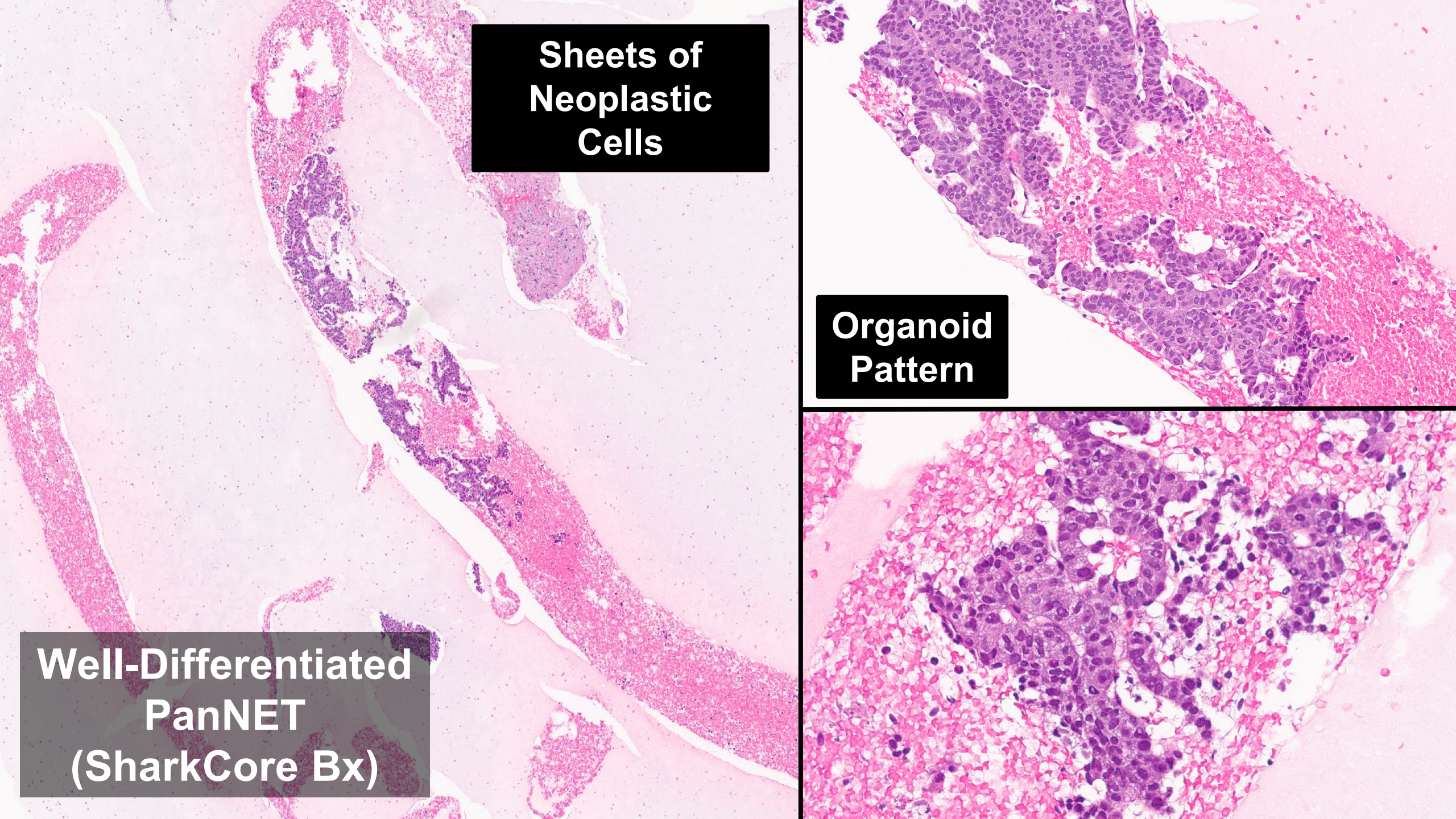




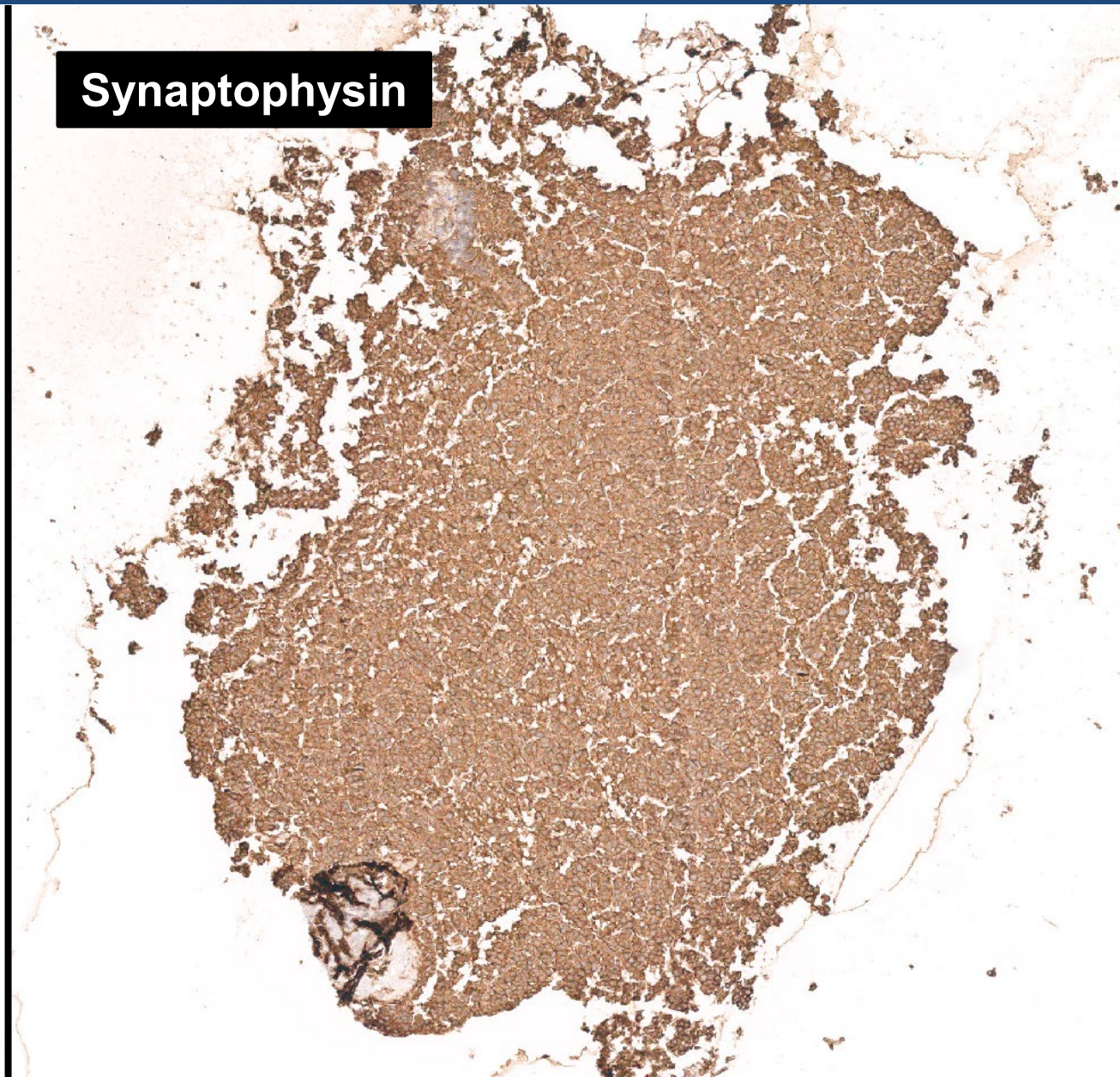
SharkCore Biopsy: SPN



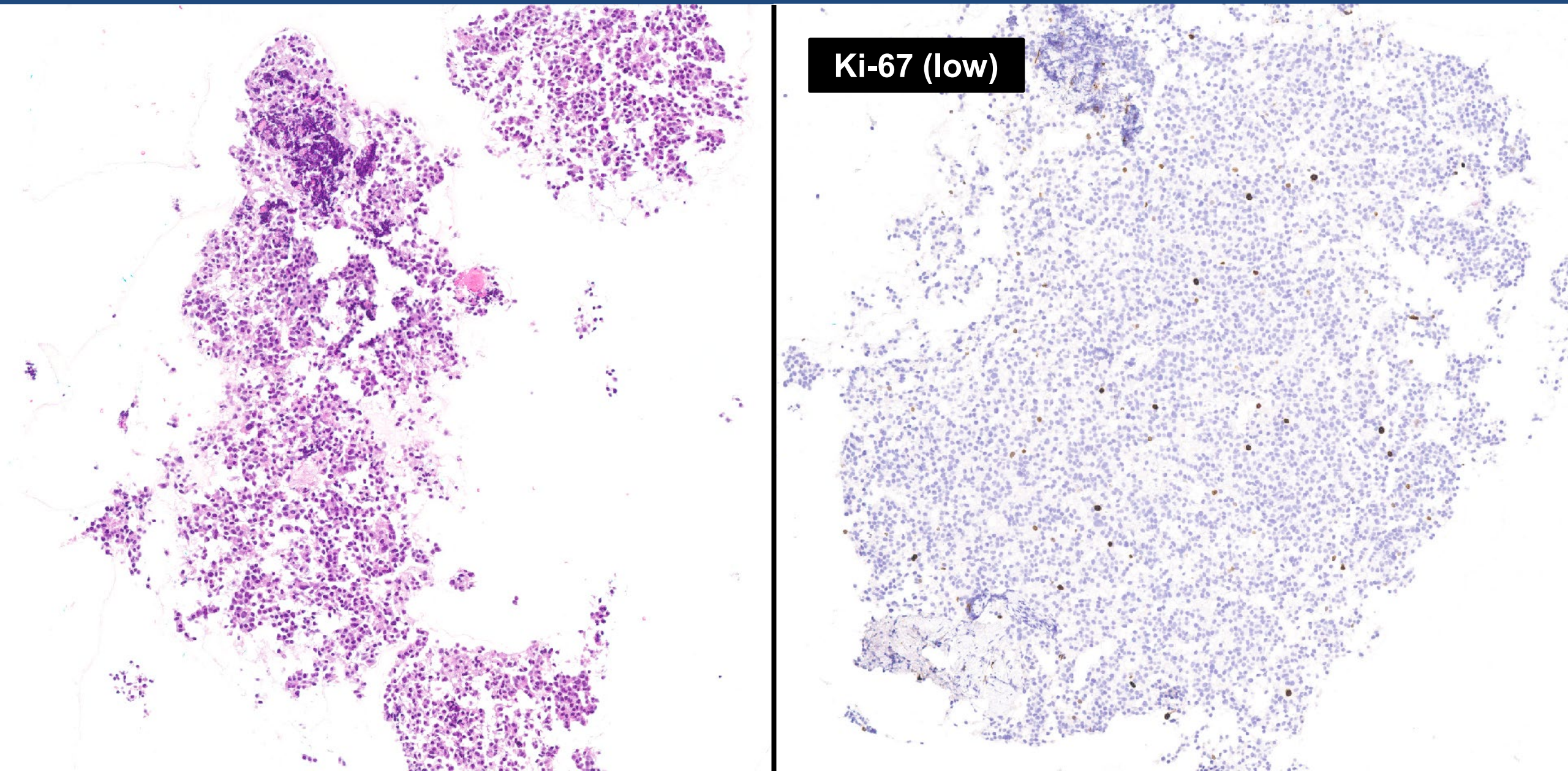



Sheets of Neoplastic Cells
Organoid Pattern
Well-Differentiated PanNET (SharkCore Bx)

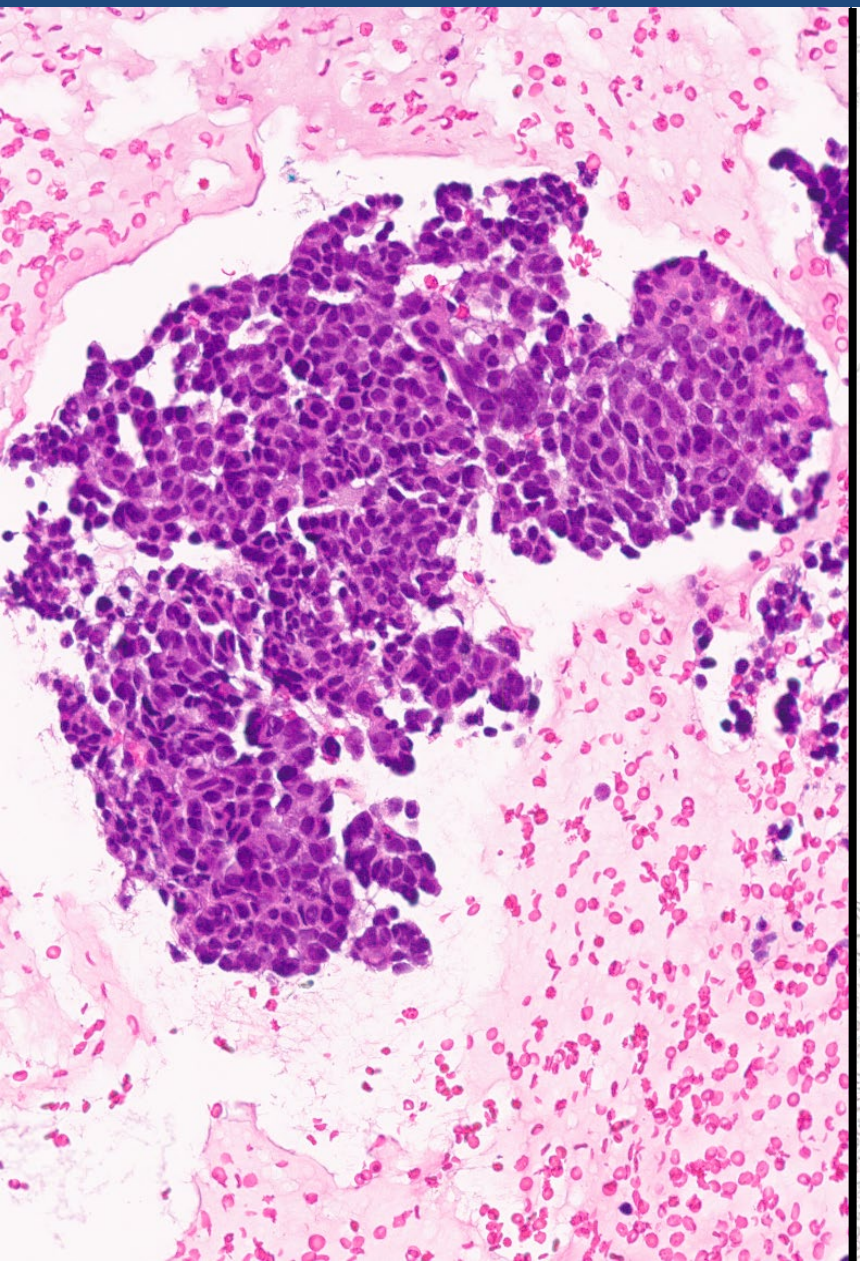
SharkCore Biopsy: Pancreatic Neuroendocrine Tumor

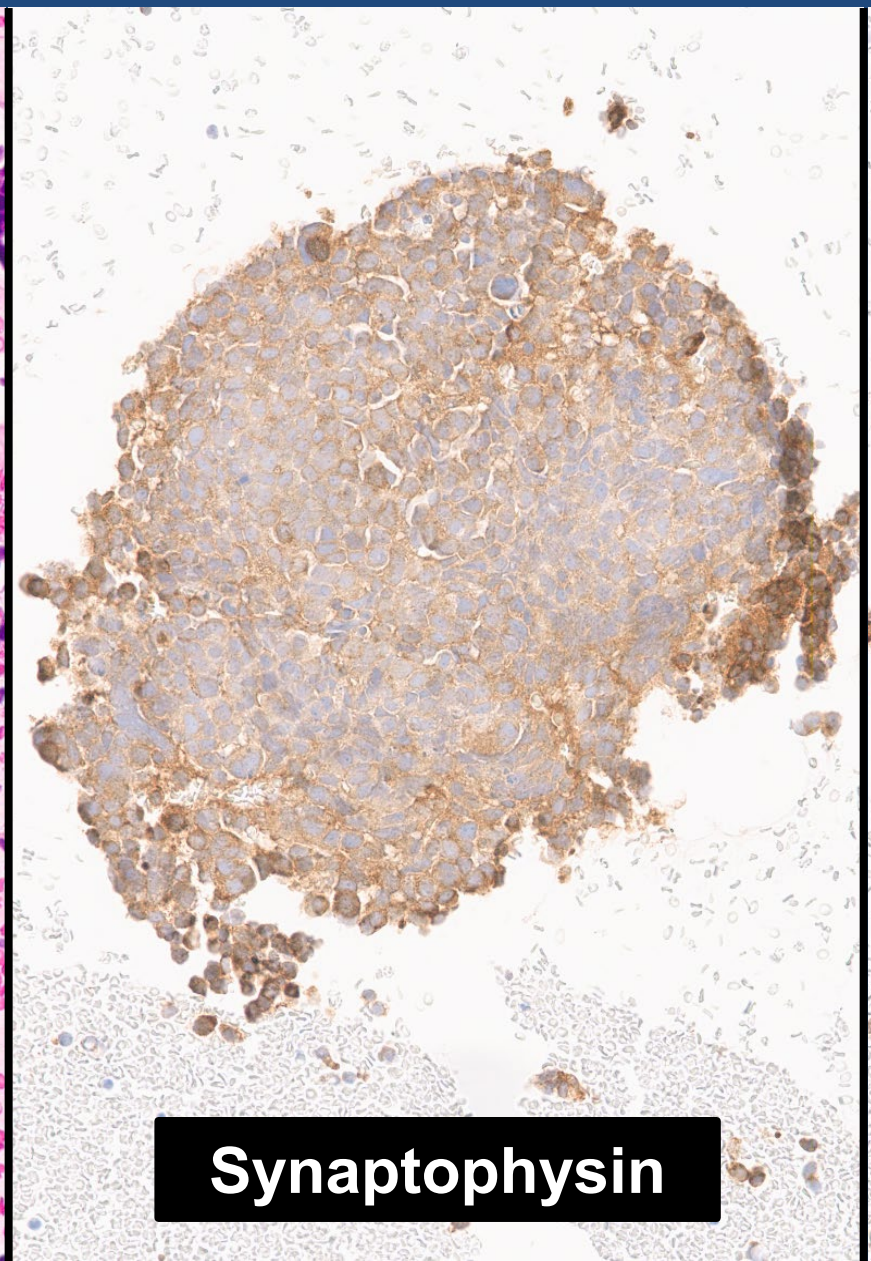


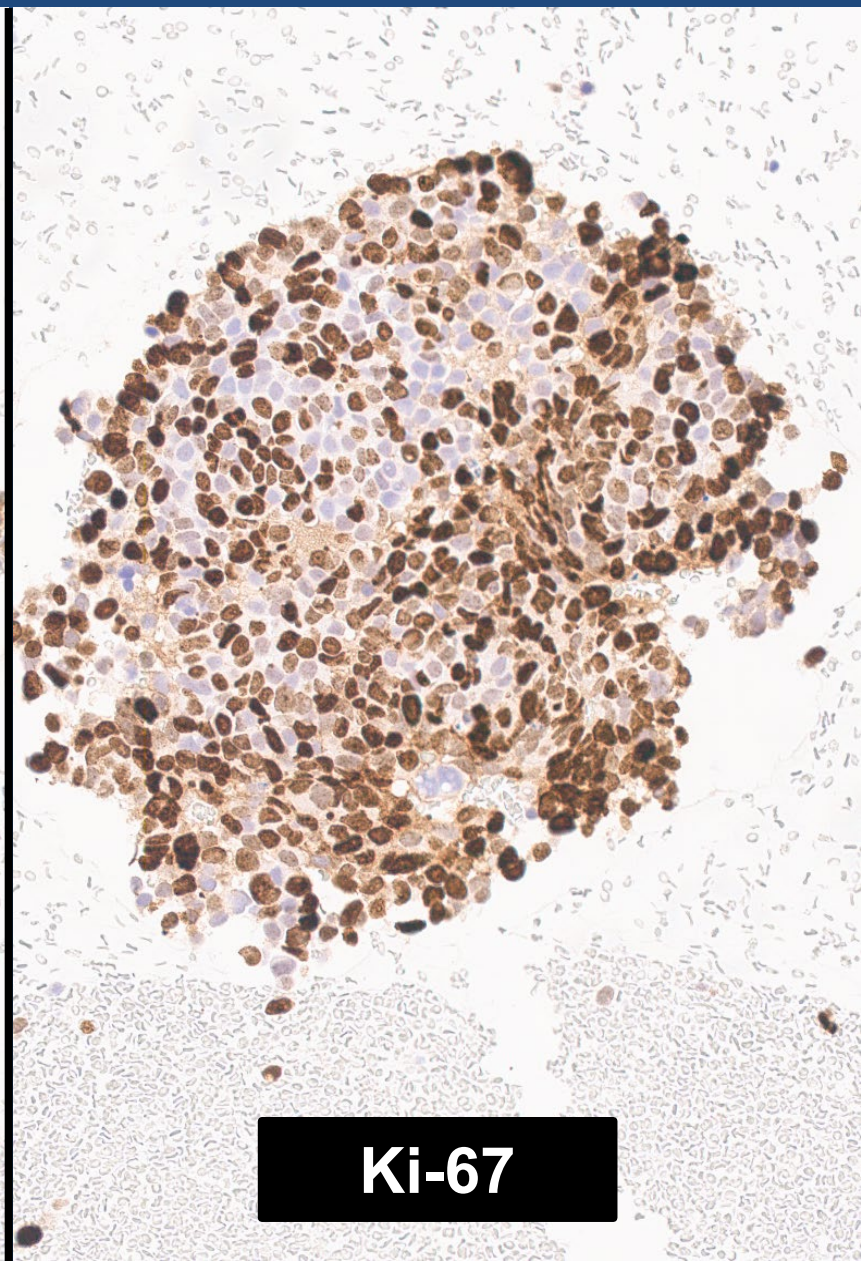
SharkCore Biopsy: Pancreatic Neuroendocrine Tumor



SharkCore Bx: Pancreatic Neuroendocrine Carcinoma

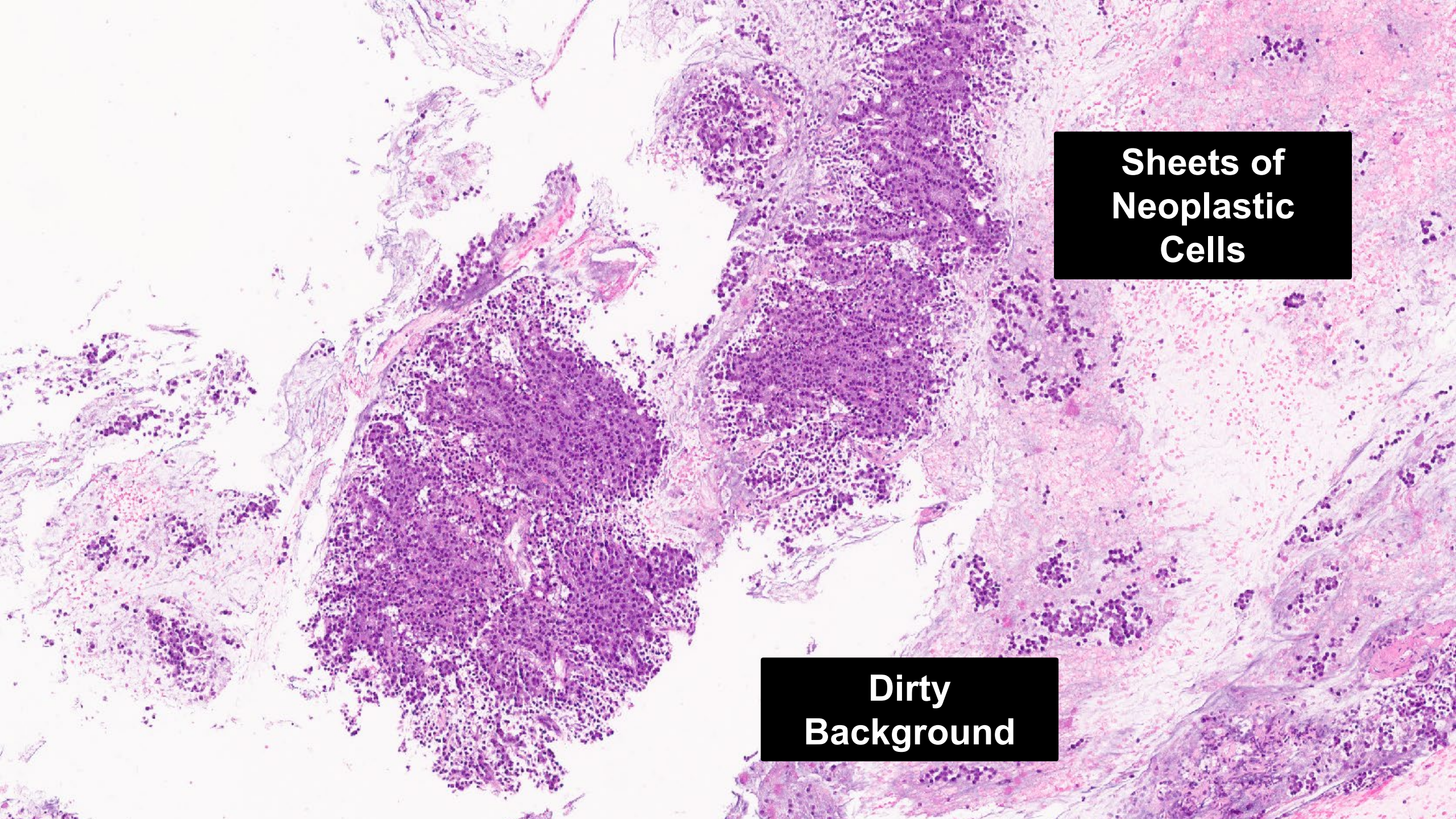


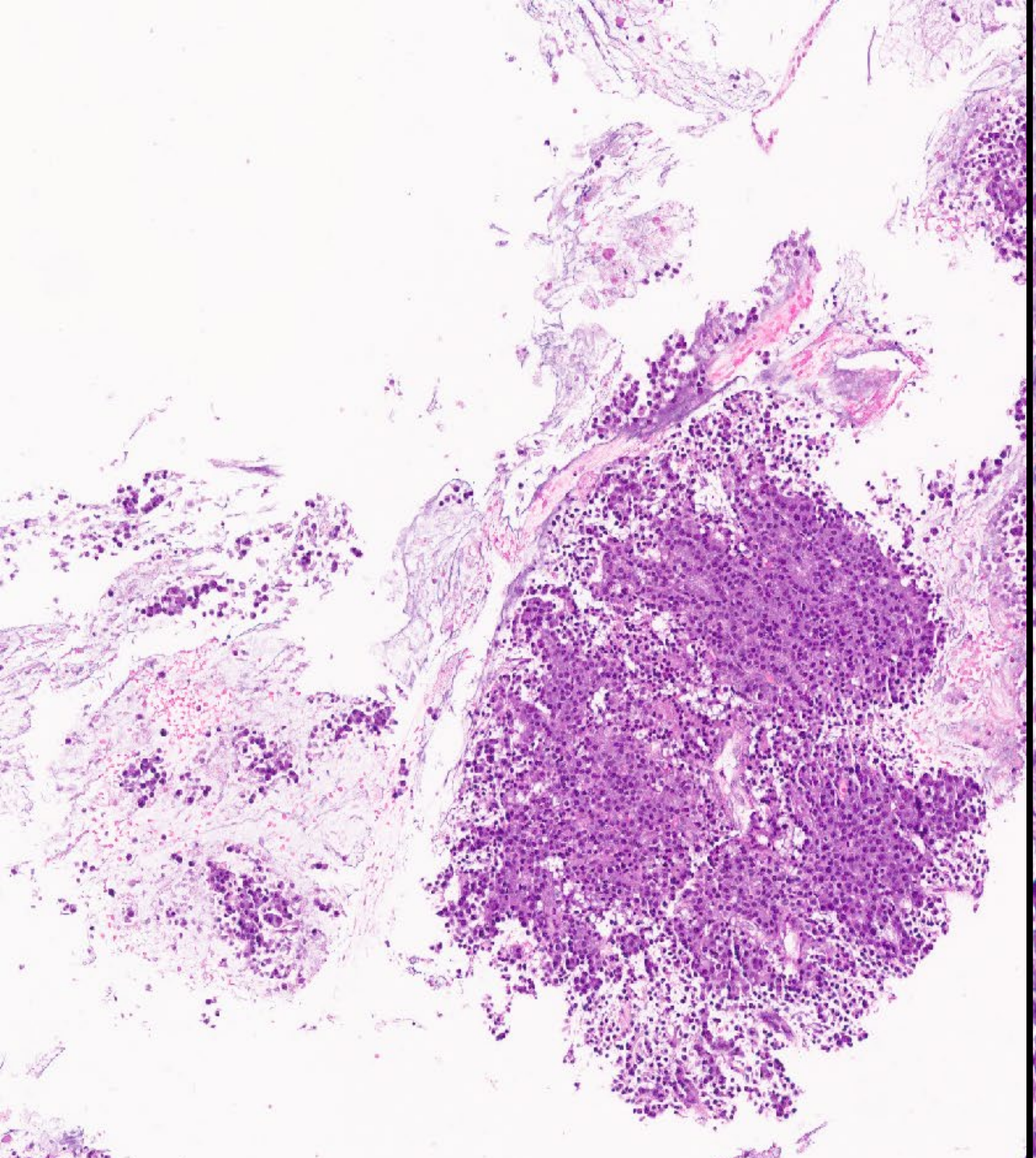


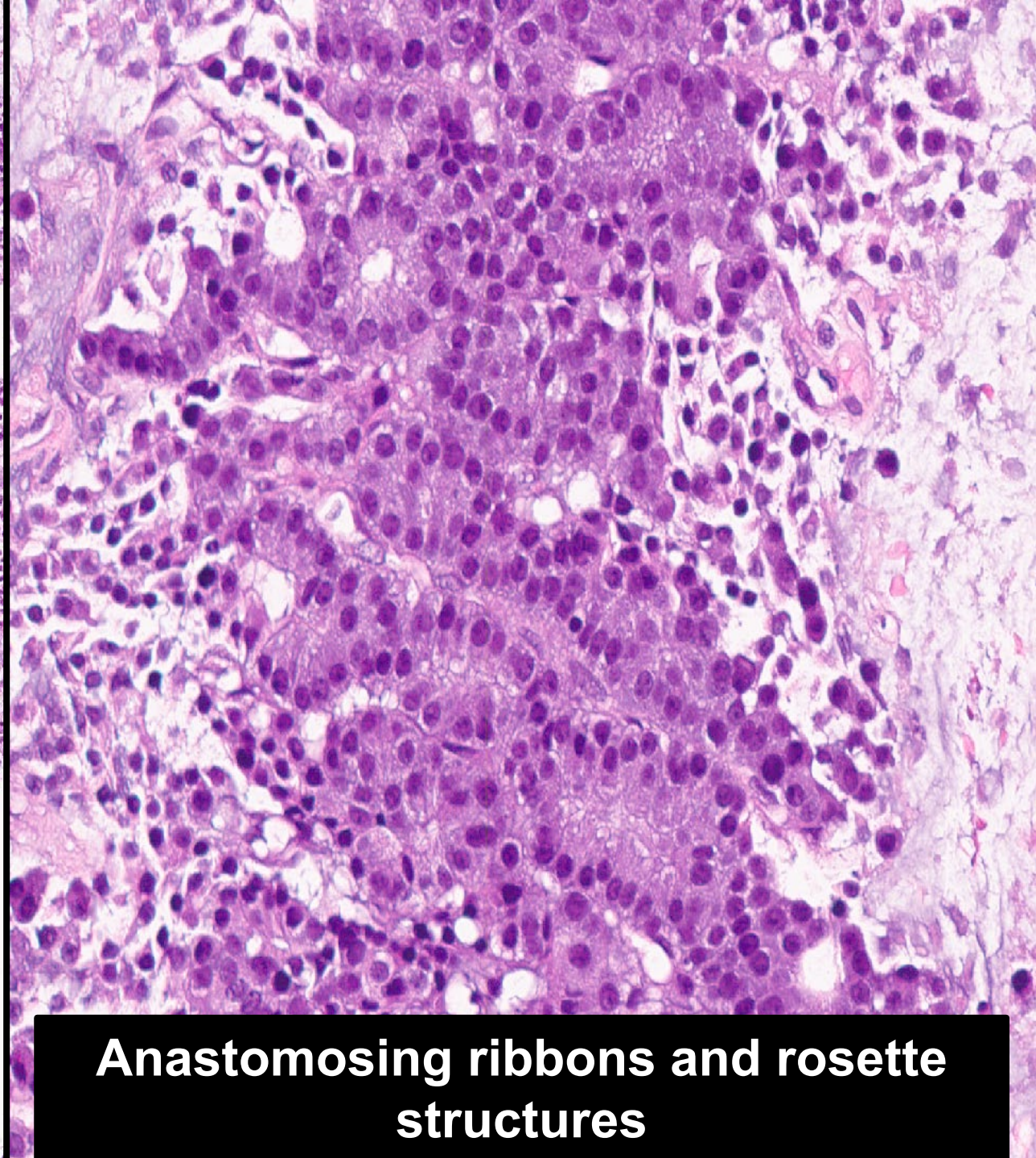


Case 2

- A 65-year-old male presents with abdominal pain, jaundice, and a 10 cm mass centered within the pancreatic head and uncinate.
- The patient also has peripheral petechiae located at his extremities.
- Serum studies for CA19-9 and CEA are within normal limits and a SharkCore™ fine-needle biopsy (FNB) was performed.

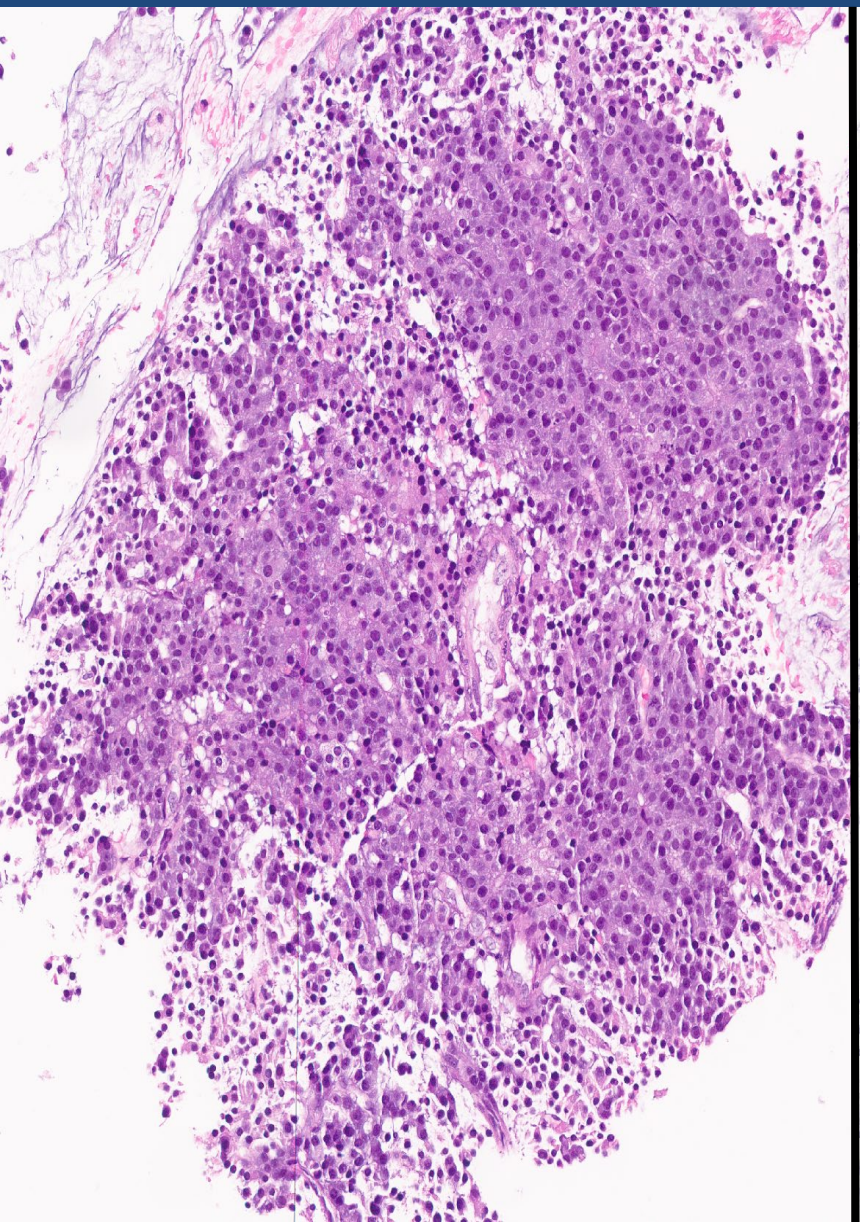

Sheets of Neoplastic Cells
Dirty Background

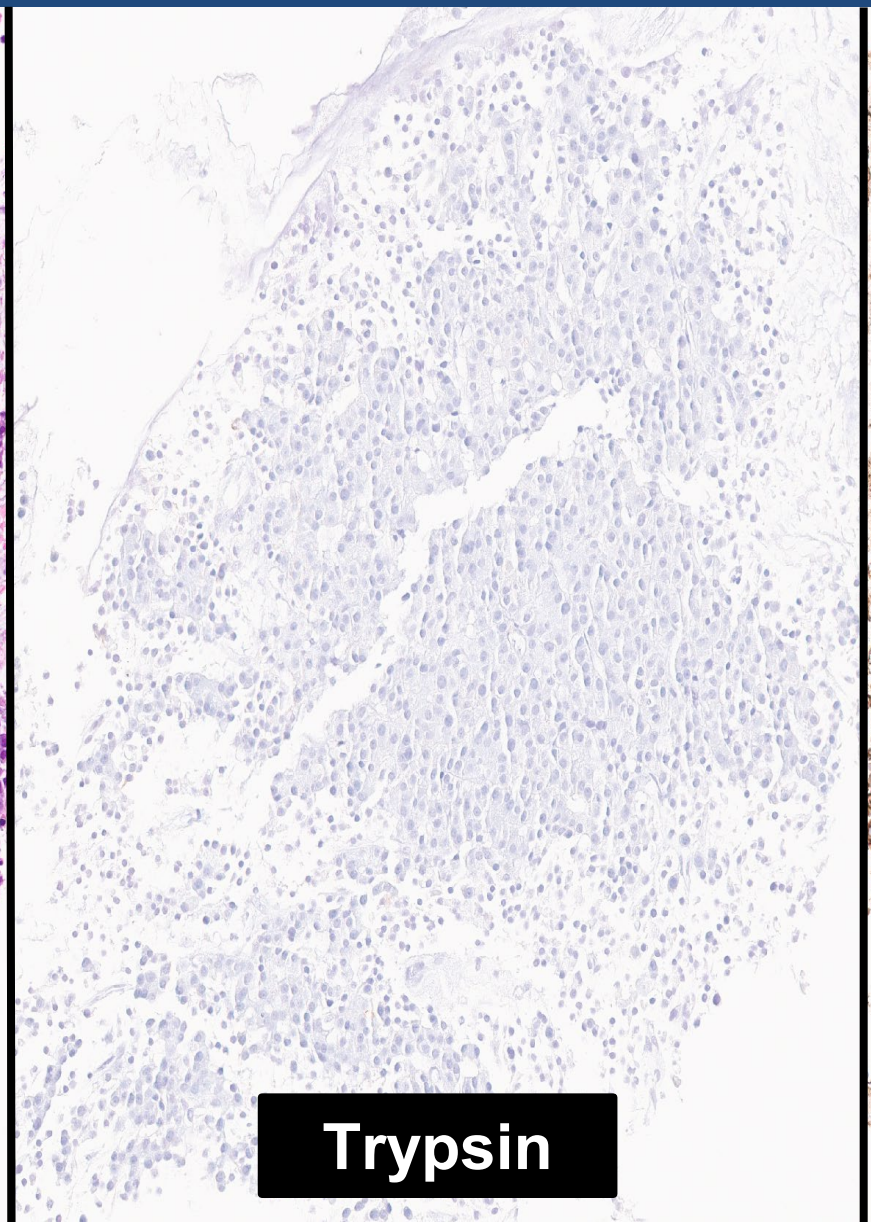


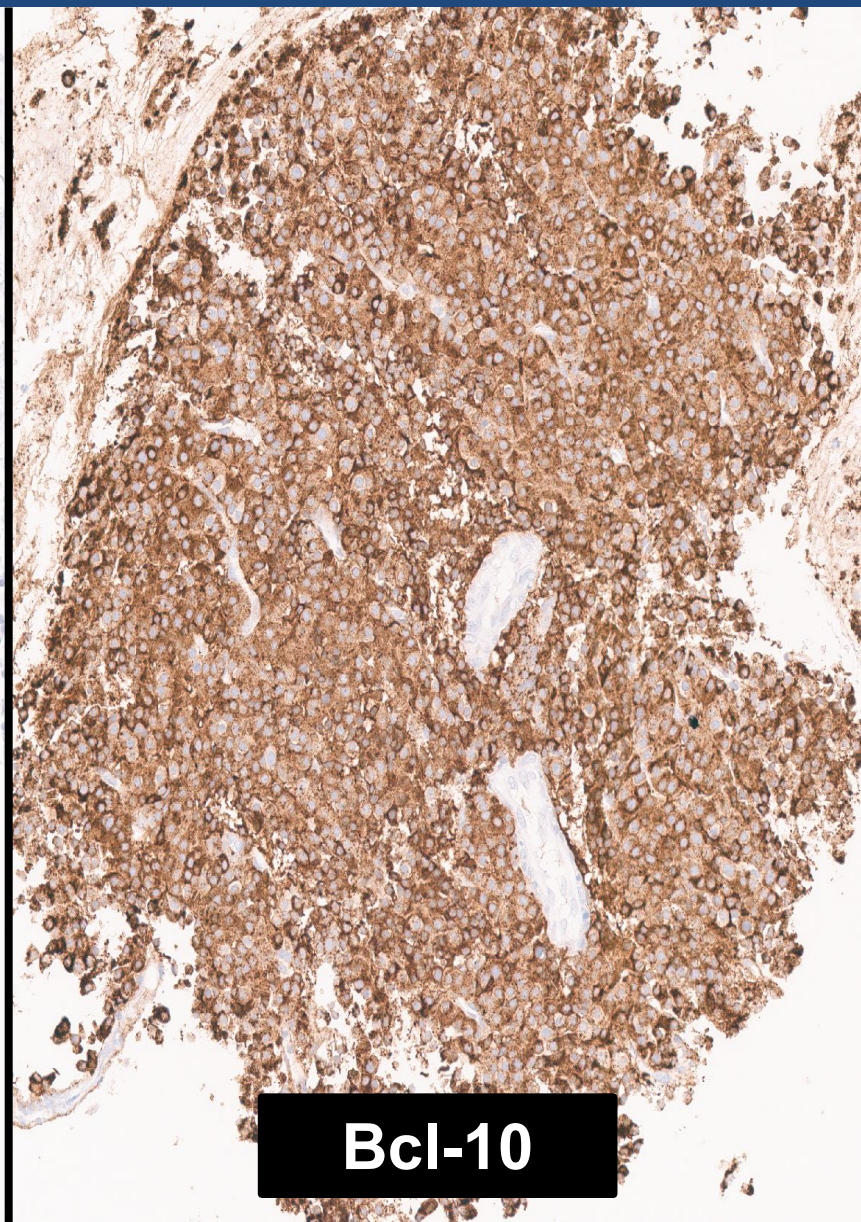


Anastomosing ribbons and rosette structures

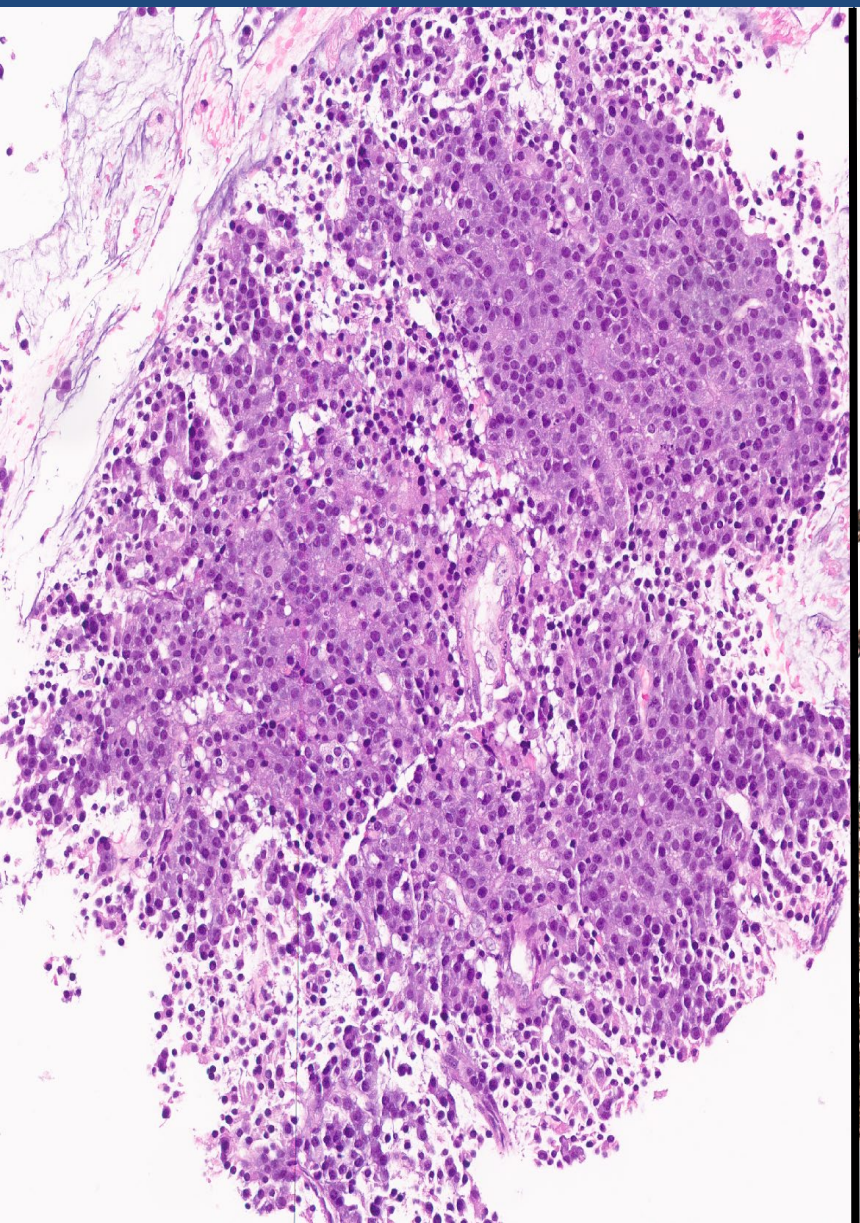
Case 2

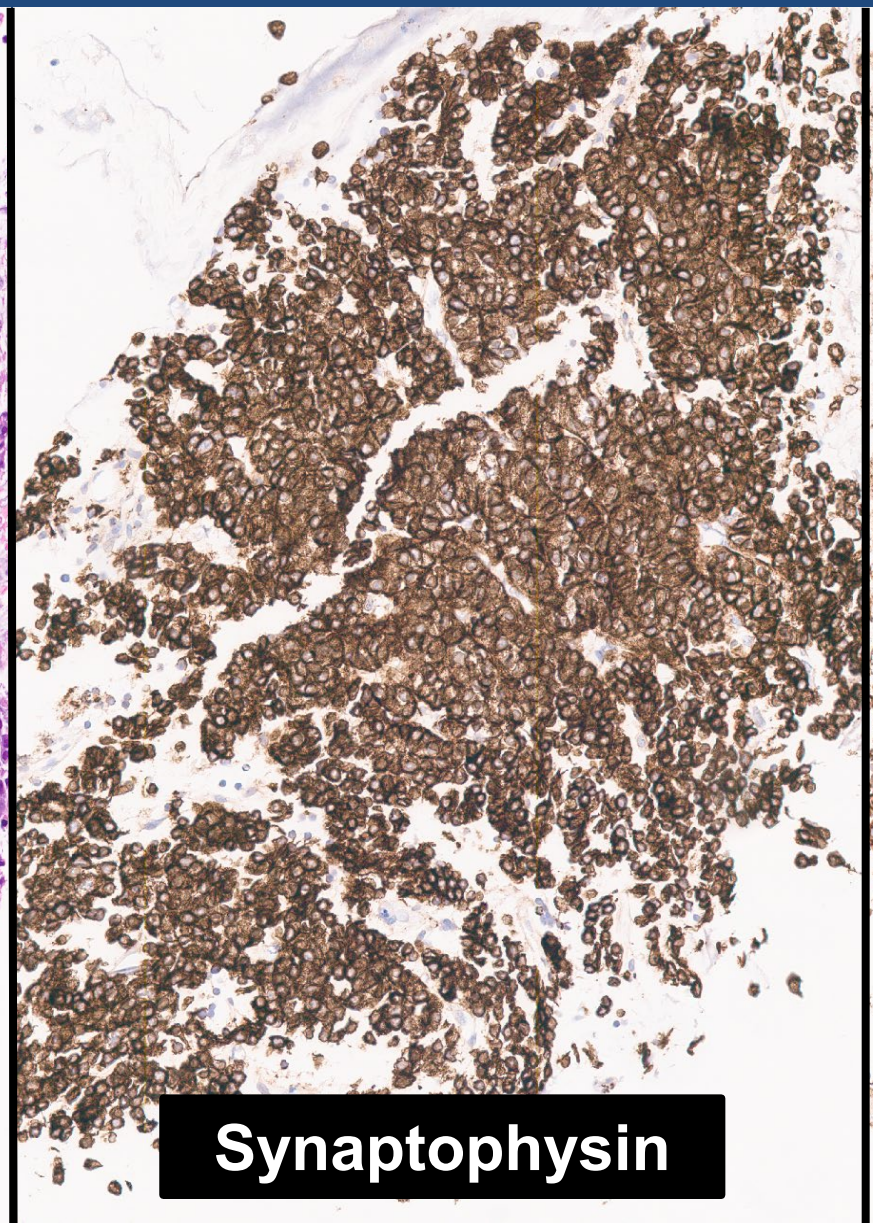


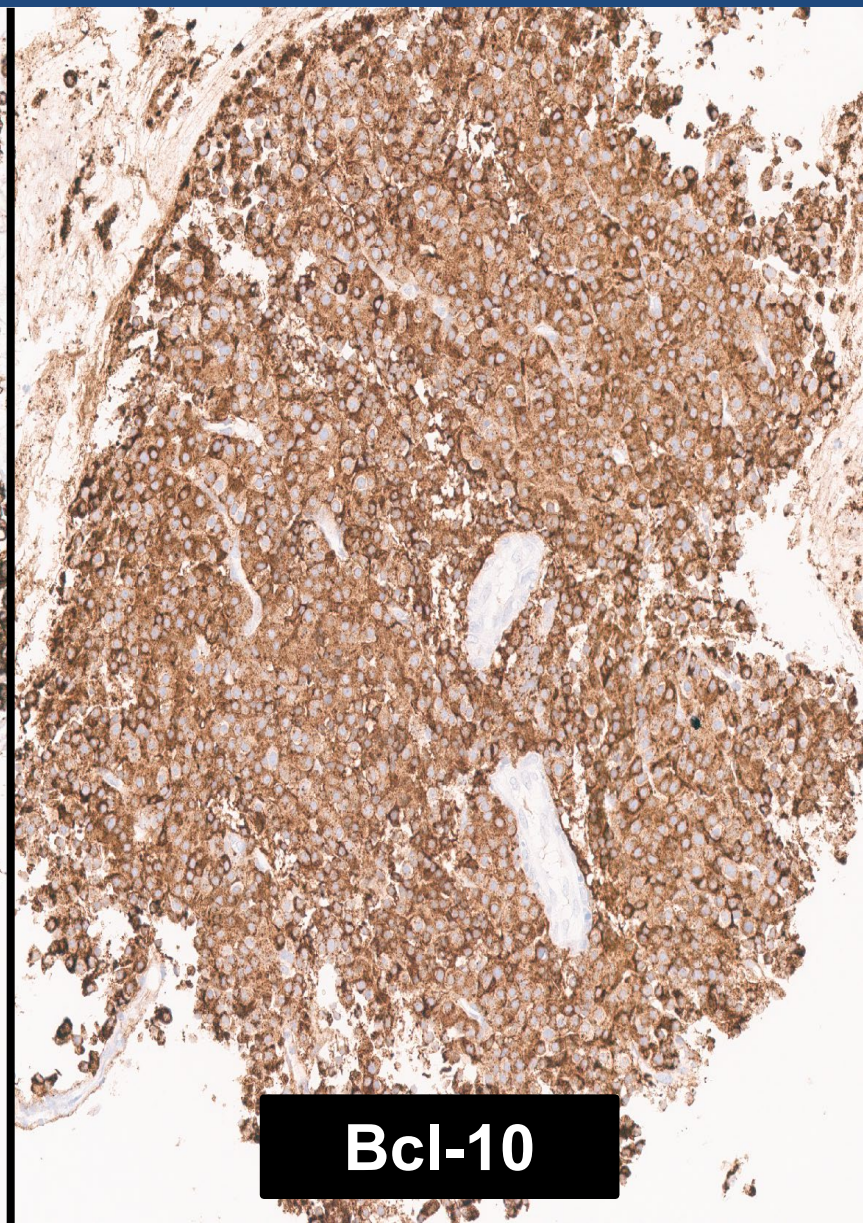




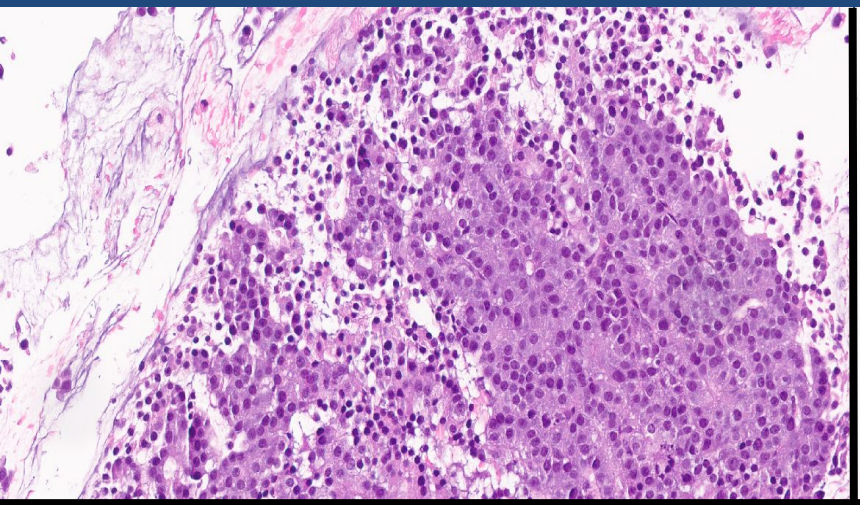
Case 2

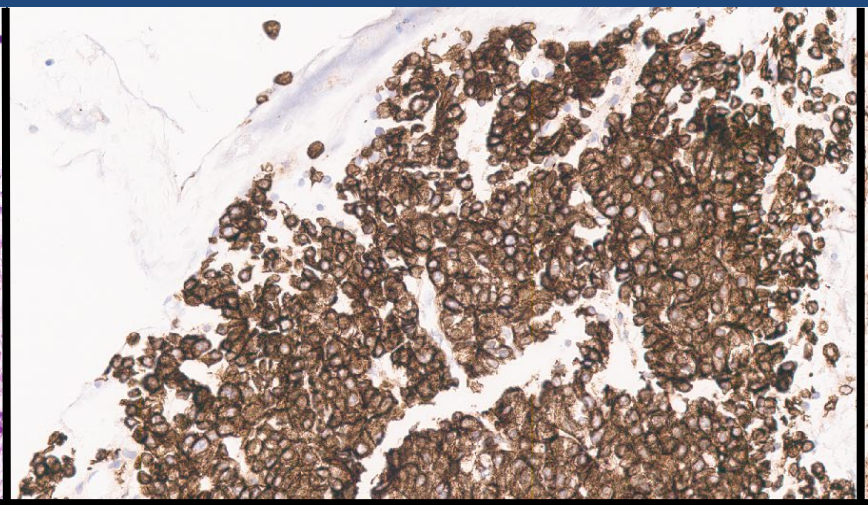


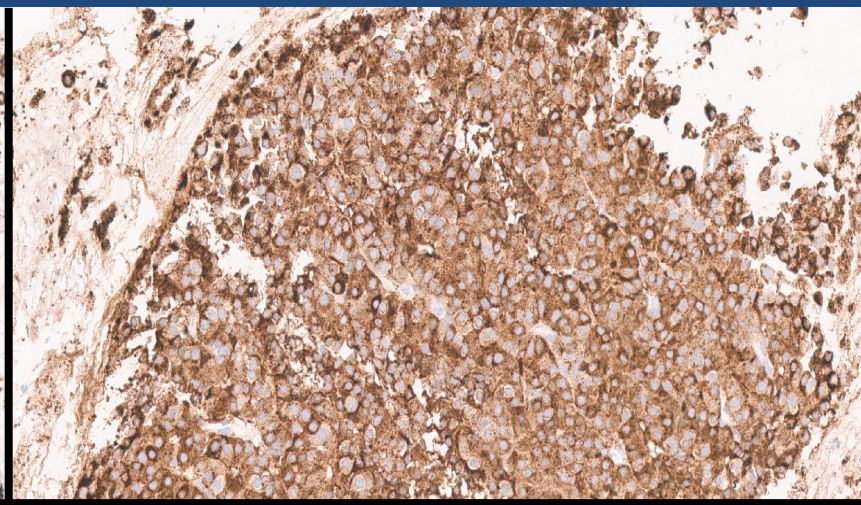




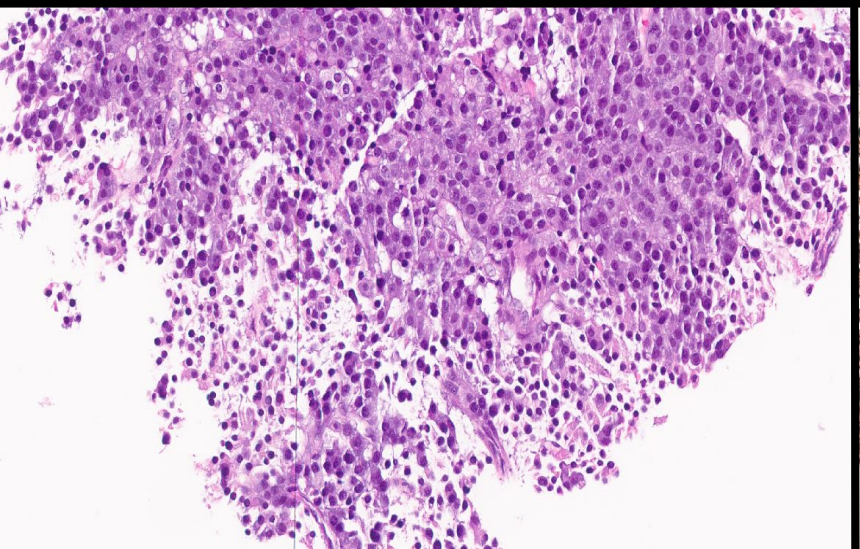
Case 2







Acinar Cell Carcinoma



MiNEN

- Mixed Neuroendocrine-Nonneuroendocrine Neoplasm (MiNEN) are rare pancreatic malignancies and consist of:
  - Both endocrine and exocrine components (ductal, acinar, or both).
  - At least 30% for each component

- Preoperative setting: Poorly-differentiated carcinoma with acinar and neuroendocrine features (see comment).

Take Home Points: Case 2

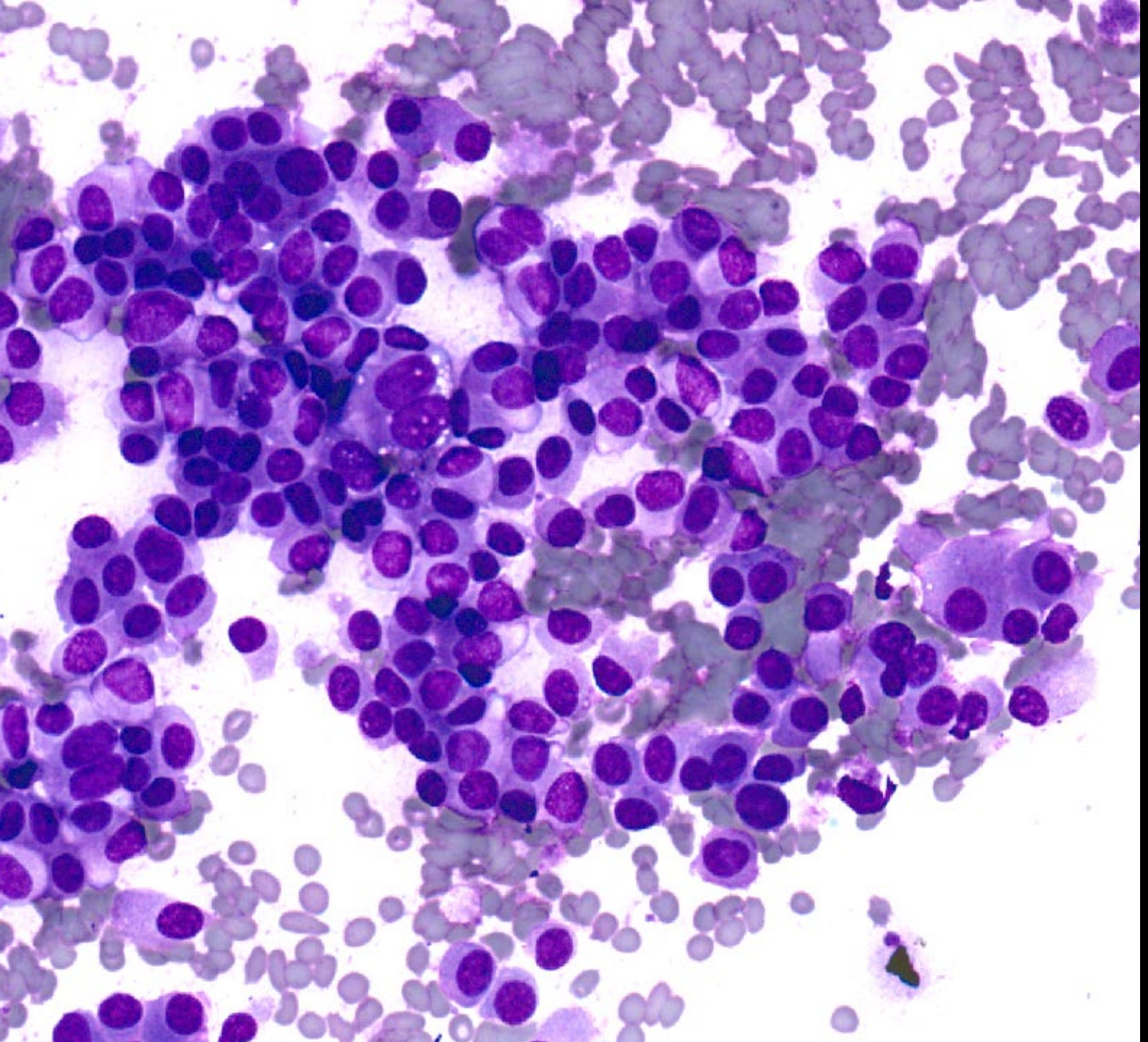
- Next-Generation Needles has improved our ability to do ancillary studies on cellular neoplasms
- Differential Diagnosis of Cellular Neoplasms:
    - Acinar Cell Carcinoma
    - Solid-Pseudopapillary neoplasm
    - Pancreatic Neuroendocrine Tumor
    - Pancreatic Neuroendocrine Carcinoma
    - Mixed Neoplasms
    - Pancreatic Ductal Adenocarcinoma*

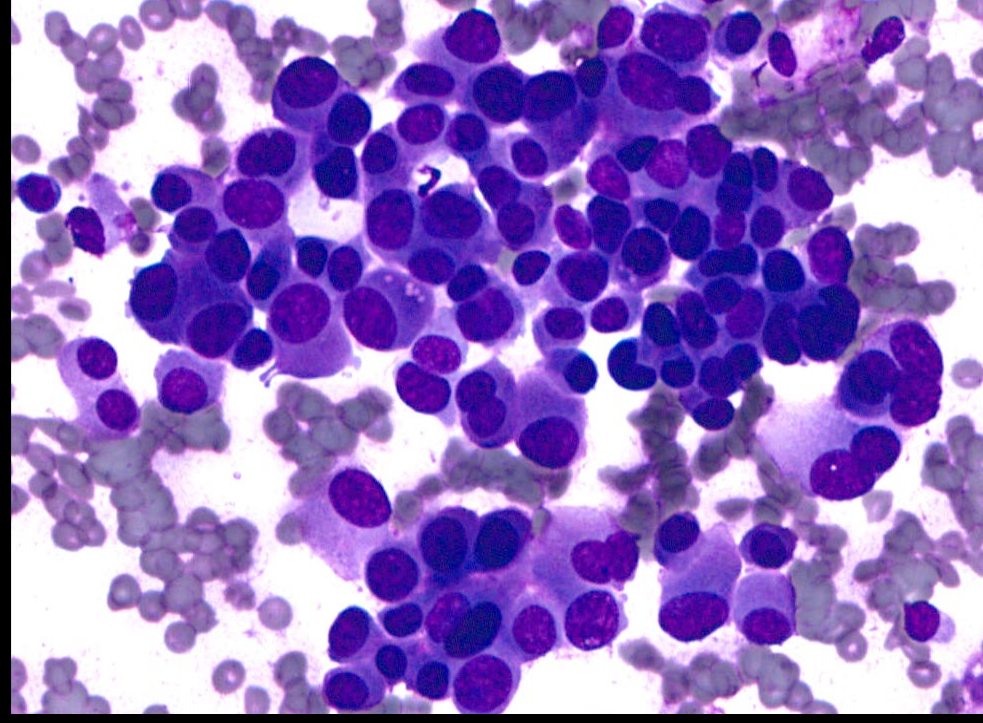
Take Home Points: Case 2

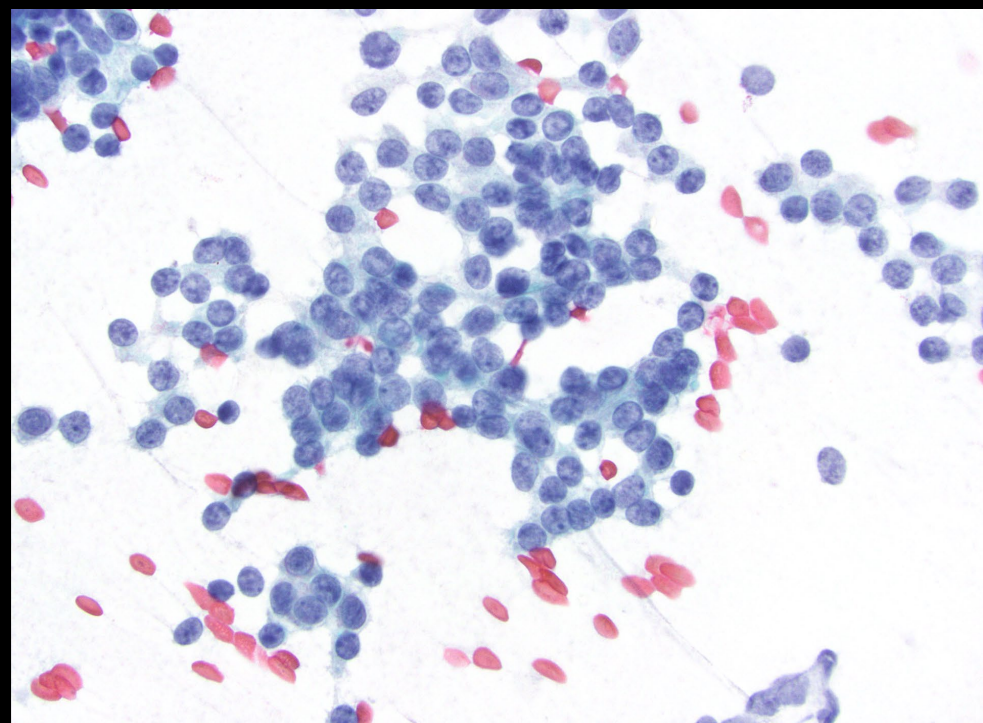
Features	ACC	PB	SPN	PanNET	PanNEC
Pathology	Rosettes; Prominent Nucleoli	Squamoid Nests	Plasmacytoid w/ Globules; Thin Vessels	Plasmacytoid w/ Stippled Chromatin	Plasmacytoid w/ Mitotic Figures
Bcl-10	Positive	Positive	Negative	Negative	Negative
Beta-catenin	Membran.	Squamoid Nests	Nuclear & Membran. (Diffuse)	Membran.	Membran.
LEF1	Negative	Squamoid Nests	Nuclear (Diffuse)	Negative	Negative
Synapto.	+/-	+/-	Positive	Positive	Positive
Ki-67*	>20%	>20%	>3%	Most <20%	>20%

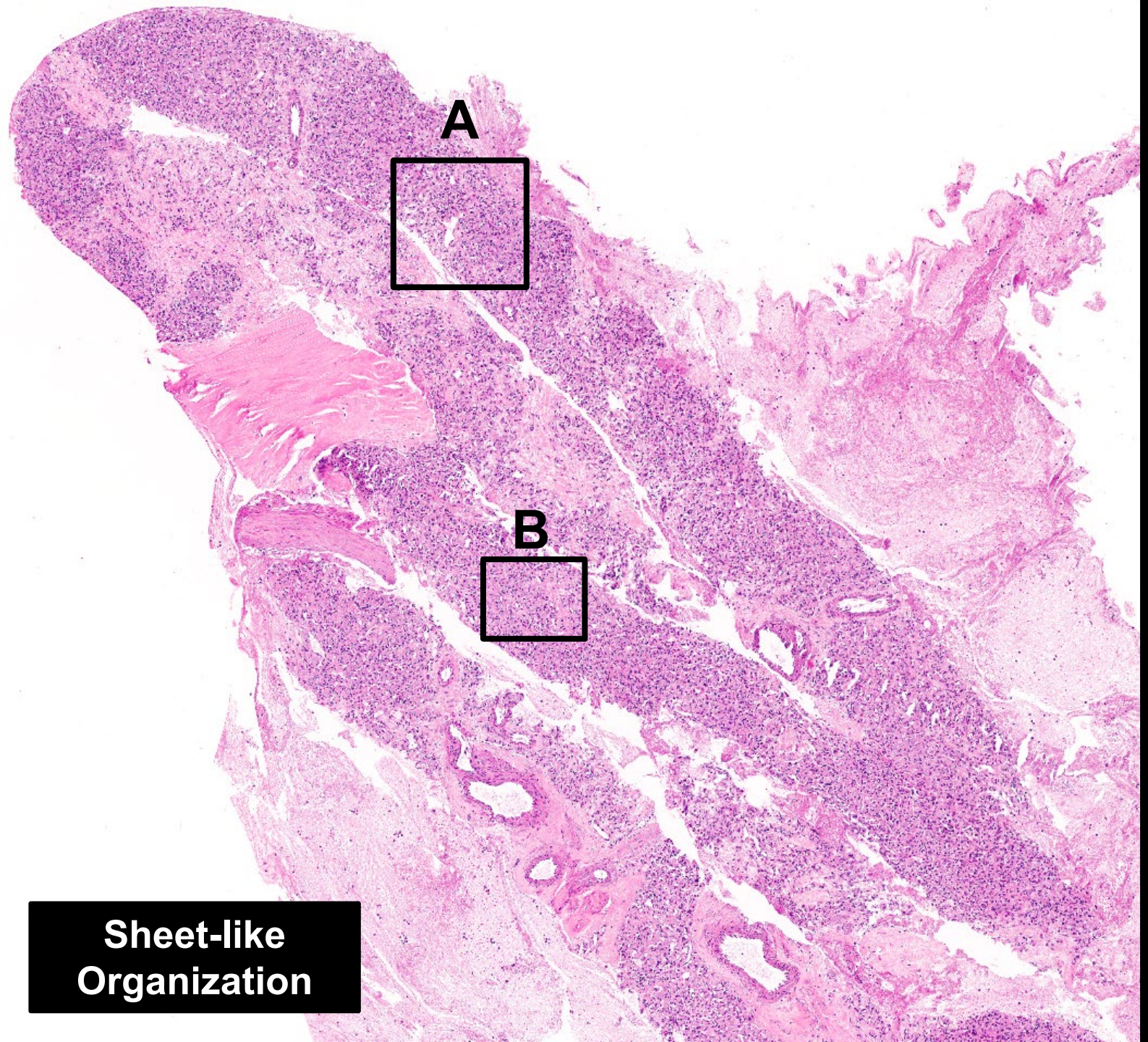
Case 3

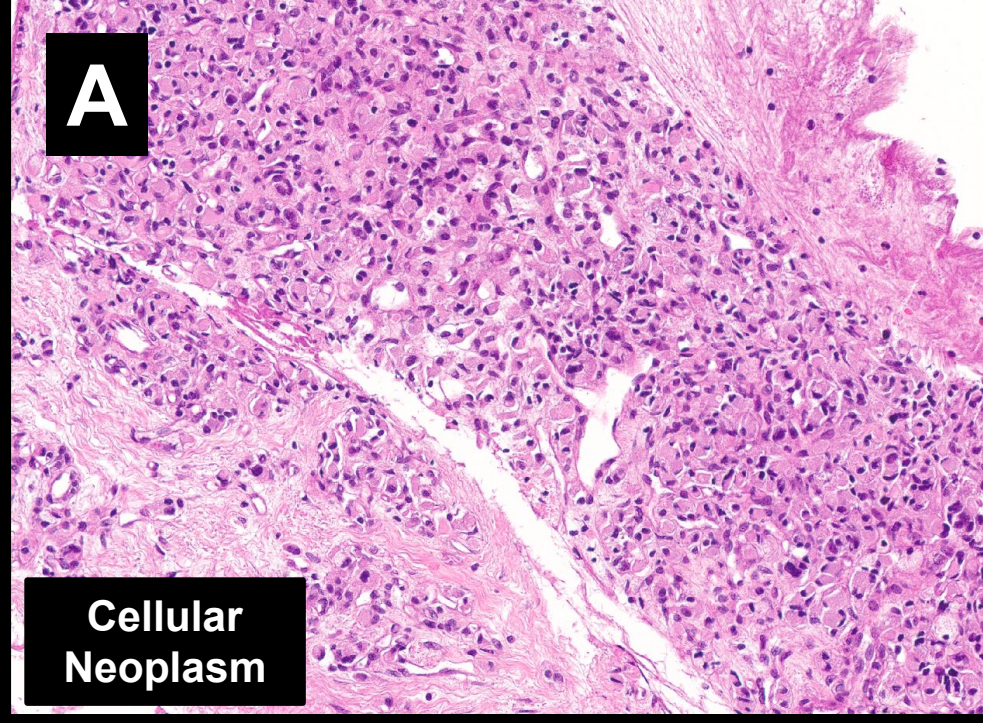
- A 54-year-old female with a history of breast cancer presents with an incidentally identified mass in the pancreatic tail and no other lesions by PET scan.
- The pancreatic tail mass measured 1.9 cm and was hypervascular within a peripheral distribution.
- A fine-needle aspirate (FNA) and a SharkCore™ fine-needle biopsy (FNB) were performed of the pancreatic mass.

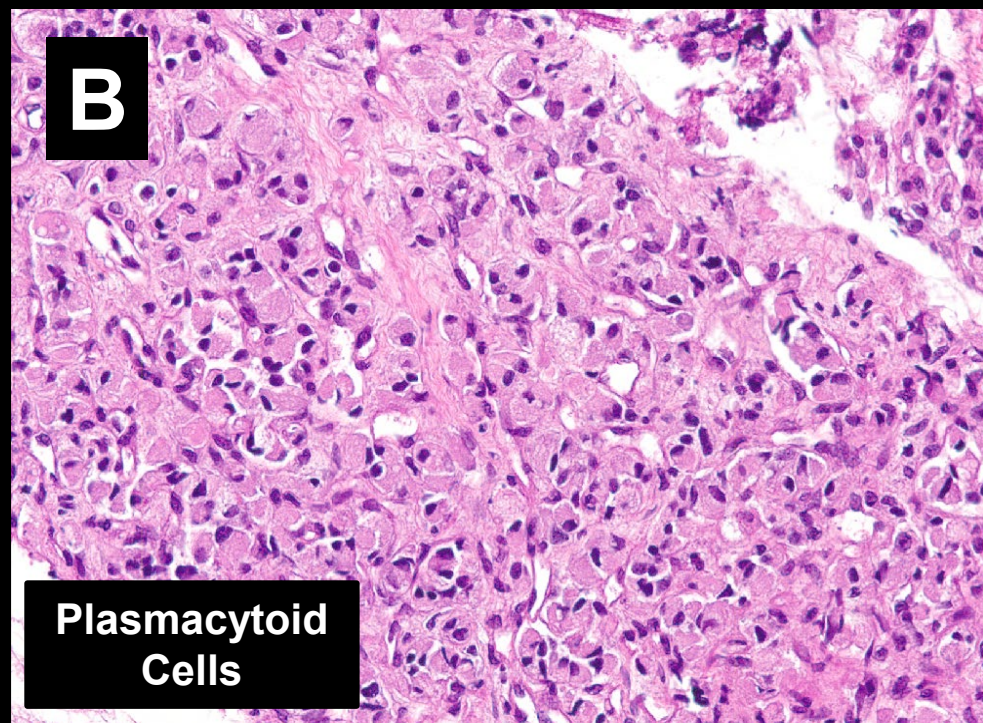


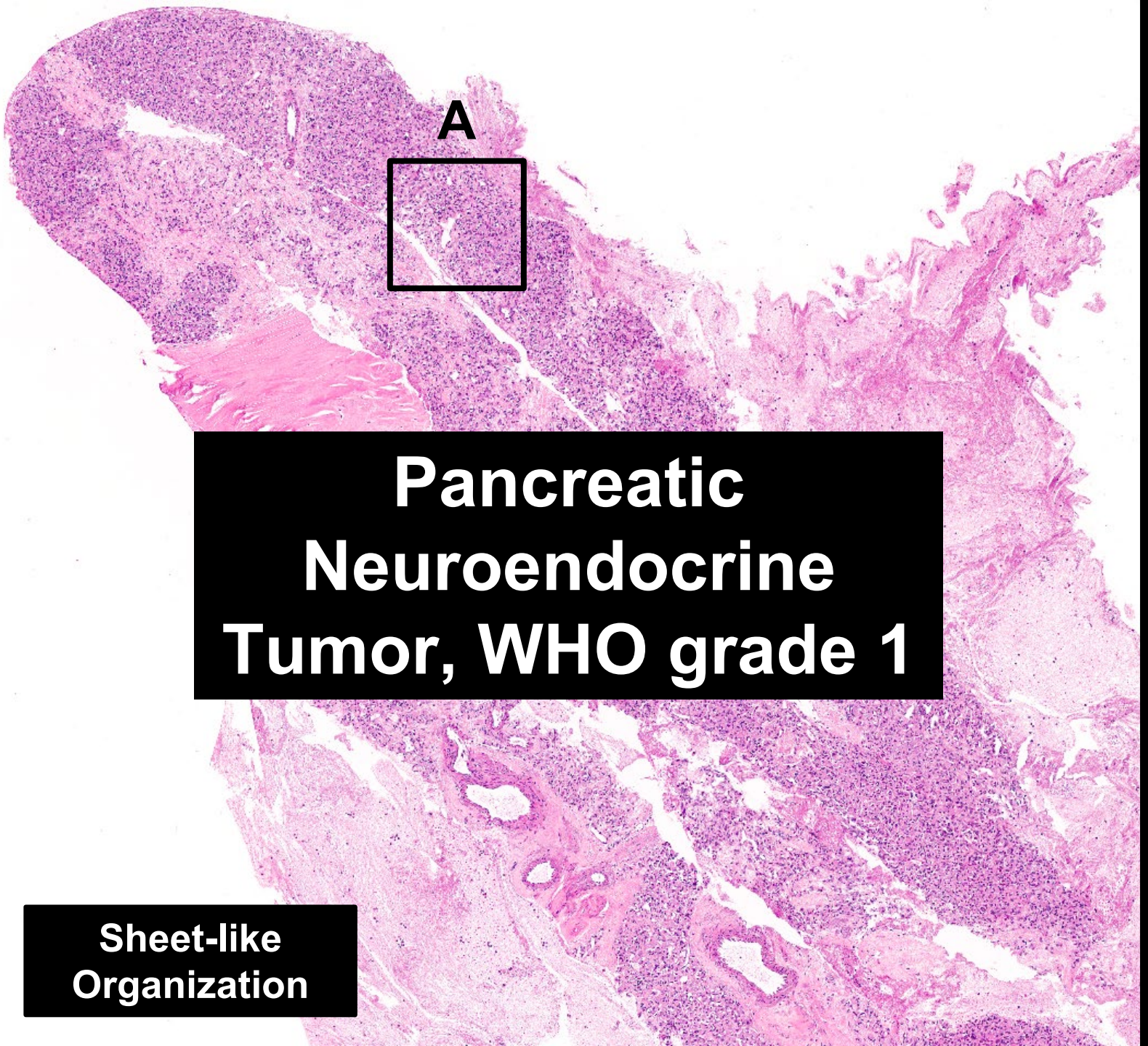





A
B
Sheet-like Organization

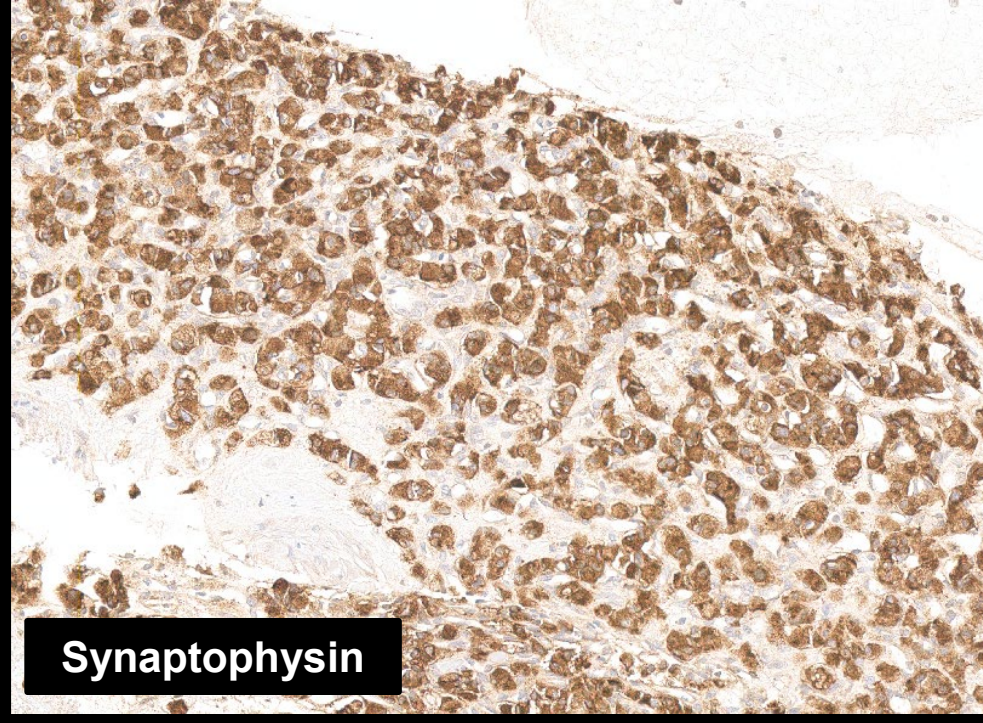

A
Cellular Neoplasm


B
Plasmacytoid Cells

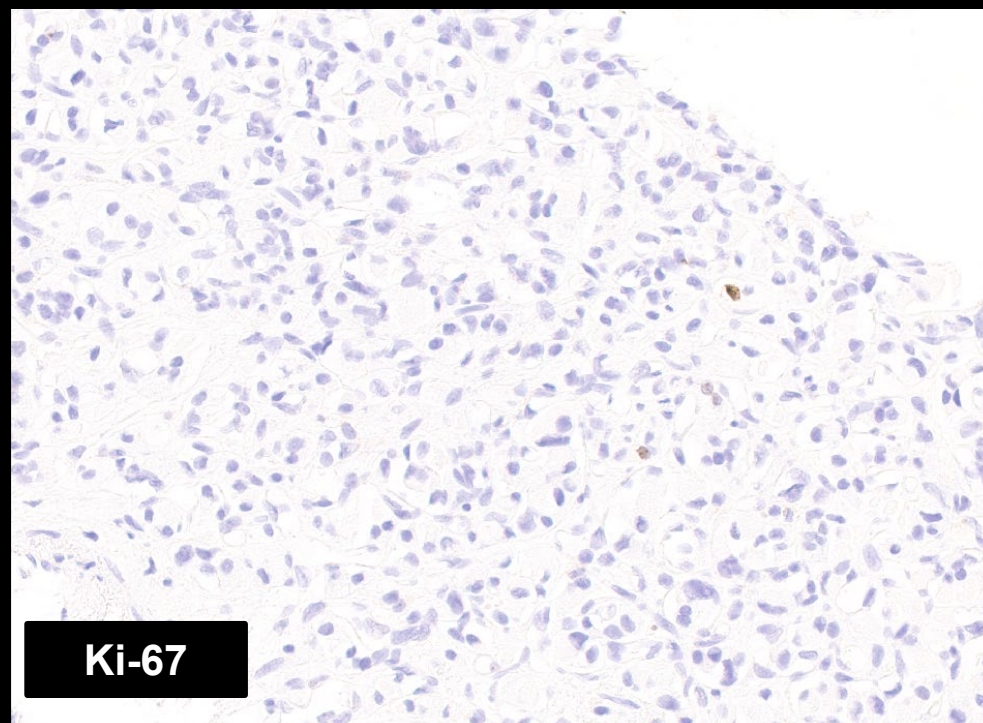


Pancreatic Neuroendocrine Tumor, WHO grade 1

Sheet-like Organization



Synaptophysin



Ki-67

Case 3: Pancreatic Neuroendocrine Tumor

- The majority of PanNETs are discovered incidentally, localized to the pancreas and often indolent in nature.
- A subset of PanNETs may behave aggressively and metastasize widely.
- Current prognostic parameters and systems include tumor size (2 cm per NCCN recommendations) and WHO grade.
- WHO grade (Ki-67 & mitotic index) may not accurately reflect the clinical behavior of these neoplasms (especially with limited material) – report what you see with a comment.

Pancreatic Neuroendocrine Tumors

- Whole-exome and whole-genome sequencing studies have focused on identifying recurrent genetic alterations in **primary** PanNETs.

DAXX/ATRX, *MEN1*, and mTOR Pathway Genes Are Frequently Altered in Pancreatic Neuroendocrine Tumors

Yuchen Jiao,[1*] Chanjuan Shi,[2*] Barish H. Edil,[3] Roeland F. de Wilde,[2] David S. Klimstra,[4] Anirban Maitra,[5] Richard D. Schulick,[3] Laura H. Tang,[4] Christopher L. Wolfgang,[3] Michael A. Choti,[3] Victor E. Velculescu,[1] Luis A. Diaz Jr.,[1,6] Bert Vogelstein,[1] Kenneth W. Kinzler,[1†] Ralph H. Hruban,[5†] Nickolas Papadopoulos[1†]

ARTICLE

doi:10.1038/nature21063

Whole-genome landscape of pancreatic neuroendocrine tumours

A list of authors and their affiliations appears at the end of the paper

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- The most frequently mutated genes are *MEN1*, *DAXX* and *ATRX*.

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- The most frequently mutated genes are *MEN1*, *DAXX* and *ATRX*.
- Alterations in *DAXX* and *ATRX* lead to loss of protein expression.

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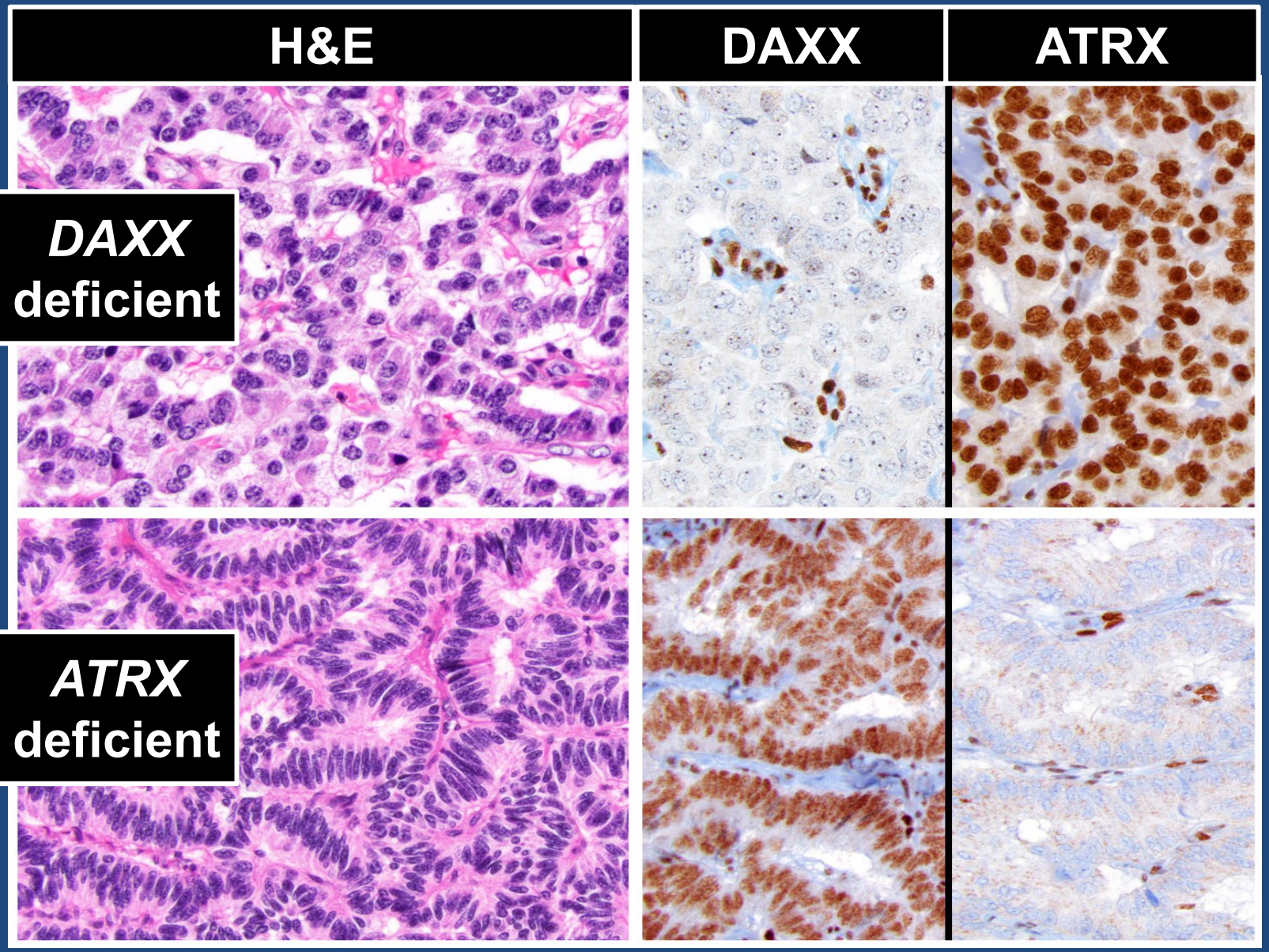
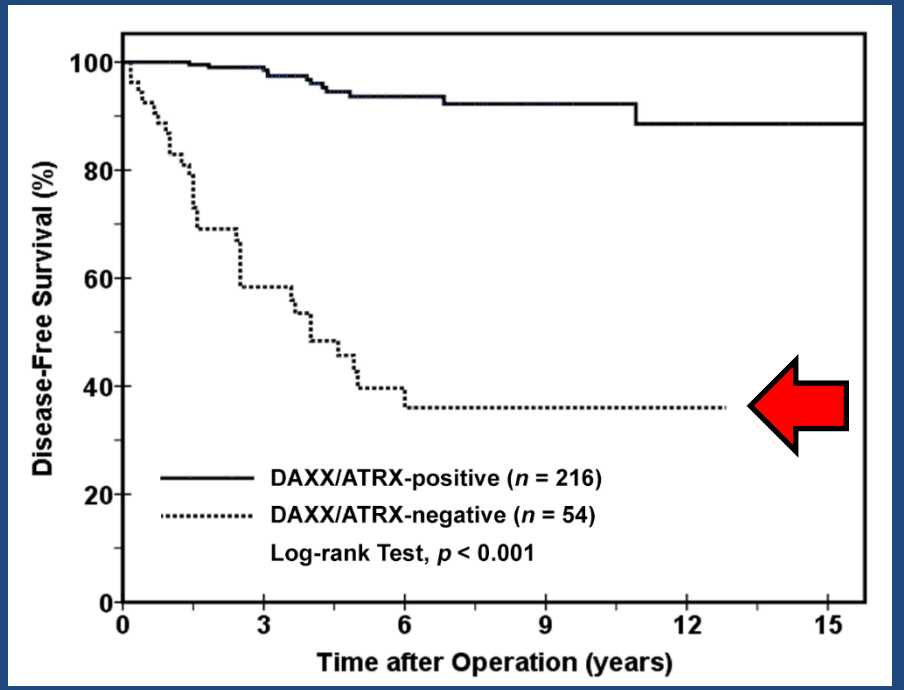
Loss of DAXX/ATRX: Poor Prognosis

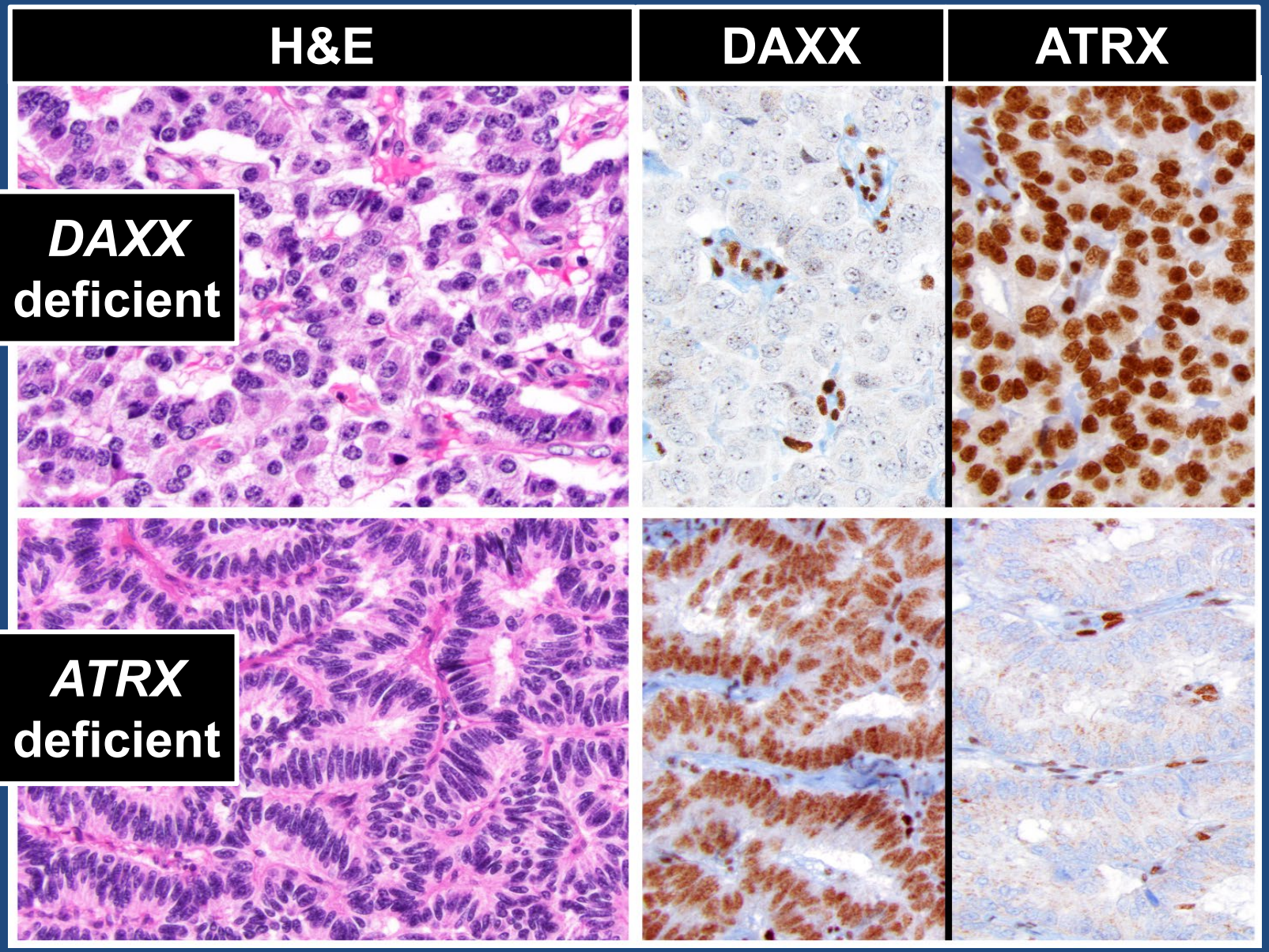


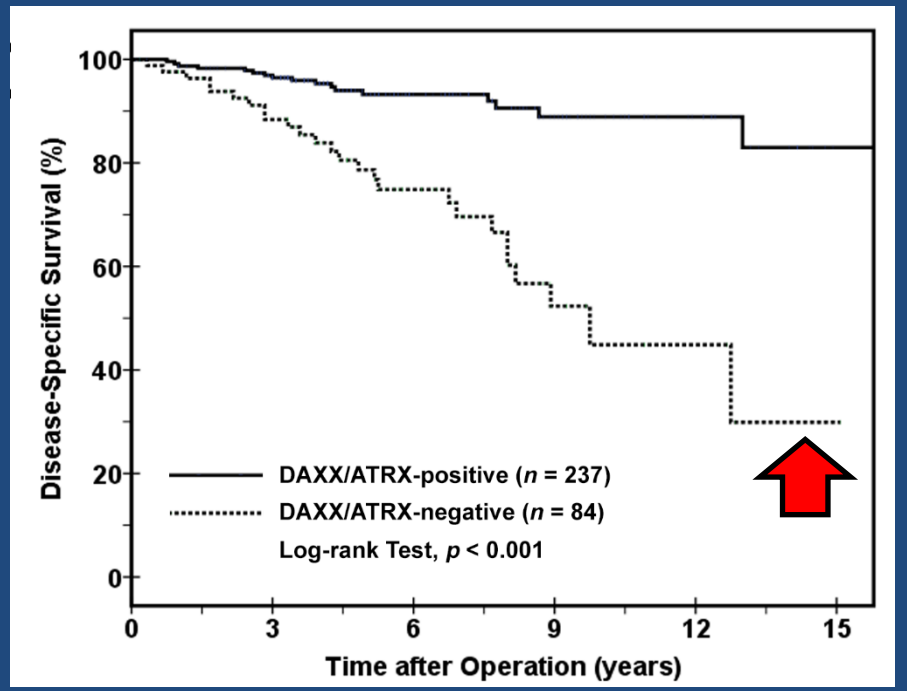
Patients with DAXX/ATRX-negative PanNETs have a shorter disease-free survival.



Singhi et al. Clin Cancer Res 2017.

Loss of DAXX/ATRX: Poor Prognosis





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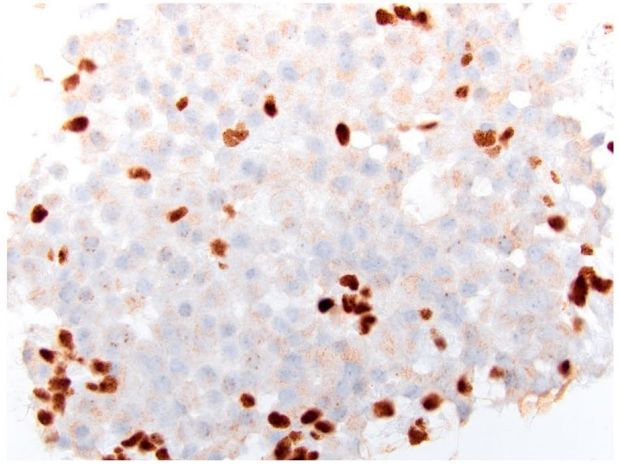
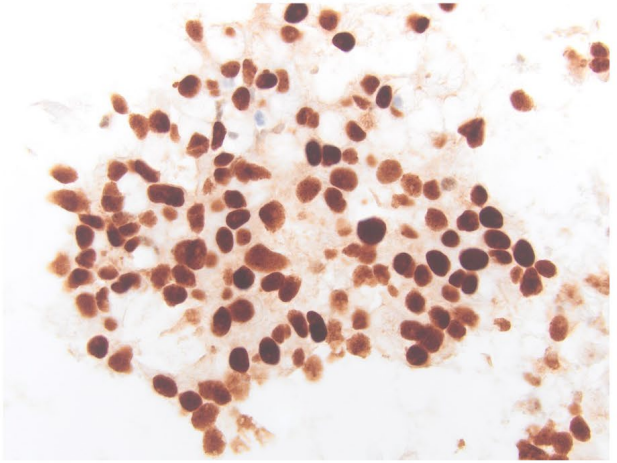
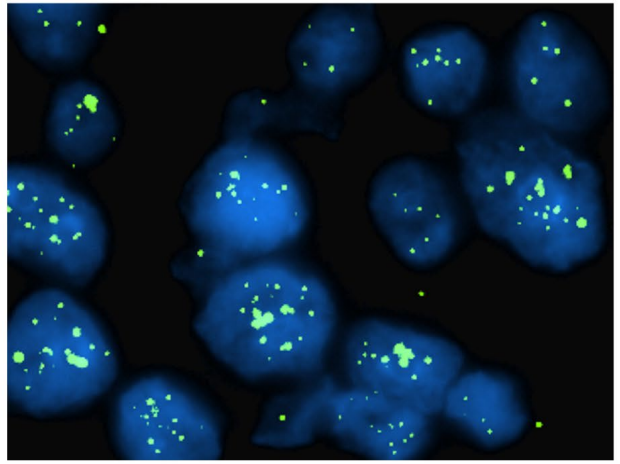
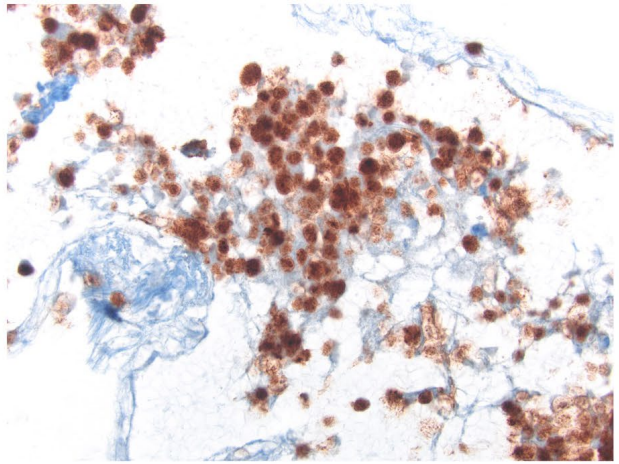
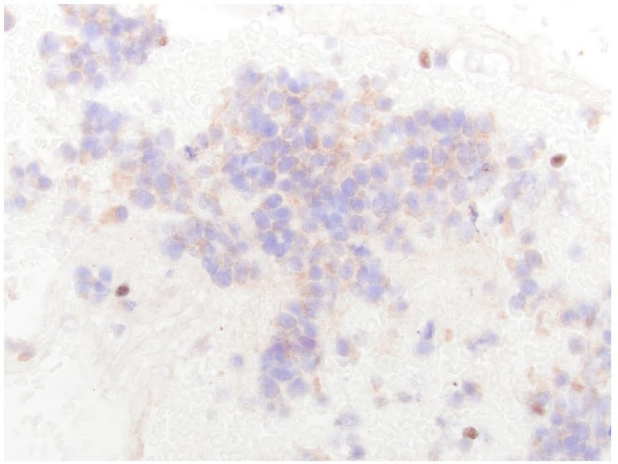
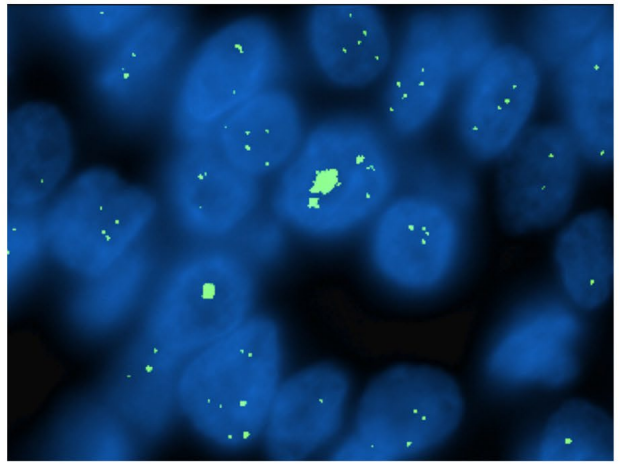
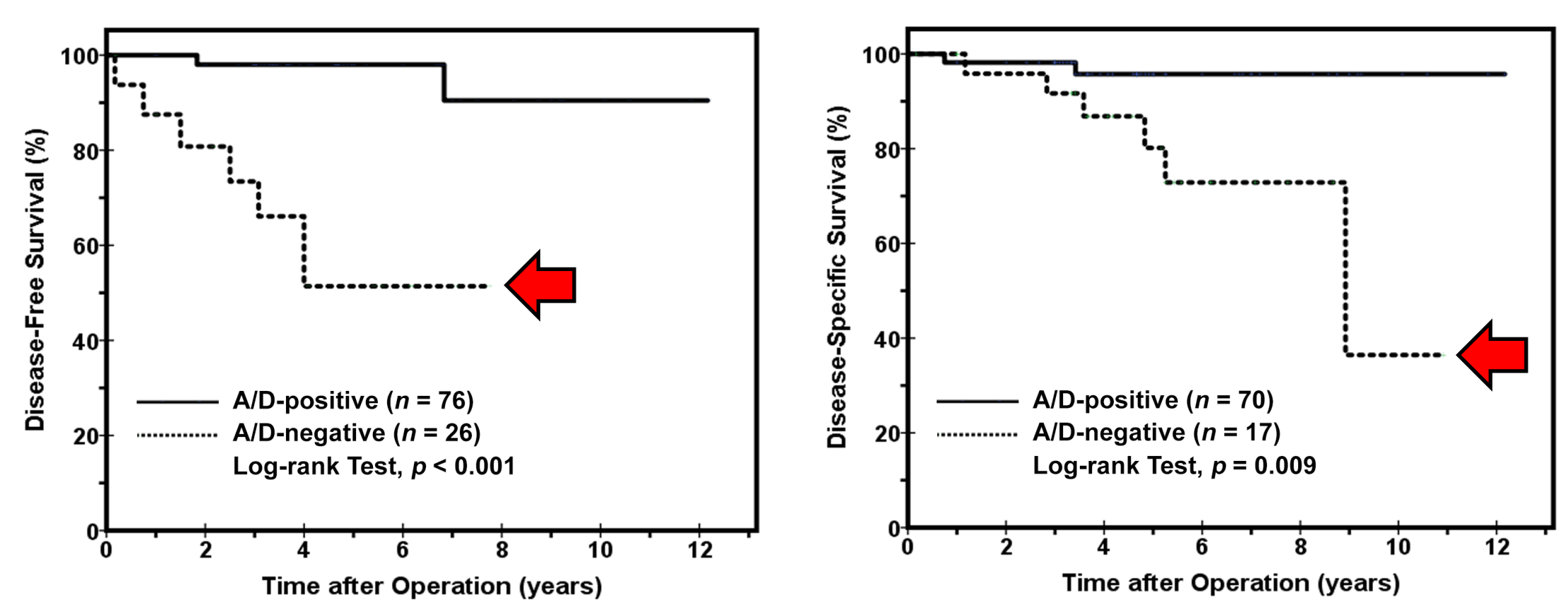
Singhi et al. Clin Cancer Res 2017.

PanNETs: EUS-FNA/B Cell Blocks

H&E	ATRX	DAXX	Telomere FISH
ATRX deficient			
DAXX deficient			

Disease-Free & Disease-Specific Survival



Loss of DAXX/ATRX on cytology specimens correlated with poor disease-free and disease-specific survival.

Case 3: Pancreatic Neuroendocrine Tumor

- Current prognostic parameters and systems include tumor size (2 cm per NCCN recommendations) and WHO grade.
- Remember: the patient's PanNET was 1.9 cm in size by EUS and based on 2019 WHO criteria, the patient's PanNET was graded as low-grade (G1).

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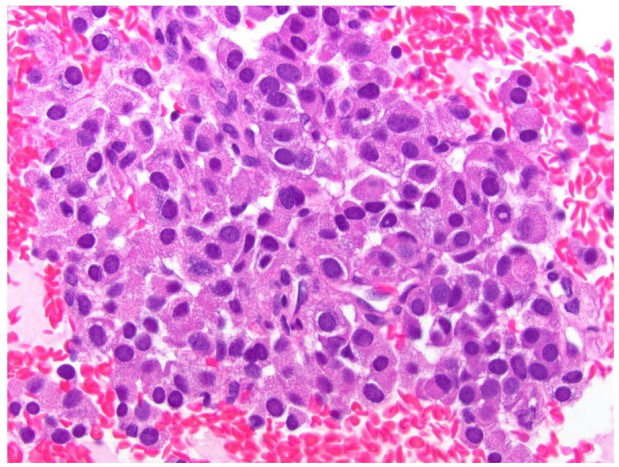
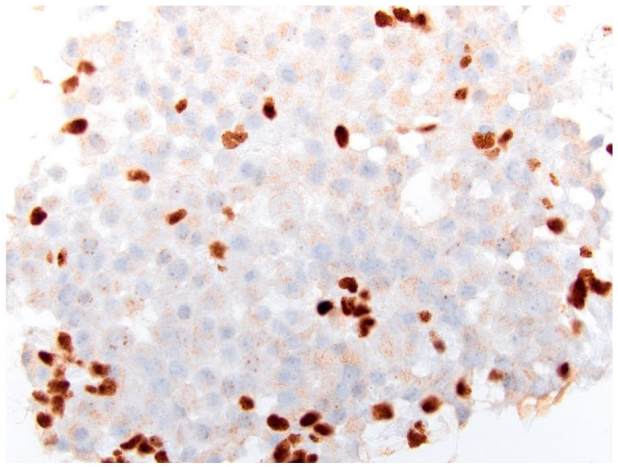
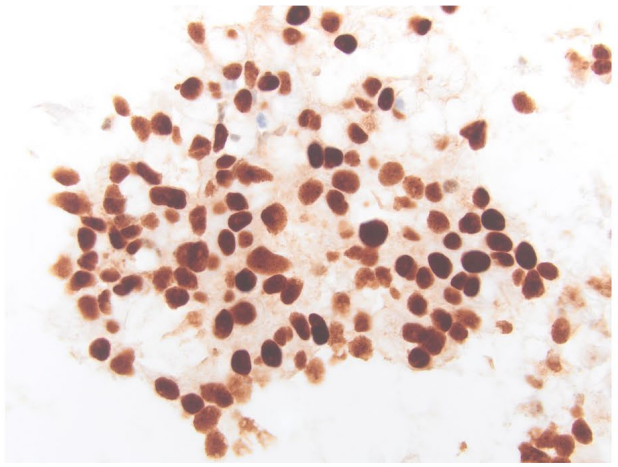
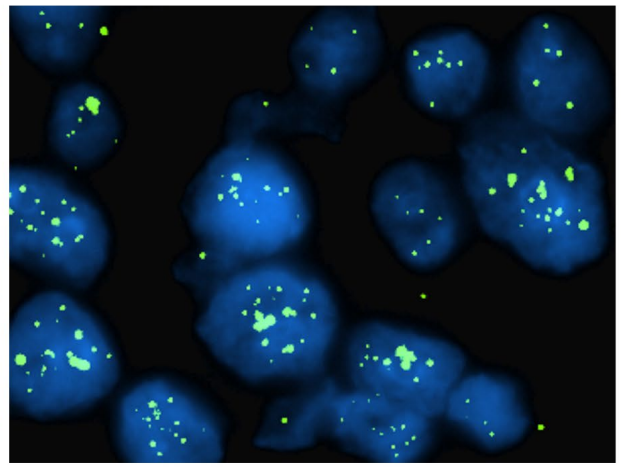
H&E	ATRX	DAXX	Telomere FISH

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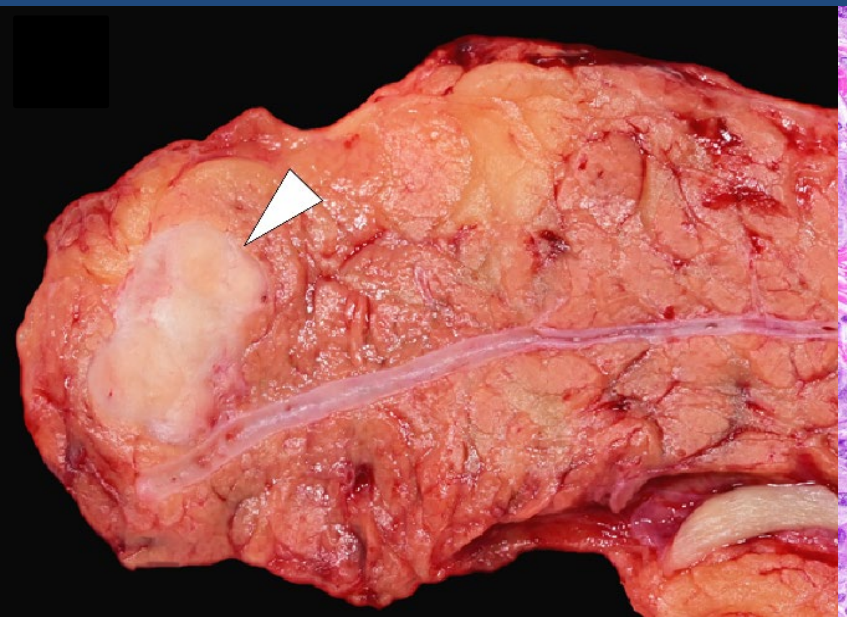
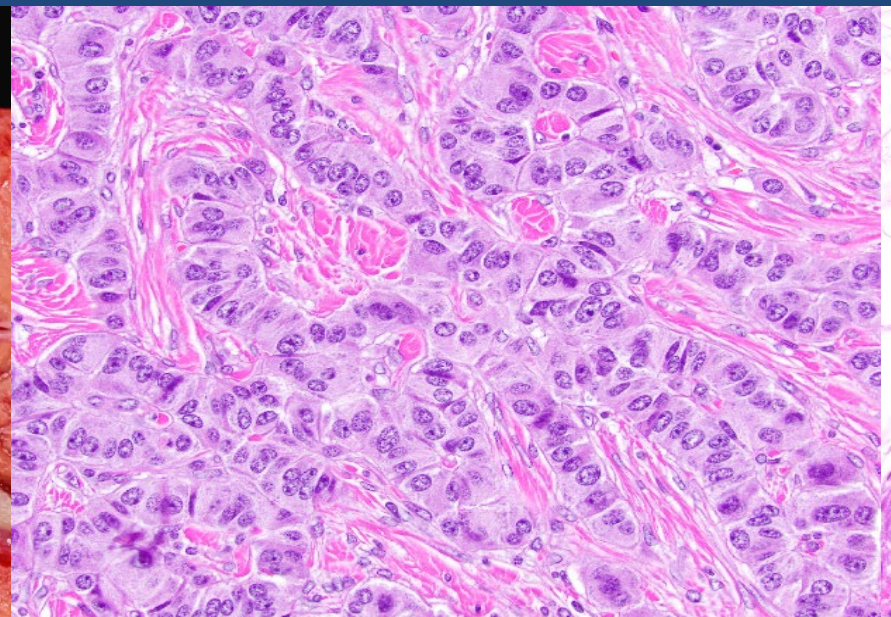
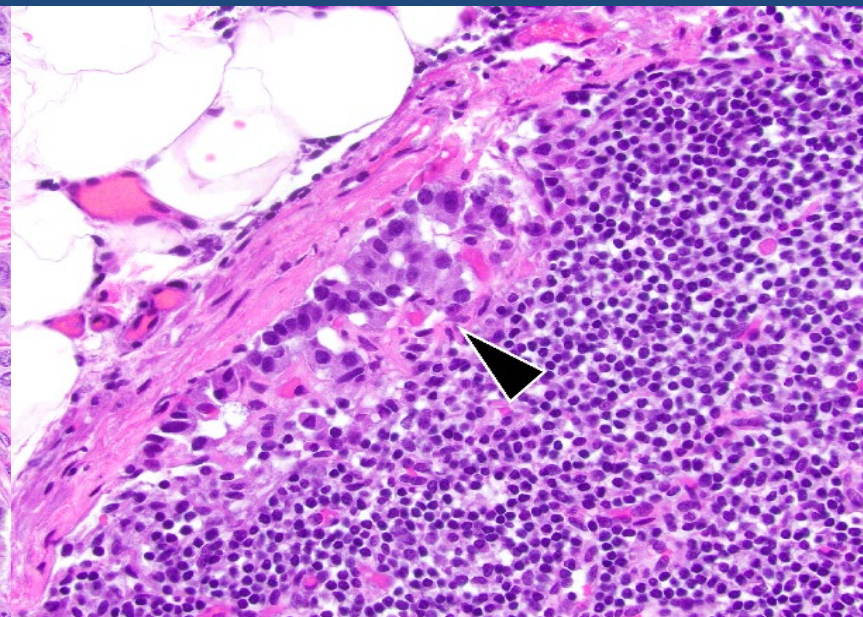
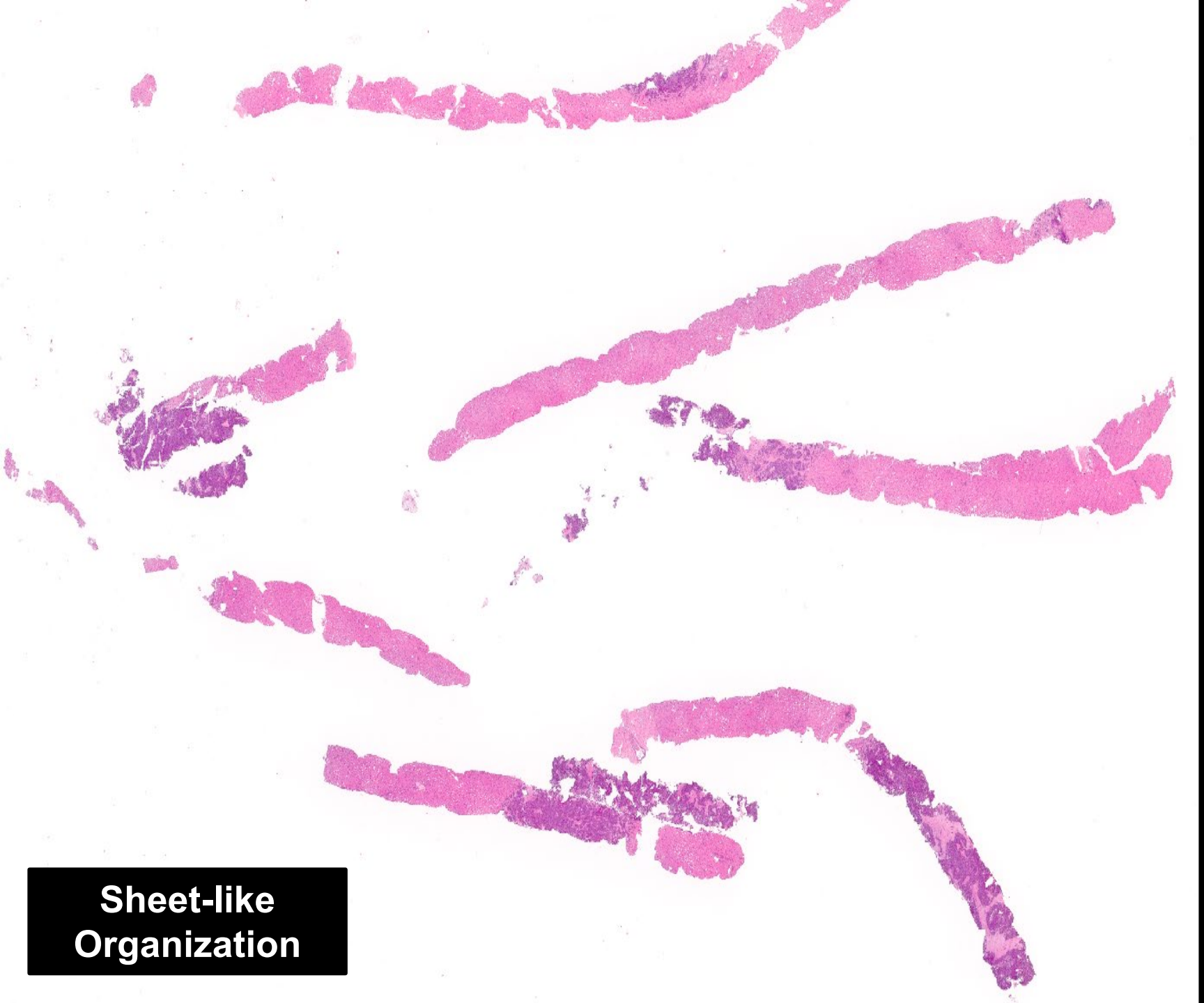


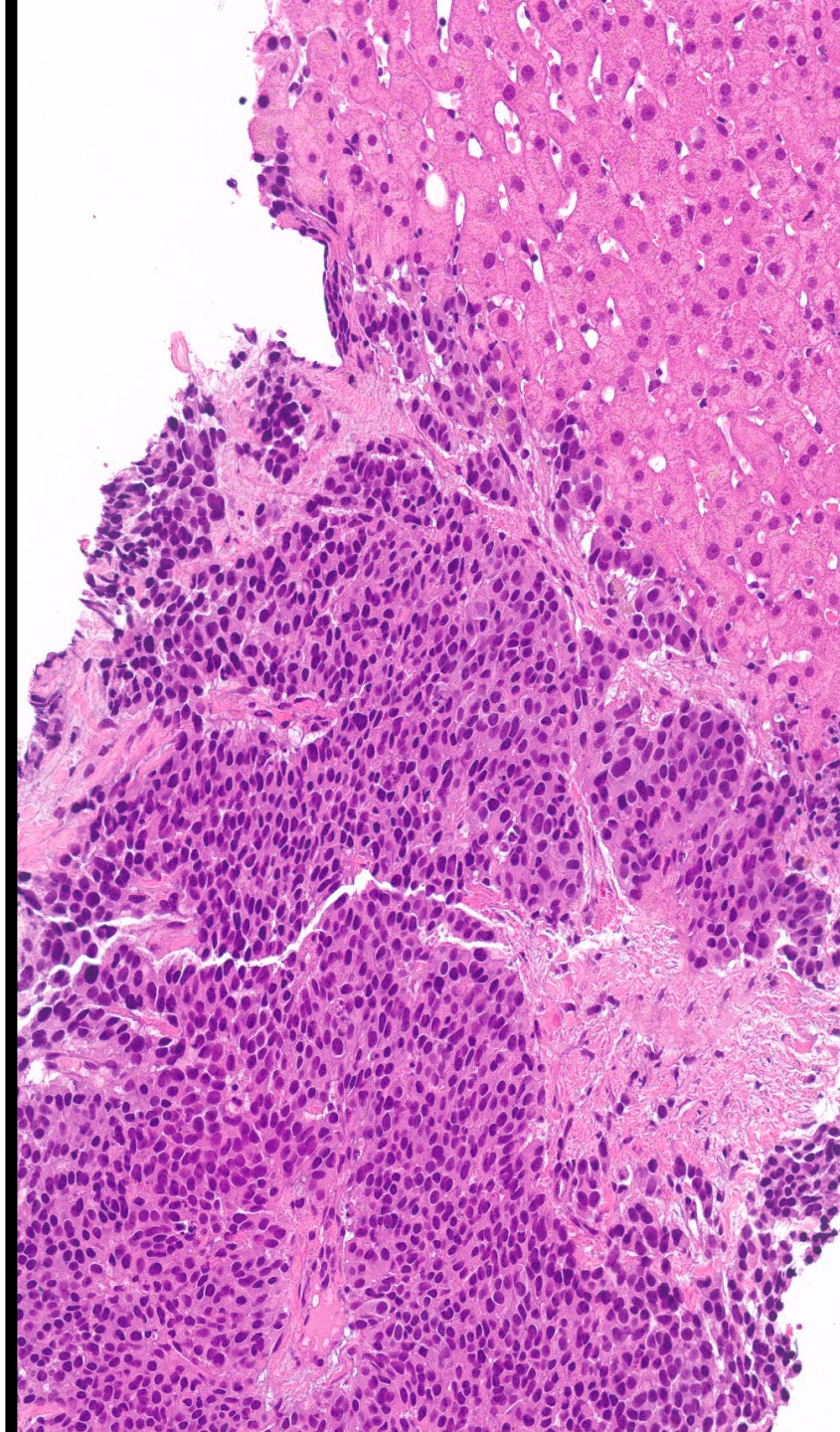




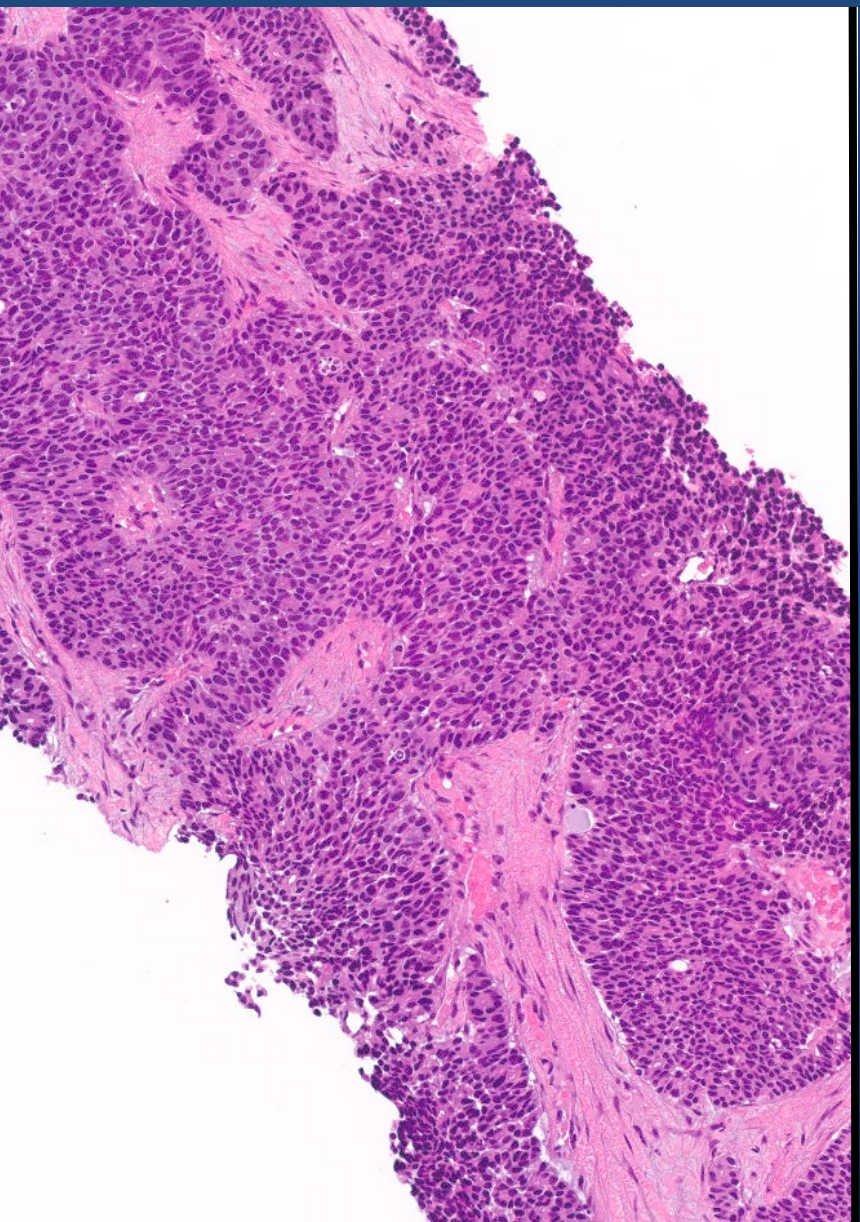
Case 4

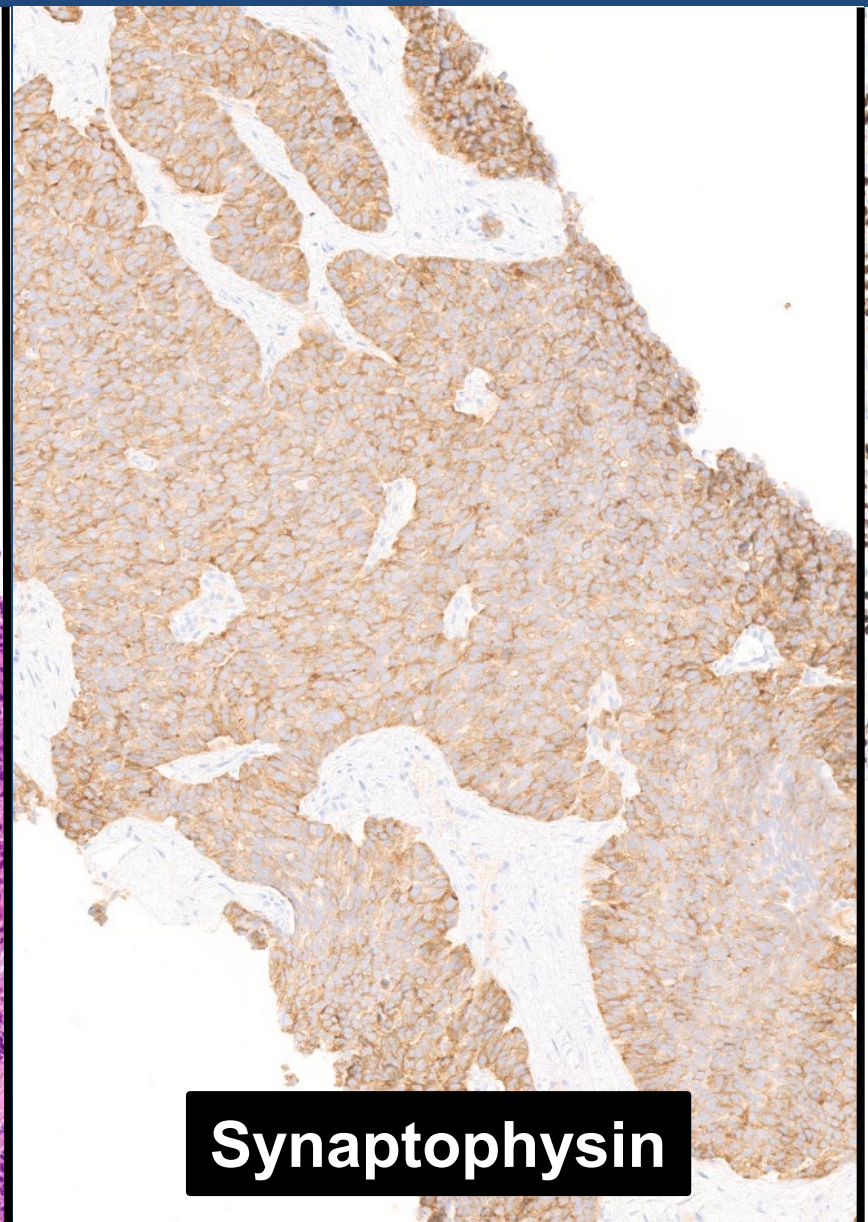
- A 67-year-old female with a history of a well-differentiated pancreatic neuroendocrine tumor, WHO grade 2, status post distal pancreatectomy.
- It is now 5 years later, and she is presenting with a 1.4 cm mass in the remnant pancreatic head and a solitary 1.2 cm liver lesion by DOTATATE scanning.
- A SharkCore™ fine-needle biopsy (FNB) was performed of the liver mass.


Sheet-like
Organization

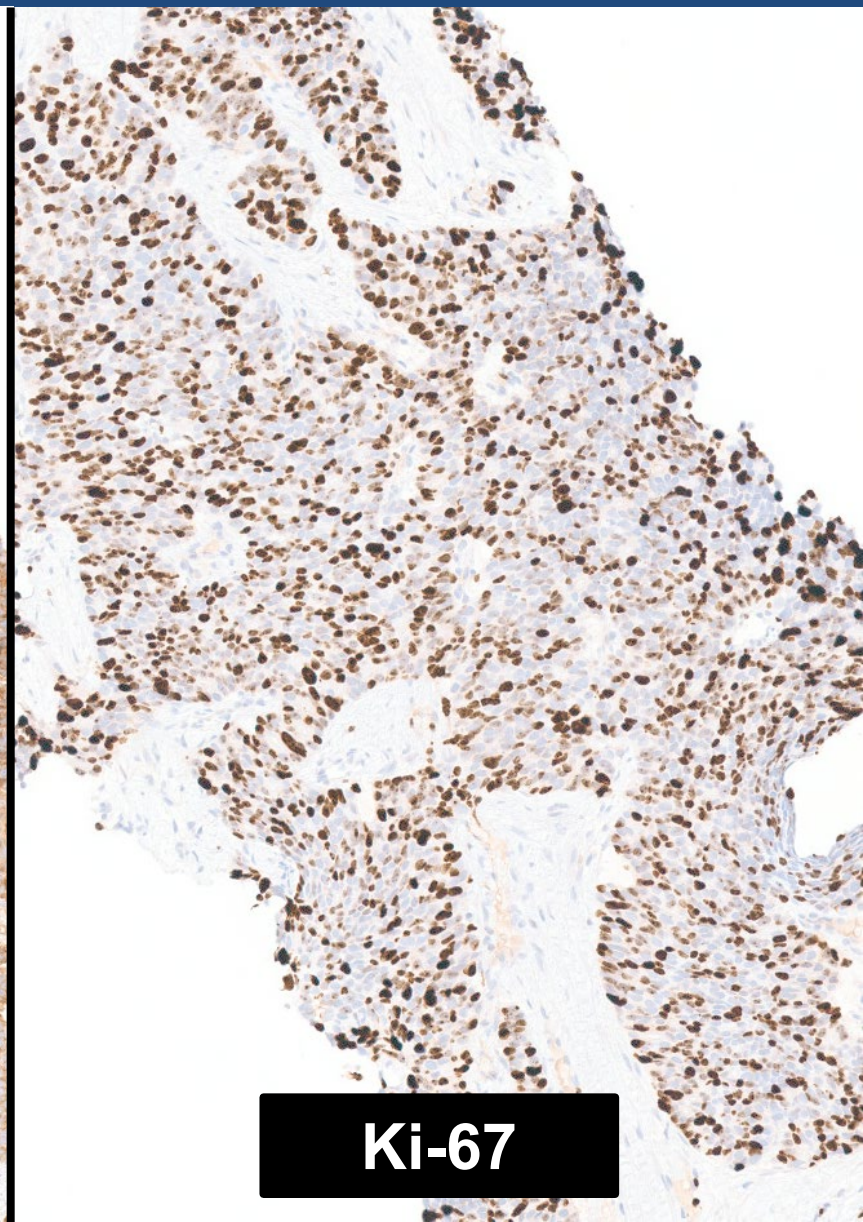


Case 4



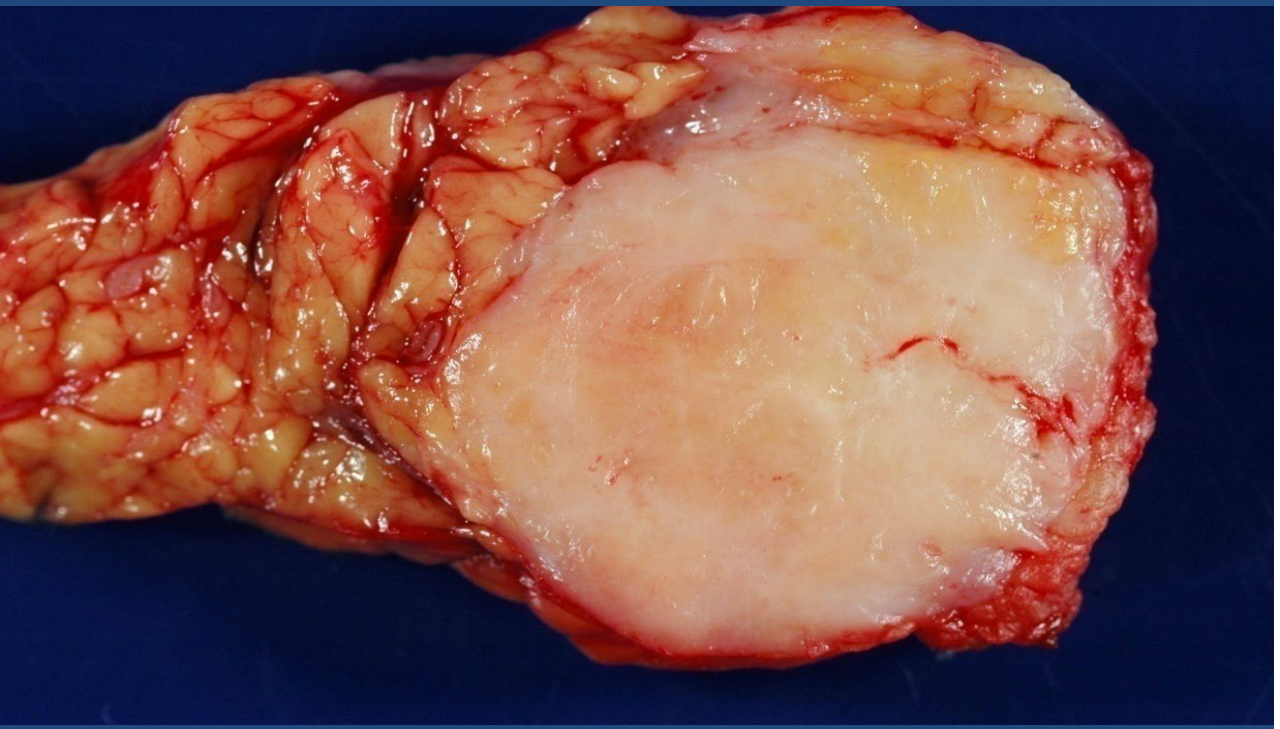


Synaptophysin



Ki-67

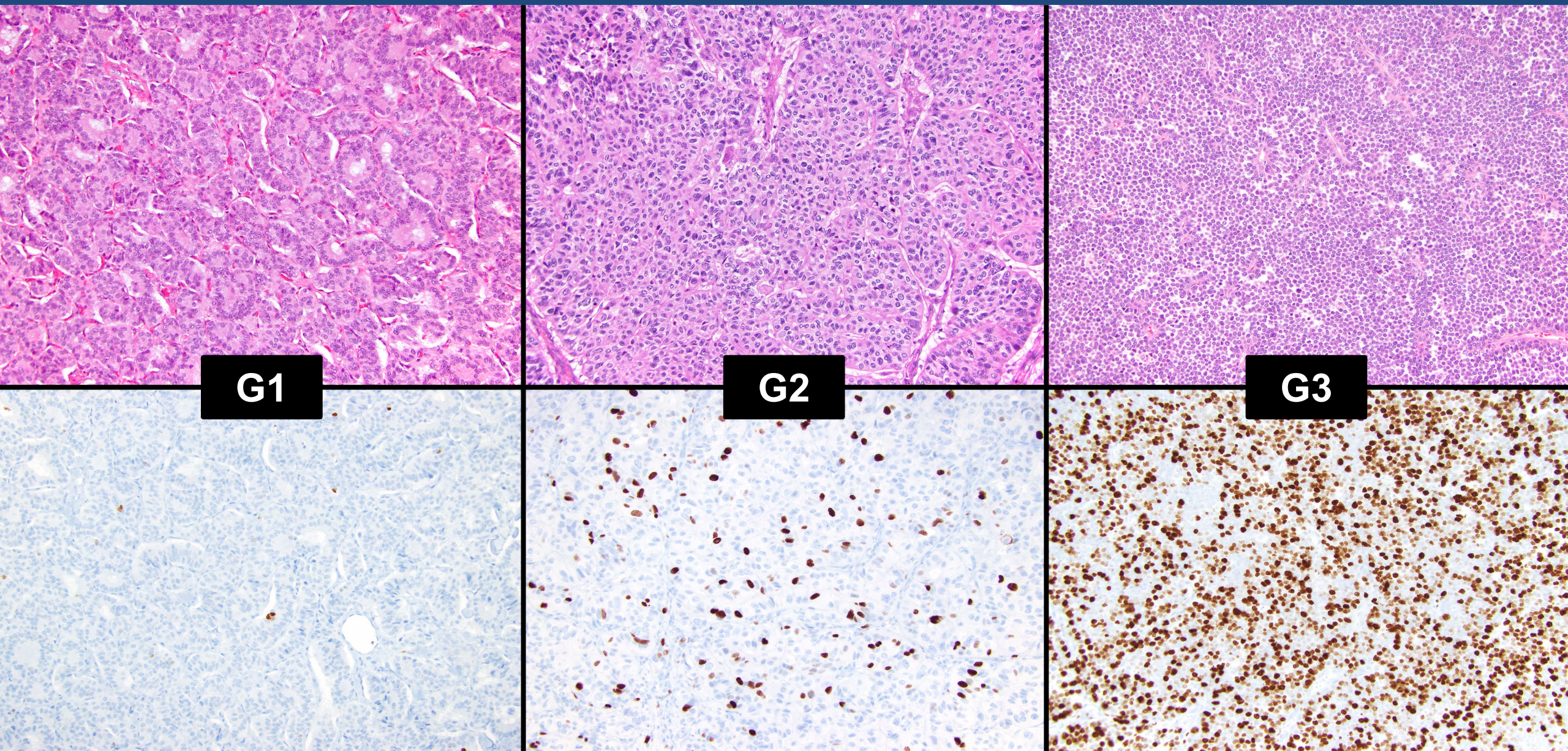
Solid



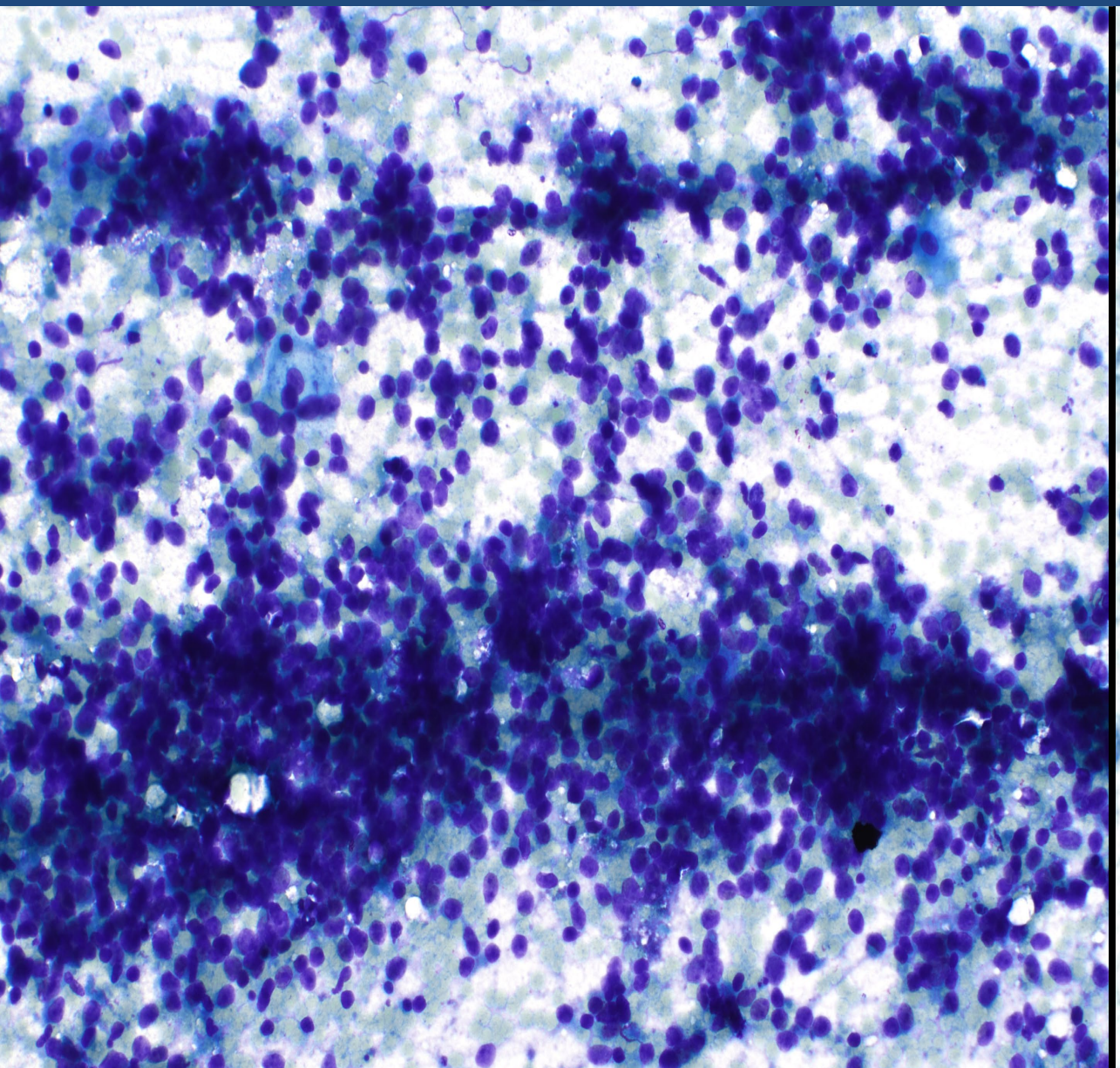
Differential Dx

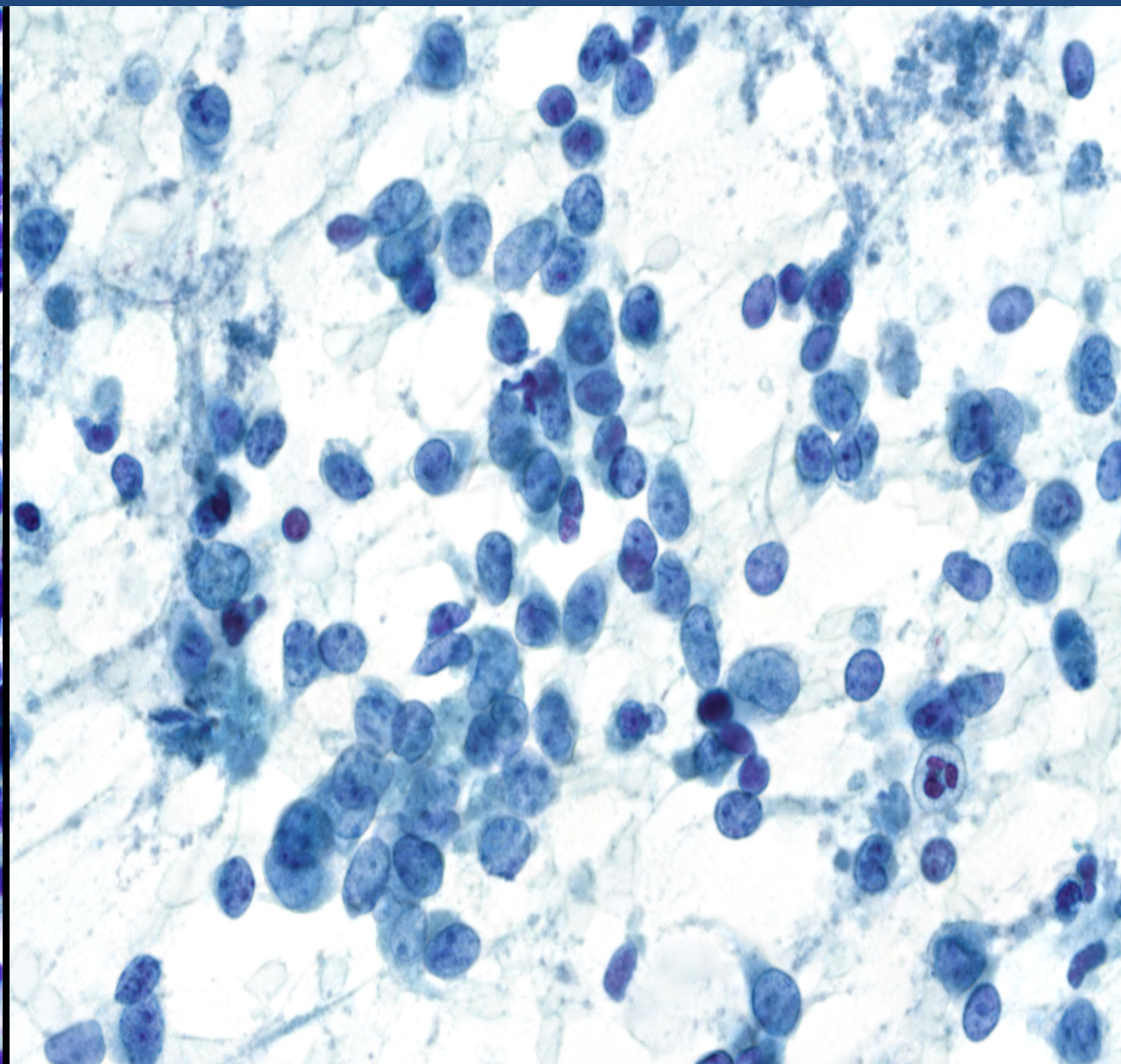
- Pancreatic Ductal Adenocarcinoma
- Acinar Cell Carcinoma
- Pancreatoblastoma
- **Well-Differentiated Neuroendocrine Tumor**
- **Poorly-Differentiated Neuroendocrine Carcinoma**
- Solid-Pseudopapillary Neoplasm

Well-Differentiated PanNETs



Poorly-Differentiated PanNECs





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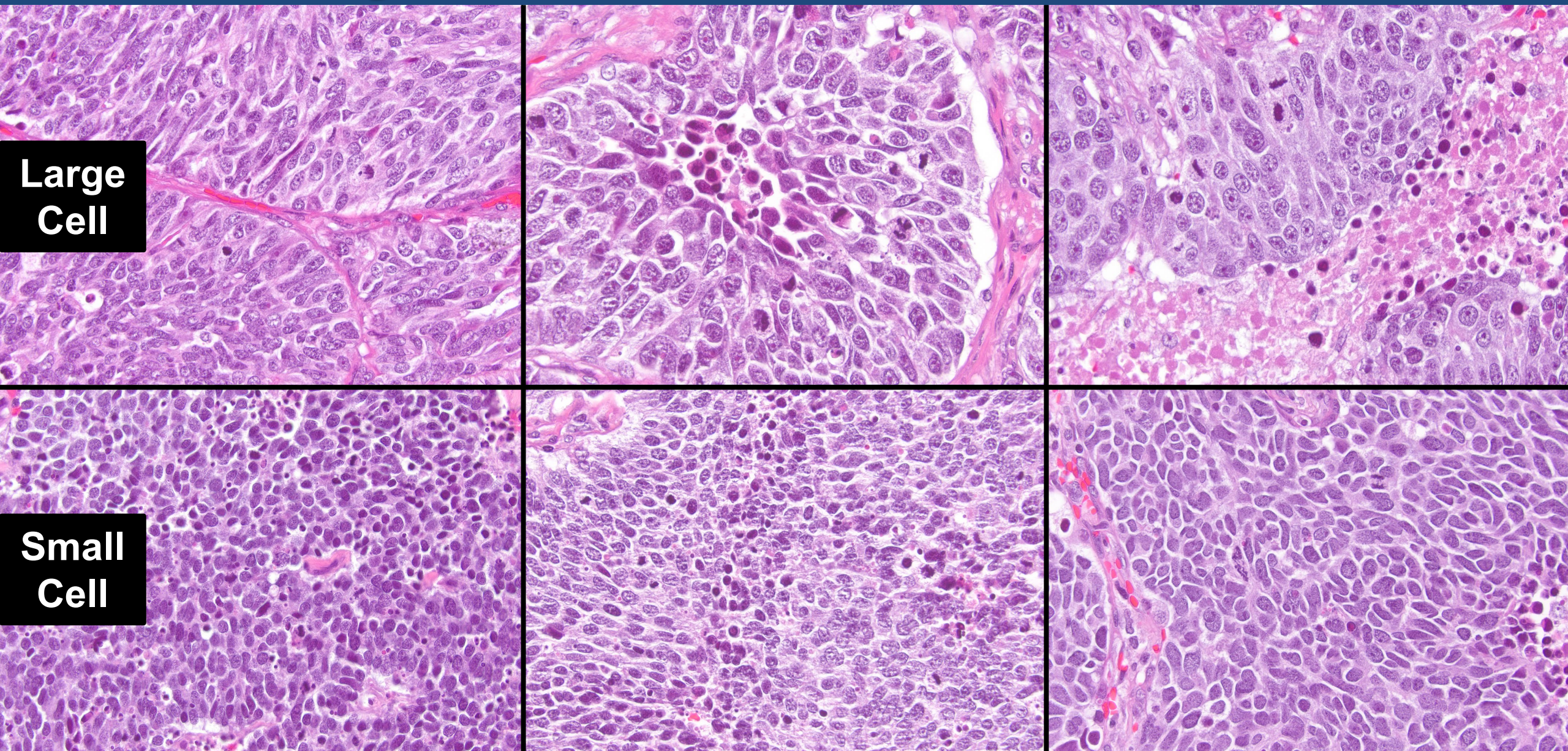

G3 WD-PanNETs vs. PD-PanNECs

Well-differentiated Neuroendocrine Tumors

- Surgical resection with curative intent
- Medical therapy:
  - Somatostatin analogues
  - Alkylating agents
  - Peptide receptor radionucleotide therapy (PRRT)

Poorly-differentiated Neuroendocrine Carcinomas

- Platinum-based chemotherapy / radiation

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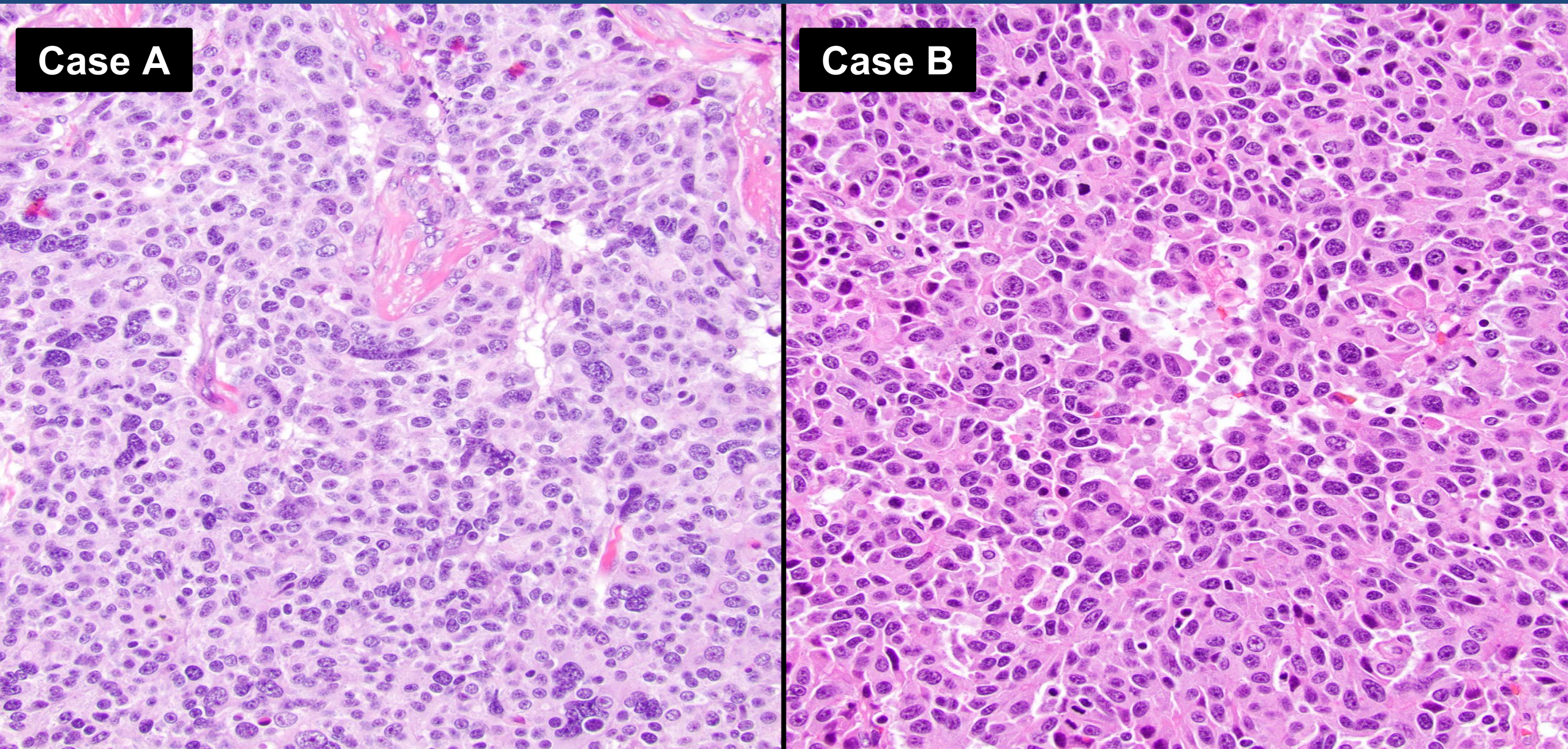

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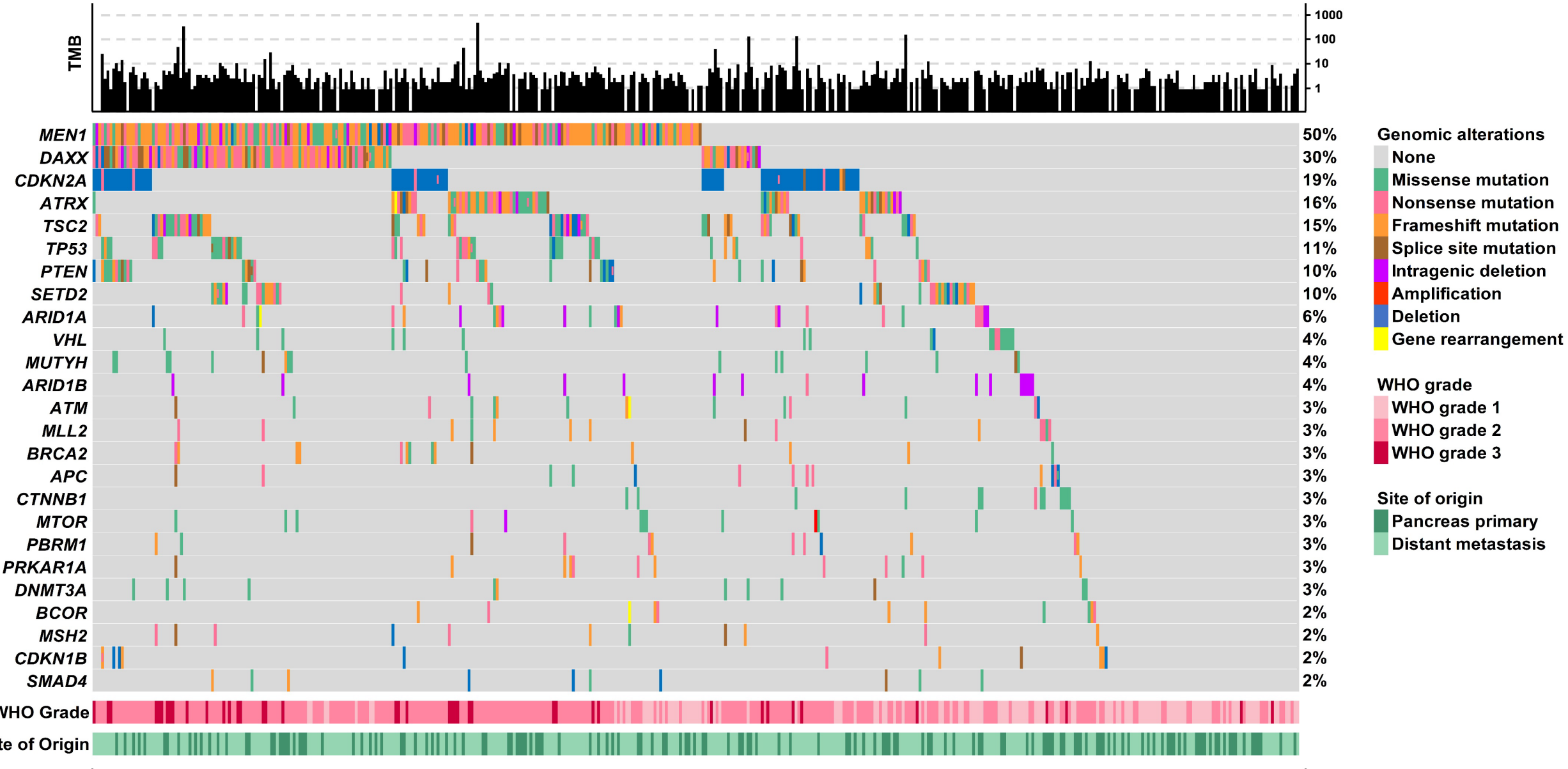

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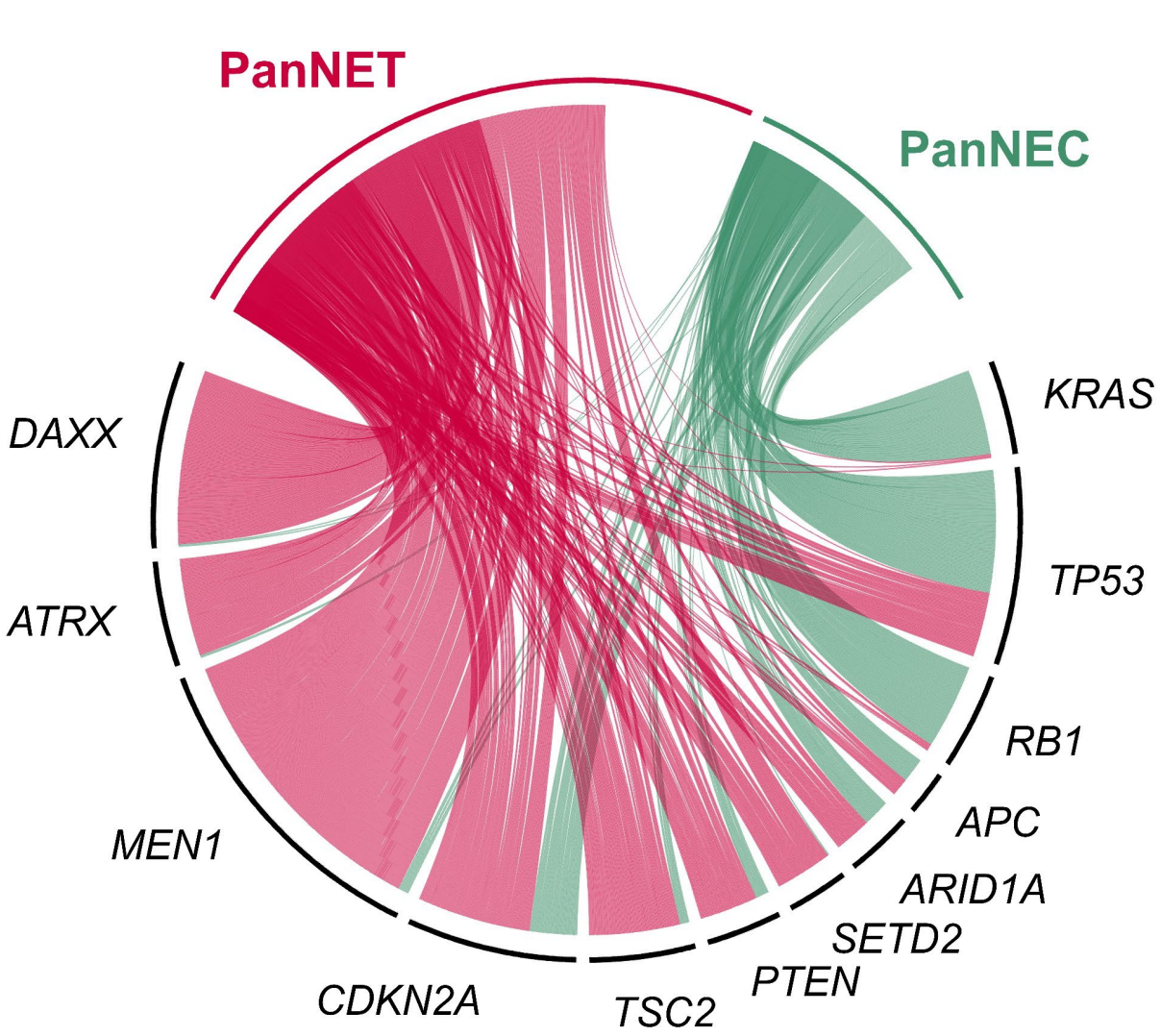

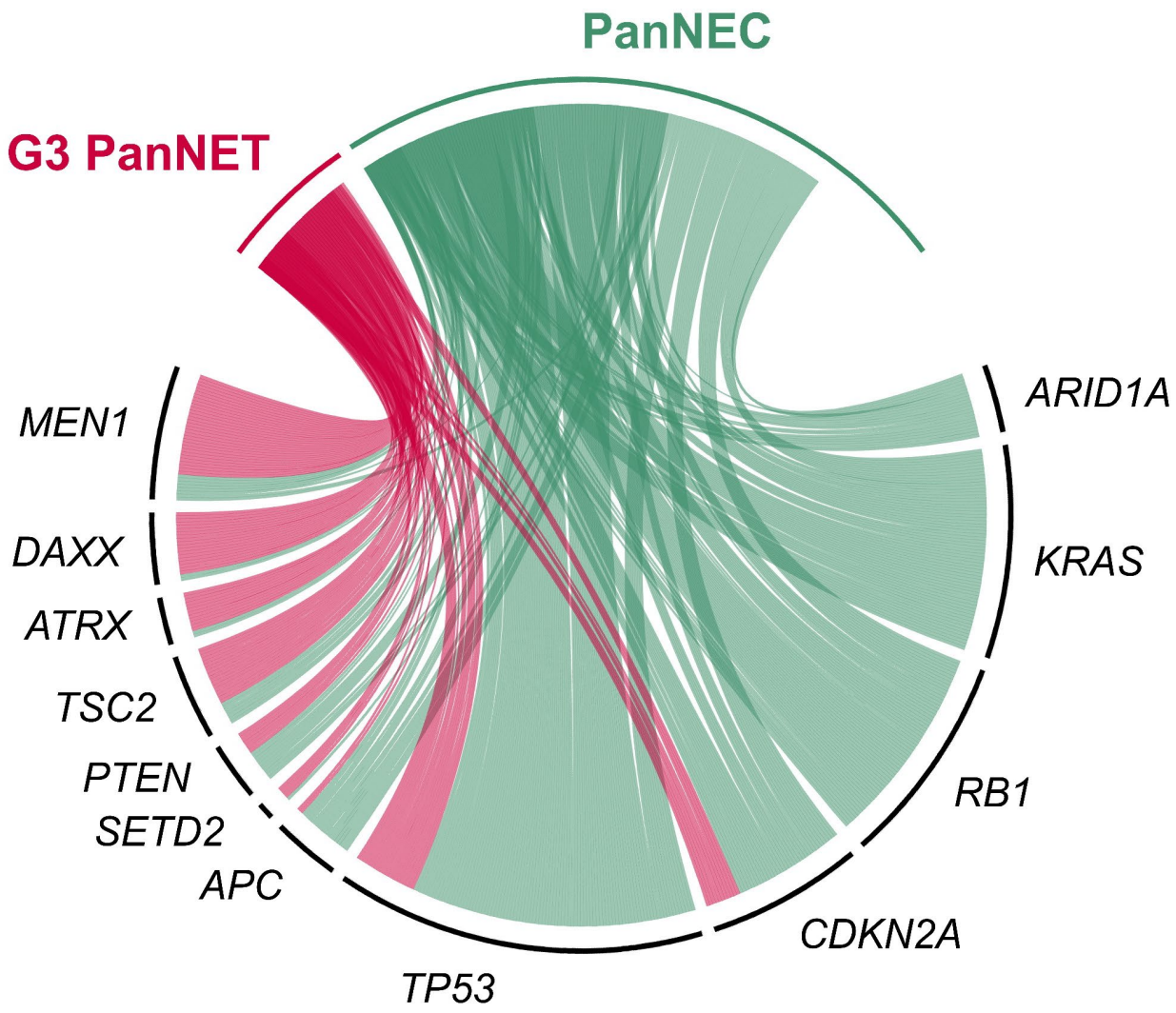

G3 WD-PanNETs vs. PD-PanNECs

G3 WD-PanNETs	
Genes	Mutation Frequency
MEN1	76%
DAXX/ATRX	78%
PIK3CA, PTEN, TSC1, & TSC2	18%
TP53	49%
RB1	2%
CDKN2A	27%
KRAS	0%
TGFBR1, TGFBR2, SMAD4	2%

PD-PanNECs	
Genes	Mutation Frequency
MEN1	4%
DAXX/ATRX	1%
PIK3CA, PTEN, TSC1, & TSC2	5%
TP53	48%
RB1	33%
CDKN2A	19%
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TGFBR1, TGFBR2, SMAD4	8%

1. Jiao Y, Shi C, de Wilde RF, et al. Science 2011; 331(6021): 1199-203.
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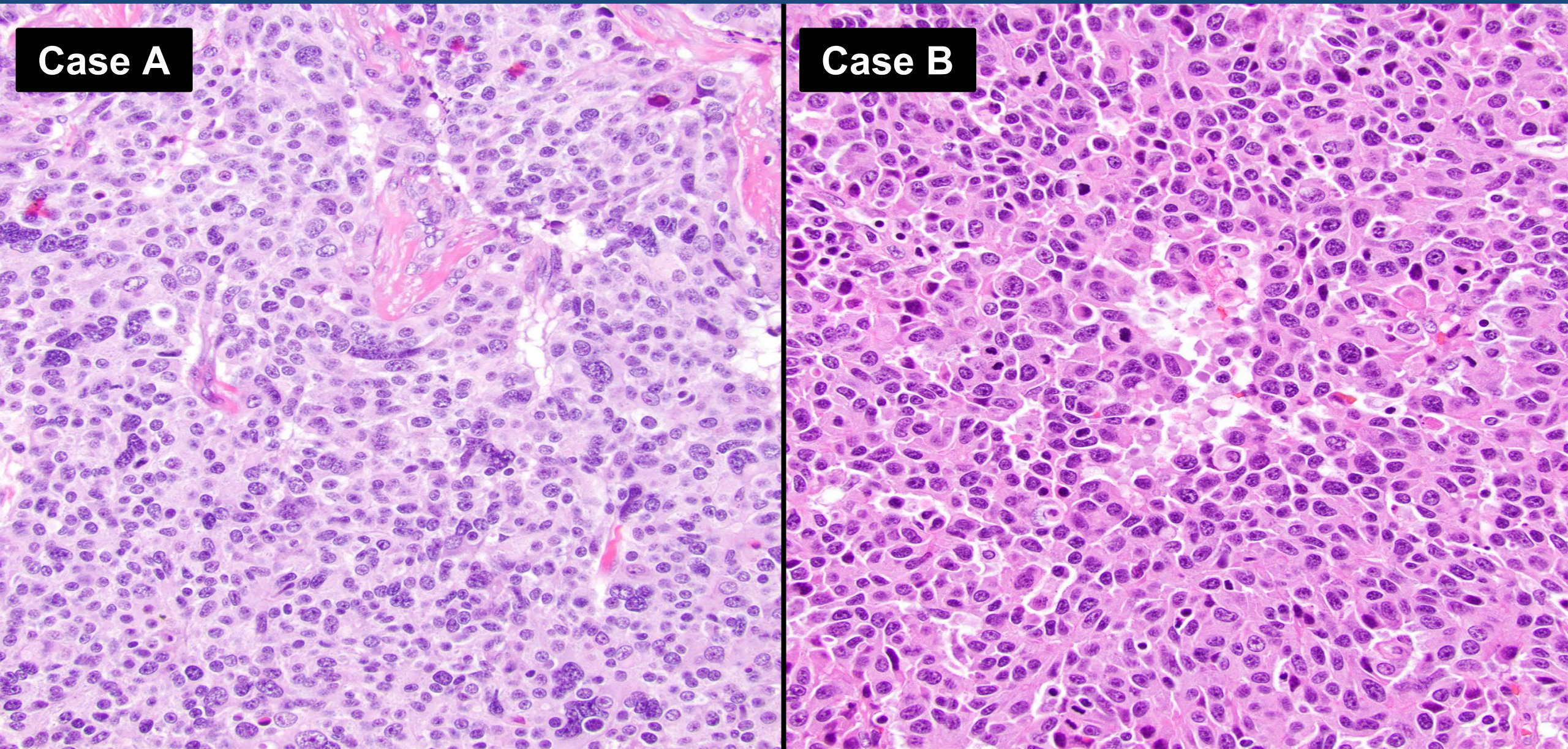

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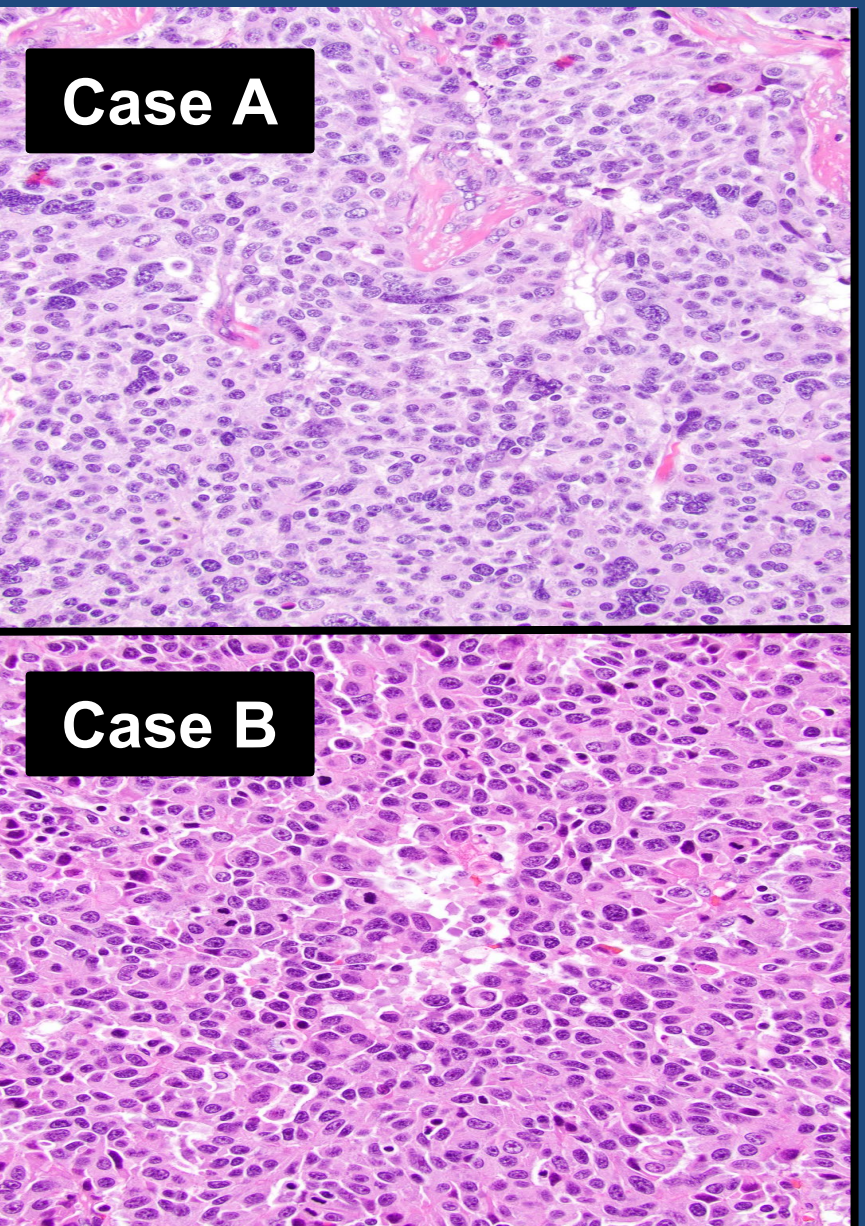

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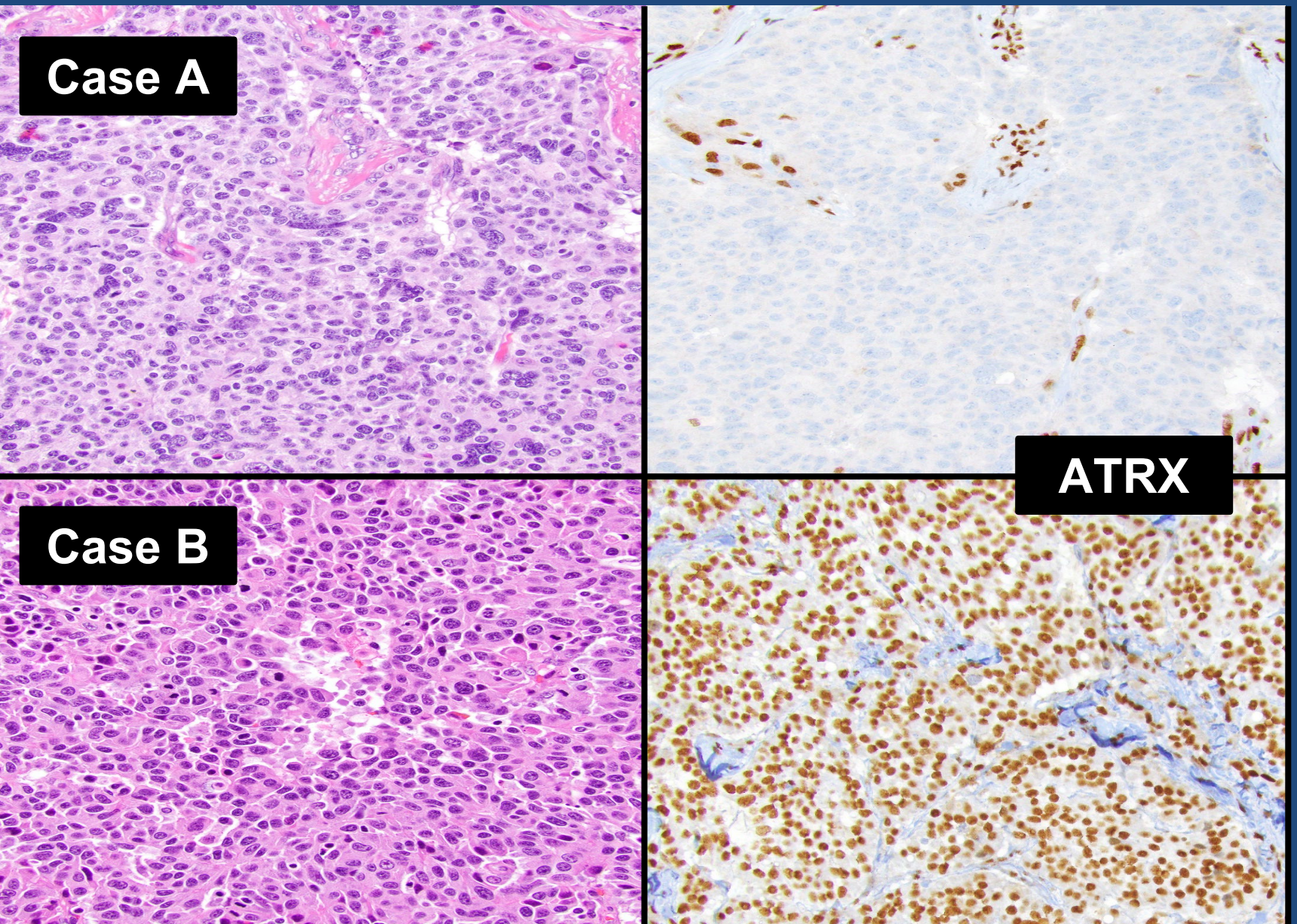

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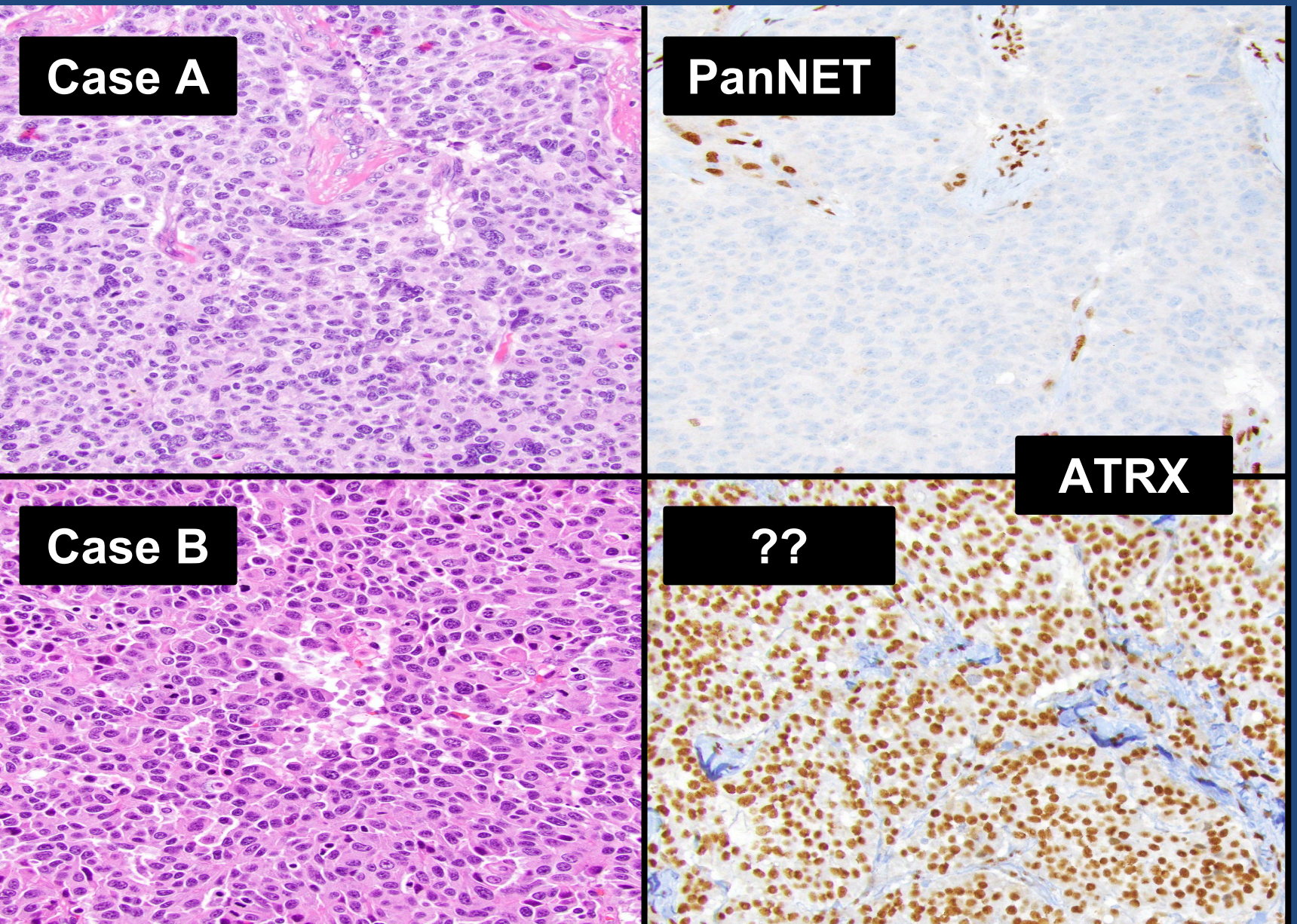

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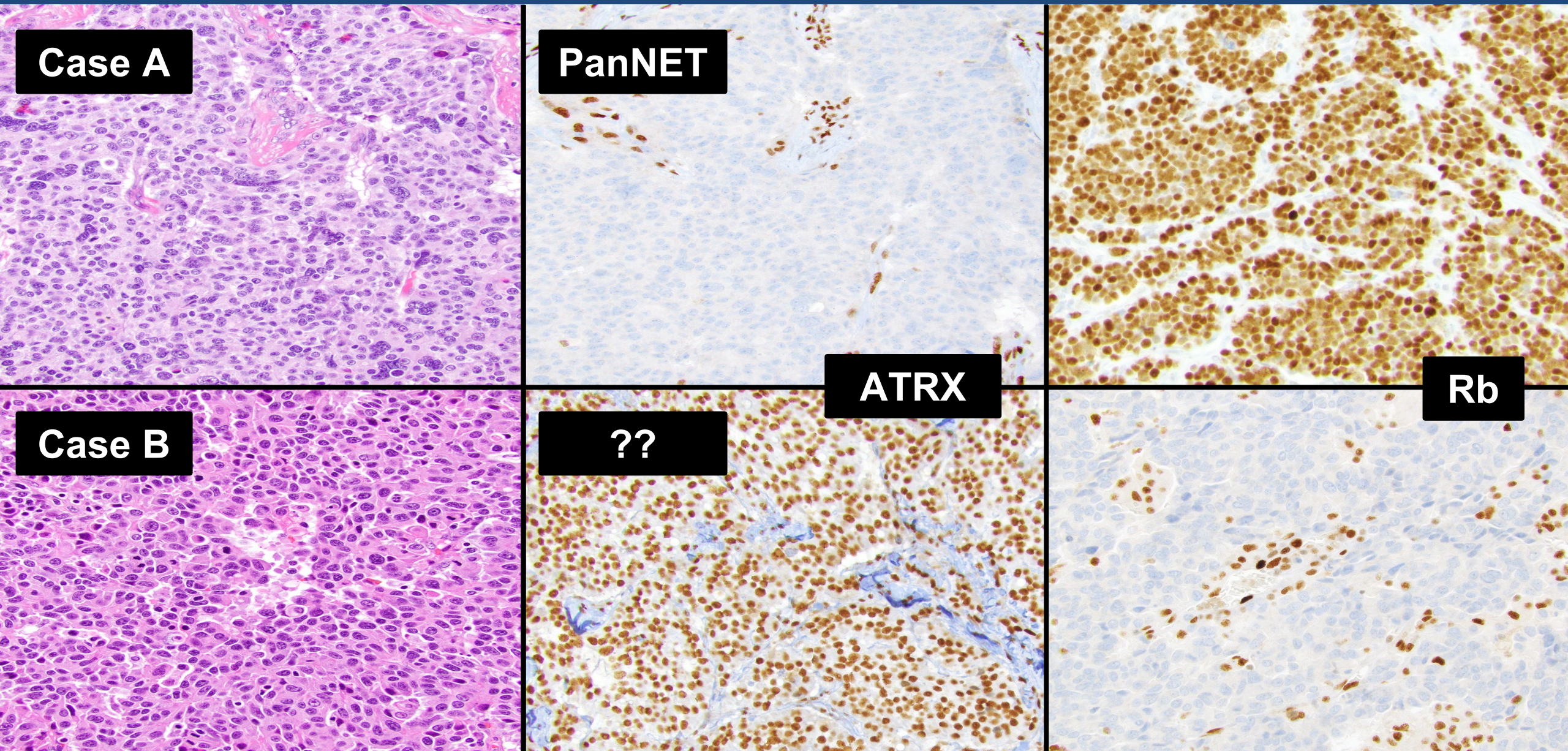

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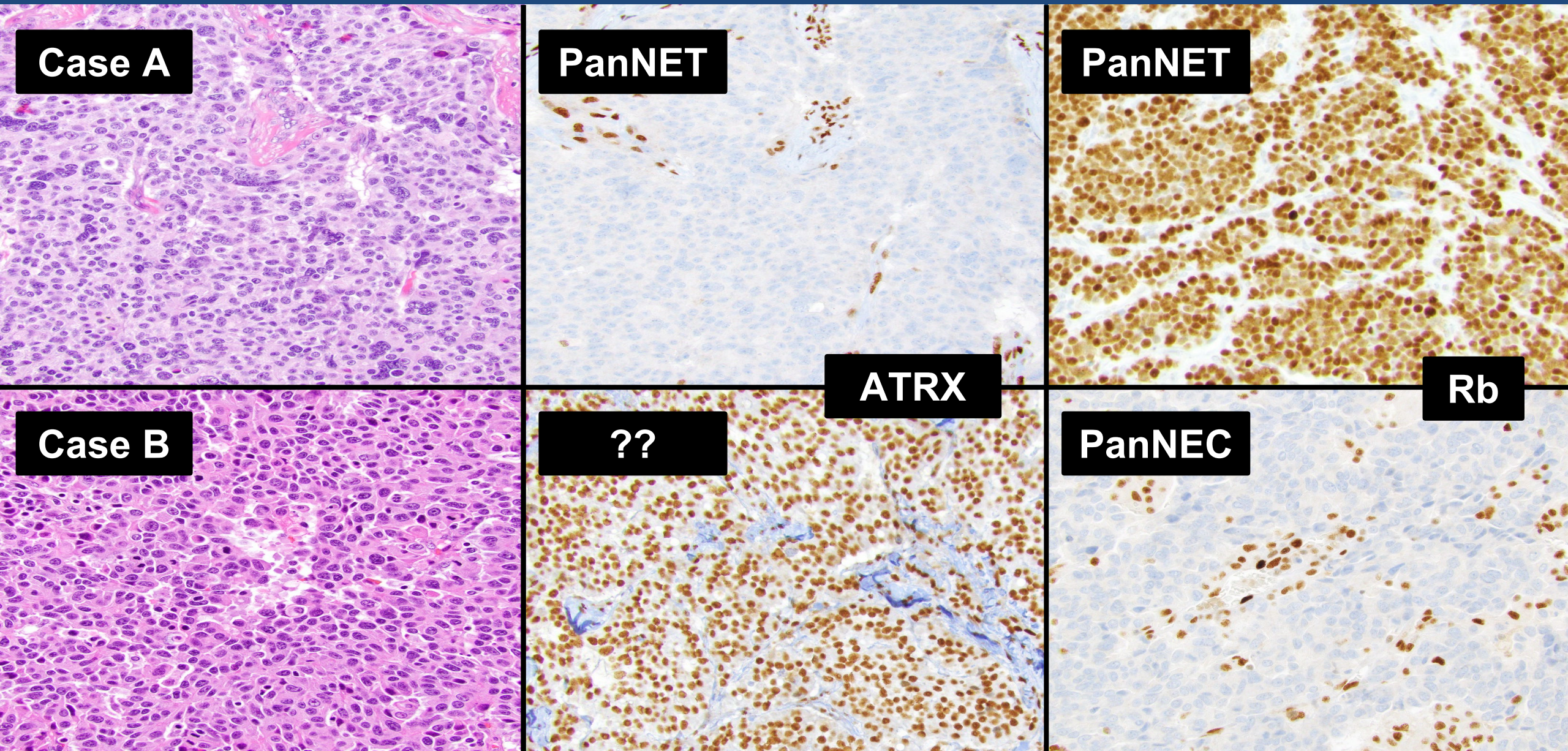
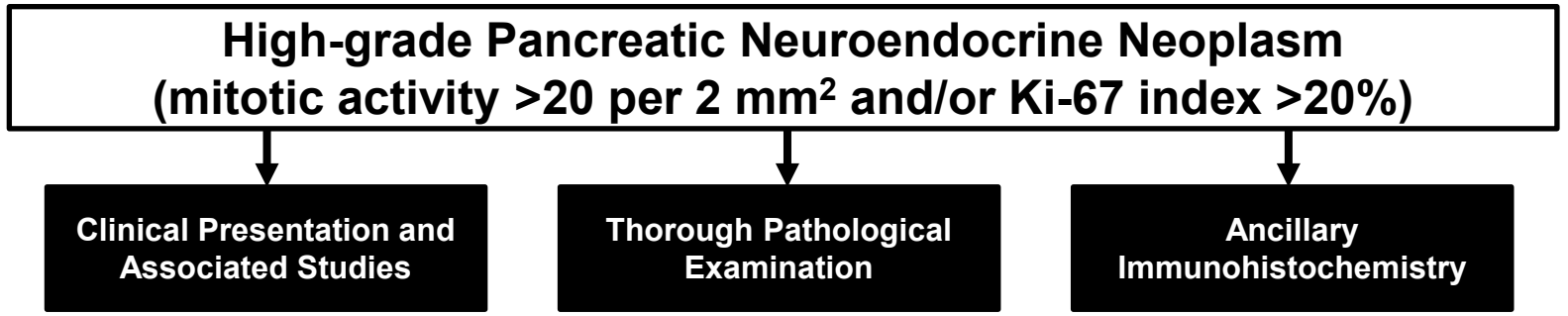
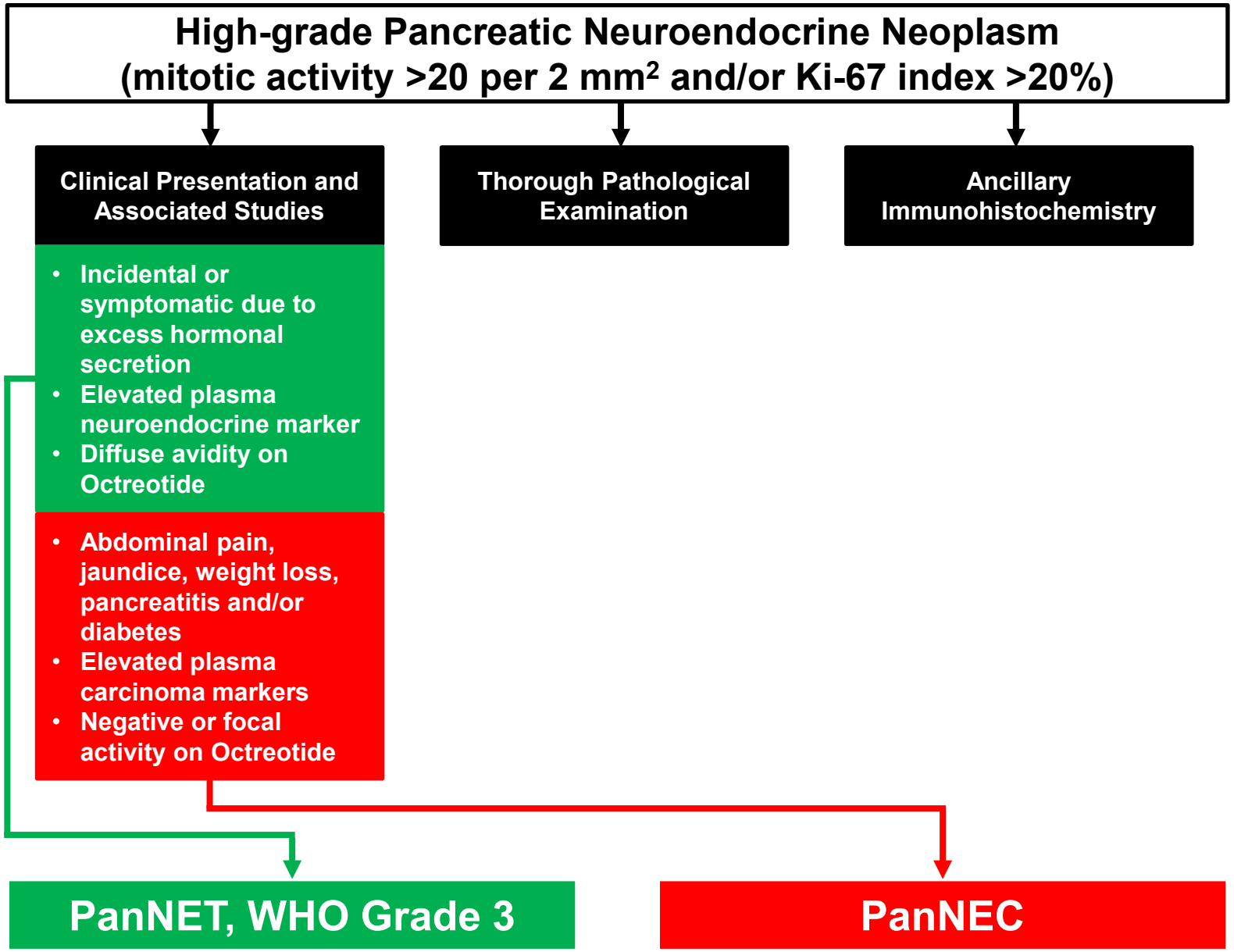



High-grade Pancreatic Neuroendocrine Neoplasm
(mitotic activity >20 per 2 mm2 and/or Ki-67 index >20%)
Clinical Presentation and Associated Studies
Thorough Pathological Examination
Ancillary Immunohistochemistry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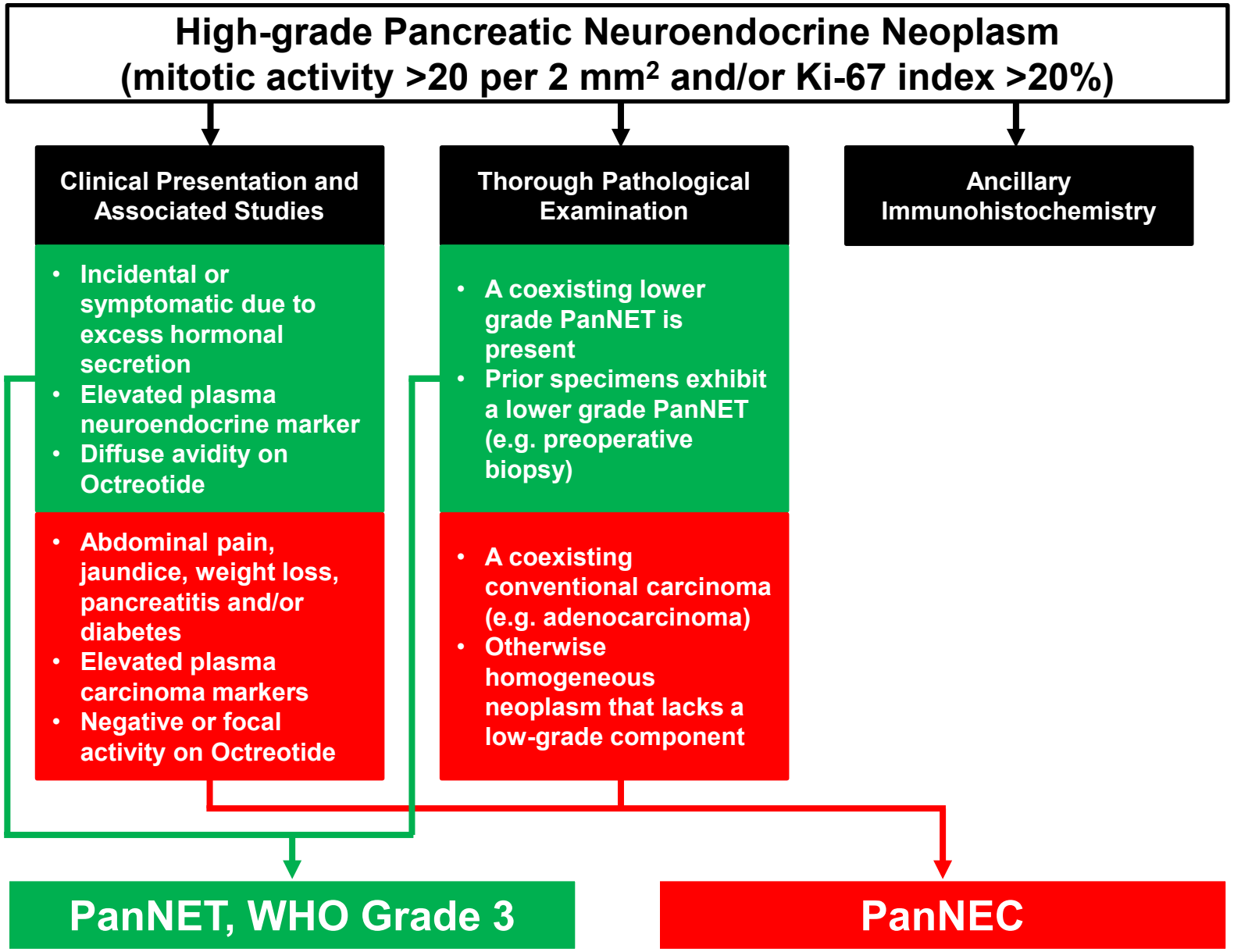
• Incidental or symptomatic due to excess hormonal secretion
• Elevated plasma neuroendocrine marker
• Diffuse avidity on Octreotide
• Abdominal pain, jaundice, weight loss, pancreatitis and/or diabetes
• Elevated plasma carcinoma markers
• Negative or focal activity on Octreotide
PanNET, WHO Grade 3
PanNEC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• A coexisting lower grade PanNET is present
• Prior specimens exhibit a lower grade PanNET (e.g. preoperative biopsy)
• Abdominal pain, jaundice, weight loss, pancreatitis and/or diabetes
• Elevated plasma carcinoma markers
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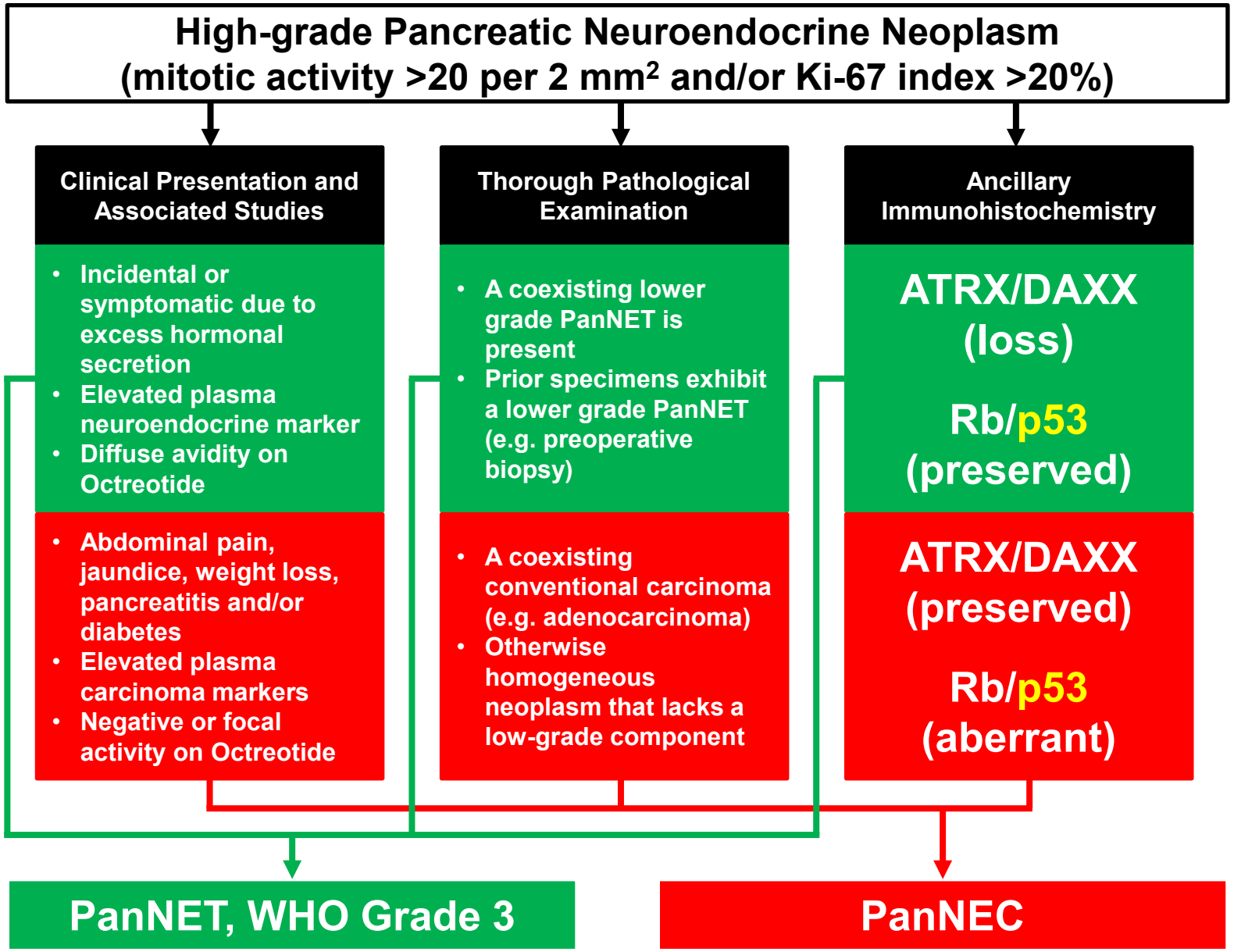
• A coexisting conventional carcinoma (e.g. adenocarcinoma)
• Otherwise homogeneous neoplasm that lacks a low-grade component
PanNET, WHO Grade 3
PanNEC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ATRX/DAXX (loss)
Rb/p53 (preserved)
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ATRX/DAXX (preserved)
Rb/p53 (aberrant)
PanNET, WHO Grade 3
PanNEC

Case 4

- A 67-year-old female with a history of a well-differentiated pancreatic neuroendocrine tumor, WHO grade 2, status post distal pancreatectomy.
- It is now 5 years later, and she is presenting with a 1.4 cm mass in the remnant pancreatic head and a solitary 1.2 cm liver lesion by DOTATATE scanning.
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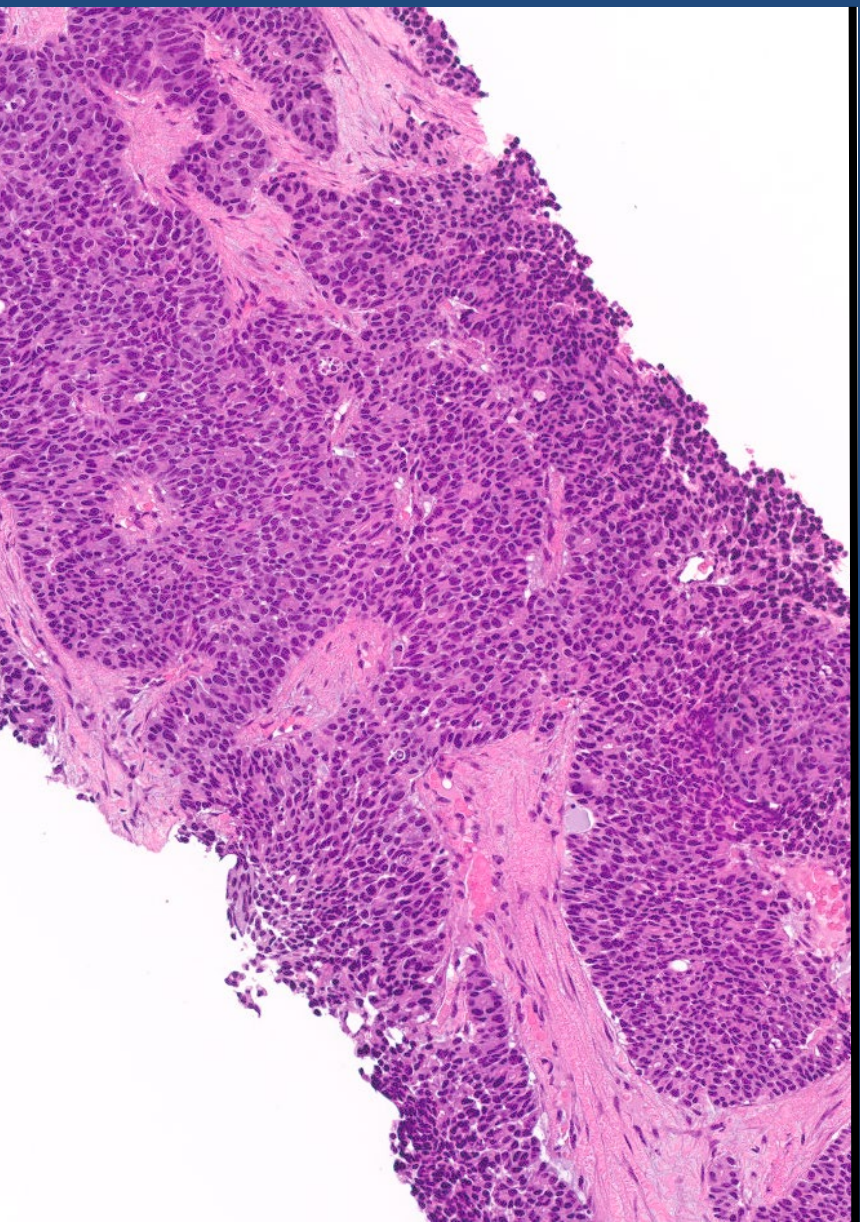
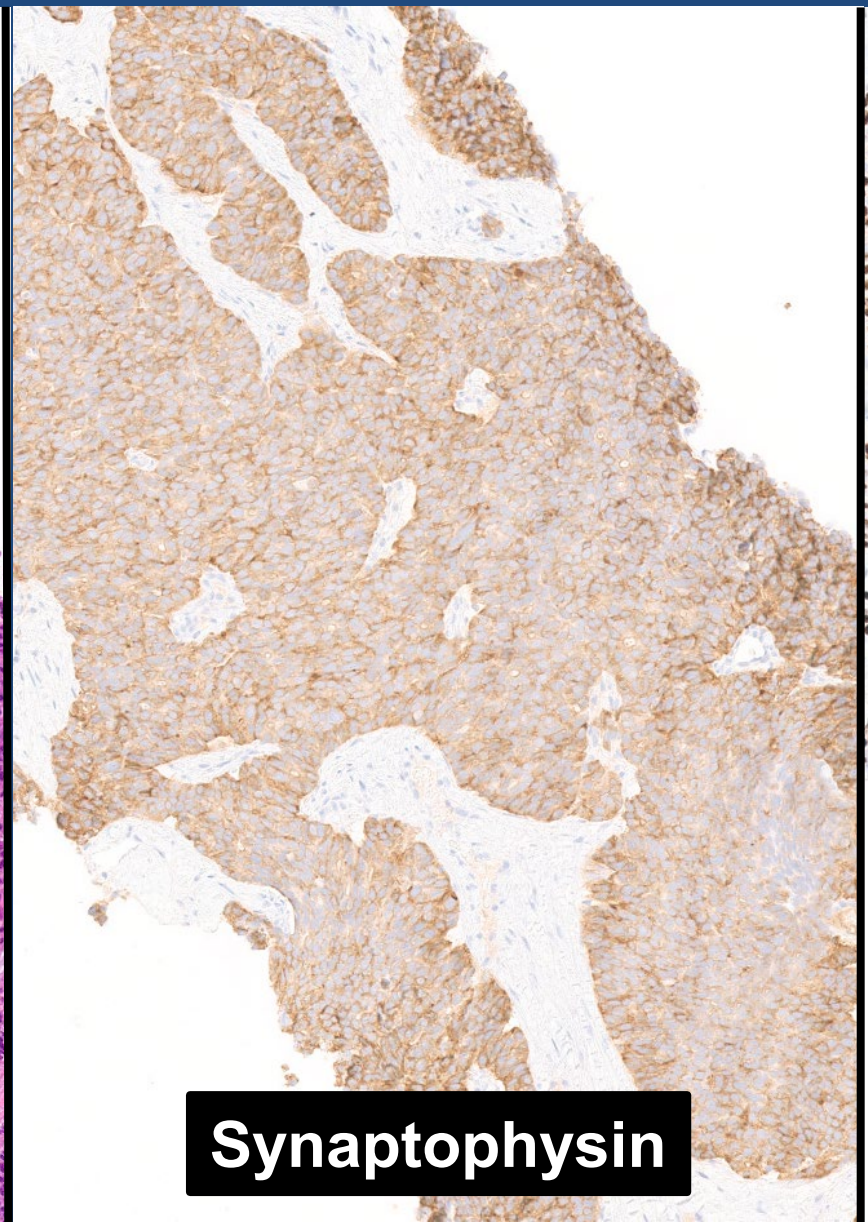
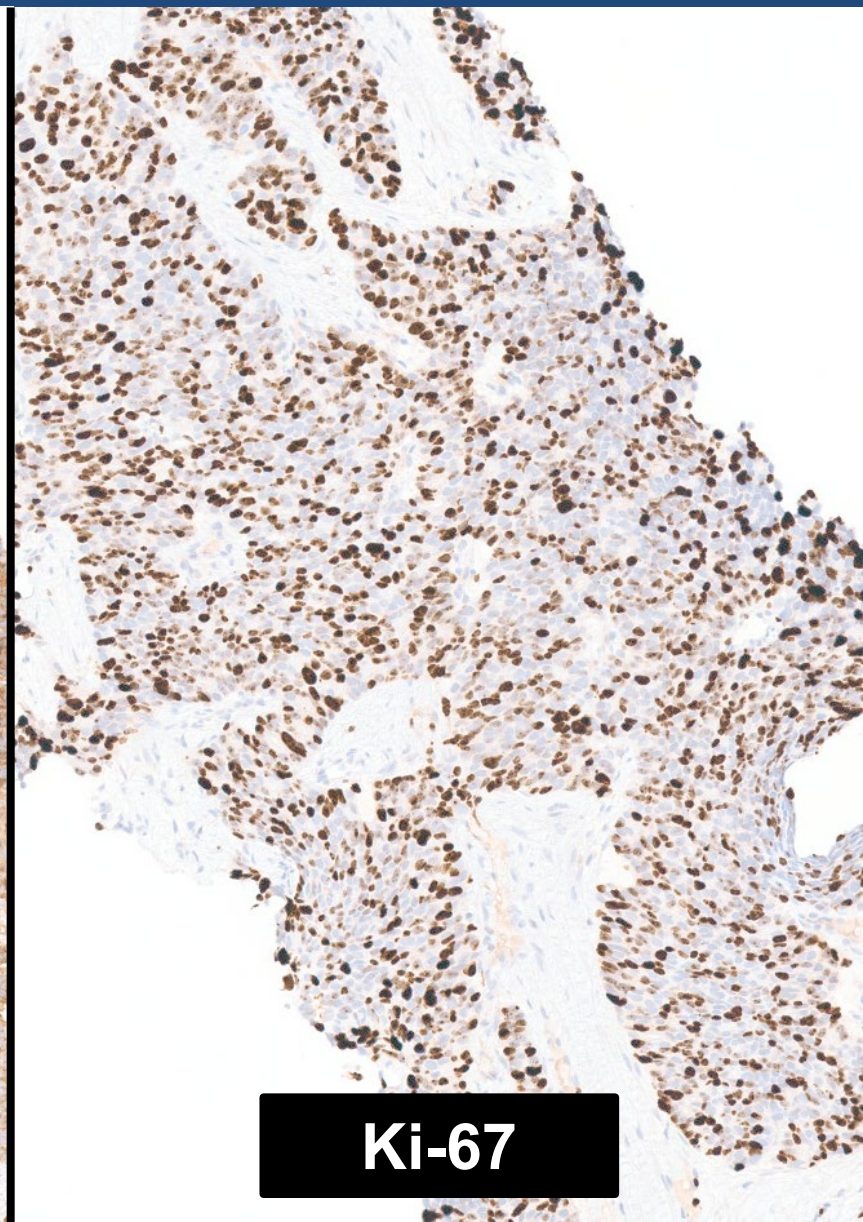


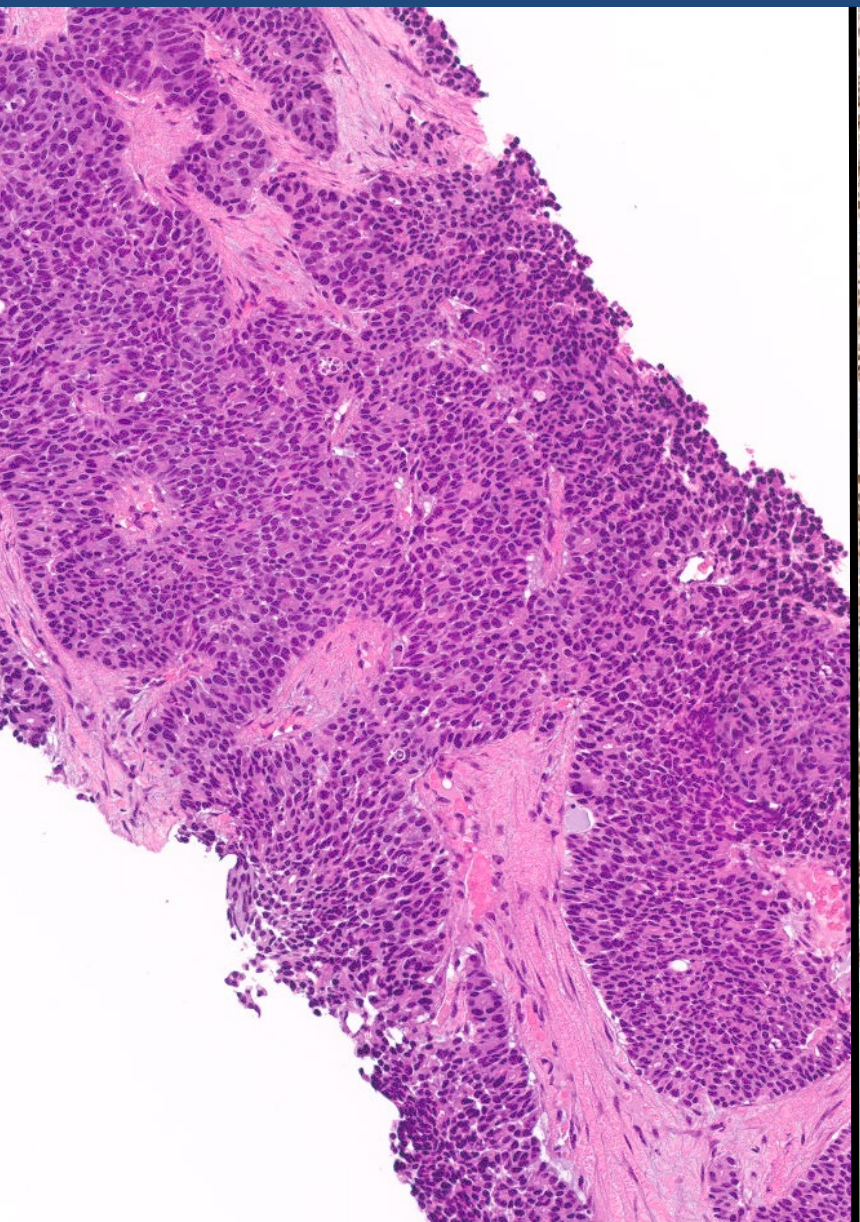


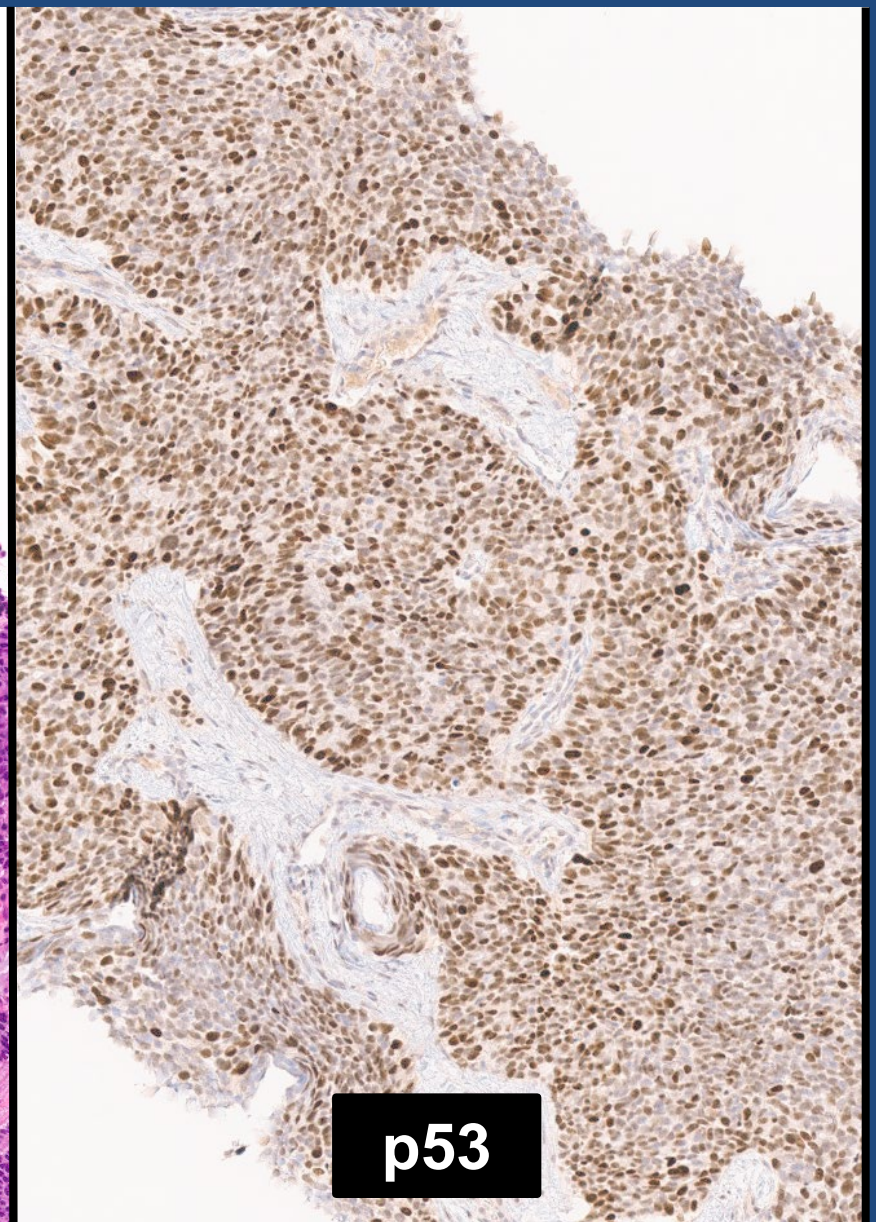
Synaptophysin



Ki-67

Case 4





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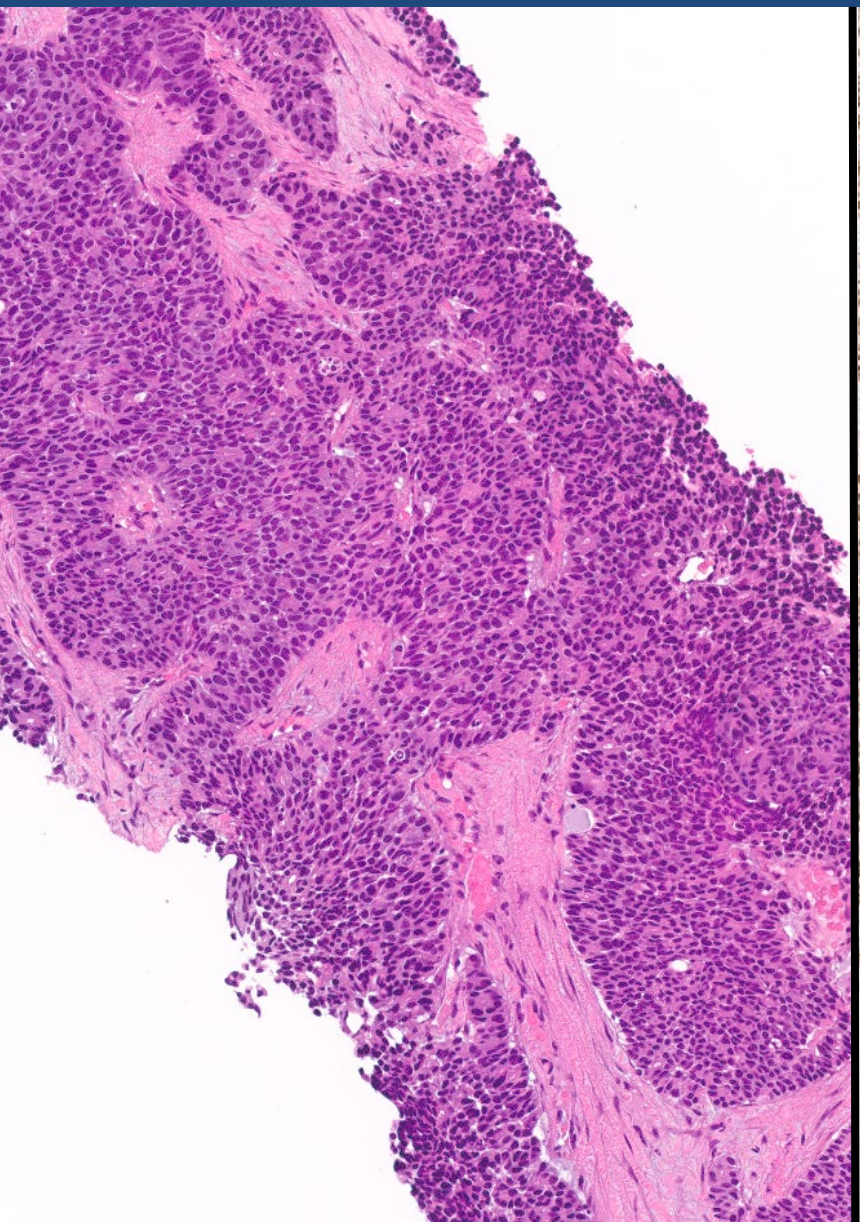
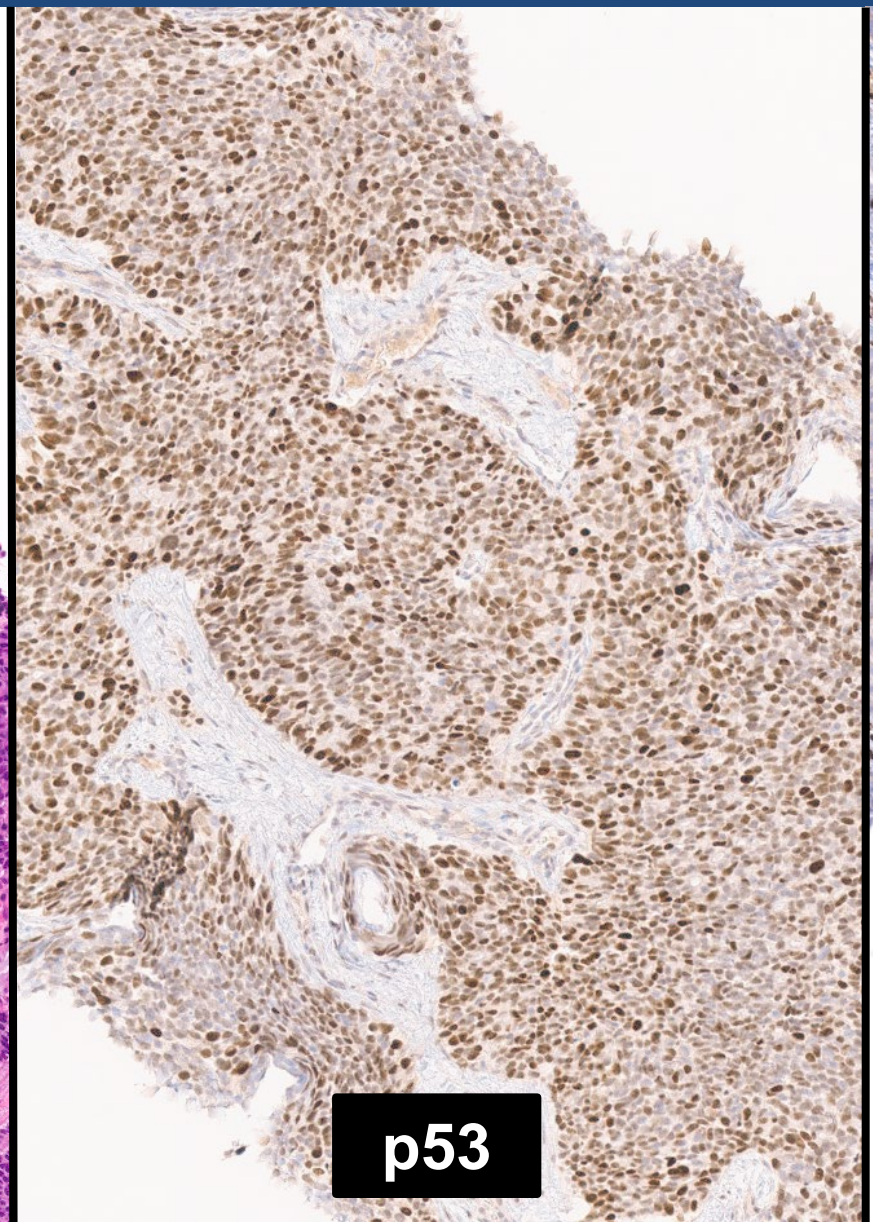
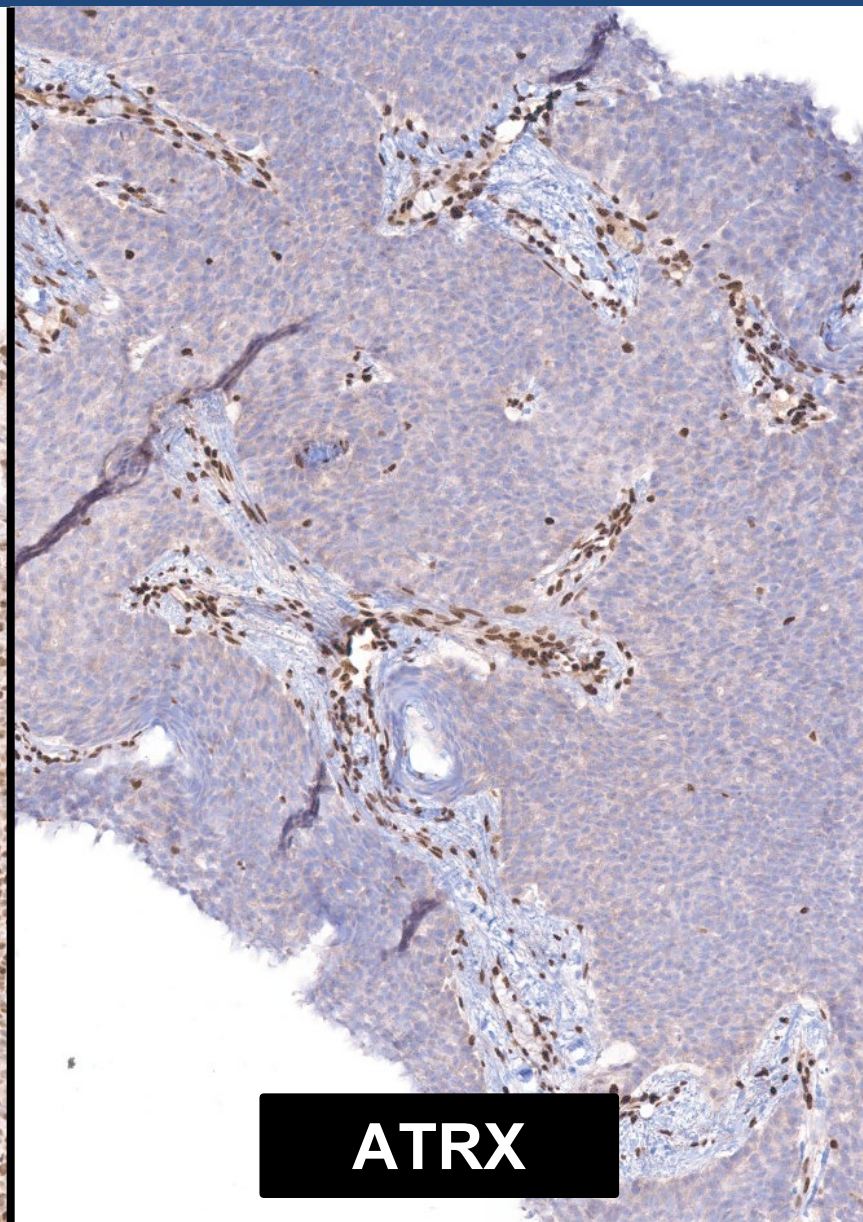
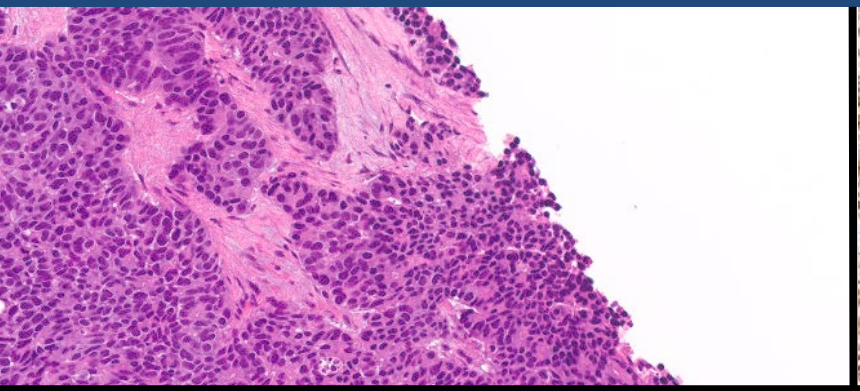
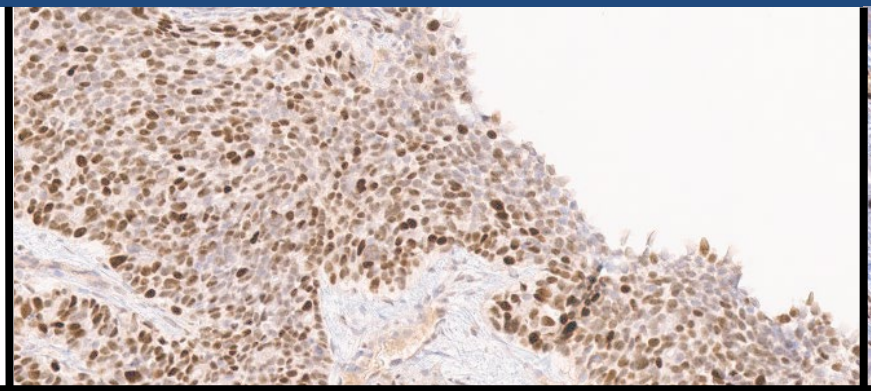


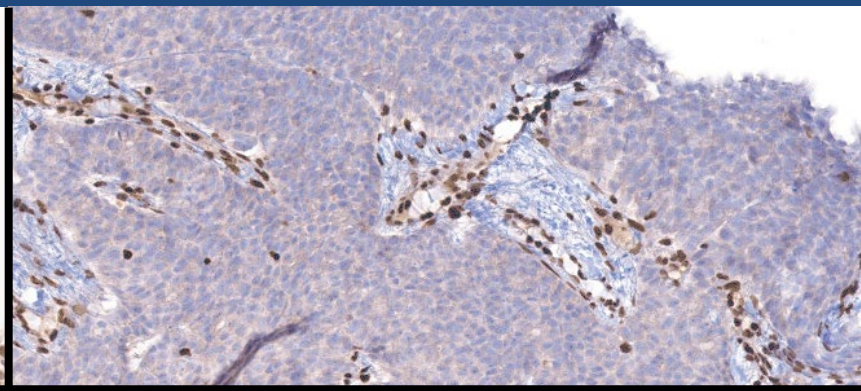




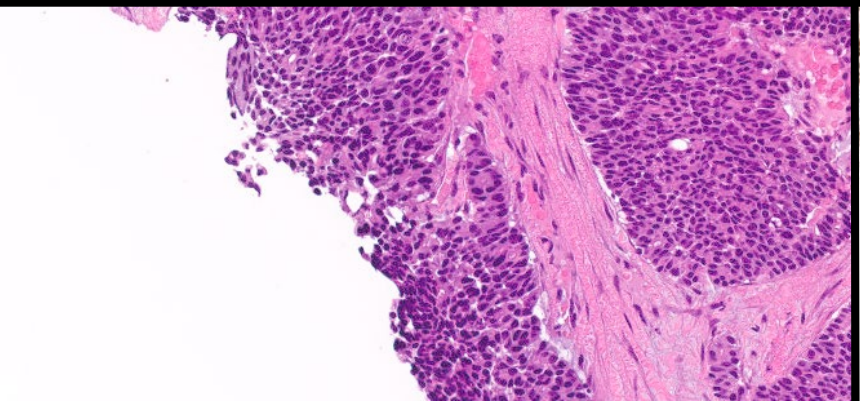
Case 4

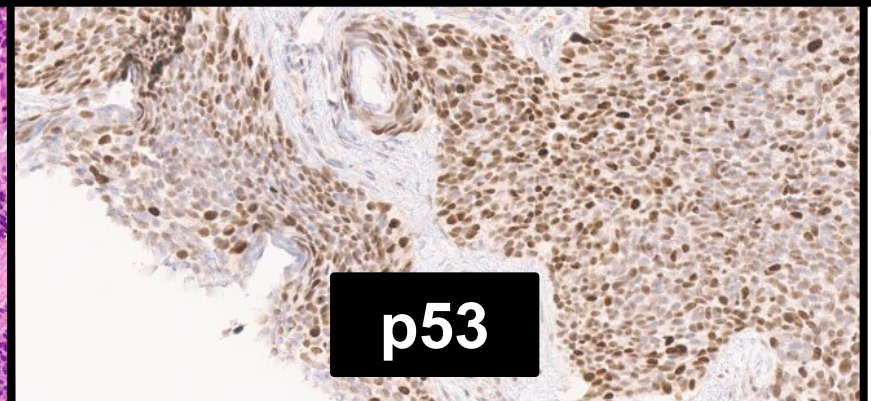


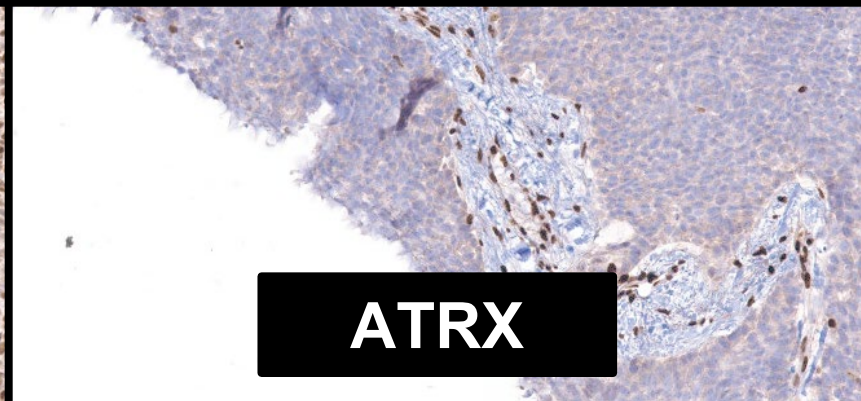


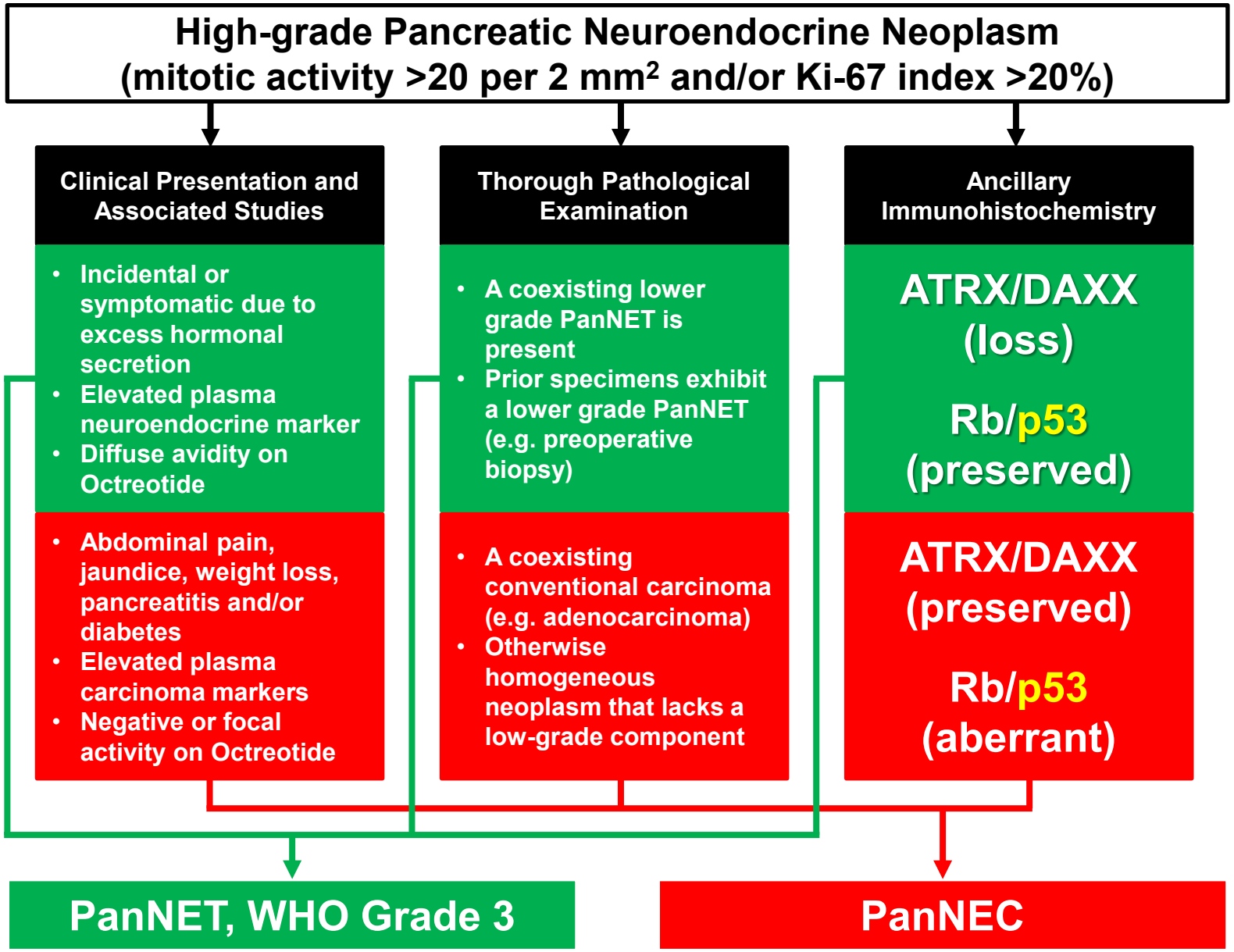


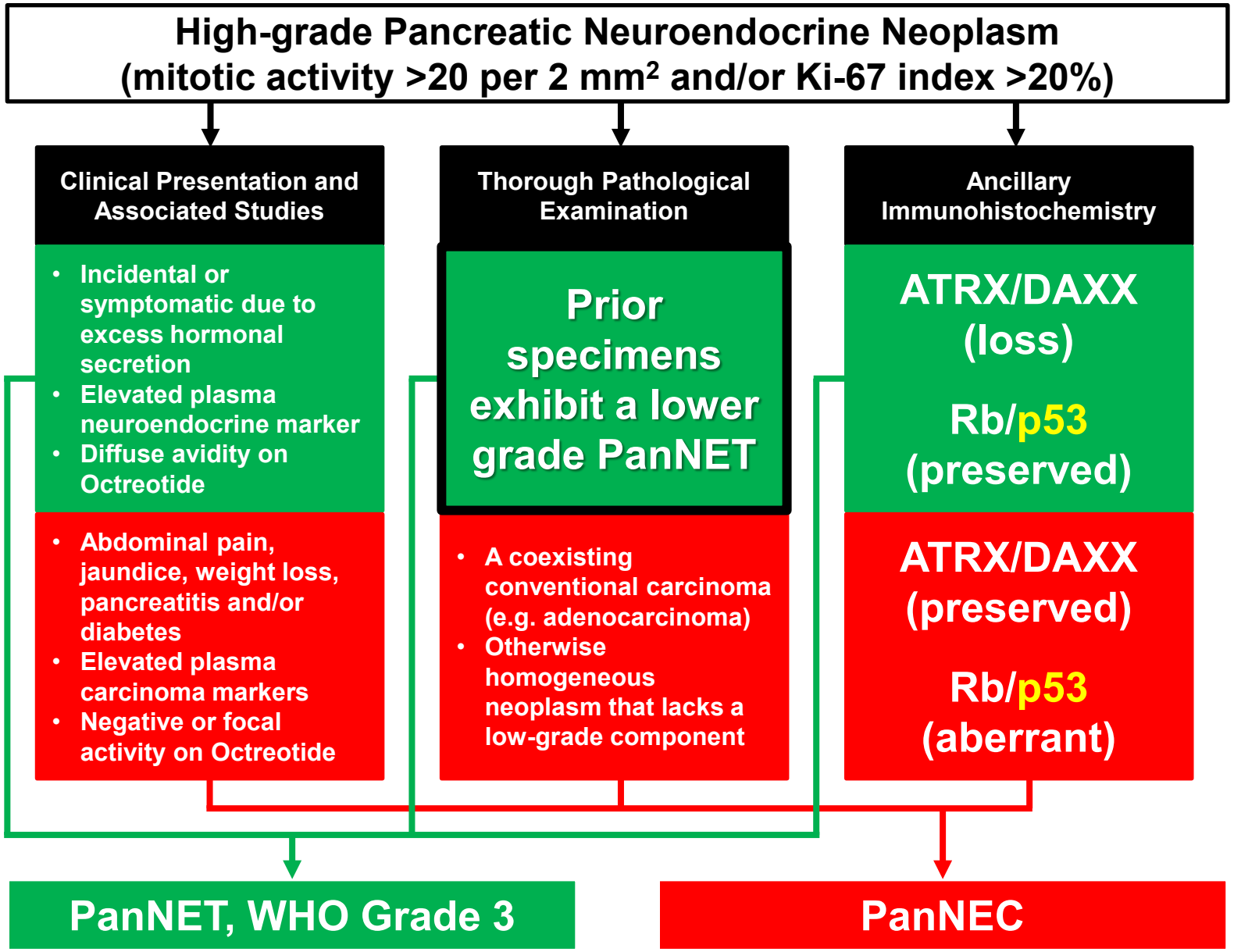
Metastatic Well-Differentiated Pancreatic Neuroendocrine Tumor, WHO Grade 3

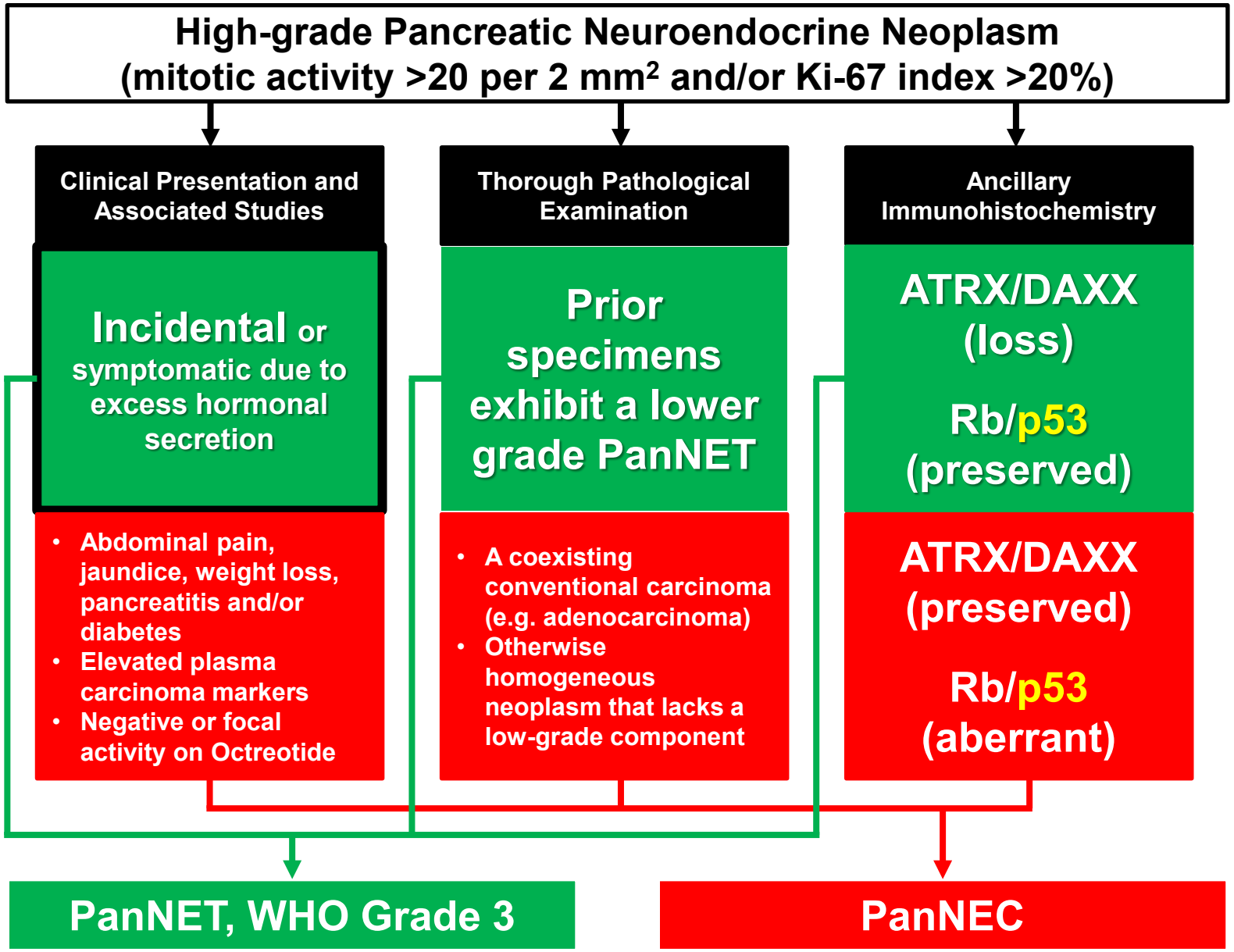







High-grade Pancreatic Neuroendocrine Neoplasm
(mitotic activity >20 per 2 mm2 and/or Ki-67 index >20%)
Clinical Presentation and Associated Studies
Incidental or symptomatic due to excess hormonal secretion
Elevated plasma neuroendocrine marker
Diffuse avidity on Octreotide
Abdominal pain, jaundice, weight loss, pancreatitis and/or diabetes
Elevated plasma carcinoma markers
Negative or focal activity on Octreotide
Thorough Pathological Examination
A coexisting lower grade PanNET is present
Prior specimens exhibit a lower grade PanNET (e.g. preoperative biopsy)
A coexisting conventional carcinoma (e.g. adenocarcinoma)
Otherwise homogeneous neoplasm that lacks a low-grade component
Ancillary Immunohistochemistry
ATRX/DAXX (loss)
Rb/p53 (preserved)
ATRX/DAXX (preserved)
Rb/p53 (aberrant)
PanNET, WHO Grade 3
PanNEC


High-grade Pancreatic Neuroendocrine Neoplasm
(mitotic activity >20 per 2 mm² and/or Ki-67 index >20%)
Clinical Presentation and Associated Studies
Thorough Pathological Examination
Ancillary Immunohistochemistry
• Incidental or symptomatic due to excess hormonal secretion
• Elevated plasma neuroendocrine marker
• Diffuse avidity on Octreotide
Prior specimens exhibit a lower grade PanNET
ATRX/DAXX (loss)
Rb/p53 (preserved)
• Abdominal pain, jaundice, weight loss, pancreatitis and/or diabetes
• Elevated plasma carcinoma markers
• Negative or focal activity on Octreotide
• A coexisting conventional carcinoma (e.g. adenocarcinoma)
• Otherwise homogeneous neoplasm that lacks a low-grade component
ATRX/DAXX (preserved)
Rb/p53 (aberrant)
PanNET, WHO Grade 3
PanNEC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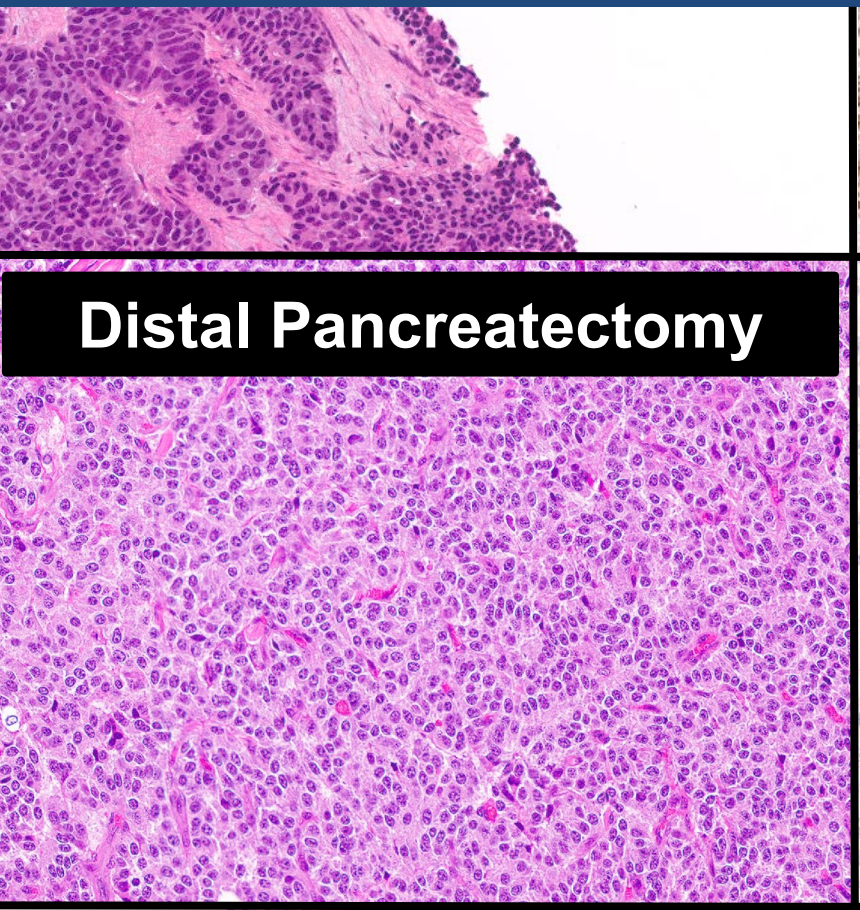
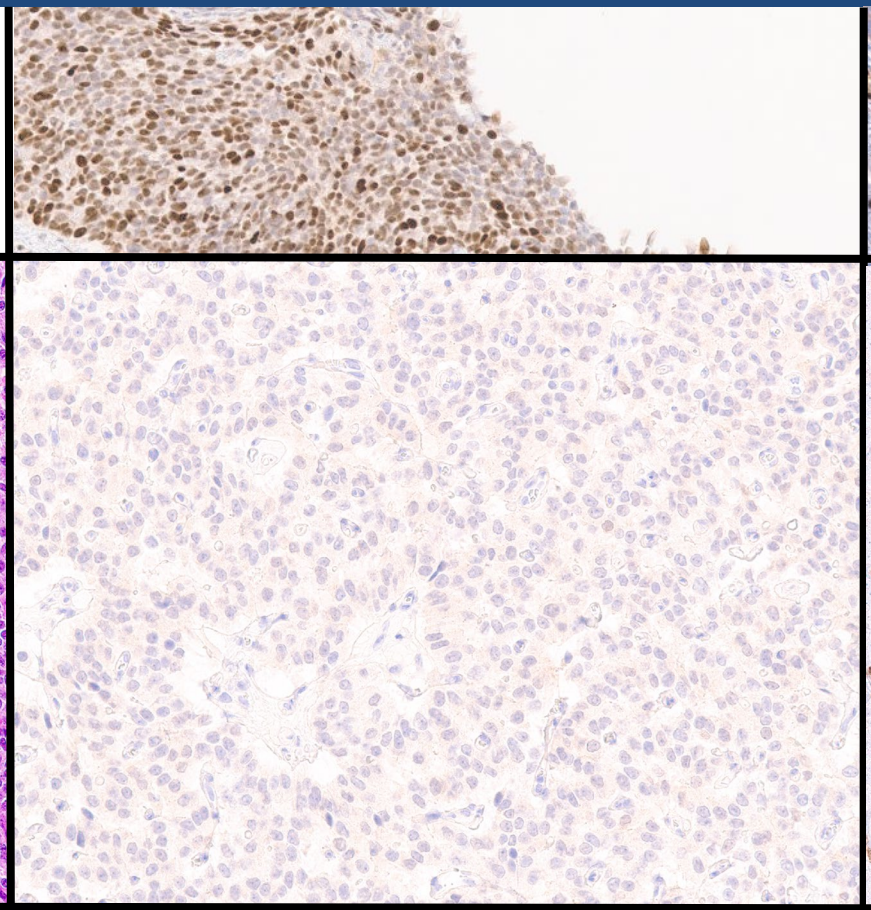
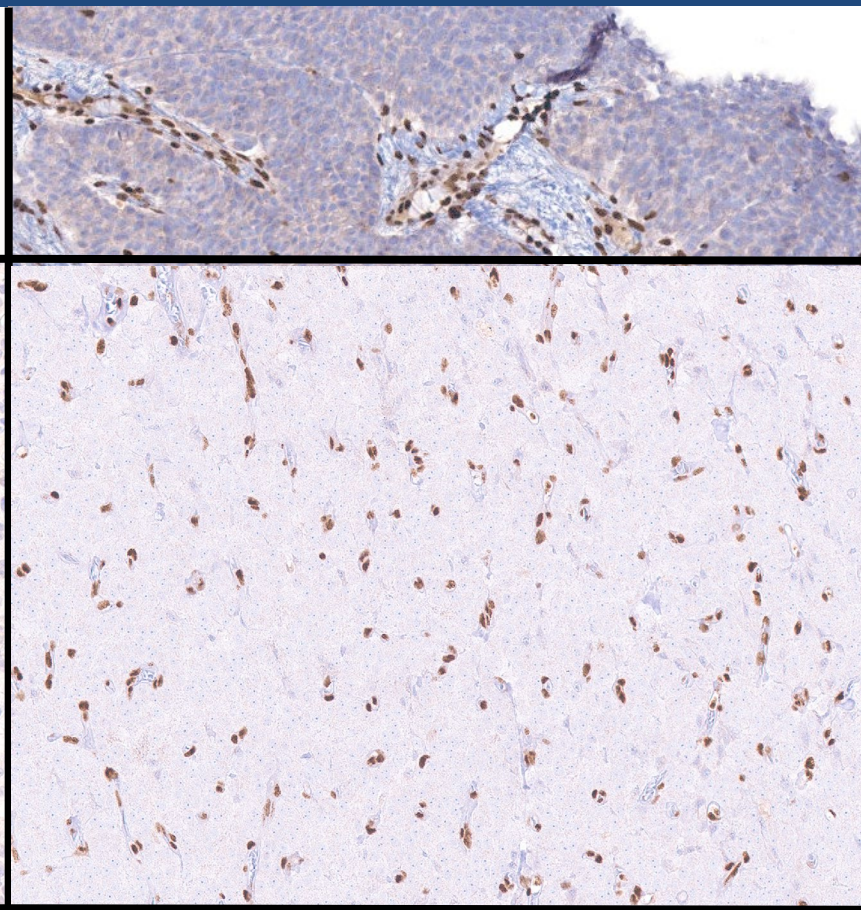
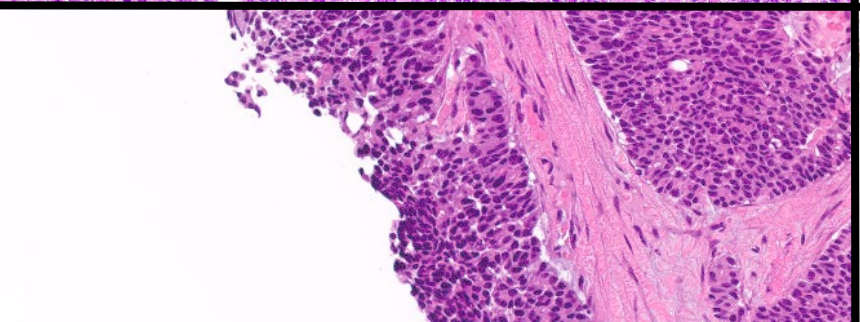
• A coexisting conventional carcinoma (e.g. adenocarcinoma)
• Otherwise homogeneous neoplasm that lacks a low-grade component
ATRX/DAXX (preserved)
Rb/p53 (aberrant)
PanNET, WHO Grade 3
PanNEC

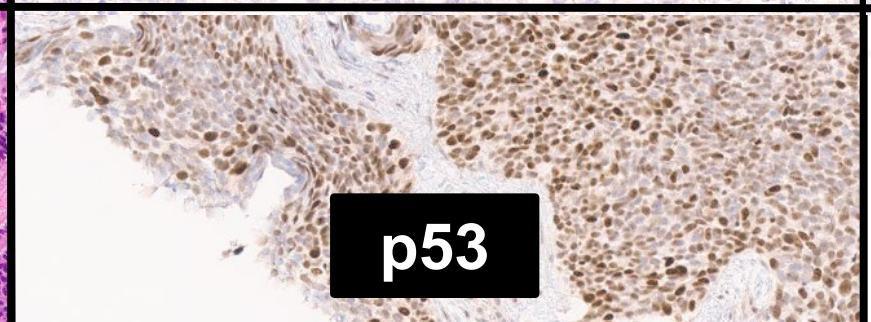
Case 4: G3 PanNET

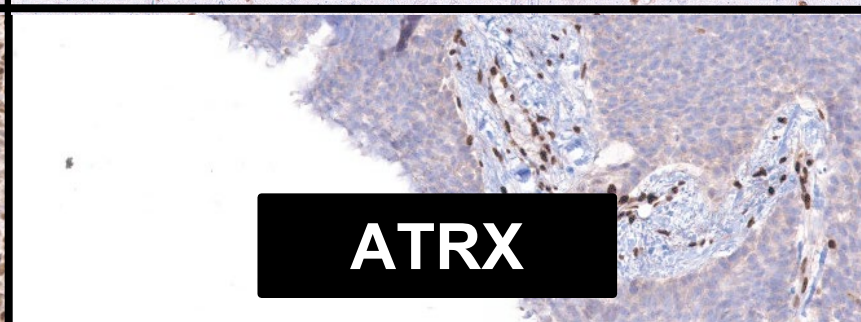




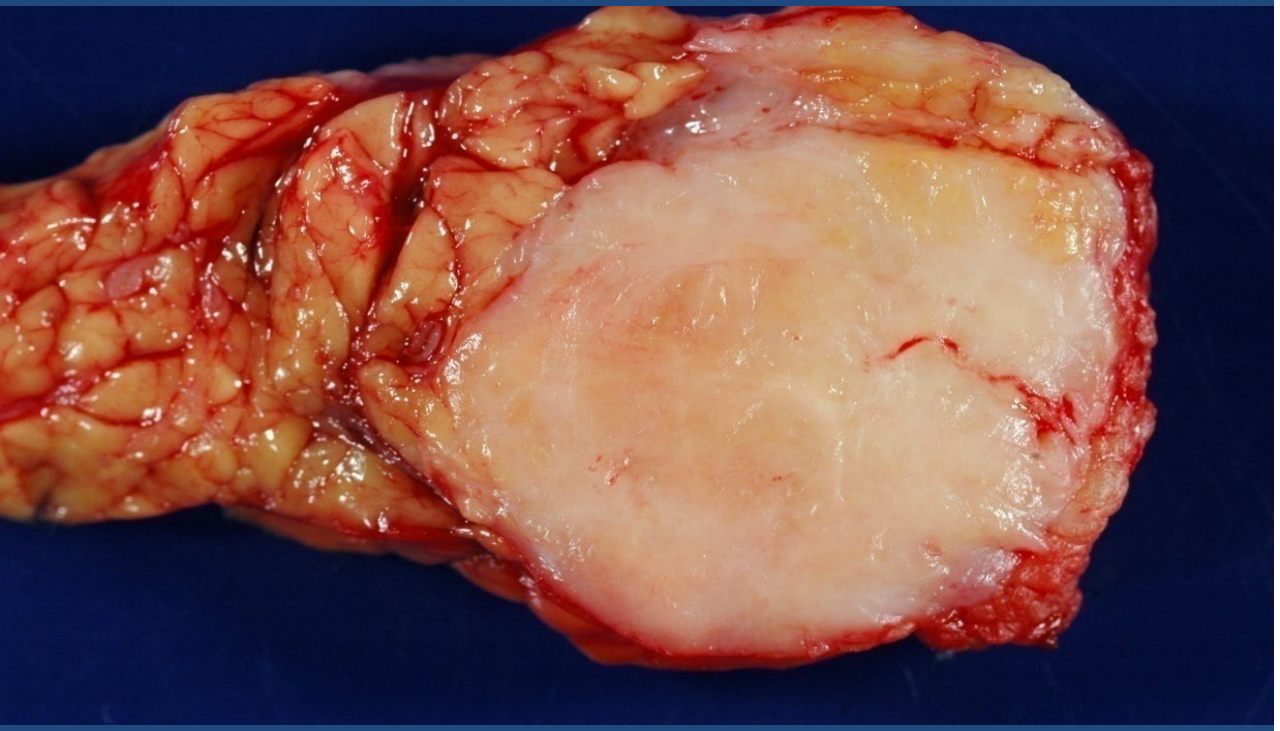








Solid



Chronic Pancreatitis*

Differential Dx

- Pancreatic Ductal Adenocarcinoma
- Acinar Cell Carcinoma
- Pancreatoblastoma
- Well-Differentiated Neuroendocrine Tumor
- Poorly-Differentiated Neuroendocrine Carcinoma
- Solid-Pseudopapillary Neoplasm

Part 1: Summary

- Next-Generation Needle Pathology:
  - Combination of cytopathology and surgical pathology
  - Adenocarcinoma:
    - Free-floating, architectural complexity, cytoplasmic clearing & nuclear abnormalities
  - Chronic pancreatitis:
    - Spectrum of histologic/cytologic findings
  - Immunohistochemical stains: p53 (strong/diffuse vs null), SMAD4 (loss), and ARID1A (loss)

Part 1: Summary

Features	ACC	PB	SPN	PanNET	PanNEC
Pathology	Rosettes; Prominent Nucleoli	Squamoid Nests	Plasmacytoid w/ Globules; Thin Vessels	Plasmacytoid w/ Stippled Chromatin	Plasmacytoid w/ Mitotic Figures
Bcl-10	Positive	Positive	Negative	Negative	Negative
Beta-catenin	Membran.	Squamoid Nests	Nuclear & Membran. (Diffuse)	Membran.	Membran.
LEF1	Negative	Squamoid Nests	Nuclear (Diffuse)	Negative	Negative
Synapto.	+/-	+/-	Positive	Positive	Positive
Ki-67*	>20%	>20%	>3%	Most <20%	>20%

Part 1: Summary

- **DAXX and ATRX are prognostic biomarkers for PanNETs**

Loss of DAXX and ATRX Are Associated With Chromosome Instability and Reduced Survival of Patients With Pancreatic Neuroendocrine Tumors

Ilaria Marinoni,[1] Anja Schmitt Kurrer,[1] Erik Vassella,[1] Matthias Dettmer,[1] Thomas Rudolph,[1] Vanessa Banz,[2] Fabio Hunger,[1] Silvan Pasquinelli,[1] Ernst–Jan Speel,[3] and Aurel Perren[1]

Biology of Human Tumors

Clinical Cancer Research

Alternative Lengthening of Telomeres in Primary Pancreatic Neuroendocrine Tumors Is Associated with Aggressive Clinical Behavior and Poor Survival

Joo Young Kim[1], Jacqueline A. Brosnan-Cashman[2], Soyeon An[3], Sung Joo Kim[3], Ki-Byung Song[4], Min-Sun Kim[5], Mi-Ju Kim[5], Dae Wook Hwang[4], Alan K. Meeker[2], Eunsil Yu[3], Song Cheol Kim[4,5], Ralph H. Hruban[2], Christopher M. Heaphy[2], and Seung-Mo Hong[3,5]

Biology of Human Tumors

Clinical Cancer Research

Alternative Lengthening of Telomeres and Loss of DAXX/ATRX Expression Predicts Metastatic Disease and Poor Survival in Patients with Pancreatic Neuroendocrine Tumors

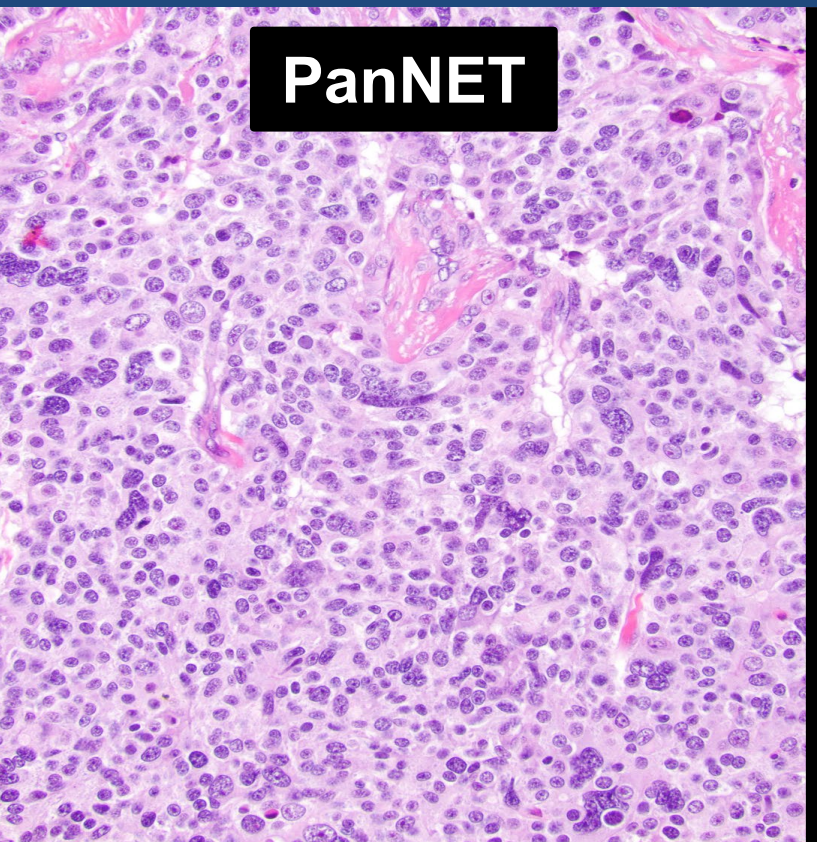
Aatur D. Singhi[1], Ta-Chiang Liu[2], Justin L. Roncaioli[3], Dengfeng Cao[2], Herbert J. Zeh[4], Amer H. Zureikat[4], Allan Tsung[4], J. Wallis Marsh[4], Kenneth K. Lee[4], Melissa E. Hogg[4], Nathan Bahary[5], Randall E. Brand[5], Kevin M. McGrath[5], Adam Slivka[5], Kristi L. Cressman[1], Kimberly Fuhrer[1], and Roderick J. O'Sullivan[3]

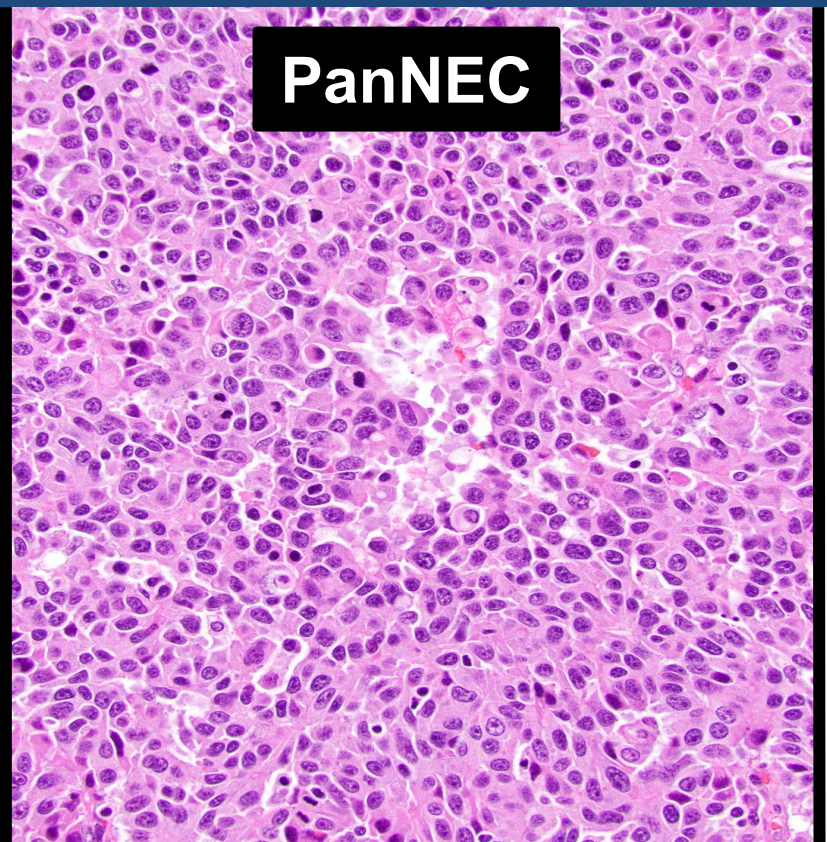
Non-functional pancreatic neuroendocrine tumours: ATRX/DAXX and alternative lengthening of telomeres (ALT) are prognostically independent from ARX/PDX1 expression and tumour size

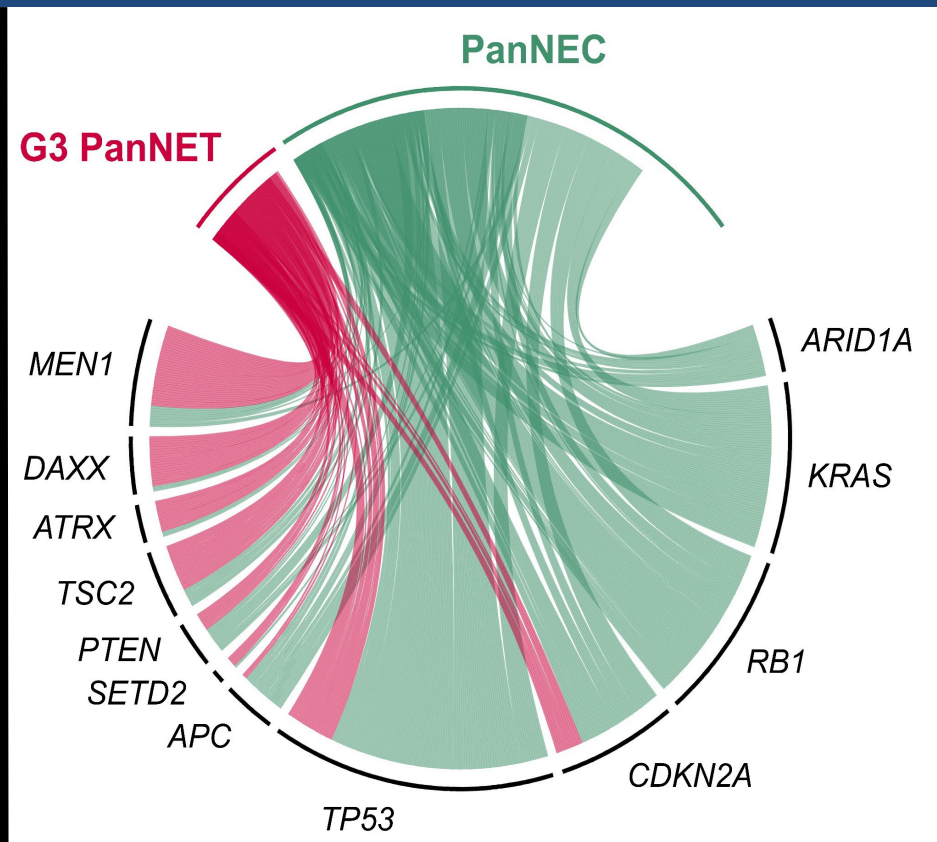
Wenzel M Hackeng ,[1] Lodewijk A A Brosens ,[1] Joo Young Kim,[2] Roderick O'Sullivan,[3] You-Na Sung,[4] Ta-Chiang Liu,[5] Dengfeng Cao,[5] Michelle Heayn,[6] Jacqueline Brosnan-Cashman,[7] Soyeon An,[8] Folkert H M Morsink,[1] Charlotte M Heidsma,[9] Gerlof D Valk,[10] Menno R Vriens,[11] Els Nieveen van Dijkum,[9] G Johan A Offerhaus ,[1] Koen M A Dreijerink,[1,12] Herbert Zeh,[13] Amer H Zureikat,[14] Melissa Hogg,[15] Kenneth Lee,[14] David Geller,[14] J Wallis Marsh,[16] Alessandro Paniccia,[14] Melanie Ongchin,[14] James F Pingpank,[14] Nathan Bahary,[17] Muaz Aijazi ,[17] Randall Brand,[17] Jennifer Chennat,[17] Rohit Das,[17] Kenneth E Fasanella,[17] Asif Khalid,[17] Kevin McGrath,[17] Savreet Sarkaria,[17] Harkirat Singh,[17] Adam Slivka,[17] Michael Nalesnik,[6] Xiaoli Han,[6] Marina N Nikiforova,[6] Rita Teresa Lawlor,[18] Andrea Mafficini,[18] Boris Rusev,[18] Vincenzo Corbo,[18,19] Claudio Luchini ,[19,20] Samantha Bersani,[19] Antonio Pea,[21] Sara Cingarlini,[21,22] Luca Landoni,[20,21] Roberto Salvia,[20,21] Massimo Milione,[23] Michele Milella,[20,22] Aldo Scarpa ,[18,19,20] Seung-Mo Hong,[4] Christopher M Heaphy ,[7,24] Aatur D Singhi [6]

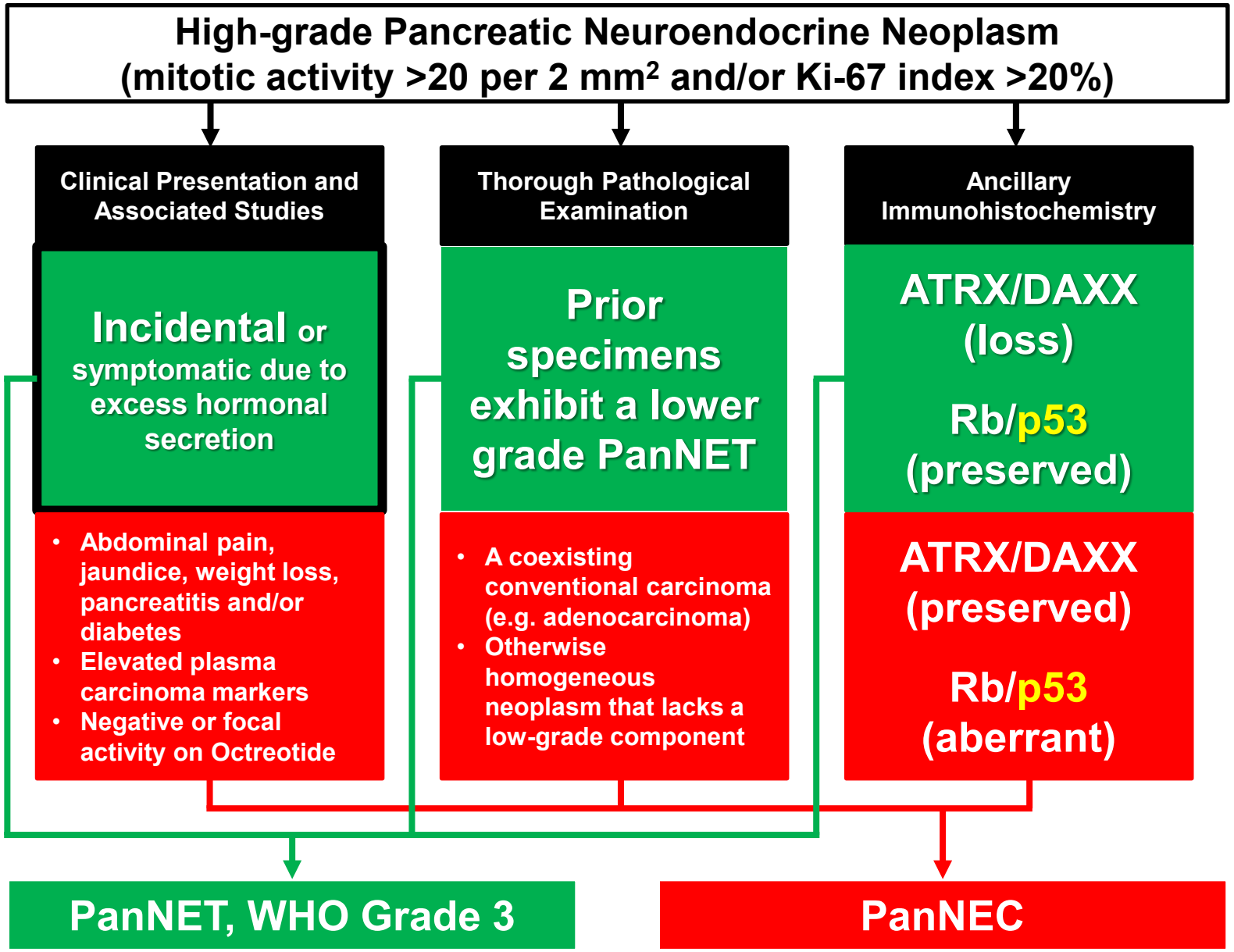
Part 1: Summary

- **The distinction between G3 WD-PanNET and PD-PanNEC can be challenging using morphology alone.**





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