

# Pancreatic Cysts

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No disclosures



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# Outline:

- Biopsy Technique
- Tissue Triage
- Biochemical testing
- Molecular testing
- Cytomorphology
- Reporting

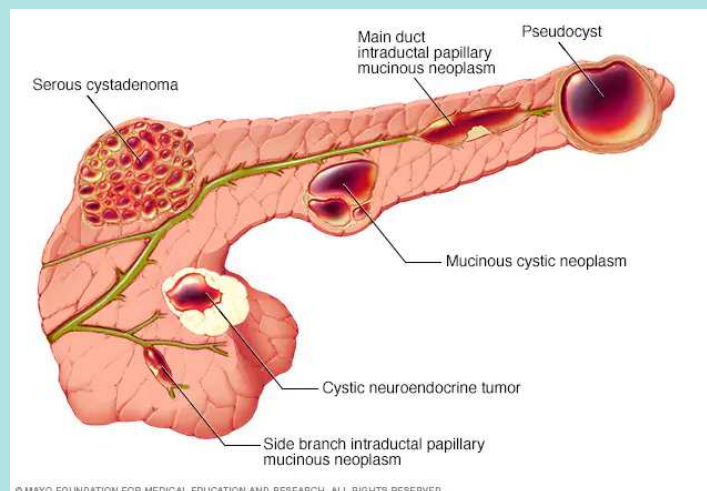


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## Pancreatic Cysts

### Differential Diagnosis

- Pseudocyst
- Lymphoepithelial cyst
- Serous cyst
- Mucinous cyst
  - (MCN and IPMN)
- Cystic degeneration of typically solid tumors
  - PanNET
  - SPN
  - other
- Other more rare cysts



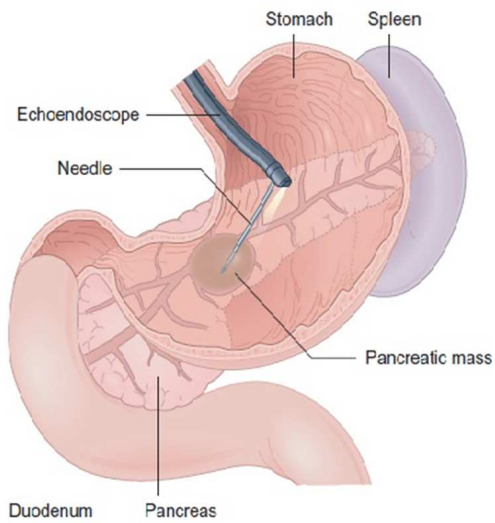
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# Biopsy Technique: EUS-FNA

Transduodenal:  
head



Transgastric:  
body and tail



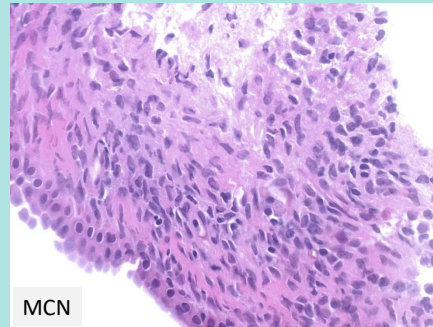
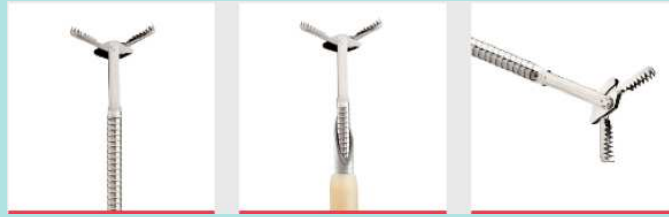
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García-García de Paredes, Ana, et al. "Current clinical and research fluid biomarkers to aid risk stratification of pancreatic cystic lesions." *Revista Española de Enfermedades Digestivas*[REED], vol. 113, no. 10, Oct. 2021, pp. 714+

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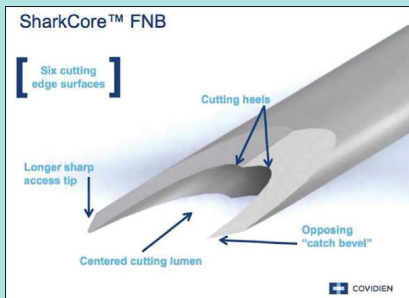
## Moray Micro-forceps biopsy



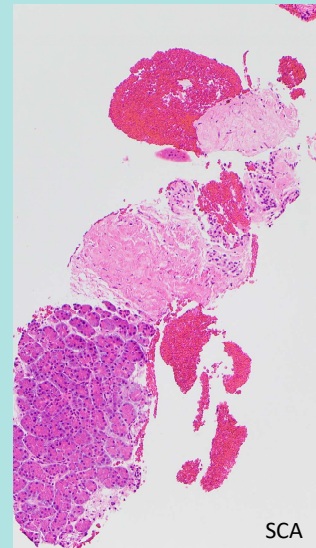
Zhang ML, Arpin RN, Brugge WR, Forcione DG, Basar O, Pitman MB. Moray micro forceps biopsy improves the diagnosis of specific pancreatic cysts. Cancer Cytopathol. 2018 Jun;126(6):414-420.

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## Next Generation Needles

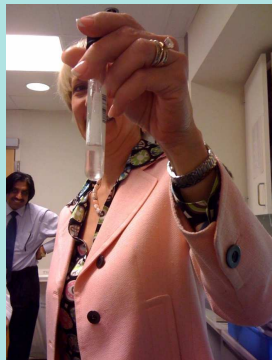


Acquire- Boston Scientific

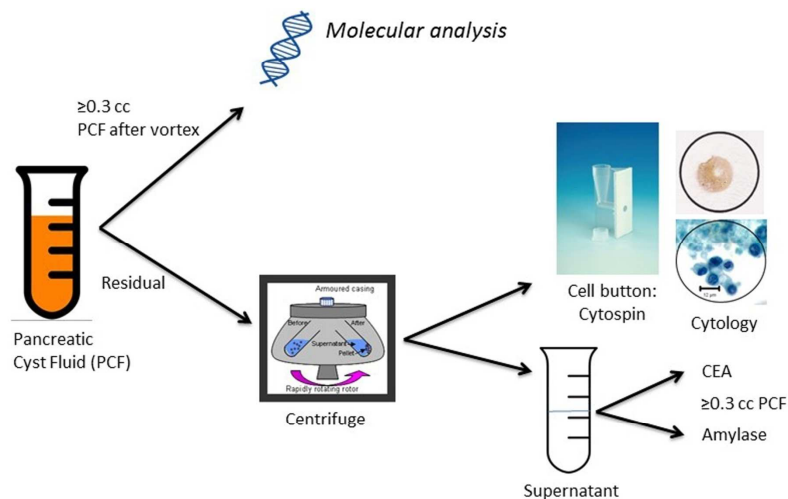


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## Pancreatic Cyst Fluid Triage



## Cytology Interpretation

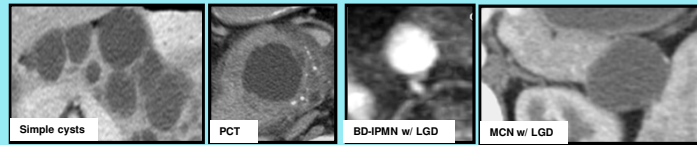
### Multimodal Approach

- Clinical Information
  - Patient age and gender
  - Symptoms
  - Past medical history
- Radiological Information
  - Location of mass in the pancreas (and thus organ traversed for EUS)
  - Cyst characteristics
    - Size, contours, invasion
    - Cyst structure: uni- or multilocular; thick/thin wall, Ca<sup>++</sup>, nodule/mass in the wall
    - Gross cyst contents: thick, viscous, thin, water, clear, brown
- Biochemical tests: CEA, amylase, glucose
- Molecular tests: *KRAS*, *GNAS*, *TP53*, *SMAD4*, *CDKN2A/p16*



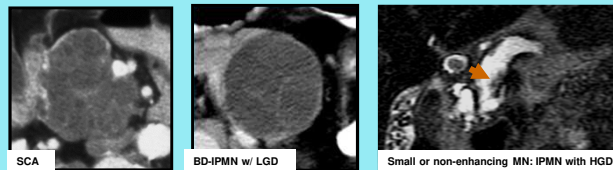
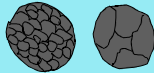
# Pancreatic Cysts: CT

## unilocular



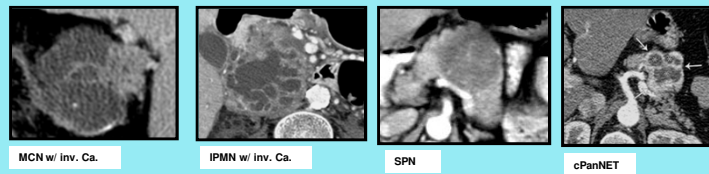
### Benign imaging

## multilocular



### Benign to Worrisome imaging

## complex

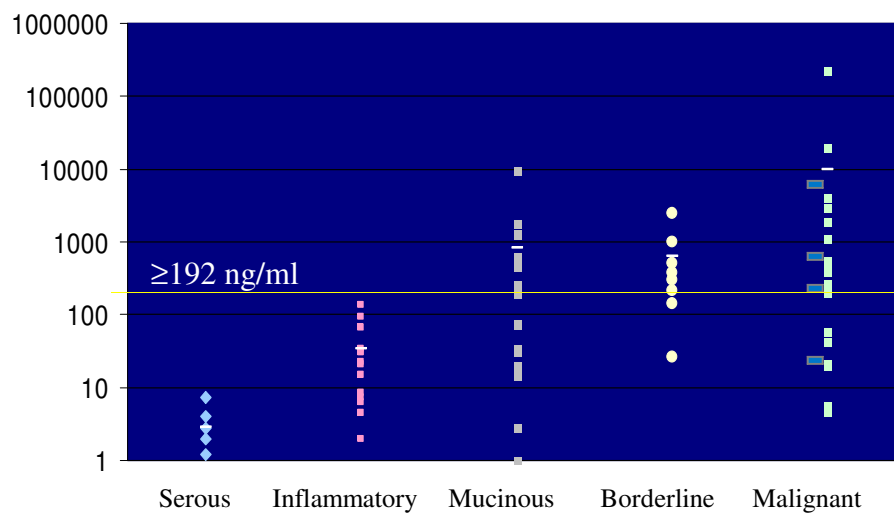


### Worrisome to High-risk imaging



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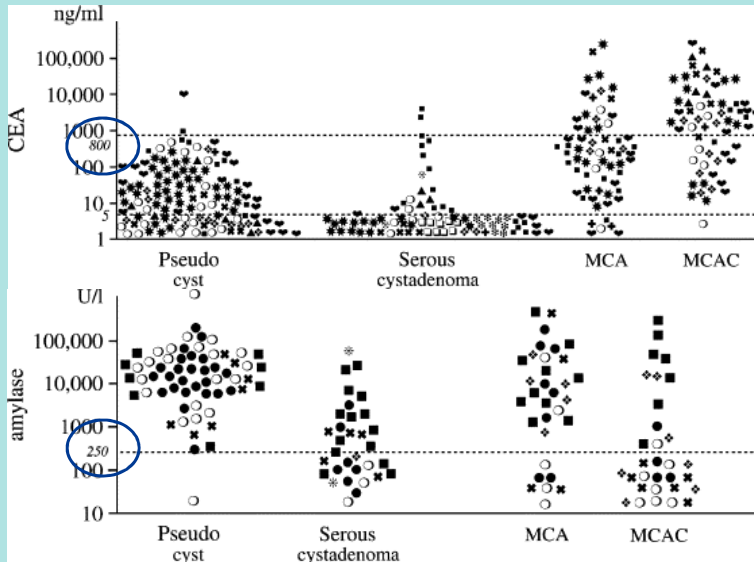
# CEA by cyst fluid analysis



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## CEA cut-off levels lab and study dependent

(van der Waaij, et. al. Cystfluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointes Endosc. 2005; 62:383)



CEA >800ng/ml	Neoplastic mucinous cysts
CEA <5ng/ml	Serous cystadenoma Pseudocyst
Amylase <250 U/L	Not a pseudocyst

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## CEA and Amylase: Key Points

Elevated CEA ( $\geq 192$  ng/ml) supports a mucinous cyst

- Does not distinguish IPMN from MCN
- Level does not correlate with malignancy
- Rare FP: PCT, GI duplication cyst, LEC

Amylase levels

- Elevated in the 1000's for most PCT
- Low amylase levels exclude a PCT
- Elevated level does not distinguish IPMN from MCN
  - MCN can have high CEA
  - IPMN can have low CEA

# Molecular Tests: Key Points

## **KRAS**

- Mutation(s) support a neoplastic mucinous cyst
  - Does not distinguish IPMN and MCN
  - Does not correlate with grade

## **GNAS**

- Mutation supports IPMN over MCN
  - Does not correlate with grade

## **RNF43**

- Mutation supports a mucinous cyst
  - Does not distinguish IPMN and MCN

## **3p deletions**

- 3p25, VHL gene, supports SCA
- Other 3p deletions also noted in SCA

## **CTNNB1** (beta-catenin) deletion

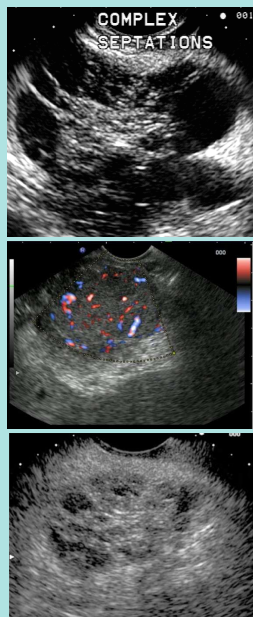
- Mutation(s) support SPN

**TP53** mutation, **CDKN2A** loss, **SMAD4** loss support a HR cyst

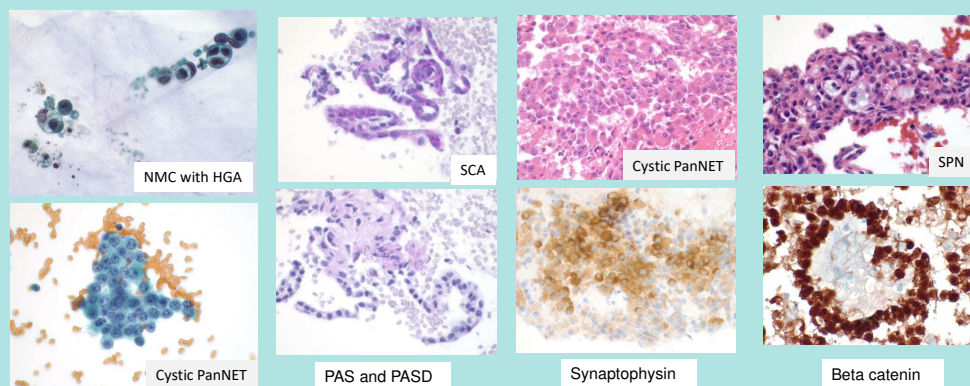


Cancer Cytopathol. 2017 Jan;125(1):41-47; Gastrointest Endosc. 2016 Jan;83(1):140-8; Surg Pathol Clin. 2022 Sep;15(3):455-468; Gastroenterology. 2023 Jan;164(1):1-11

## Clinical and Imaging Features



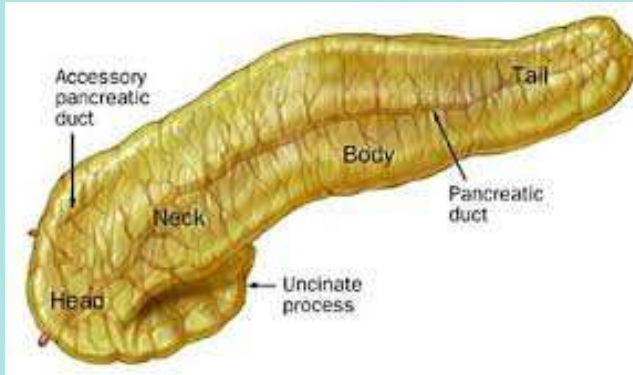
## Multimodal Approach: Cytomorphology, Special Stains and Immunohistochemistry



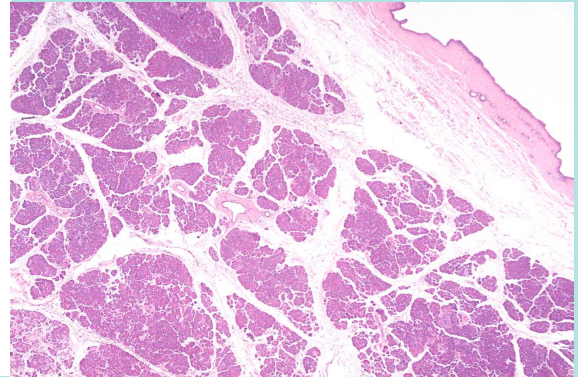
## Biochemical and Molecular analysis of Cyst Fluid

Cyst	Biochemical tests		Molecular Tests					
	CEA	Amy	KRAS	GNAS	3p25 (VHL)	P53	P16 (CDKN2A/INK4A)	SMAD4
PCT	↓	↑↑	-	-	-	-	-	-
SCA	↓↓	↓↓	-	-	+	-	-	-
IPMN	↑↓	↑↑	+	+	-	+ <sup>a</sup>	+ <sup>a</sup>	+ <sup>a</sup>
MCN	↑↓	↓↑	+	-	-	+ <sup>a</sup>	+ <sup>a</sup>	+ <sup>a</sup>

# Normal Pancreas



<https://www.hopkinsmedicine.org>



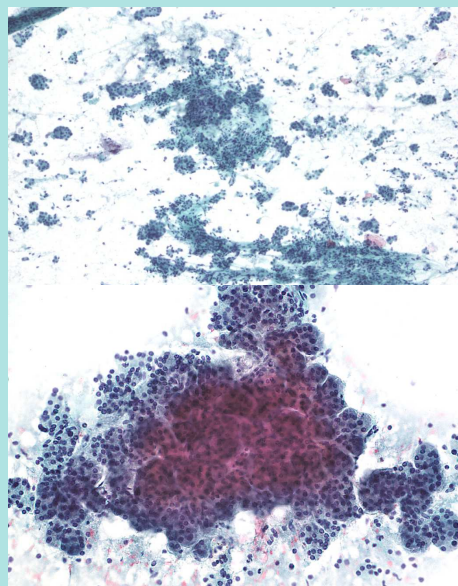
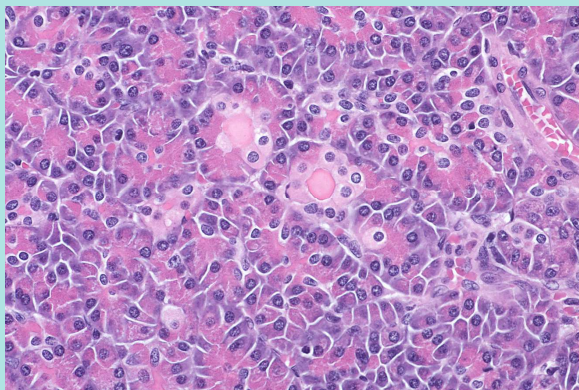
4th Series AFIP Fascicle on Tumors of the Pancreas



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# Normal Pancreas

## Acini and intercalated cells

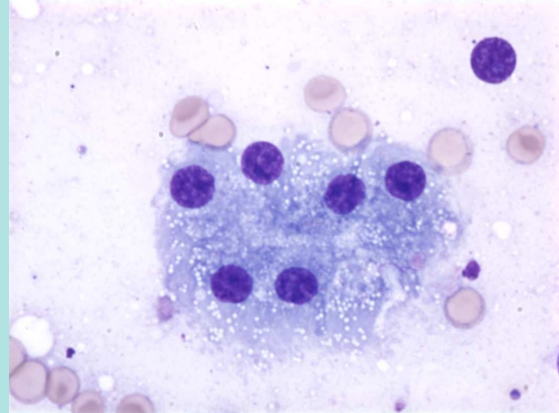
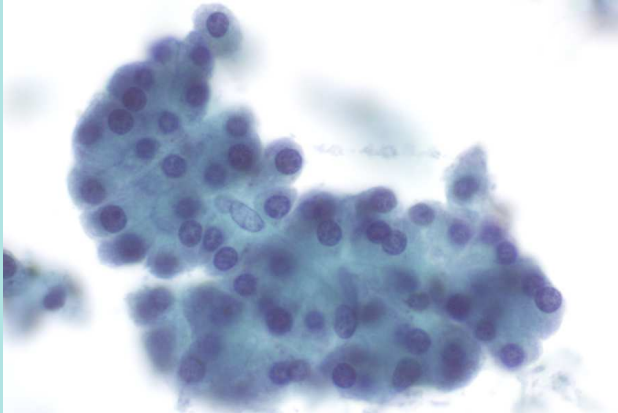


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## Normal Pancreas

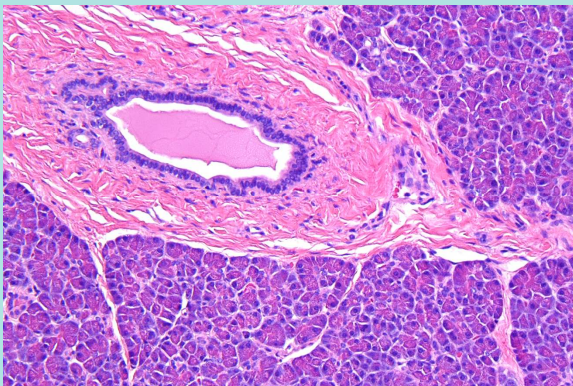
### Acinar Cells



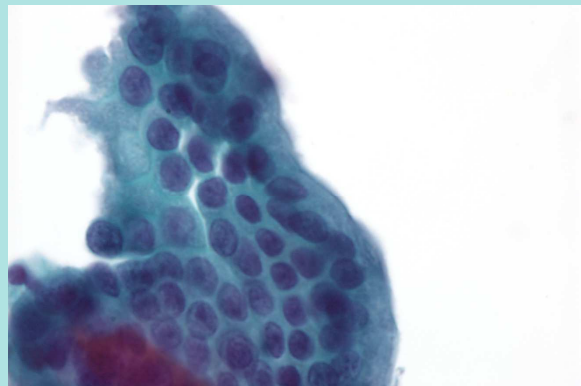
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## Normal Pancreas

### Pancreatic Ducts



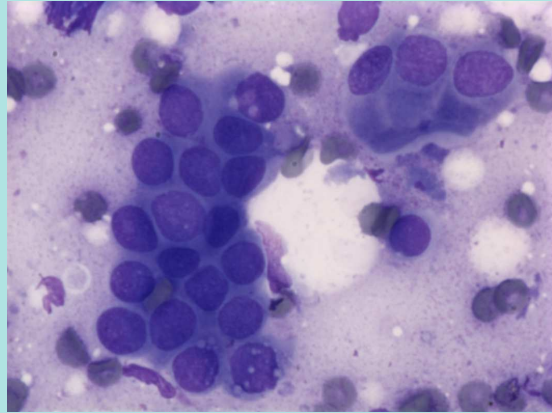
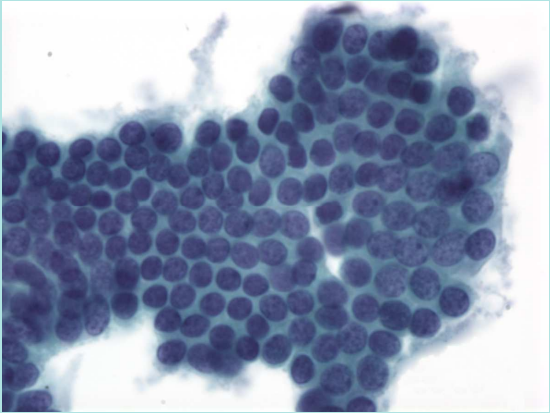
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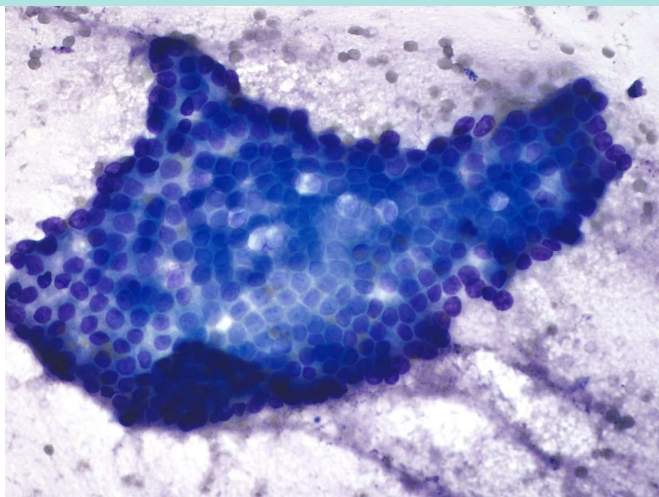
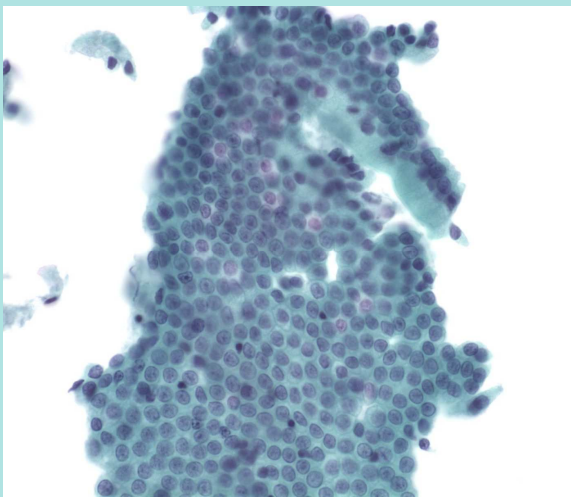


## Normal Pancreas Ductal Cells



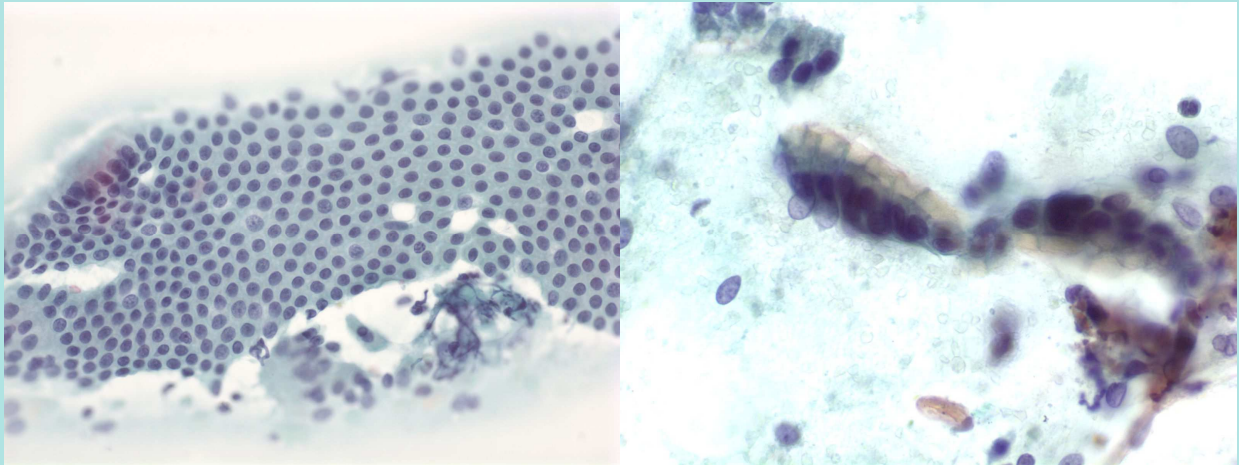
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## Duodenal Contamination



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## Gastric Contamination



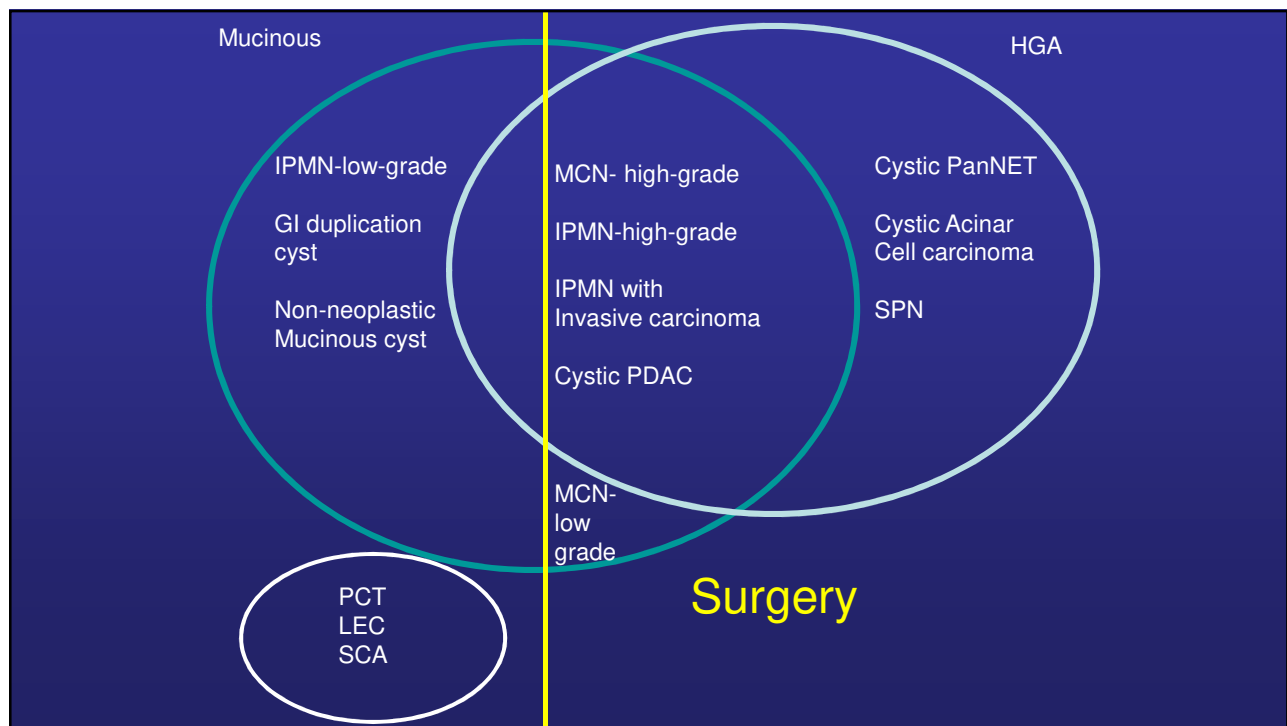
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## Two basic questions for Cyst analysis

- 1) Is the cyst mucinous or non-mucinous?
- 2) Is the cyst low-risk/grade or high-risk/grade?



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## Solid-Pseudopapillary Neoplasm

- **Clinical: young female**
  - Up to 2.7% of exocrine tumors; 5% of cystic neoplasms
  - 89% in young women, mean age ~ 28 years
- **Radiology: solid and cystic**
  - shows complex, large solid and cystic neoplasm
  - Slight preference for the pancreatic tail

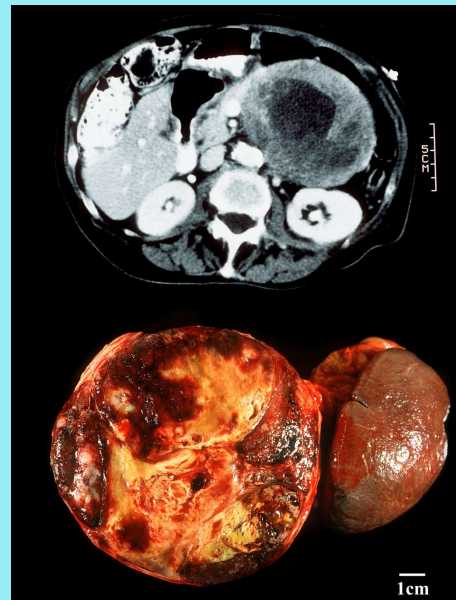
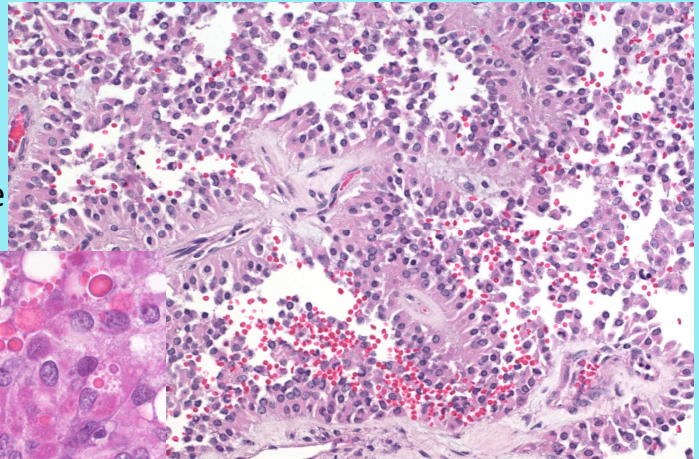
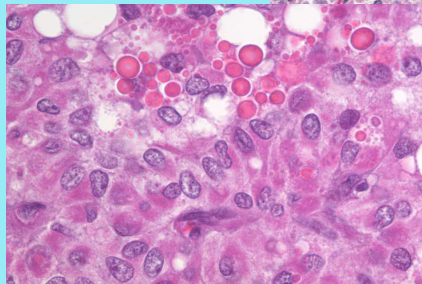


Image: AFIP Pancreas fascicle 2007



## Solid-Pseudopapillary Neoplasm

- Secondly cystic
- Pseudopapillae
- Cells cling to myxoid or hyalinized vessels
- Perinuclear vacuoles; hyaline globules

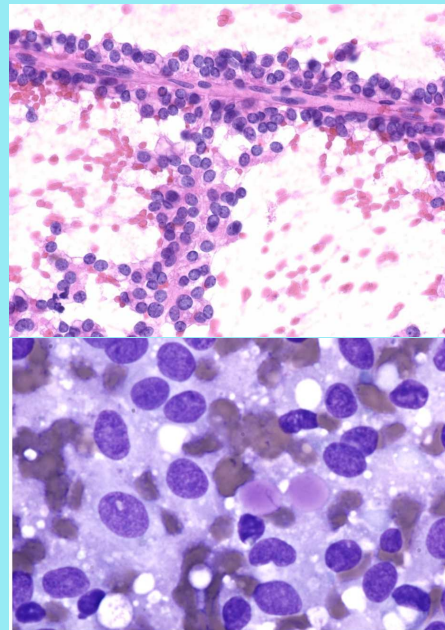
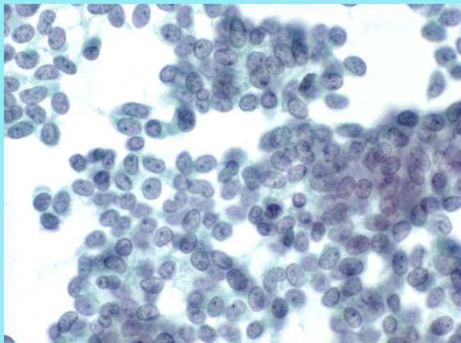


Images: AFIP Pancreas fascicle 2007

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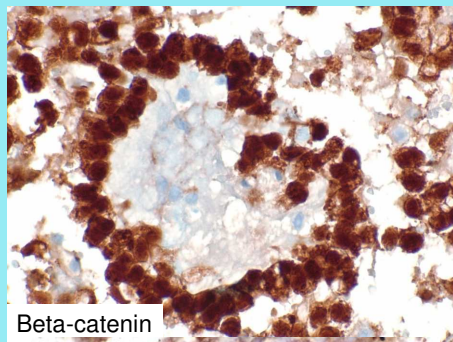
## Classic Morphology: SPN

- Papillary branching
- Myxoid stroma
- Clinging cells and single cells
- Euchromatin
- Oval, indented, grooved nuclei
- Perinuclear vacuoles/globules

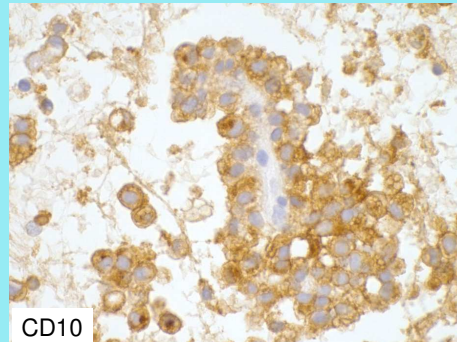


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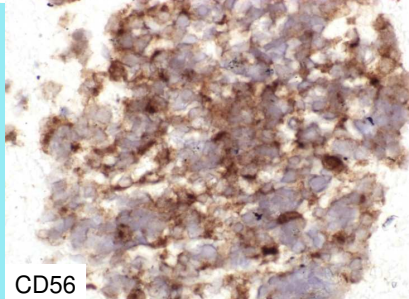
## IHC: SPN



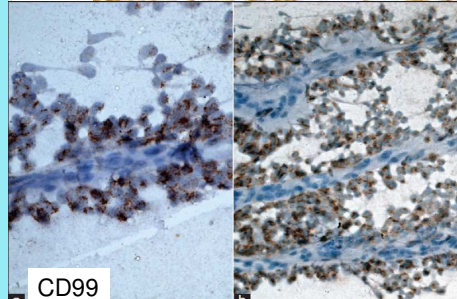
Beta-catenin



CD10



CD56



CD99

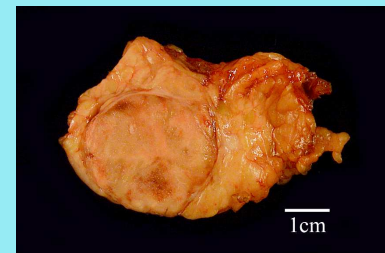
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## Well-Differentiated Pancreatic Neuroendocrine Tumor

- Clinical: **middle age adult**
  - Any age; 40-50 y.o.; M=F
  - Slow growing
- Radiological: **round mass**
  - Pancreatic tail > head/body
  - well-circumscribed
- Functional imaging-high levels of somatostatin receptor 2 (SSTR2) expression
  - Indium-111 ( $^{111}\text{In}$ ) pentetreotide scan (Octreoscan<sup>TM</sup>)- radiolabeled- use scintigraphy
  - Gallium-68 ( $^{68}\text{Ga}$ ) DOTATATE- positron emitter- use PET/CT



<https://radiologykey.com/pancreatic-neuroendocrine-tumors>

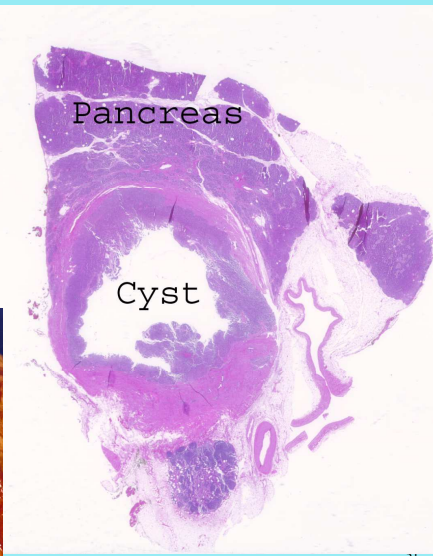
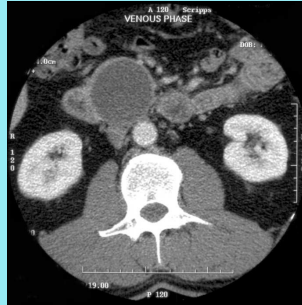


Images: AFIP Pancreas fascicle 2007

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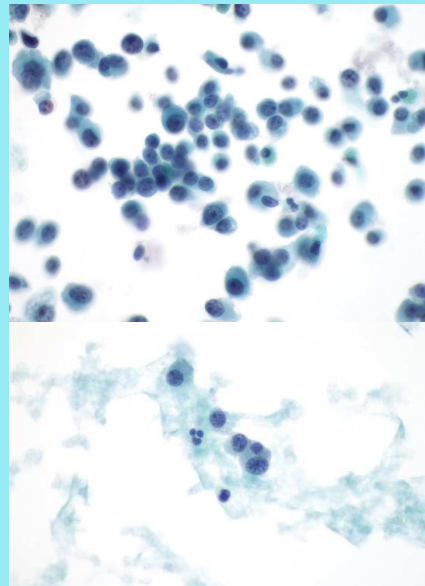
## Cystic PanNET

- 10% of tumors are cystic
- Secondary change
- Can mimic primary cysts
- Clue to diagnosis on imaging is **“thick cyst wall”**



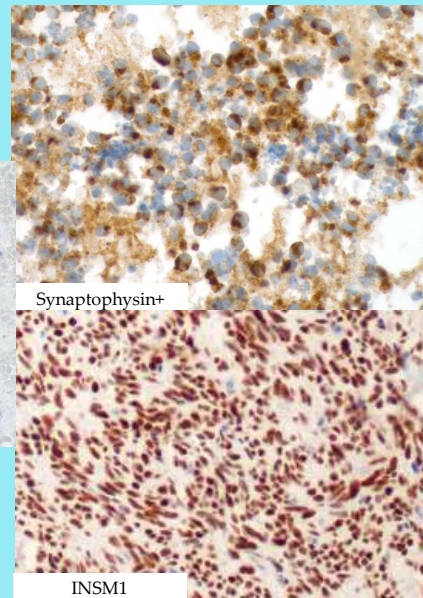
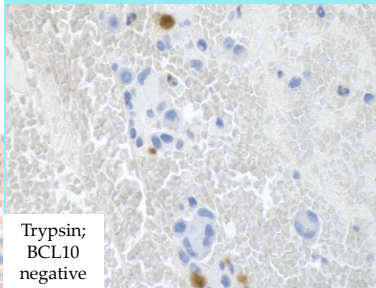
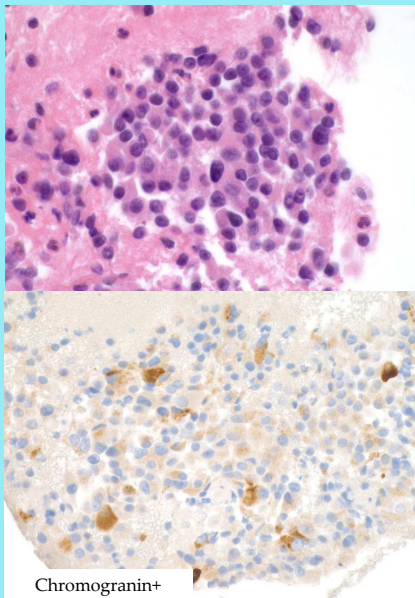
## Cystic PanNET

- Cytology is THE diagnostic test
  - CEA low
  - Amylase low
  - KRAS/GNAS negative
- Cells usually diagnostic when present



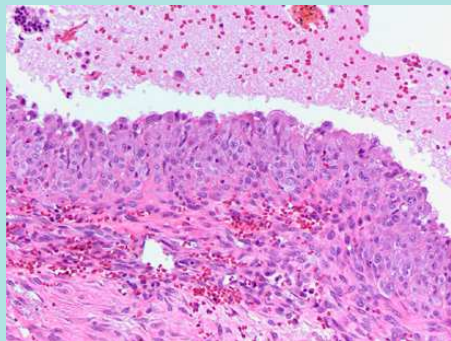


## Ancillary Studies: PanNET

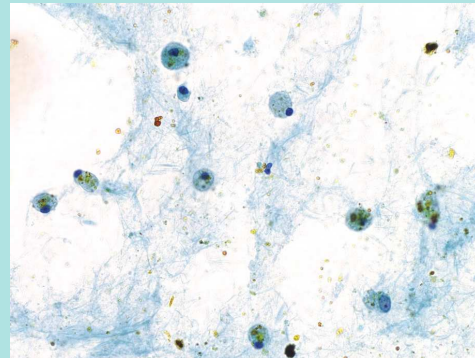
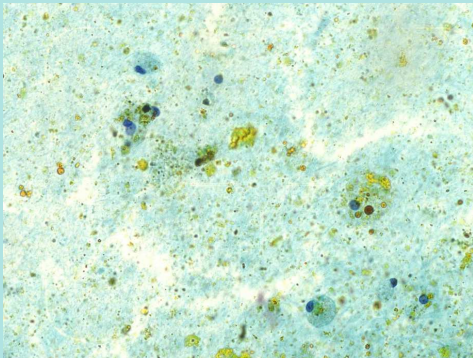


## Pancreatic Pseudocyst

- Clinical: **pancreatitis**
  - From alcohol, trauma, surgery
- Radiology: **large cyst, high volume fluid**
  - Unilocular, non-septated
  - Thick walled
  - No mural nodule
- Histology
  - Cyst lining of
  - histiocytes and
  - inflammatory
  - cells



## Pancreatic Pseudocyst: Cytology



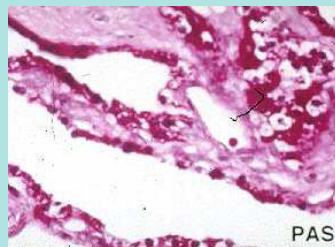
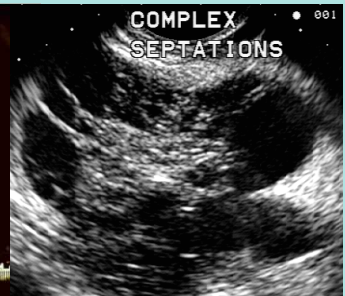
- cyst debris with blood, proteinaceous material and yellow hematoidin-like pigment (grossly brown and thin fluid)
- variable inflammation
- NO cyst lining epithelium (beware of contamination, mucin and epithelium)
- CEA low; amylase usually in the 1000's; no mutations



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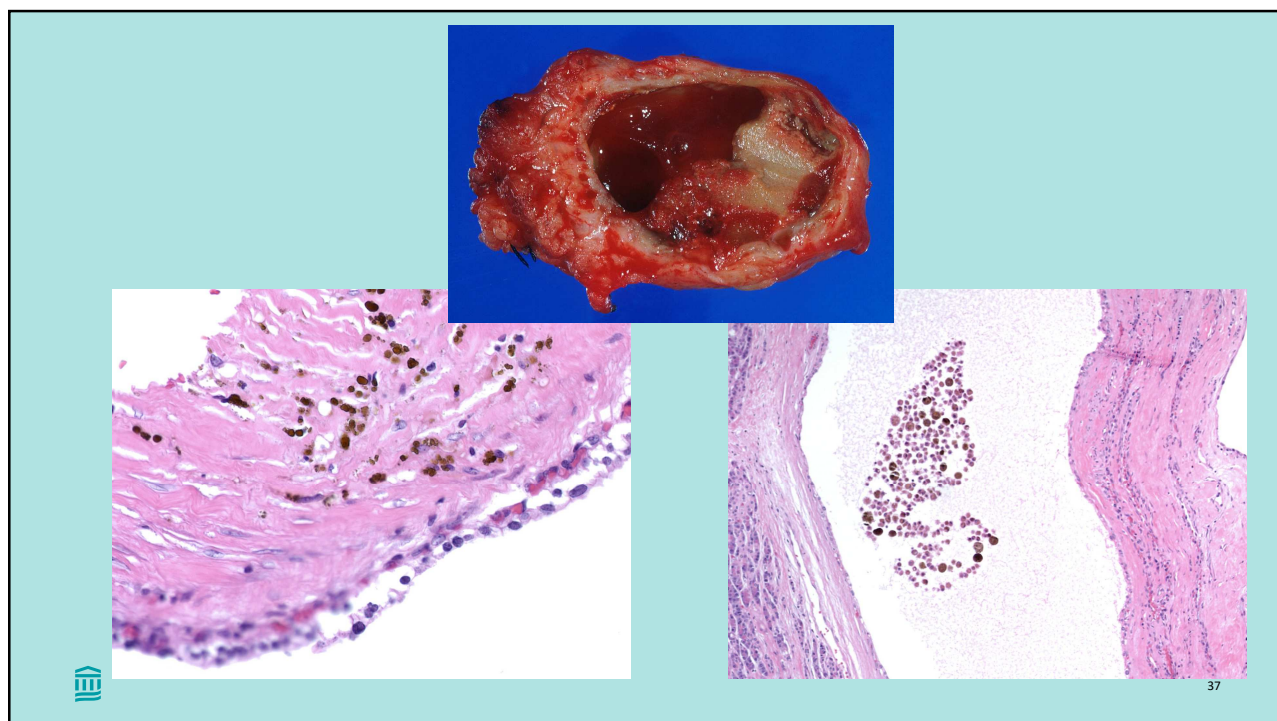
## Serous Cystadenoma

- Clinical: **asymptomatic, elderly female**
  - Benign, slow growing neoplasm women >> men, mean age 7<sup>th</sup> decade
  - Associated with VHL with deletion of 3p25 in most cases
  - Often asymptomatic, but can hemorrhage and cause pain
- Radiology: **multi-lobulated**
  - circumscribed
    - Microcystic with fibrous septae, central scar, calcifications in ~30-40%
- Histology
  - “glycogen-rich”
  - dPAS+ cuboidal epithelium



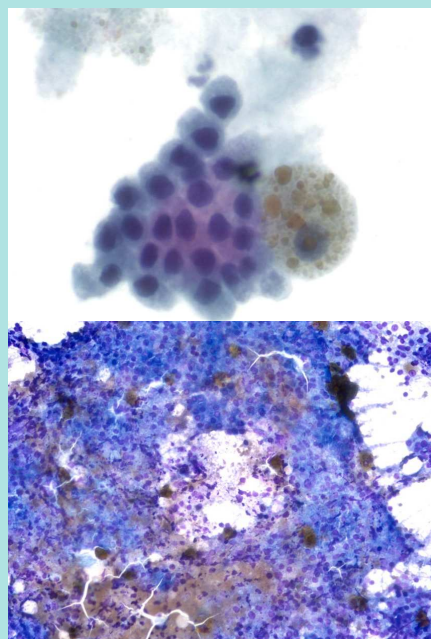
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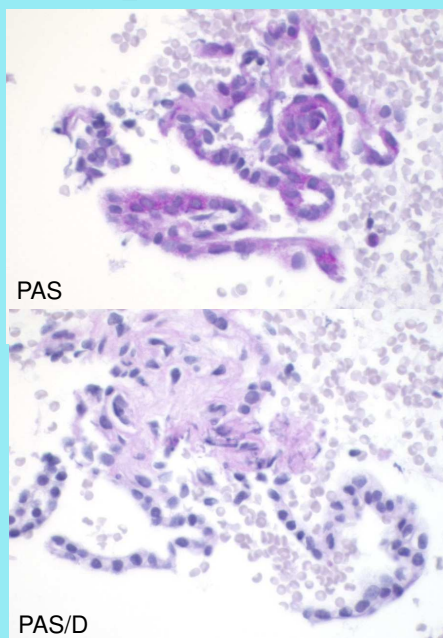
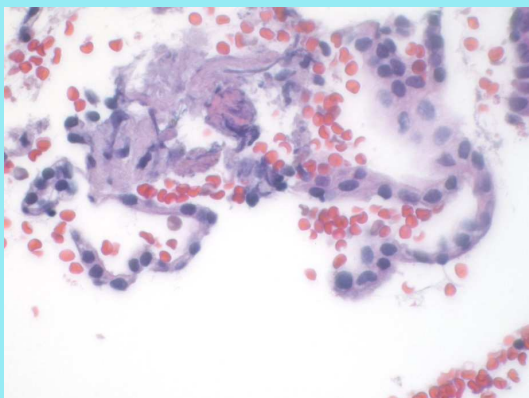


## Serous Cystadenoma

- Cuboidal non-mucinous epithelial cells
- Hemosiderin-laden macrophages in a clean or bloody, non-pseudocyst like background
- Grossly bloody or thin and clear
- CEA and amylase low
- NO *KRAS*/*GNAS*
- 3p deletions (3p25, VHL)

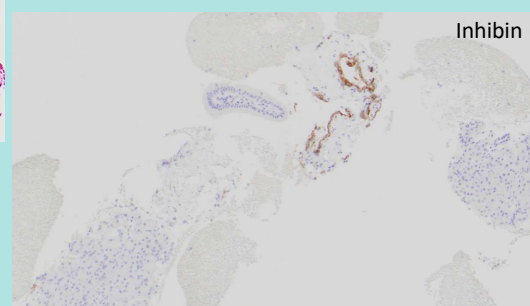
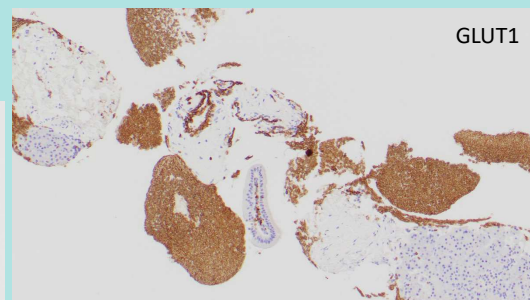
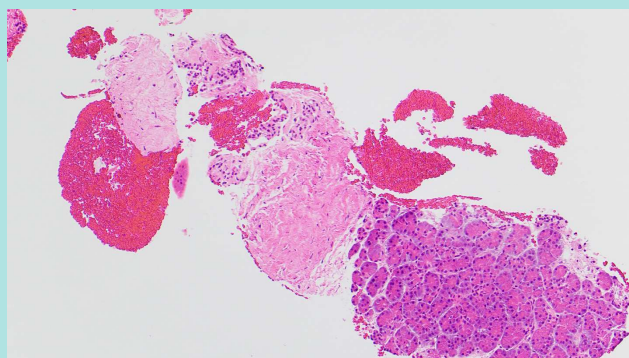


## Serous Cystadenoma: Special Stains



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## Serous Cystadenoma: Immunostains

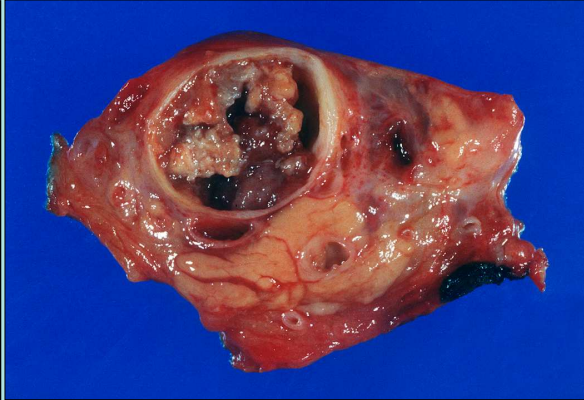


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## Neoplastic Mucinous Cysts



MCN

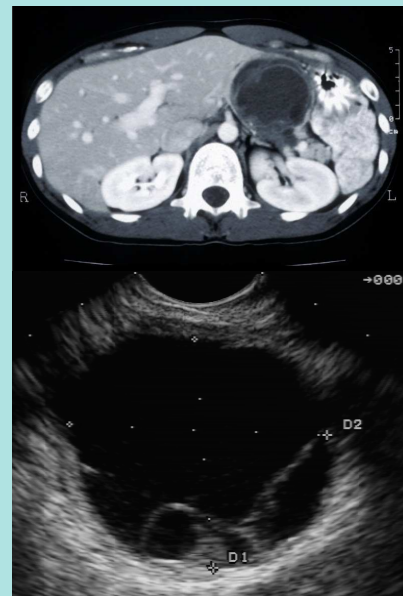


IPMN



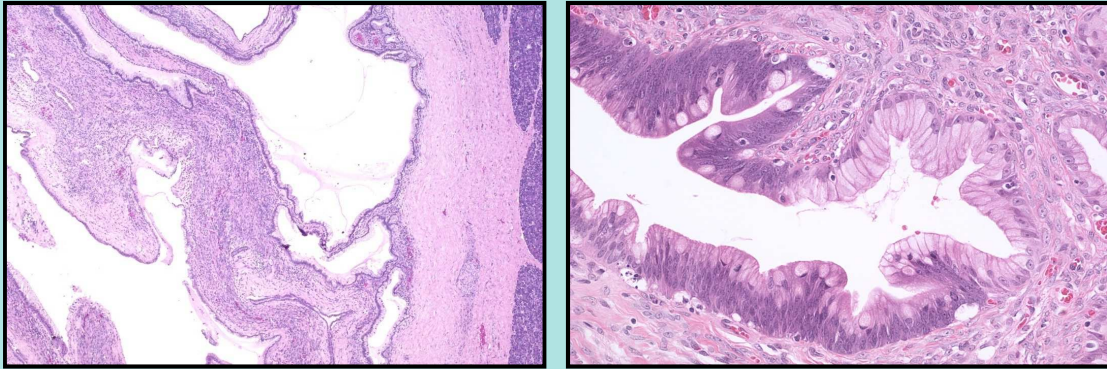
## Mucinous Cystic Neoplasm

- Clinical: **middle age female**
  - F:M=20:1
  - Most are benign
  - Prognosis excellent for non-invasive completely resected tumors
  - Resection recommended despite grade
- Radiology: **multiloculated**
  - body and tail (90%)
  - do not communicate with the pancreatic ductal system
  - thick walled (Ca++ in 20%)
  - thin or thick septa





## Mucinous Cystic Neoplasm



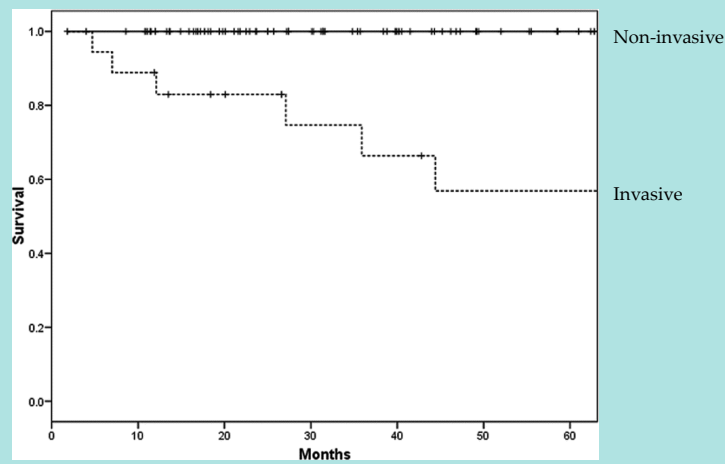
- Not associated with the pancreatic ducts
- Lined by mucinous, generally non-papillary epithelium
- Subepithelial “ovarian-like stroma” required
- Atypia may be very heterogeneous; invasion may be very focal, so the entire cyst should be submitted for histology



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## Mucinous Cystic Neoplasm is not an Aggressive Entity

(Crippa, et.al. Annals of Surgery 2008; 247:571-579)

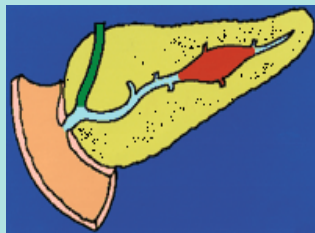


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# Intraductal Papillary Mucinous Neoplasm

Clinical: **elderly adult**; M:F ~ 1:1 in US



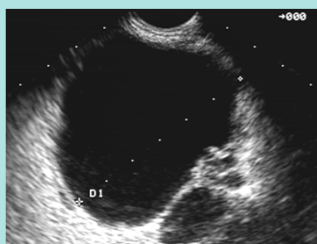
Main duct



Branch duct



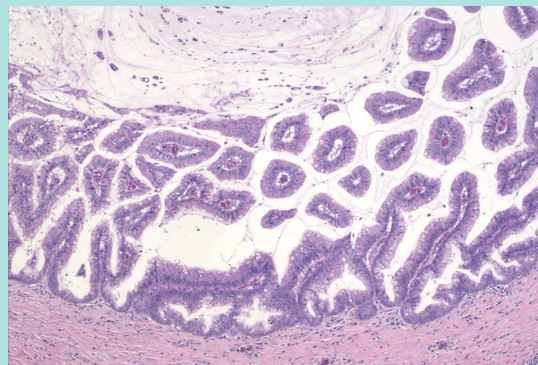
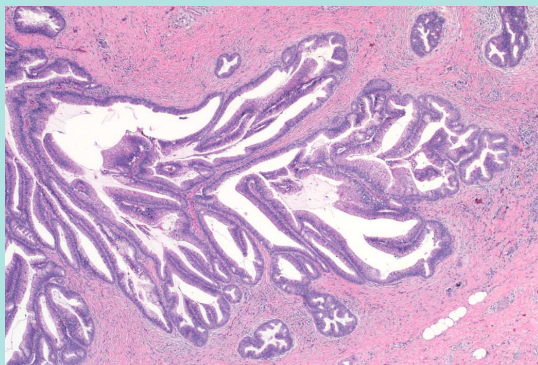
Combined



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# Intraductal Papillary Mucinous Neoplasm



- Various papillary mucinous epithelium of variable cell type and heterogenous atypia
- No association with ovarian-like stroma under the epithelium



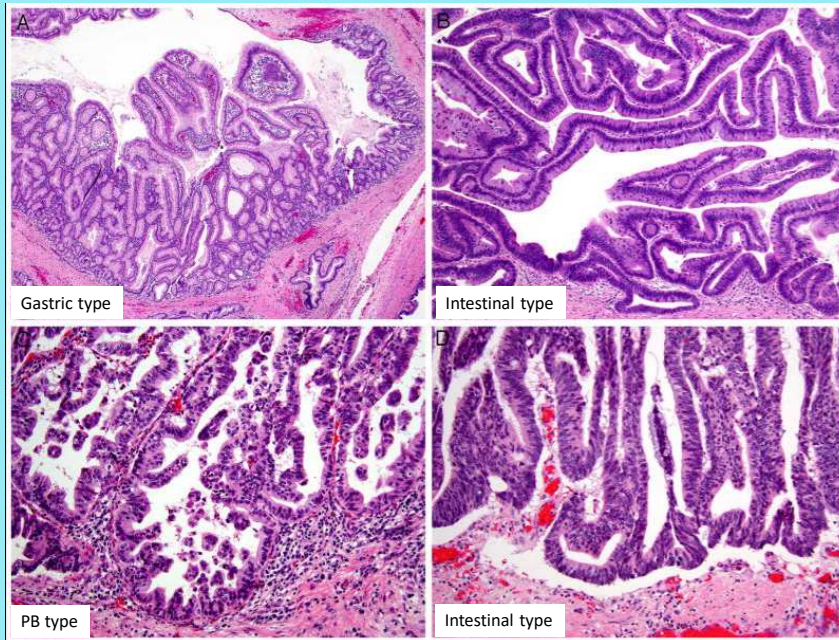
Two-tiered Grading of IPMN:

**Low-grade**

(low-intermediate grade dysplasia)

**High-grade**

(high-grade dysplasia/carcinoma in-situ)



Am J Surg Pathol. 2015 Dec;39(12):1730-41.

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## Intraductal Oncocytic Papillary Neoplasm

**Clinical:** average 60 yo, M=F

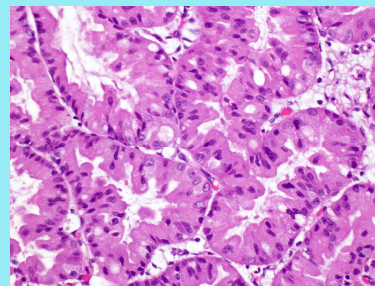
**Imaging:** Cystic to solid and cystic  
Pancreatic head; High PET uptake

**Cytology** = High risk/grade

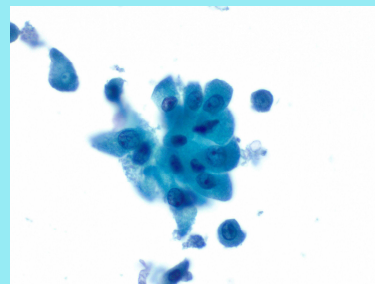
**Biochemical:** Low CEA

**Molecular:** recurrent rearrangements in  
*PRKACA* and *PRKACB*; no *KRAS* or *GNAS*

**Prognosis:** invasive carcinoma in about 30%  
of cases, but 5-year disease-specific survival  
rate approaches 100%



Olca Bastuck from WHO 5<sup>th</sup> edition of GI Tumours



Michelle Reid from WHO 1<sup>st</sup> edition of PB Reporting System

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# Management Guidelines for IPMN and MCN

(International consensus guidelines (revised)  
Pancreatology. 2017;17(5):738-753.

**MCN** • All MCNs are resected regardless of grade

## Indication for Resection

**IPMN**

- Cytology suspicious or positive for malignancy, includes cytology with features of HGEA
- Jaundice (tumour-related)
- Enhancing mural nodule (> 5 mm)
- MPD dilatation  $\geq 10$  mm

## Indication for EUS-FNA

- Growth rate  $\geq 5$  mm over 2 years
- Increased levels of serum CA19-9
- MPD dilatation between 5 and 9 mm
- Cyst diameter  $\geq 30$  mm
- Acute pancreatitis (caused by IPMN)
- Enhancing mural nodule (< 5 mm)
- Abrupt change in diameter of MPD with distal atrophy
- Lymphadenopathy
- Thickened or enhancing cyst walls



Modified from Barbara Centeno and the 1<sup>st</sup> edition of the WHO Reporting System for Pancreaticobiliary Cytopathology

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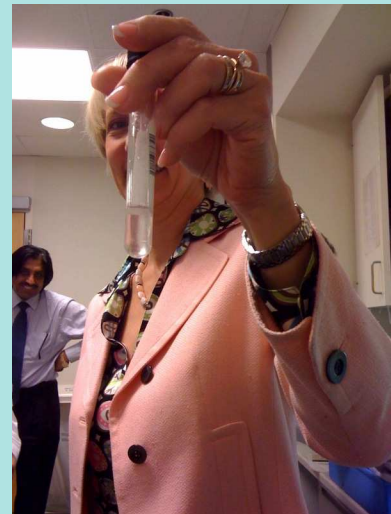
## Two basic questions for Cyst analysis

1. Is the cyst mucinous or non-mucinous?

1. **Gross examination**
2. **Cytology**
3. **CEA**
4. ***KRAS/GNAS/RNF43***

2. Is the cyst low-grade or high-grade?

1. **Cytology!!**
2. **Molecular analysis**

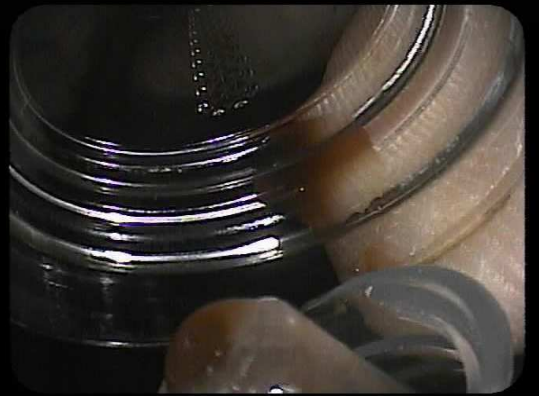




## Gross Cyst Fluid



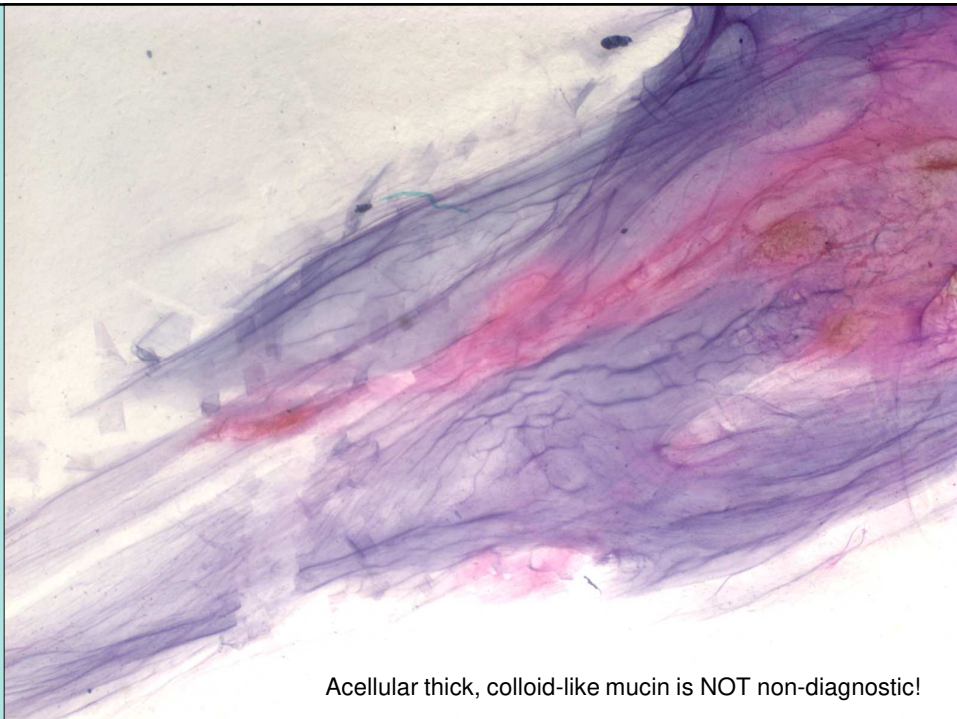
Mucinous cyst fluid



Pseudocyst fluid



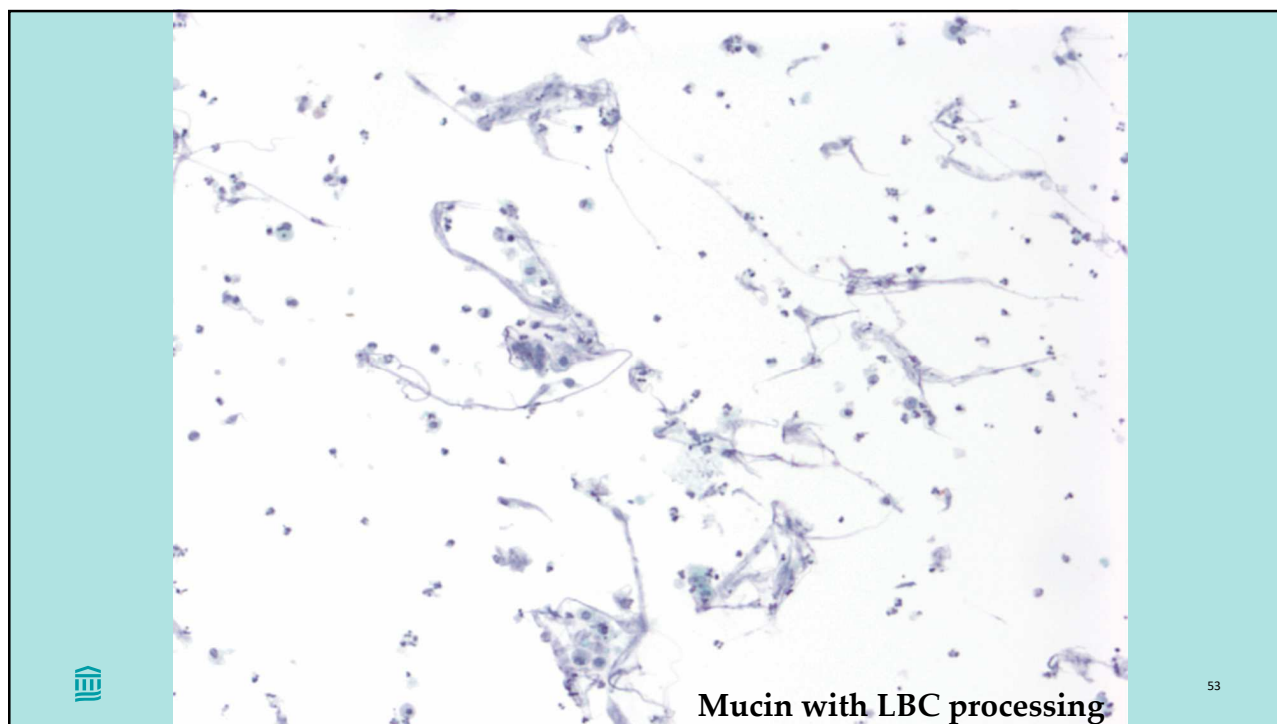
51



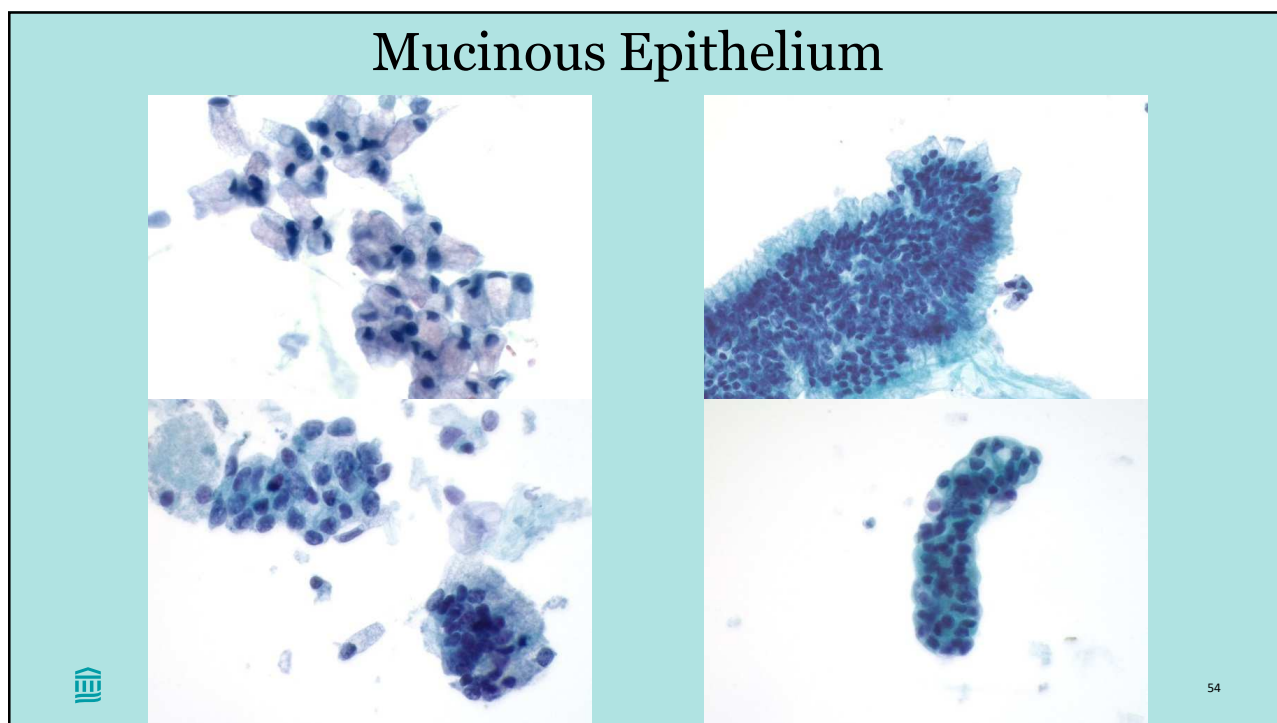
Acellular thick, colloid-like mucin is NOT non-diagnostic!



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## Mucinous Epithelium



## Ancillary Tests for Mucinous Neoplasia

CEA > 192 ng/ml

Molecular Analysis

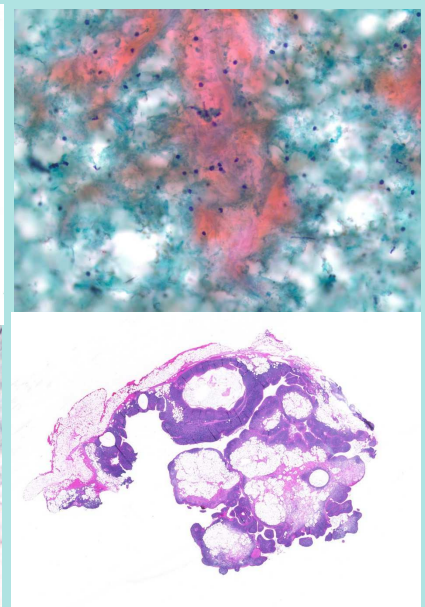
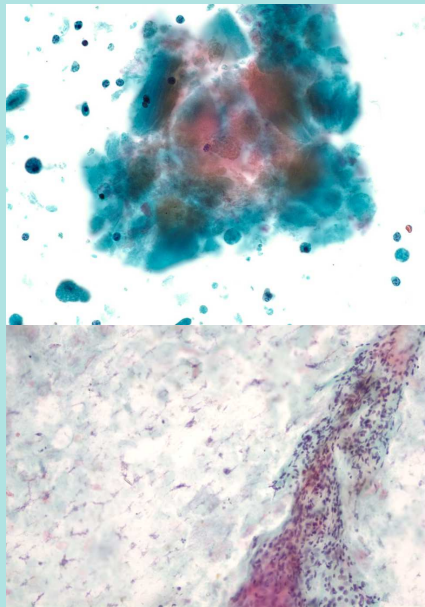
- *KRAS* mutation
- *GNAS* mutation
- *RNF43* mutation



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## Lymphoepithelial cyst

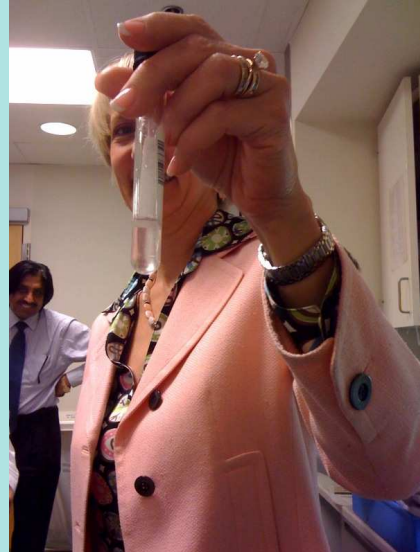
- Anucleate squames and abundant keratinous debris
- Mature superficial squamous cells
- Lymphocytes variable and may be quite scant
- +/-Cholesterol clefts
- Elevated CEA (pitfall!)





## Two basic questions for Cyst analysis

1. Is the cyst mucinous or non-mucinous?
  1. Gross examination
  2. Cytology
  3. CEA
  4. *KRAS/GNAS/RNF43*
2. Is the cyst low-grade or high-grade?
  1. Cytology!!
  2. Molecular analysis

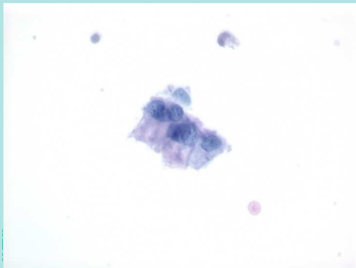
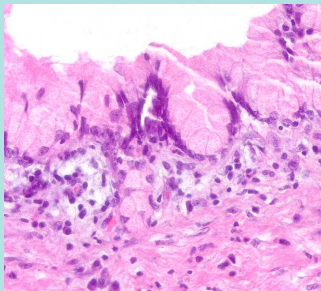


57

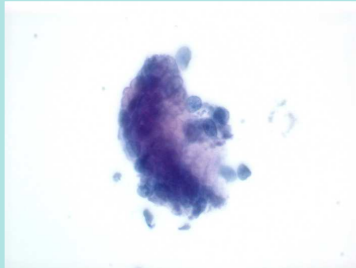
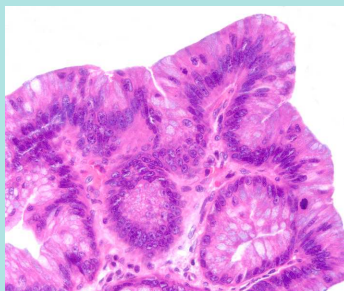
### Intraductal Papillary Mucinous Neoplasm of the Pancreas: Cytologic Analysis and Correlation with Histologic Grade

PJ Michaels, EF Brachtel, BC Bounds, WR Brugge, and MB Pitman  
(Cancer Cytopathol 2006; 108:174-179.)

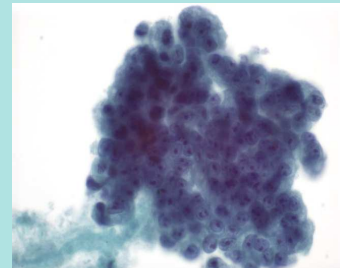
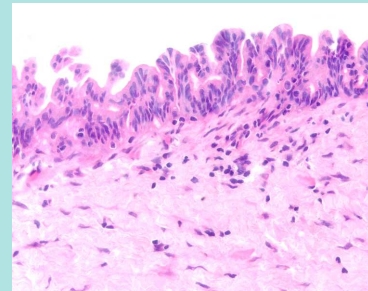
Low grade dysplasia



Intermediate dysplasia



HGD/Carcinoma



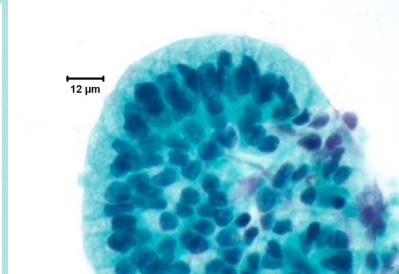
58

## Cytological Criteria of High-Grade Epithelial Atypia in the Cyst Fluid of Pancreatic Intraductal Papillary Mucinous Neoplasms

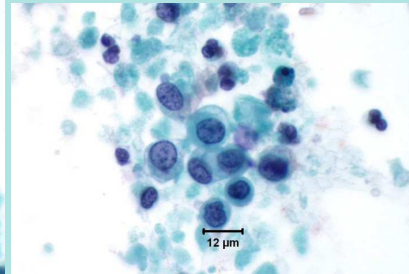
Martha B. Pitman, MD, Barbara A. Centeno, MD, Ebubekir S. Daglilar, MD, William R. Brugge, MD, and Mari Mino-Kenudson, MD  
Cancer Cytopathology 2014;122(1):40-47.



Reference duodenal enterocyte



Low-grade



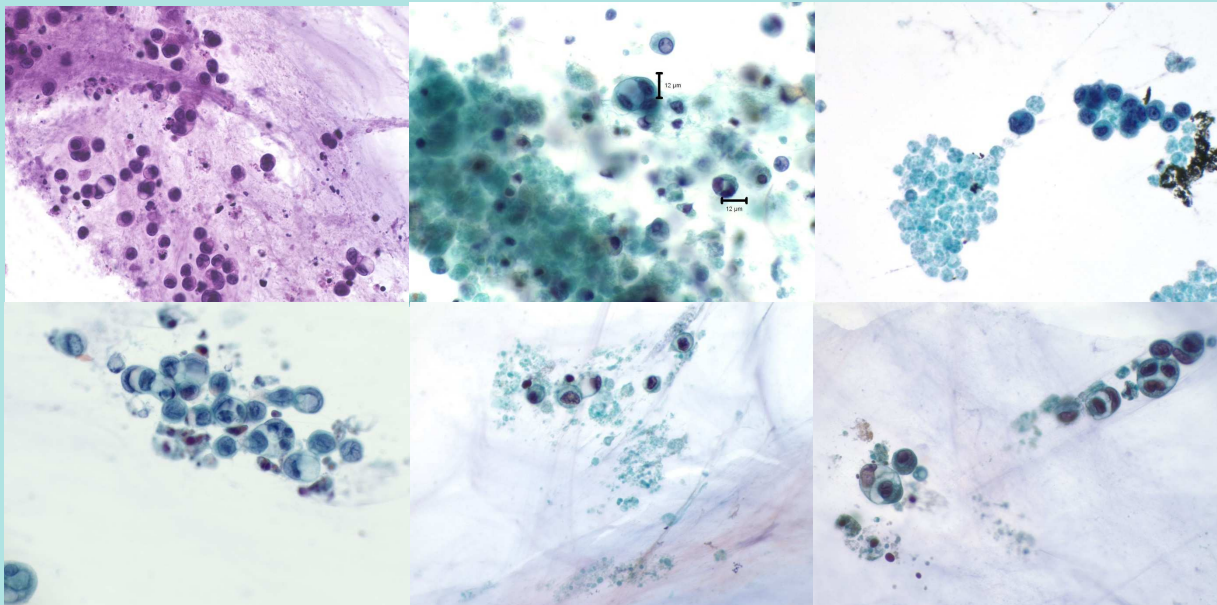
High-grade

HGA is most accurately identified in mucinous cyst fluids by:

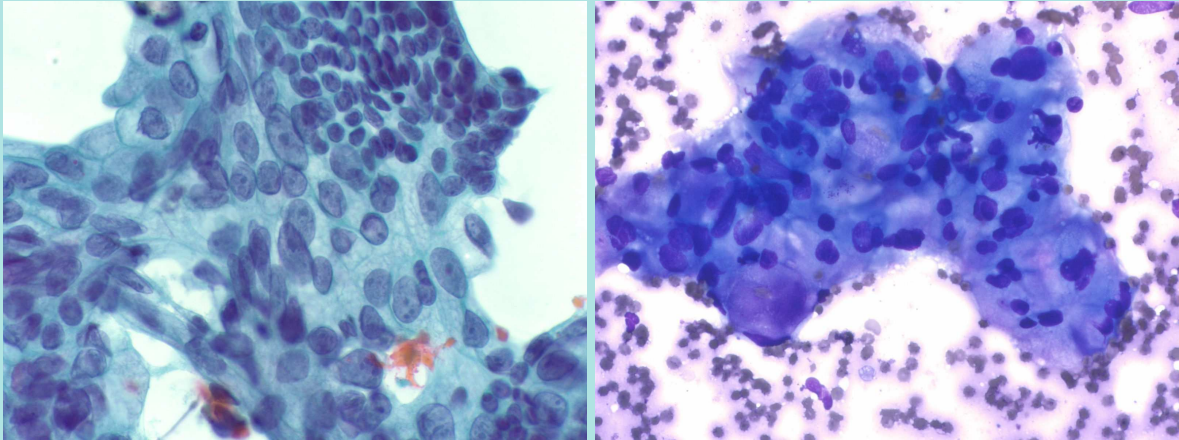
1. an increased N/C ratio,
2. an abnormal chromatin pattern
3. background necrosis



## HGA in Mucinous Cysts



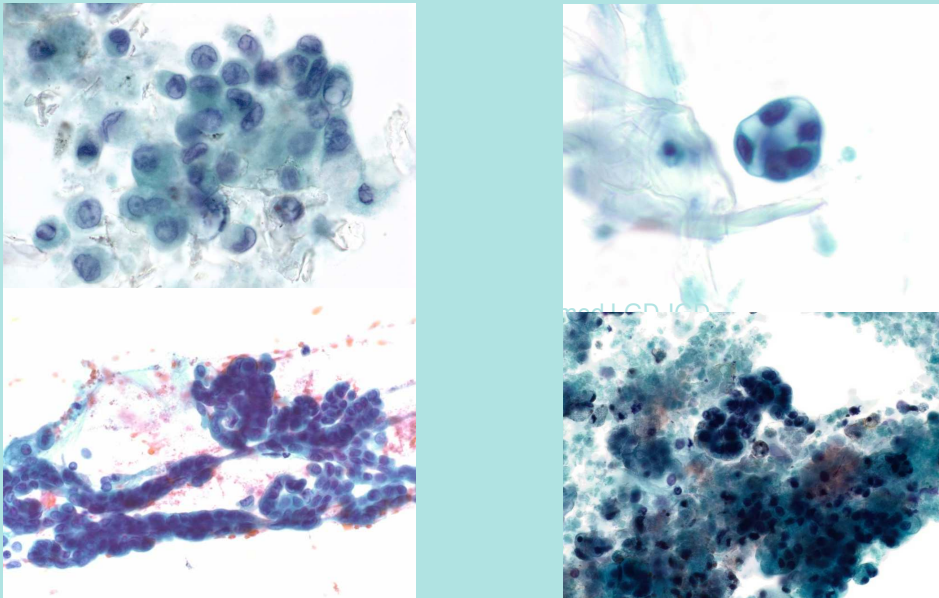
## Diagnostic Morphology of Carcinoma



Already invasive- prognosis decreases ~50%

61

## Morphological Overlap with LGA and HGA



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## Grading Epithelial Atypia in EUS-FNA of Intraductal Papillary Mucinous Neoplasms: An international interobserver concordance study

Martha B Pitman MD<sup>1</sup>, Barbara A Centeno MD<sup>2</sup>, Muriel Genevay MD<sup>3</sup>, Ricardo Fonseca, MD<sup>4</sup> and Mari Mino-Kenudson MD<sup>1</sup>.  
Cancer Cytopathology 2013;121(12):729-736.

Table 3. Kappa Coefficient for Two-Tiered Cytological Grading of Branch-Duct IPMN Cyst Fluids

Grade	Four Reviewers	Randolph's Multirater Kappa	Two Reviewers*	Cohen's Kappa
0-2, 3-4	54%	0.45	87%	0.74
0-1, 2-4	52%	0.44	88%	0.71

\* Two most experienced reviewers

0= GI contamination; 1=LGD; 2= IGD; 3= HGD and 4= PDAC



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J. 2019 May-Jun;8(3):120-127  
\*. 2019 May-Jun;8(3):120-127

## Risk of Malignancy in the Categories of *The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology*

Raza S. Hoda, M.D., Elizabeth B. Finer, Ronald N. Arpin III, M.S. SCT(ASCP), Matthew Rosenbaum, M.D., Martha B. Pitman, M.D.  
J Am Soc Cytopathol; 2019 May-Jun;8(3):120-127

**Table 3.** Absolute Risk and Relative Risk of Malignancy of the Diagnostic Categories in *The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology*

Diagnostic Category	Absolute Risk of Malignancy (%)	Relative Risk	p-value (Relative to Benign Category)
I. Nondiagnostic	7.7	7.7	0.07
II. Negative (for Malignancy)	1.0	1.0	—
III. Atypical	28.0	28.0	0.001*
IV. Neoplastic: Benign	0.0	0.0	1
IV. Neoplastic: Other, all grades of atypia	30.3	30.3	<0.001*
With Low-Grade Atypia	4.3	4.3	0.23
With High-Grade Atypia	90.0	90.0	<0.001*
V. Suspicious (for Malignancy)	100.0	100.0	<0.001*
VI. Positive or Malignant	100.0	100.0	<0.001*

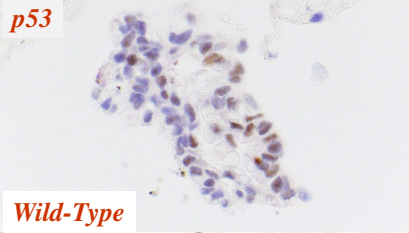
\* Denotes a statistically significant p-value <0.05.



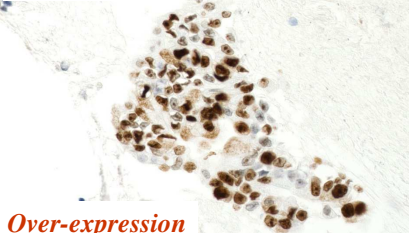
64



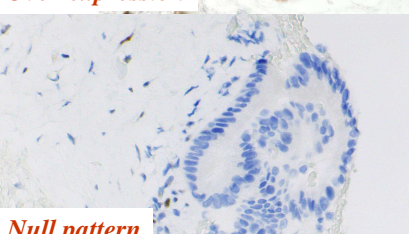
**p53**



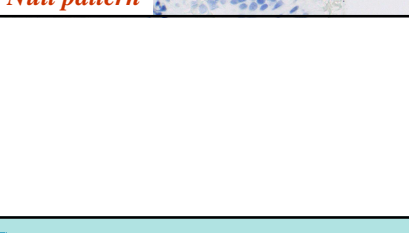
**Wild-Type**



**Over-expression**

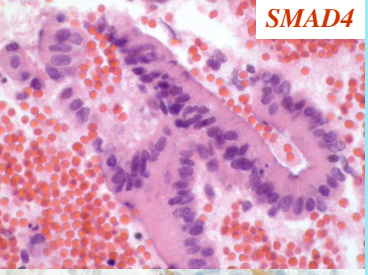


**Null pattern**

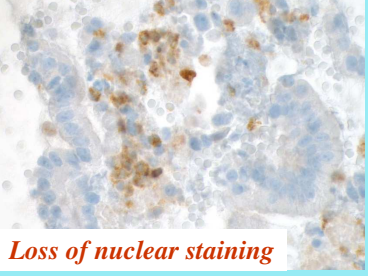


### Ancillary Studies: HGA

**SMAD4**




**Loss of nuclear staining**




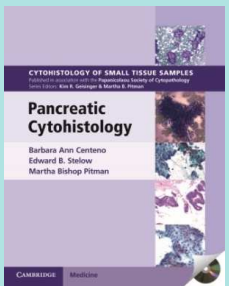
Others:

- p16- loss if nuclear staining
- MTAP- loss if nuclear staining
- Keratin 18-positive cytoplasmic staining<sup>65</sup>

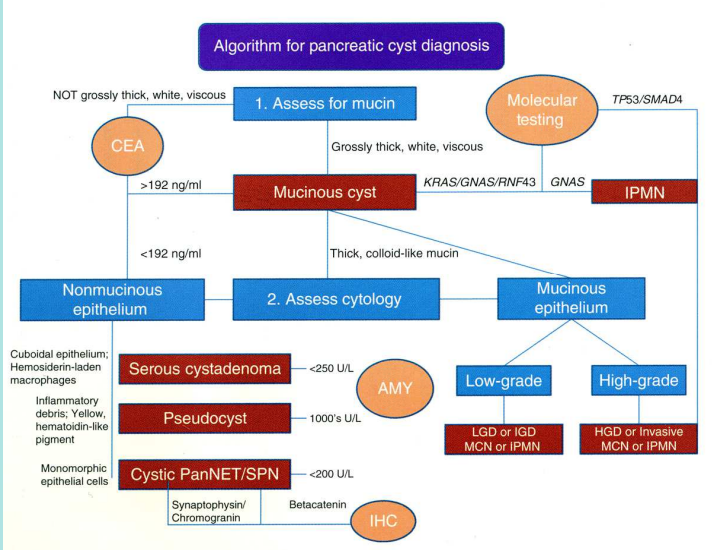


*Advancing Diagnosis and Discovery*






### Algorithm for pancreatic cyst diagnosis




```

graph TD
    Start([Algorithm for pancreatic cyst diagnosis]) --> Step1[1. Assess for mucin]
    Step1 -- "NOT grossly thick, white, viscous" --> CEA((CEA))
    Step1 -- "Grossly thick, white, viscous" --> MC[Mucinous cyst]
    CEA -- ">192 ng/ml" --> MC
    CEA -- "<192 ng/ml" --> NE[Nonmucinous epithelium]
    MC --> Molecular[Molecular testing]
    Molecular -- "TP53/SMAD4" --> IPMN[IPMN]
    Molecular -- "KRAS/GNAS/RNF43" --> MC
    Molecular -- "GNAS" --> IPMN
    MC -- "Thick, colloid-like mucin" --> Step2[2. Assess cytology]
    Step2 --> NE
    Step2 --> ME[Mucinous epithelium]
    NE -- "Cuboidal epithelium; Hemosiderin-laden macrophages" --> SC[Serous cystadenoma]
    SC -- "<250 U/L" --> IHC1((IHC))
    NE -- "Inflammatory debris; Yellow, hematoidin-like pigment" --> P[Pseudocyst]
    P -- "1000's U/L" --> IHC1
    NE -- "Monomorphic epithelial cells" --> CP[Cystic PanNET/SPN]
    CP -- "<200 U/L" --> IHC1
    IHC1 -- "Synaptophysin/Chromogranin" --> IHC1
    IHC1 -- "Betacatenin" --> IHC1
    ME --> LowGrade[Low-grade]
    ME --> HighGrade[High-grade]
    LowGrade -- "LGD or IGD MCN or IPMN" --> IHC2((IHC))
    HighGrade -- "HGD or Invasive MCN or IPMN" --> IHC2
    
```



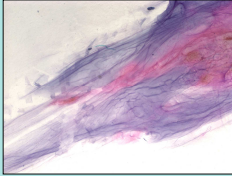
HARVARD MEDICAL SCHOOL



# Diagnosis of a Mucinous Cyst

## Mucin Production Established

- o Thick, colloid-like extracellular mucin



- o Cellular or inflammatory debris within the mucin
- o Thin mucin covering the slide confirmed with

❖ special stains for mucin (mucicarmin or Alcian blue pH2.5)

❖ Elevated CEA (192 ng/ml is ~ 80% accurate)

OR

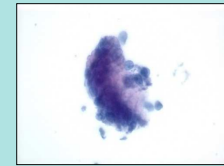
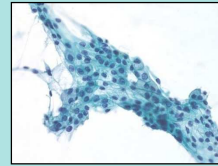
❖ KRAS/GNAS mutation

And/OR

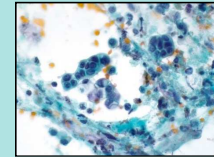
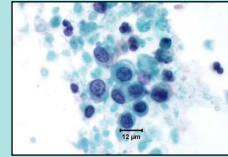


## Neoplastic Epithelial Cells identified

- o Low-grade mucinous epithelium, e.g. low-grade atypia (low-grade to intermediate-grade dysplasia)

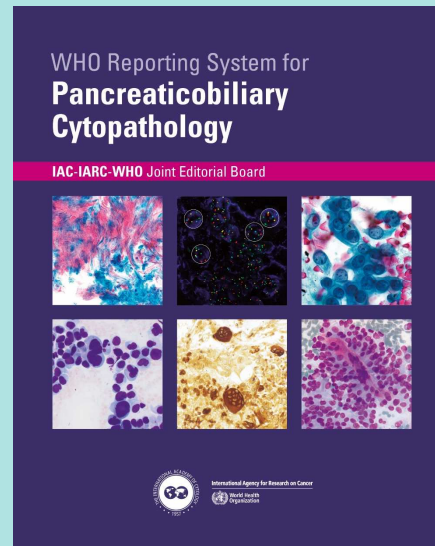
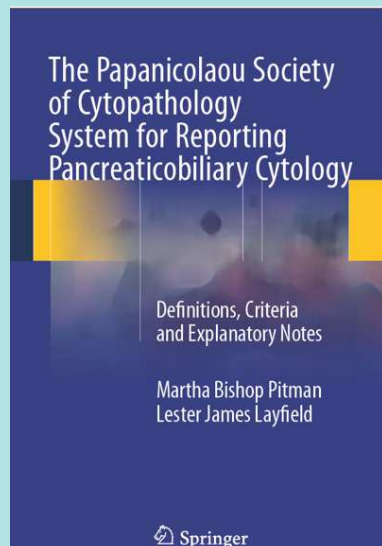


- o High-grade epithelium, e.g. high-grade atypia (at least high-grade dysplasia/carcinoma in-situ, but quality and quantity of atypia is insufficient for diagnosis of adenocarcinoma)



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# Reporting Systems for Pancreaticobiliary Cytology



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	PSC System		WHO System		
1	Nondiagnostic			Inadequate/insufficient/ nondiagnostic	1
2	Negative (for Malignancy)	Non-neoplastic only	Non-neoplastic and neoplastic (SCA)	Benign/Negative (for Malignancy)	2
3	Atypical			Atypical	3
4	Neoplastic				
4a	Neoplastic:Benign	SCA	low-grade MCN Low-grade IPMN Also, low-grade PanIN, BiIN	Pancreaticobiliary Neoplasm- low risk/low-grade (Pan-Low)	4
4b	Neoplastic:Other	IPMN,MCN, PanNET, SPN	High-grade MCN High-grade IPMN IOPN ITPN Also, high-grade PanIN, BiIN	Pancreaticobiliary Neoplasm- high risk/high-grade (Pan-High)	5
5	Suspicious (for malignancy)			Suspicious (for malignancy)	6
6	Positive (for malignancy)		PDAC, Acinar Cell ca., PanNET, PanNEC, SPN, PBL, other	Malignant	7

**Table 1.** The World Health Organization System for Reporting Pancreatic Cytopathology: implied risk of malignancy and clinical management options by diagnostic category for Pancreatic FNAB.

Diagnostic category	Estimated risk of malignancy (%) <sup>a</sup>	Clinical Management Options <sup>b</sup>
Insufficient/inadequate/nondiagnostic	5 – 25	Repeat FNAB
Benign/Negative for Malignancy	0 – 15	Correlate clinically
Atypical	30 – 40	Repeat FNAB
Pancreatic Neoplasm: low risk/low-grade (PaN-Low)	5 – 20	Correlate clinically
Pancreatic Neoplasm: high risk/high-grade (PaN-High)	60 – 95	Surgical Resection in surgically fit patients Conservative management optional
Suspicious for Malignancy	80 – 100	If patient to be surgically managed, treat as positive If patient requires pre-operative therapy, repeat FNAB
Malignant	99 – 100	Per clinical stage

Abbreviation: FNAB, fine-needle aspiration biopsy.

<sup>a</sup> Estimated risks of malignancy are based on retrospective and prospective studies with risk analysis based on pancreatic neoplasia with low-grade and high-grade cytopathological atypia.

<sup>b</sup> Management options for patients with pancreatic lesions may depend on a variety of factors, including clinical and imaging characteristics and the overall functional status of the patient. Some clinical management suggestions are outlined as above.

**Table 2.** The World Health Organization International System for Reporting Pancreaticobiliary Cytopathology: implied risk of malignancy and clinical management options by diagnostic category for Bile Duct Brushing Specimens.

Diagnostic category	Estimated risk of malignancy (%) <sup>a</sup>	Clinical management options <sup>b</sup>
Insufficient/inadequate/nondiagnostic	28 – 69	Repeat ERCP with cholangioscopy, brushing, and biopsies
Benign/Negative for Malignancy	26 – 55	Correlate clinically
Atypical	25 – 77	Repeat ERCP with cholangioscopy, brushing, and biopsies; consider ancillary testing with FISH and/or NGS
Pancreatic Neoplasm-low-grade (PaN-low)	NA <sup>c</sup>	NA
Pancreatic Neoplasm-high-grade (PaN-high)	NA <sup>c</sup>	NA
Suspicious (for malignancy)	74 – 100	Repeat sampling with ancillary testing (FISH and/or NGS) or, if other factors support malignancy, surgical intervention; for neoadjuvant therapy, repeat ERCP with cholangioscopy/brushings/biopsies/ancillary studies
Malignant	96 – 100	Per clinical stage

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography; FNAB, fine-needle aspiration biopsy; FISH, fluorescence in-situ hybridization; NA, not available/not applicable; NGS, next-generation sequencing.

<sup>a</sup> Estimated risks of malignancy are based on retrospective and prospective studies with risk analysis based on pancreatic neoplasia with low-grade and high-grade cytologic atypia { 10049415,24167030,26596524,28411396,32649050,34800330,35163571 }.

<sup>b</sup> Management options for patients with bile duct strictures may depend on a variety of factors, including clinical and imaging characteristics and overall functional status of the patient. Some clinical management suggestions are outlined as above.

<sup>c</sup> Cytological criteria for premalignant neoplasms of the bile duct are lacking and, thus, there are no data on bile duct categorization in the PaN-low and PaN-high categories.





**71st Annual Scientific Meeting**  
American Society of Cytopathology

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