INTEGRATING DNA MOLECULAR TESTING INTO THE ROUTINE EVALUATION OF PANCREATIC CYSTS

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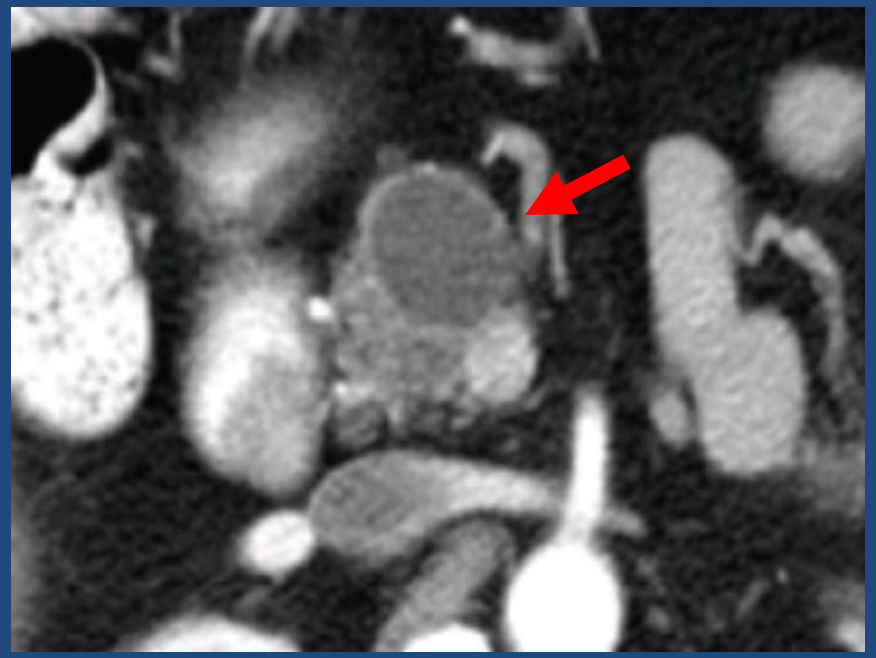
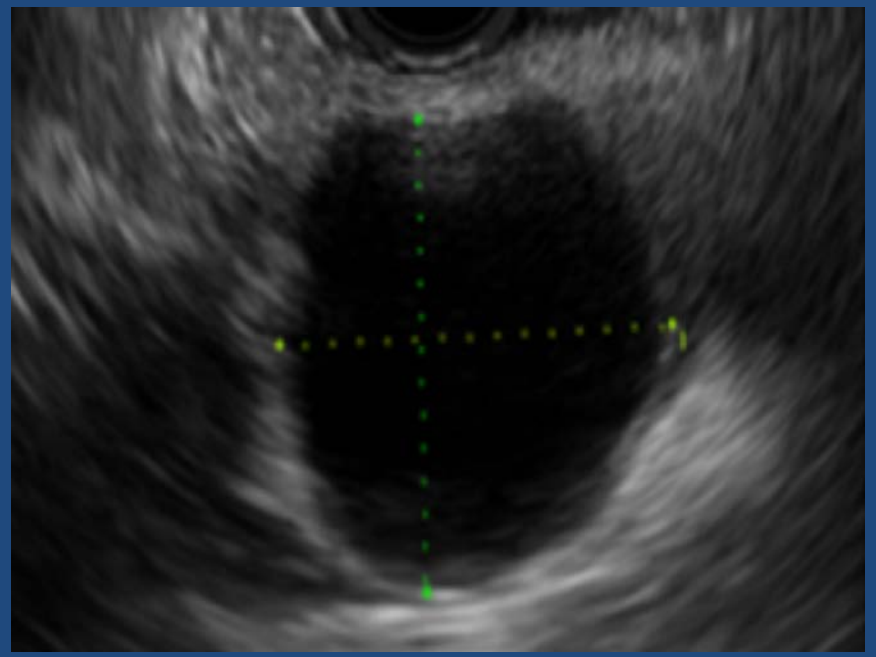
Disclosures

- **None of the presenters have financial relationships or interests to disclose.**

Clinical Case

- 61 yo WM with 3 cm incidental pancreatic head cyst
- No associated main duct dilation or mural nodule
- EUS-FNA cytology: atypical cells, no mucin
- CEA 157 ng/ml
- DNA analysis
  - *GNAS* (Allele Freq. 51%)
  - *PIK3CA* (Allele Freq. 50%)

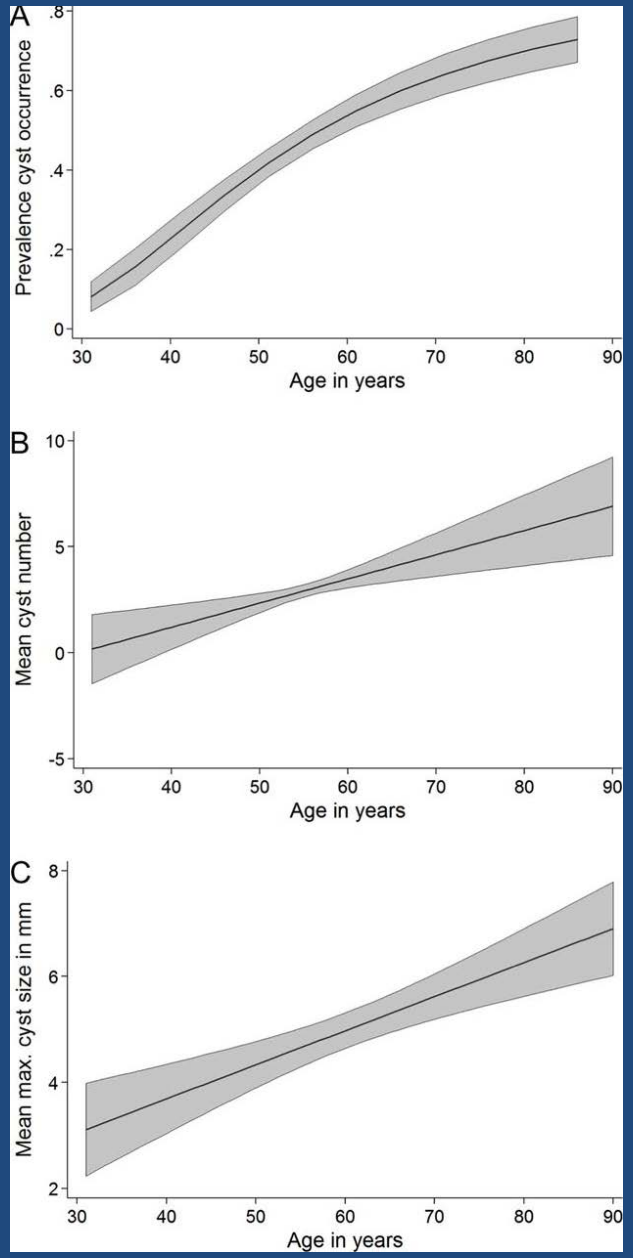




Pancreatic Cyst Prevalence

- ~ 70% discovered incidentally
- MRI: 13.5%-19.6%
- Autopsy: up to 50% in elderly
- Meta-analysis: 49K pts, 17 studies
  - Pooled prevalence: 8%

- Study of Health in Pomerania
  - 1077 pts underwent MRI
  - 49.1% prevalence (cysts > 2 mm)
  - 12.9% incidence during 5 yr f/u
  - > 80 yrs: 75.7%, mean size 4.3 mm
  - 30-39 yrs: 17.1%, mean size 6.8 mm
  - 0.7% had cysts > 2 cm



Zerboni et al. Pancreatology 2019;19:2-9
Kromrey et al. Gut 2018;67:138-145

Pancreatic Cyst Classification

- **Mucinous**
  - Mucinous cystic neoplasm (MCN)
  - Intraductal papillary mucinous neoplasm (IPMN)
- **Non-mucinous**
  - Serous cystadenoma (SCA)
  - Cystic pancreatic neuroendocrine tumor
  - Solid pseudopapillary neoplasm (SPN)
  - Lymphoepithelial cyst
  - Retention cyst
  - Pseudocyst

Most Common Pancreatic Cystic Neoplasm?

- 376 pts
  - Resected between 2005 – 2011

  - ***IPMN 49%***
  - MCN 16%
  - SCA 12%
  - SPN 5%

  - Cystic pancreatic neuroendocrine tumor 8%

Valsangkar et al. Surgery 2012;152:S4-12

Guidelines for Evaluation / Management

- International Association of Pancreatology
  - Sendai guidelines 2006
  - Fukuoka guidelines 2012
    - Cyst fluid analysis is still investigational, but is recommended for evaluation of small BD-IPMNs without “worrisome features” in centers with expertise in EUS-FNA and cytological interpretation
  - Revised Fukuoka guidelines 2017

Tanaka et al. Pancreatology 2006;6:17-32
Tanaka et al. Pancreatology 2012;12:183-97
Tanaka et al. Pancreatology 2017;17:738-53

Revised Fukuoka Guidelines

- High risk stigmata
  - Obstructive jaundice in a pt with a pancreatic head cyst
  - Enhanced mural nodule ≥ 5 mm
  - MPD size ≥ 10 mm
- Worrisome features
  - Cyst size ≥ 3 cm
  - Enhancing mural nodule < 5 mm
  - MPD size 5 - 9 mm
  - Abrupt change in MPD caliber with distal pancreatic atrophy
  - Lymphadenopathy
  - Elevated CA 19-9
  - Rapid cyst growth > 5 mm / 2 yrs

Tanaka et al. Pancreatology 2017;17:738-53

Guidelines for Evaluation / Management

- AGA
- ACG
- ASGE
- UPMC

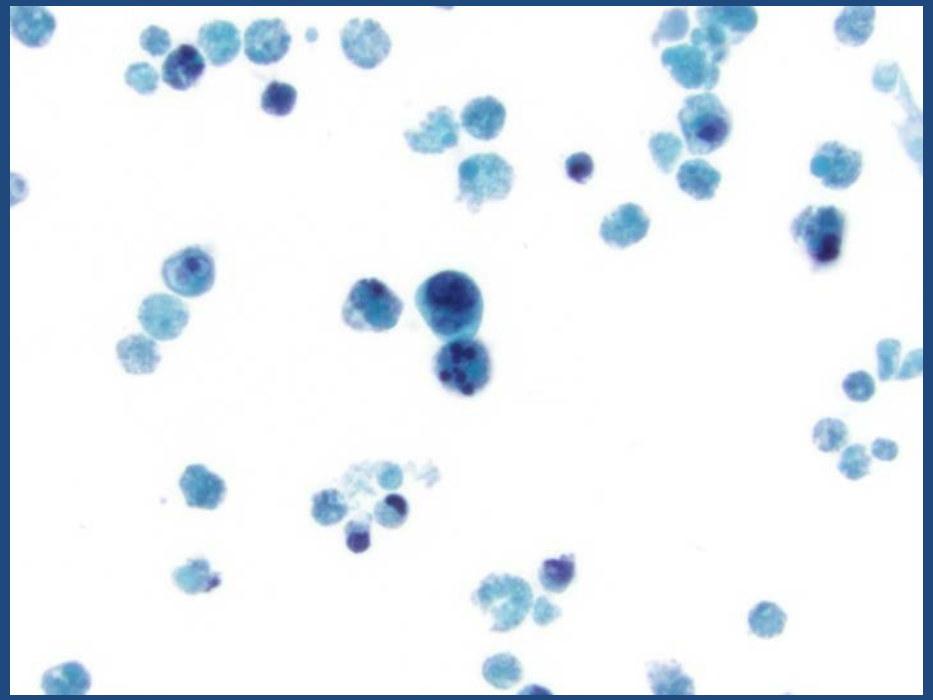
Vege et al. Gastroenterology 2015;148:819-22
Elta et al. Am J Gastroenterol 2018;113:464-79
Jacobson et al. Gastrointest Endosc 2005;61:363-70
Singhi et al. Gastrointest Endosc 2016;83:1107-1117

Cytology: Mucinous vs Non-Mucinous Cysts

- Paucicellular specimen
- Viscosity dependent?

- CPC
  - sens 35%, spec 83%, accuracy 59%

- MGH
  - sens 43%, spec 96% , accuracy 58%



Brugge et al. Gastroenterology 2004;126:1330-6
Cizginer et al. Pancreas 2011;40:1024-8

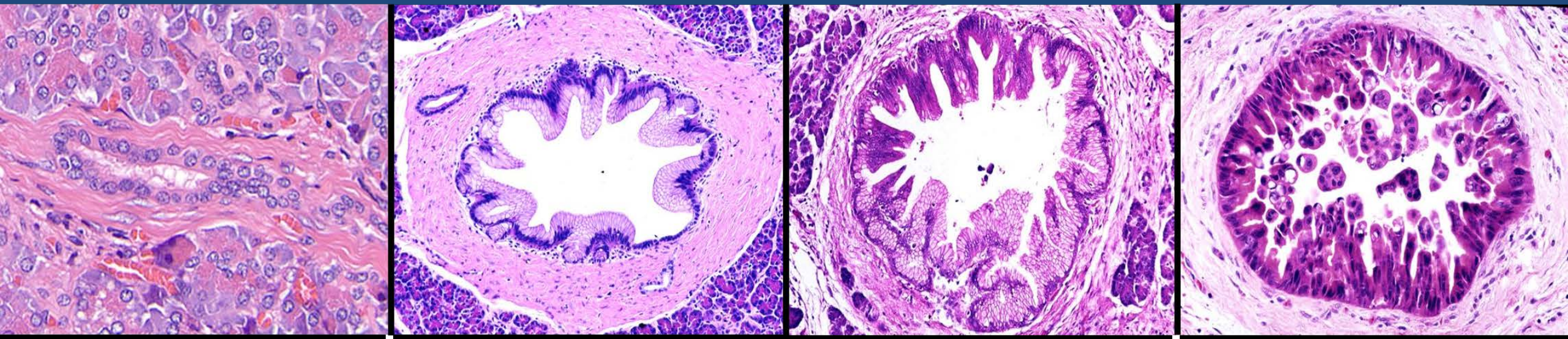
CEA: Differentiating Mucinous Cysts

- CPC
  - 112 pts
  - CEA optimal cutoff of **192** ng/mL (AUC 0.79, 73% sens, 83% spec)
- MGH
  - 198 pts
  - CEA optimal cutoff **110** ng/ml (AUC 0.93, 81% sens, 98% spec)
- Multicenter
  - 226 pts
  - CEA optimal cutoff **105** ng/ml (AUC 0.77, sens 70%, spec 63%)

Brugge et al. Gastroenterology 2004;126:1330-6
Cizginer et al. Pancreas 2011;40:1024-8
Gaddam et al. Gastrointest Endosc 2015;82:1060-9

Pancreatic Cystic Neoplasms

- Neoplastic transformation in cell morphology is preceded / paralleled by genetic alterations



Normal Duct | **Low-Grade** | **High-Grade**

- Hypothesis: Detection of established DNA mutations in cyst fluid may improve the yield of EUS-FNA and reflect biologic behavior

Hruban et al. Clin Can Res 2000;6:2969-72

Pancreatic Cyst Fluid Molecular Testing

The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology:

- 2005 pilot study
- Cyst fluid does harbor DNA for molecular analysis
- DNA quantity / quality
- *KRAS* point mutations
- Tumor suppressor gene Loss of Heterozygosity (LOH)
- Sequence – first hit *KRAS* followed by LOH predicts malignancy as does number of mutations and DNA quantity

Khalid et al. Clin Gastroenterol Hepatol 2005;3:967-73

PANDA

- Multicenter study of cyst fluid DNA analysis
  - 113 patients
  - CEA (AUC 0.74; optimal value >148 ng/mL)
  - *KRAS*: predictive of mucinous cyst
  - Predictive of malignancy:
    - Elevated DNA amount
    - High amplitude mutations
    - Sequence of mutations
  - Consider DNA analysis when cytology is negative

Khalid et al. Gastrointest Endosc 2009;69:1095-102

Molecular Analysis: 10 yrs ago

- Molecular profiles may allow:
  - Differentiation of mucinous vs non-mucinous cysts
    - *KRAS*
  - Selection of high-risk lesions for surgical resection
    - DNA quantity / quality
    - LOH
  - Prediction of the malignant potential of mucinous cysts

Table 1. k-ras-2 Gene and Tumor Suppressor Genes (With Associated Markers) With Chromosomal Location and Mutation Type

Proximity cancer gene[a]	Mutation type	Locus[b]	Marker 1	Marker 2
k-ras	Point mutation[c]	12p12		
CMM/RIZ	Allelic imbalance[d]	1p36–1p34	D1S407	MYCL
VHL	Allelic imbalance[d]	3p26–3p25	D3S1539	D3S2303
APC	Allelic imbalance[d]	5q23–5q23	D5S592	D5S615
P16	Allelic imbalance[d]	9p21–9p23	D9S251	D9S254
PTCH[e]	Allelic imbalance[d]	9q22	D9S252	
PTEN	Allelic imbalance[d]	10q23–10q23	D10S520	D10S1173
P53	Allelic imbalance[d]	17p13–17p13	D17S974	D17S1289

Khalid et al. Clin Gastroenterol Hepatol 2005;3:967-73

Pancreatic Cyst Molecular Testing

Whole-exome sequencing of neoplastic cysts o pancreas reveals recurrent mutations in compo of ubiquitin-dependent pathways

Jian Wu[a,1], Yuchen Jiao[a,1], Marco Dal Molin[b,1], Anirban Maitra[b], Roeland F. de Wilde[b], Laura D. Wood[b], James R. Eshleman[b], Michael G. Goggins[b,c], Christopher L. Wolfgang[d], Marcia I. Canto[c], Richard D. Schu
Barish H. Edil[d], Michael A. Choti[d], Volkan Adsay[e], David S. Klimstra[f], G. Johan A. Offerhaus[g], Alison P.
Levy Kopelovich[h], Hannah Carter[i], Rachel Karchin[i], Peter J. Allen[j], C. Max Schmidt[k], Yoshiki Naito[l], Luis
Kenr

Targeted DNA Sequencing Reveals Patterns of Local Progression in the Pancreatic Remnant Following Resection of Intraductal Papillary Mucinous Neoplasm (IPMN) of the Pancreas

Antonio Pea, MD,† Jun Yu, MD,‡ Neda Rezaee, MD,* Claudio Luchini, MD,‡§ Jin He, MD, PhD,* Marco Dal Molin, MD,‡ James F. Griffin, MD,* Helen Fedor,‡ Shahriar Fesharakizadeh,‡*

Digital next-generation sequencing identifies ns in pancreatic juice the duodenum of patients and intraductal papillary

indo,[1] Masaya Suenaga,[1] Aaron Brant,[1]
hael Borges,[1] Thomas Barkley,[1]
ord,[1] Ralph H Hruban,[1,2] Eun Ji Shin,[3]
Canto,[2,3] Michael Goggins[1,2,3]

om the prospective ZYSTEUS biomarker

Endris[1] | Matthias M. Gaida[1] | Jonas Leichsenring[1] |
äuer[1] | Moritz von Winterfeld[1] | Roland Penzel[1] |
lt[1] | Olaf Neumann[1] | Holger Sültmann[2] |
i[3] | Daniel Schmitz[3†] | Albrecht Stenzinger[1,4†]

A Combination of Molecular Markers and Clinical Features Improve the Classification of Pancreatic Cysts

Simeon Springer,[1,2,*] **Yuxuan Wang**,[1,2,*] **Marco Dal Molin**,[2,3,*] **David L. Masica**,[2,4,5,*]
Yuchen Jiao,[1,2] Isaac Kinde,[1,2] Amanda Blackford,[6] Siva P. Raman,[7]
Christopher L. Wolfgang,[2,8,9] Tyler Tomita,[4,5] Noushin Niknafs,[4,5] Christopher Douville,[4,5]
Janine Ptak,[1,2] Lisa Dobbyn,[1,2] Peter J. Allen,[10] David S. Klimstra,[11] Mark A. Schattner,[12]
C. Max Schmidt,[13] Michele Yip-Schneider,[14] Oscar W. Cummings,[14] Randall E. Brand,[15]
Herbert J. Zeh,[16] Aatur D. Singhi,[17] Aldo Scarpa,[18,19] Roberto Salvia,[20] Giuseppe Malleo,[20]
Giuseppe Zamboni,[19,21] Massimo Falconi,[22] Jin-Young Jang,[23] Sun-Whe Kim,[23]
Wooil Kwon,[23] Seung-Mo Hong,[24] Ki-Byung Song,[25] Song Cheol Kim,[25] Niall Swan,[26]
Jean Murphy,[26] Justin Geoghegan,[27] William Brugge,[28] Carlos Fernandez-Del Castillo,[29]
Mari Mino-Kenudson,[30] Richard Schulick,[31] Barish H. Edil,[31] Volkan Adsay,[32] Jorge Paulino,[33]
Jeanin van Hooft,[34] Shinichi Yachida,[35] Satoshi Nara,[35] Nobuyoshi Hiraoka,[35] Kenji Yamao,[36]
Susuma Hijioka,[36] Schalk van der Merwe,[37] Michael Goggins,[2,9,38] Marcia Irene Canto,[38]
Nita Ahuja,[8] Kenzo Hirose,[8] Martin Makary,[8] Matthew J. Weiss,[8] John Cameron,[8] Meredith Pittman,[2,3]
James R. Eshleman,[1,2] Luis A. Diaz Jr.,[1,2,8] Nickolas Papadopoulos,[1,2] Kenneth W. Kinzler,[1,2]
Rachel Karchin,[2,4,5,9] Ralph H. Hruban,[1,2,3,9] Bert Vogelstein,[1,2] and Anne Marie Lennon[2,8,38]

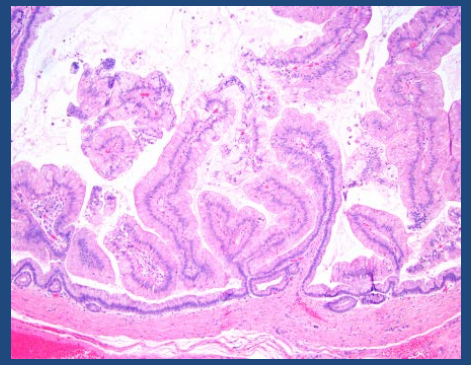
Pancreatic Cyst Molecular Testing

	KRAS	*GNAS*	*VHL*	*CTNNB1*
IPMN	+	+	-	-
MCN	+	-	-	-
SCA	-	-	+	-
SPN	-	-	-	+
Non	-	-	-	-

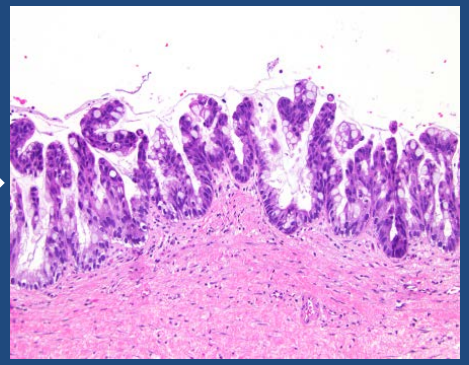
- Intraductal papillary mucinous neoplasms (IPMN):
  KRAS and *GNAS*
- Mucinous cystic neoplasms (MCN):
  KRAS
- Serous cystadenomas (SCA):
  VHL
- Solid pseudopapillary neoplasms (SPN):
  CTNNB1
- Non-neoplastic cysts:
  Absent

Pancreatic Cyst Molecular Testing

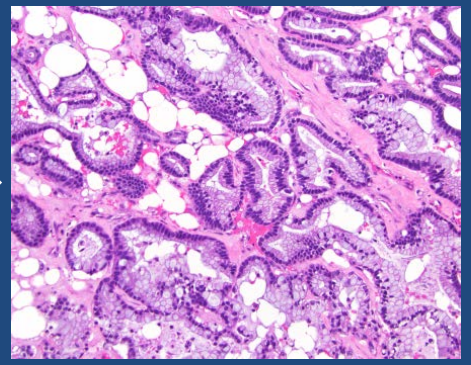
	KRAS	*GNAS*	*VHL*	*CTNNB1*
IPMN	+	+	-	-
MCN	+	-	-	-



Low-grade Dysplasia



High-grade Dysplasia

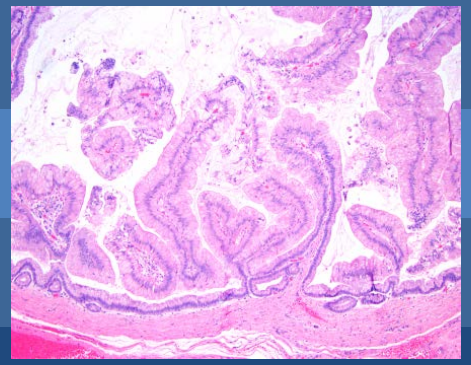


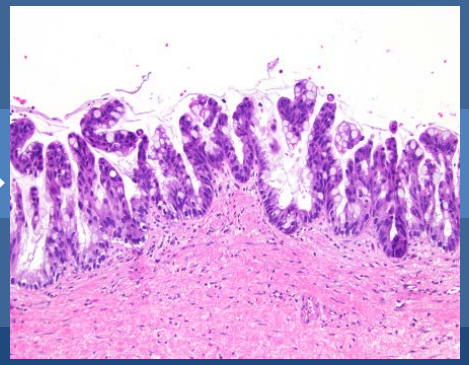
AdenoCA

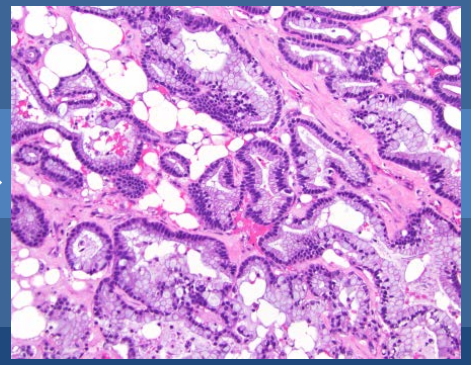
KRAS & GNAS

Pancreatic Cyst Molecular Testing

	KRAS	*GNAS*	*VHL*	*CTNNB1*	*TP53*	*PIK3CA*	*PTEN*
IPMN	+	+	-	-	HR	HR	HR
MCN	+	-	-	-	HR	HR	HR
		-			-		
		-			-		







Low-grade Dysplasia

High-grade Dysplasia

AdenoCA

HR = High-risk of malignancy

KRAS & GNAS

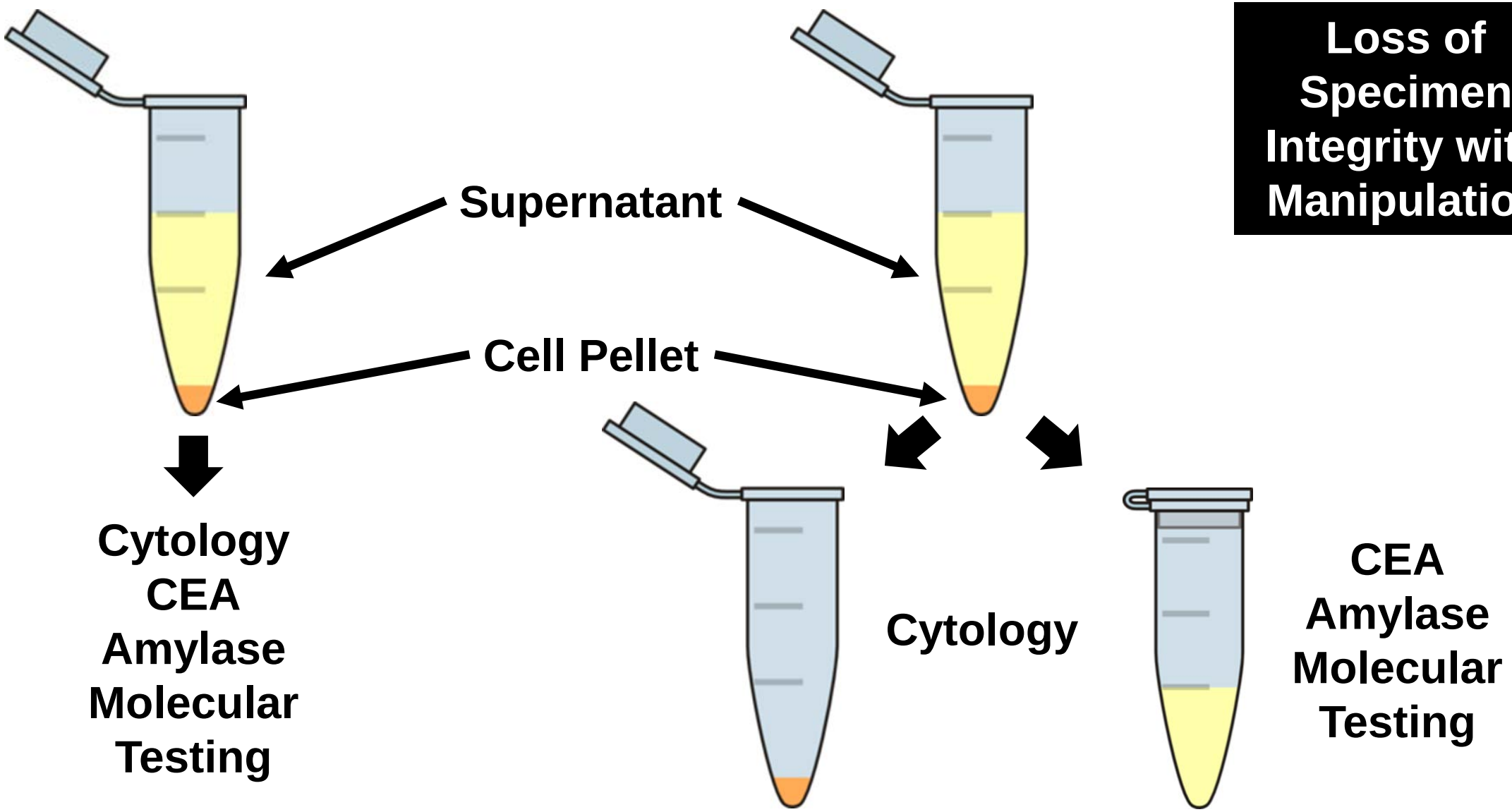
TP53, *PIK3CA* & *PTEN*

Pancreatic Cyst Molecular Testing

KRAS GNAS VHL CTNNB1 TP53 PIK3CA PTEN

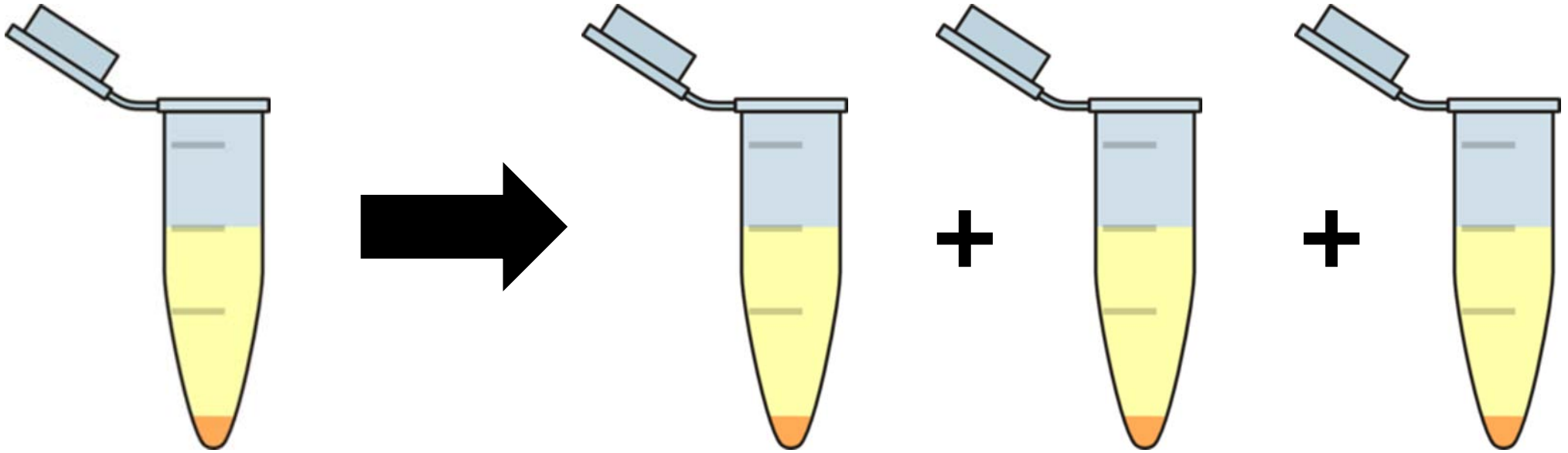
- **Next-generation sequencing panel (PancreaSeq) to assess preoperative EUS-FNA obtained pancreatic cyst fluid designed in 2013.**
- **Exons 1 through 3 of *VHL* were assessed by Sanger sequencing, limit of detection 10-20%.**
- **>1,000 hot spot mutations with over 1000x to 500x depth of coverage, corresponding to a limit of detection of 3% to 5%, respectively.**
- **Samples below 500x were not interpreted.**

Pancreatic Cyst Fluid: Triaging



Loss of Specimen Integrity with Manipulation

Pancreatic Cyst Fluid: Triaging

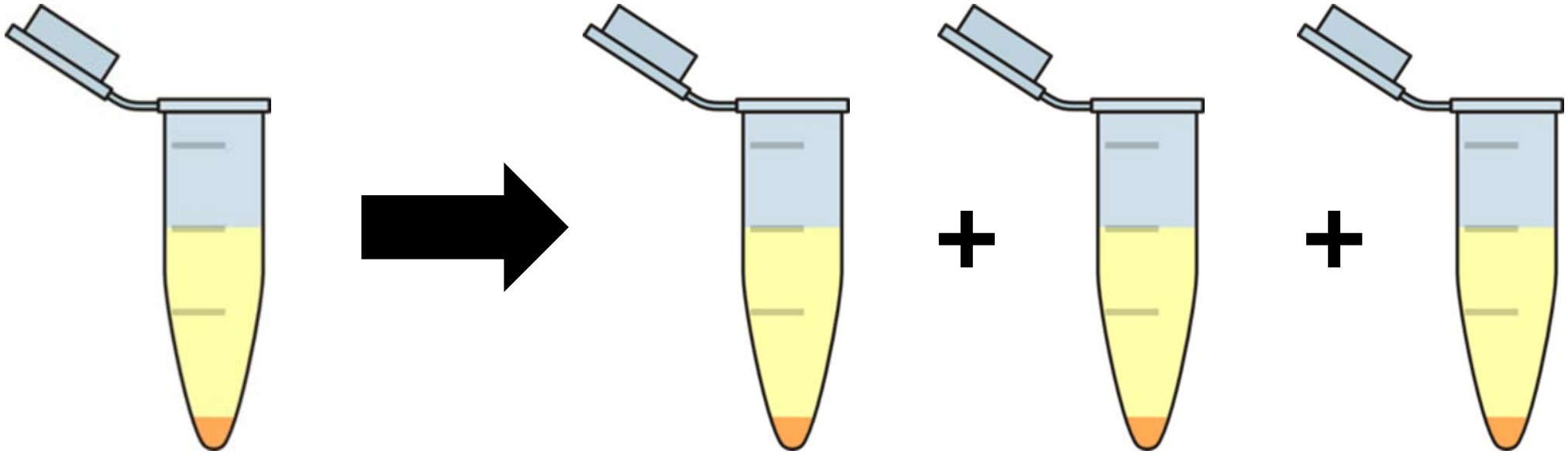


Cytology

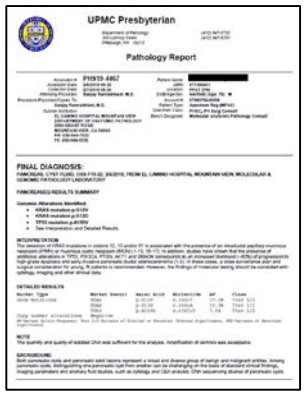
Molecular Testing (Stabilization Buffer)

CEA Amylase

Pancreatic Cyst Fluid: Triaging



Report


UPMC Presbyterian

Pathology Report

FINAL DIAGNOSIS:

10 days

Cytology

Molecular Testing (Stabilization Buffer)

CEA Amylase

PancreaSeq: Pancreatic Cyst Fluid

KRAS GNAS VHL CTNNB1 TP53 PIK3CA PTEN

- Over a 43-month period, **673 EUS-FNA** pancreatic cyst fluid specimens from 642 patients were prospectively analyzed for genetic alterations.
- Among the 673 specimens, **626** (**93%**) pancreatic cysts were satisfactory for molecular analysis (**PancreaSeq**).
- In comparison, **452** (**72%**) pancreatic cysts were sufficient for CEA analysis and **251** (**40%**) pancreatic cysts were satisfactory for cytopathologic evaluation.
- Follow-up was available for **102** (**18%**) patients.

PancreaSeq: Pancreatic Cyst Fluid

Surgical Resection Dx	Total, n = 102 (18%)
AdenoCA arising in an IPMN	13
IPMN with HGD	4
MCN with HGD	2
IPMN with LGD	39
MCN with LGD	8
Serous cystadenoma	3
Cystic PanNET	9
Acinar cell cystadenoma	1
Pseudocyst	17
Retention cyst	2
Lymphoepithelial cyst	2
Epidermoid cyst	1
Squamoid cyst	1

PancreaSeq: Pancreatic Cyst Fluid

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66 Mucinous Cysts:
56 IPMNs
10 MCNs

PancreaSeq: Pancreatic Cyst Fluid

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Retention cyst	2
Lymphoepithelial cyst	2
Epidermoid cyst	1
Squamoid cyst	1

66 Mucinous Cysts:
56 IPMNs
10 MCNs

36 Non-Mucinous Cysts

PancreaSeq: Pancreatic Cyst Fluid

Surgical Resection Dx	Total, n = 102 (18%)	*KRAS/GNAS* wildtype	*KRAS/GNAS* mutant
AdenoCA arising in an IPMN	13	0 (0%)	13 (100%)
IPMN with HGD	4	0 (0%)	4 (100%)
MCN with HGD	2	0 (0%)	2 (100%)
IPMN with LGD	39	0 (0%)	39 (100%)
MCN with LGD	8	7 (87%)	1 (13%)
Serous cystadenoma	3	3 (100%)	0 (0%)
Cystic PanNET	9	9 (100%)	0 (0%)
Acinar cell cystadenoma	1	1 (100%)	0 (0%)
Pseudocyst	17	17 (100%)	0 (0%)
Retention cyst	2	2 (100%)	0 (0%)
Lymphoepithelial cyst	2	2 (100%)	0 (0%)
Epidermoid cyst	1	1 (100%)	0 (0%)
Squamoid cyst	1	1 (100%)	0 (0%)

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MCN with LGD	8	7 (87%)	1 (13%)
Se		3 (100%)	0 (0%)
C		9 (100%)	0 (0%)
A		1 (100%)	0 (0%)
P		17 (100%)	0 (0%)
R		2 (100%)	0 (0%)
Ly		2 (100%)	0 (0%)
E		1 (100%)	0 (0%)
Sq		1 (100%)	0 (0%)

IPMNs & MCNs

KRAS **&/or** ***GNAS*** **mutations**

- **Sensitivity: 89%**
- **Specificity: 100%**

Elevated CEA*

- **Sensitivity: 57%**
- **Specificity: 80%**

PancreaSeq: Pancreatic Cyst Fluid

Surgical Resection Dx	Total, n = 102 (18%)	*KRAS/GNAS* wildtype	*KRAS/GNAS* mutant
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Se			
C			
A			
P			
R			
Ly			
E			
Sq			

IPMNs & MCNs

***KRAS* &/or *GNAS* mutations**

- **Sensitivity: 89%**
- **Specificity: 100%**

Elevated CEA

- **Sensitivity: 57%**
- **Specificity: 80%**

IPMNs

***KRAS* &/or *GNAS* mutations**

Sensitivity: 100%

MCNs

***KRAS* mutations**

Sensitivity: 30%

PancreaSeq: Pancreatic Cyst Fluid

Surgical Resection Dx	Total, n = 102 (18%)	*TP53/PIK3CA/PTEN* wildtype	*TP53/PIK3CA/PTEN* mutant
AdenoCA arising in an IPMN	13	0 (0%)	13 (100%)
IPMN with HGD	4	2 (50%)	2 (50%)
MCN with HGD	2	2 (100%)	0 (0%)
IPMN with LGD	39	36 (92%)	3 (8%)
MCN with LGD	8	8 (100%)	0 (0%)
Epidermoid cyst	1	1 (100%)	0 (0%)
Squamoid cyst	1	1 (100%)	0 (0%)

Alterations in *TP53*/*PIK3CA*/*PTEN* were preoperatively detected in all 13 (100%) adenocarcinomas.

PancreaSeq: Pancreatic Cyst Fluid

Surgical Resection Dx	Total, n = 102 (18%)	*TP53/PIK3CA/PTEN* wildtype	*TP53/PIK3CA/PTEN* mutant
AdenoCA arising in an IPMN	13	0 (0%)	13 (100%)
IPMN with HGD	4	2 (50%)	2 (50%)
MCN with HGD	2	2 (100%)	0 (0%)
IPMN with LGD	39	36 (92%)	3 (8%)
MCN with LGD	8	8 (100%)	0 (0%)
Epidermoid cyst	1	1 (100%)	0 (0%)
Squamoid cyst	1	1 (100%)	0 (0%)

Alterations in *TP53*/*PIK3CA*/*PTEN* were detected in 2 (50%) IPMNs with HGD

PancreaSeq: Pancreatic Cyst Fluid

Surgical Resection Dx	Total, n = 102 (18%)	*TP53/PIK3CA/PTEN* wildtype	*TP53/PIK3CA/PTEN* mutant
AdenoCA arising in an IPMN	13	0 (0%)	13 (100%)
IPMN with HGD	4	2 (50%)	2 (50%)
MCN with HGD	2	2 (100%)	0 (0%)
IPMN with LGD	39	36 (92%)	3 (8%)
MCN with LGD	8	8 (100%)	0 (0%)
Epidermoid cyst	1	1 (100%)	0 (0%)
Squamoid cyst	1	1 (100%)	0 (0%)

Alterations in *TP53*/*PIK3CA*/*PTEN* were detected in 2 (50%) IPMNs with HGD and 3 (8%) IPMNs with LGD (*PIK3CA* mutations).

PancreaSeq: Pancreatic Cyst Fluid

Surgical Resection Dx	Total, n = 102 (18%)	*TP53/PIK3CA/PTEN* wildtype	*TP53/PIK3CA/PTEN* mutant
AdenoCA arising in an IPMN	13	0 (0%)	13 (100%)
IPMN with HGD	4	2 (50%)	2 (50%)
MCN with HGD	2	2 (100%)	0 (0%)
IPMN with LGD	39	36 (92%)	3 (8%)
M		8 (100%)	0 (0%)
S		3 (100%)	0 (0%)
C		9 (100%)	0 (0%)
A		1 (100%)	0 (0%)
R		17 (100%)	0 (0%)
R		2 (100%)	0 (0%)
L		2 (100%)	0 (0%)
E		1 (100%)	0 (0%)
Sq		1 (100%)	0 (0%)

Advanced Neoplasia

KRAS **and/or** ***GNAS*** **and** ***TP53***, ***PIK3CA***, **and/or** ***PTEN***

- **Sensitivity: 79%**
- **Specificity: 96%**

Cytology

- **Sensitivity: 32%**
- **Specificity: 98%**

PancreaSeq: Pan

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P	
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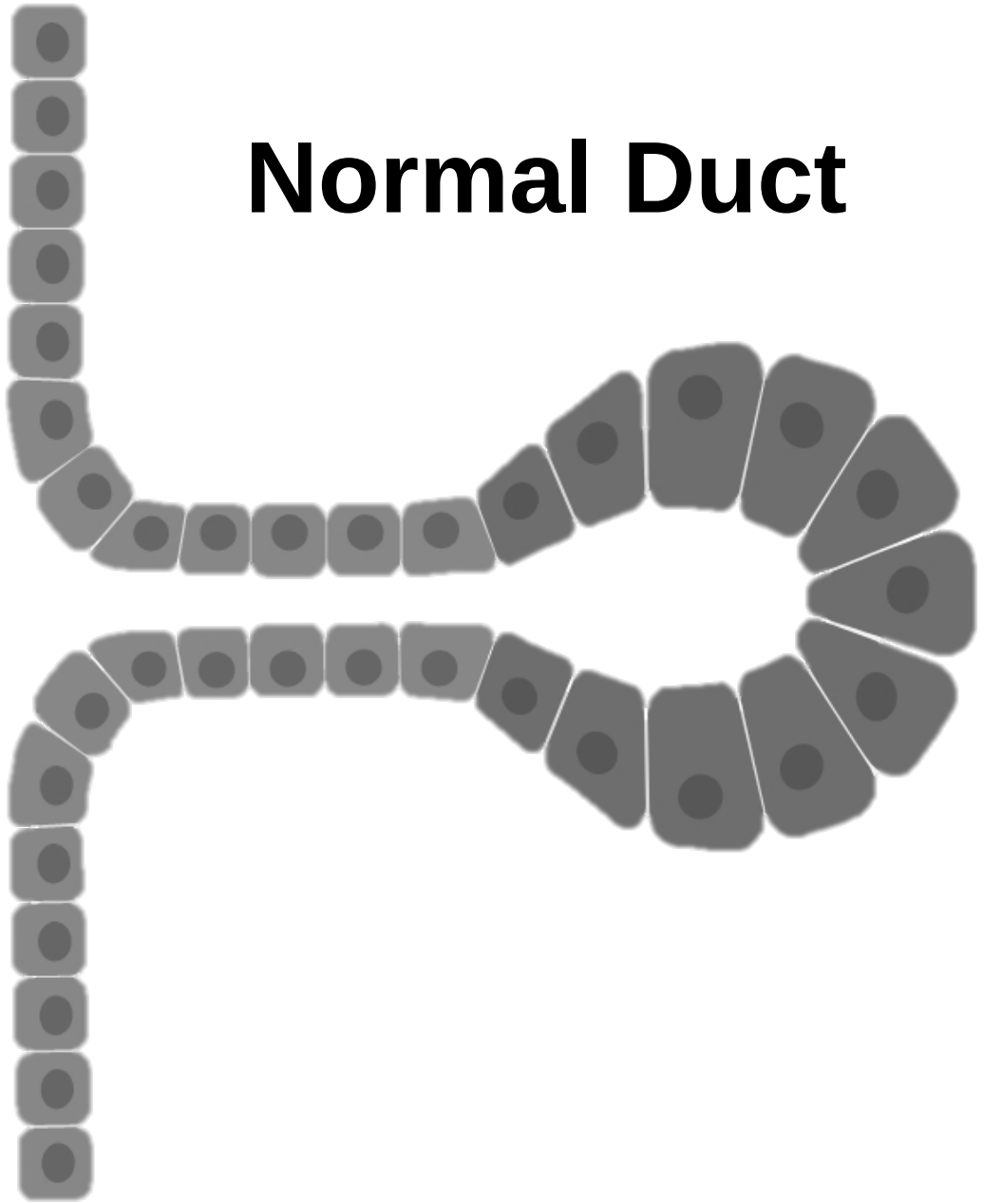
Normal Duct



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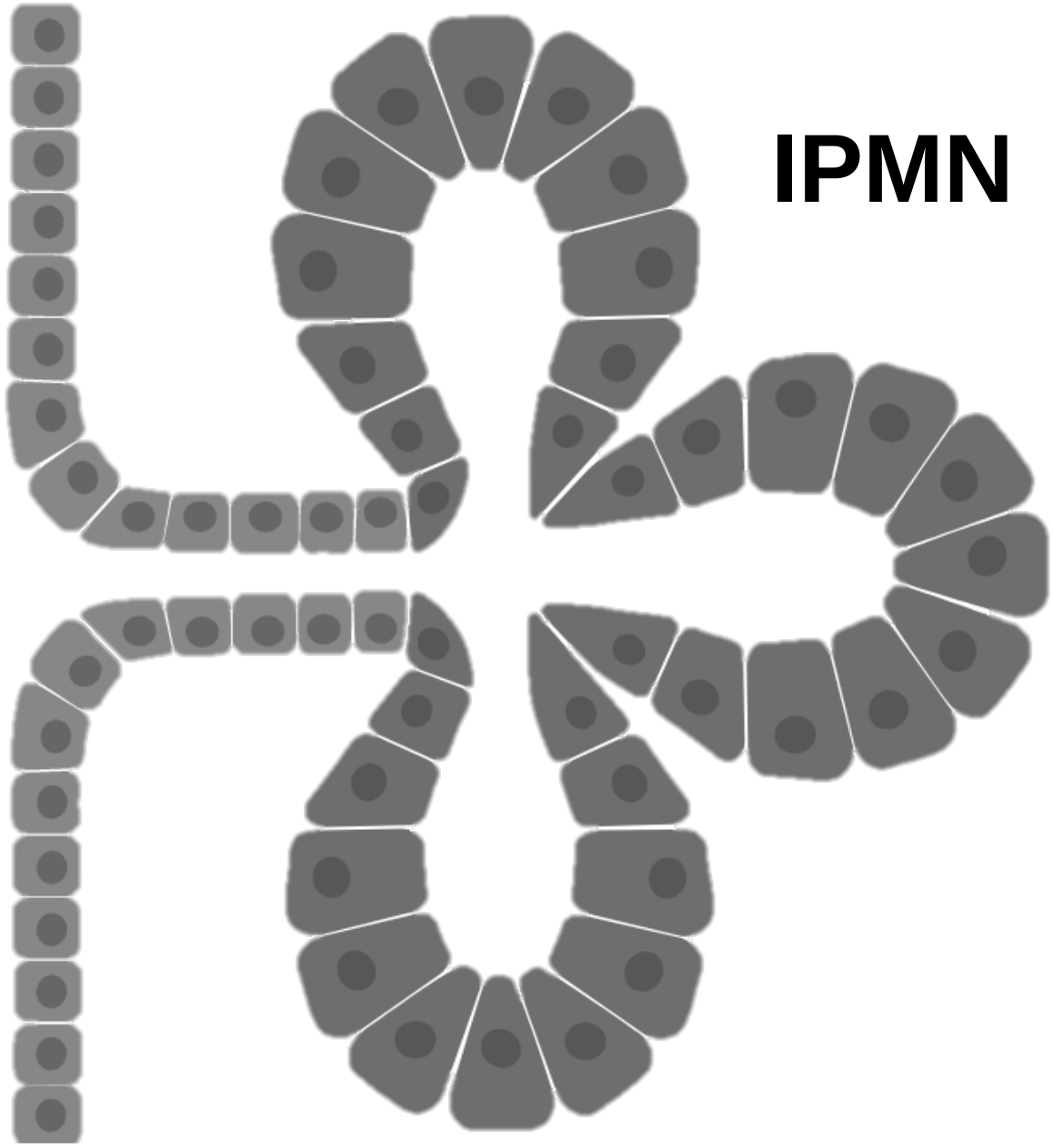

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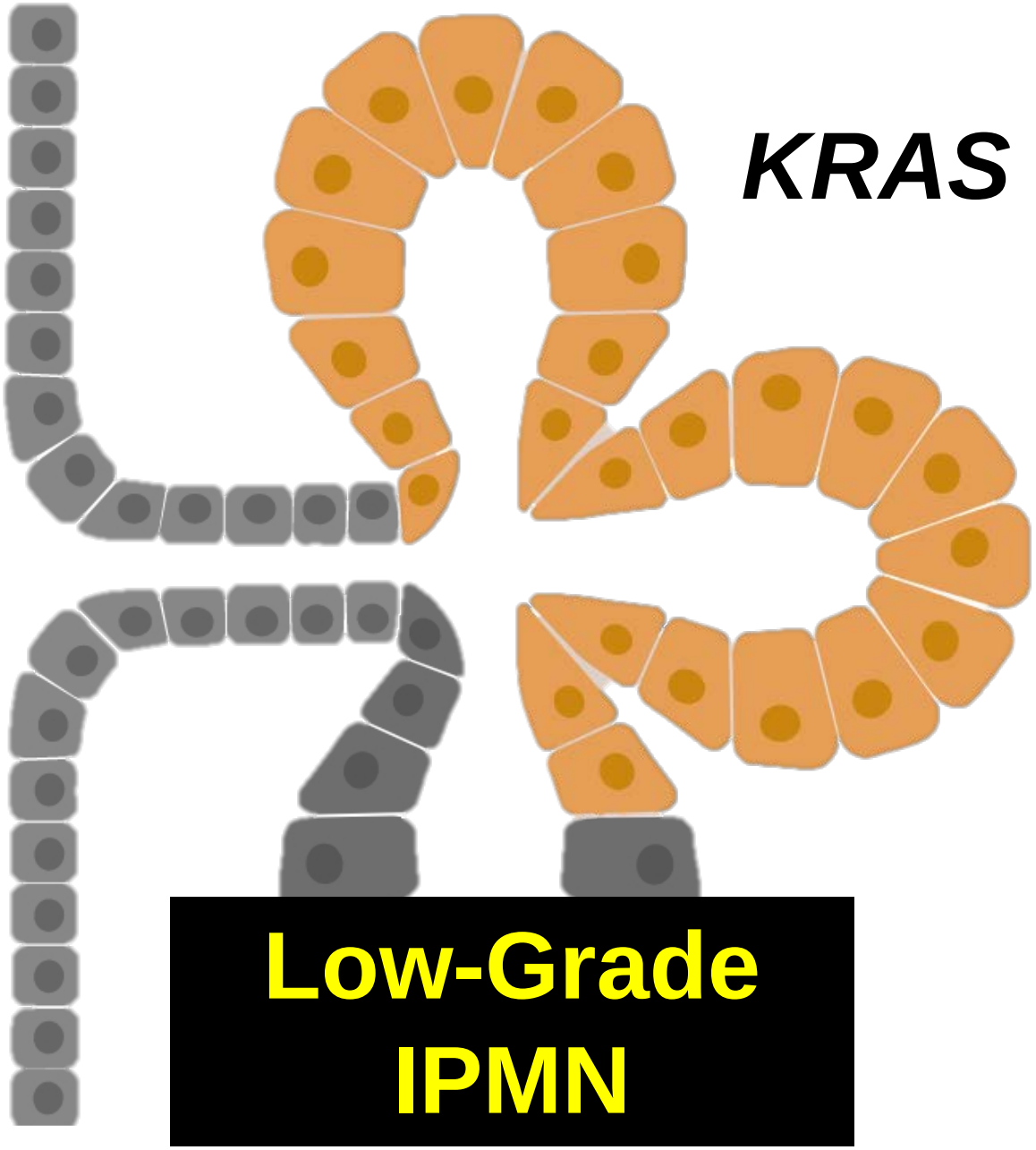

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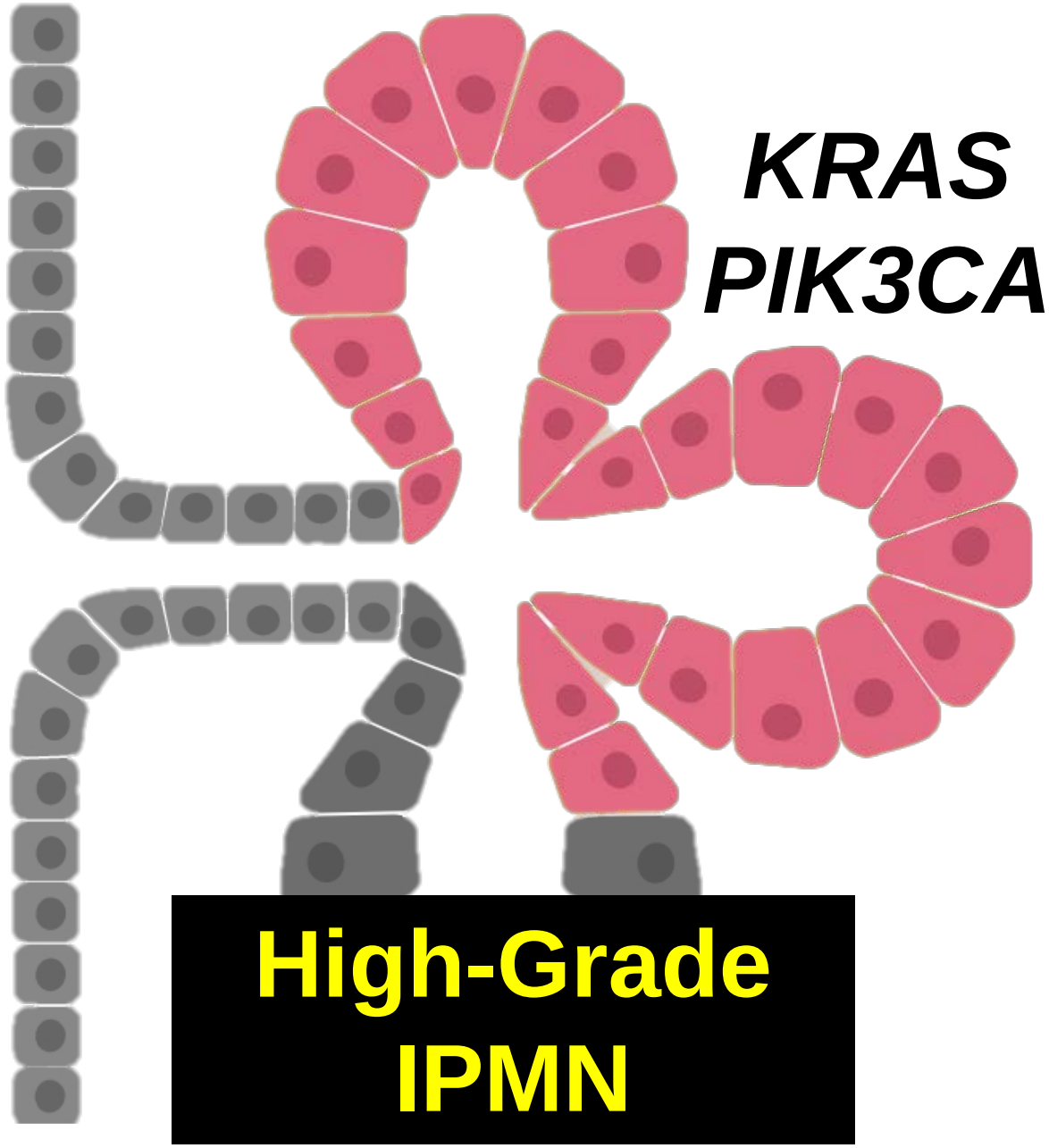

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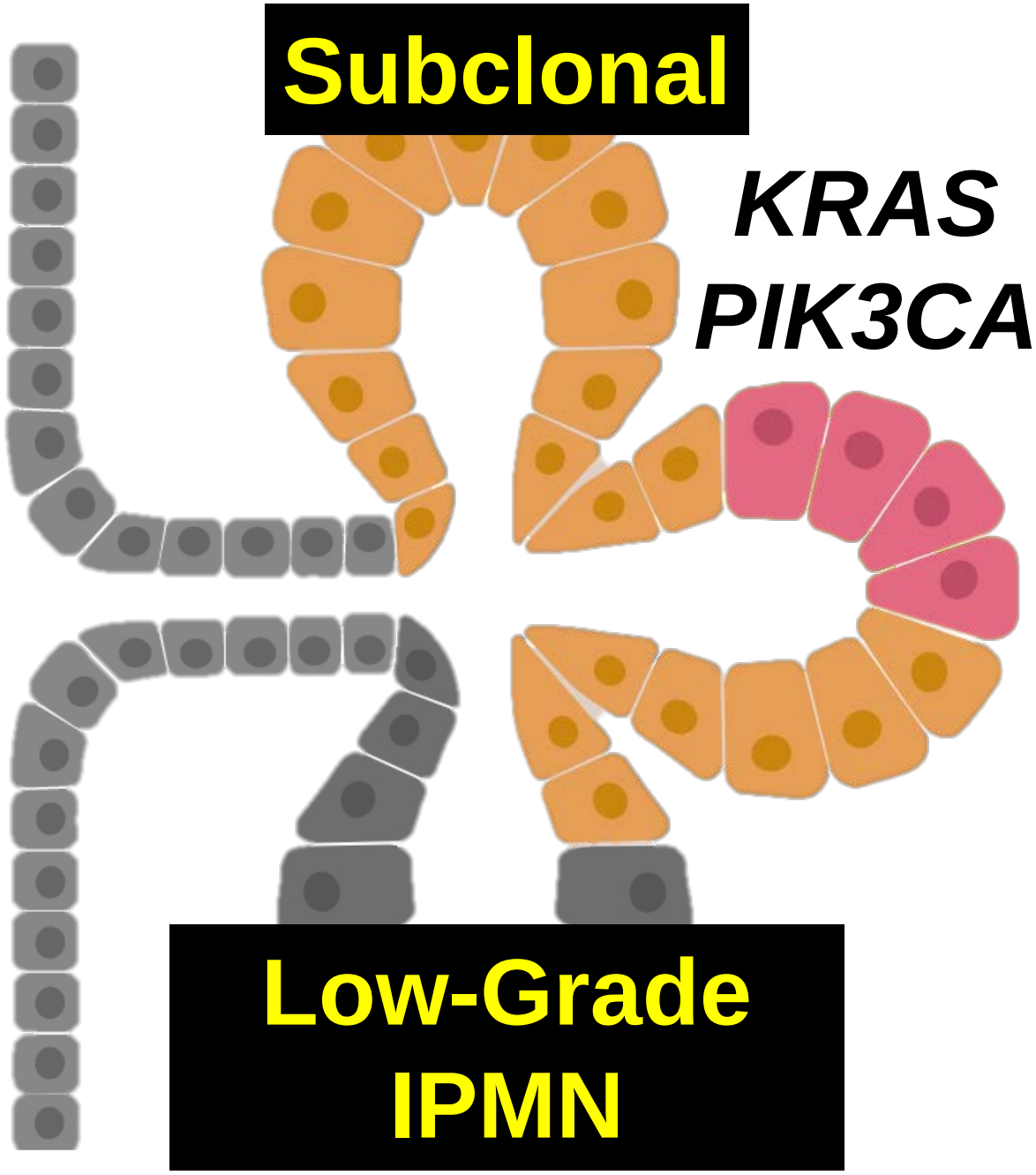

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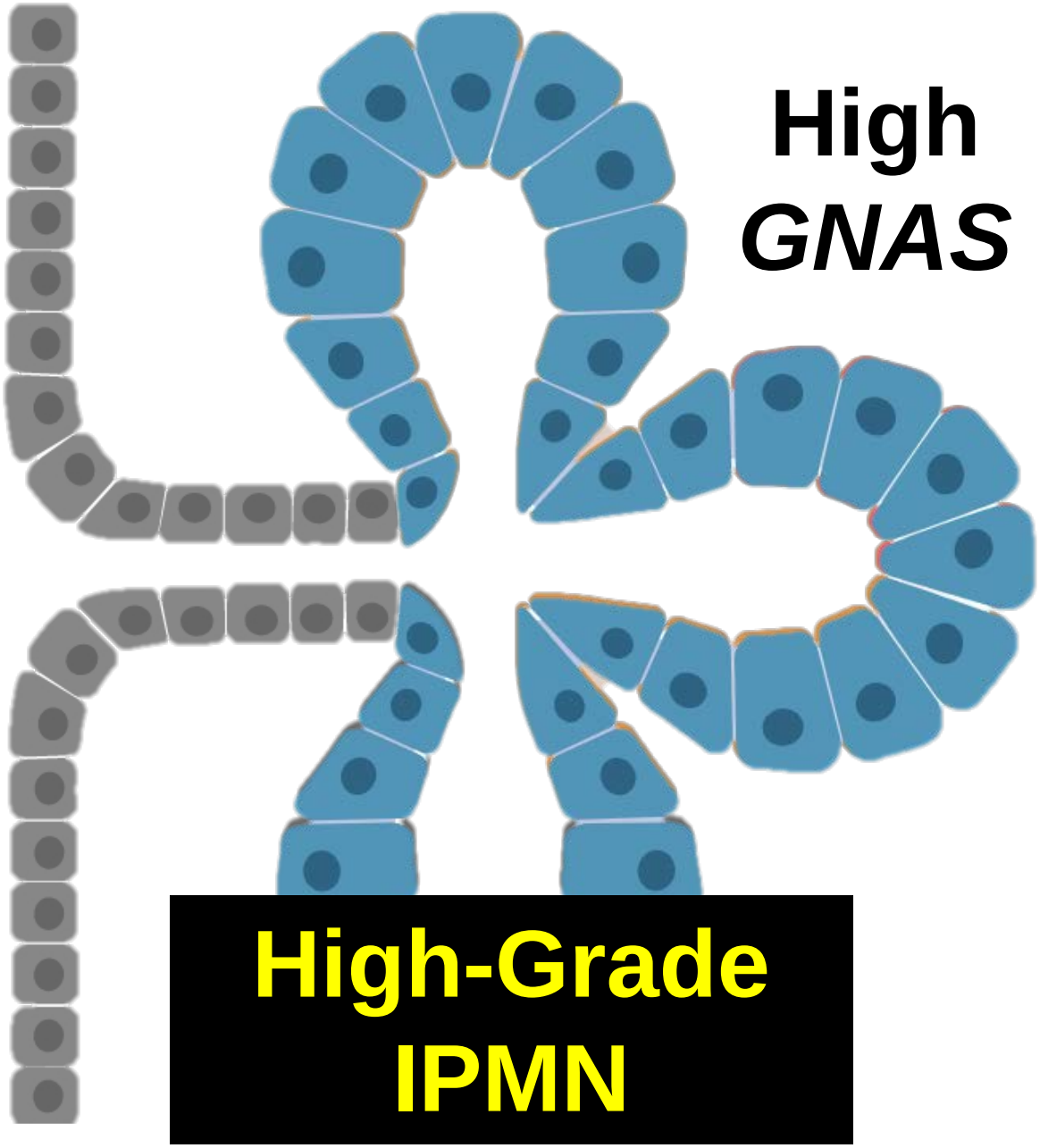
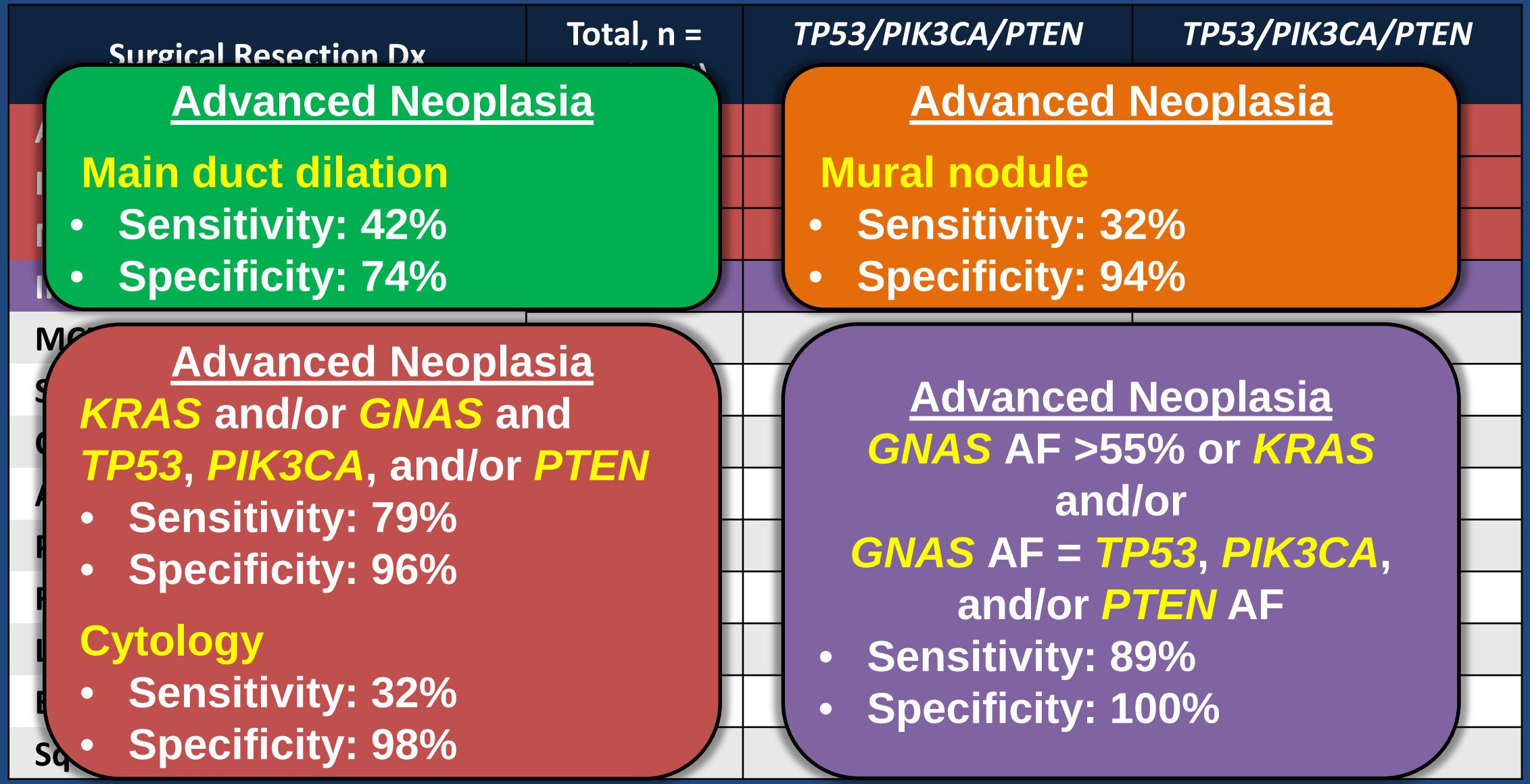
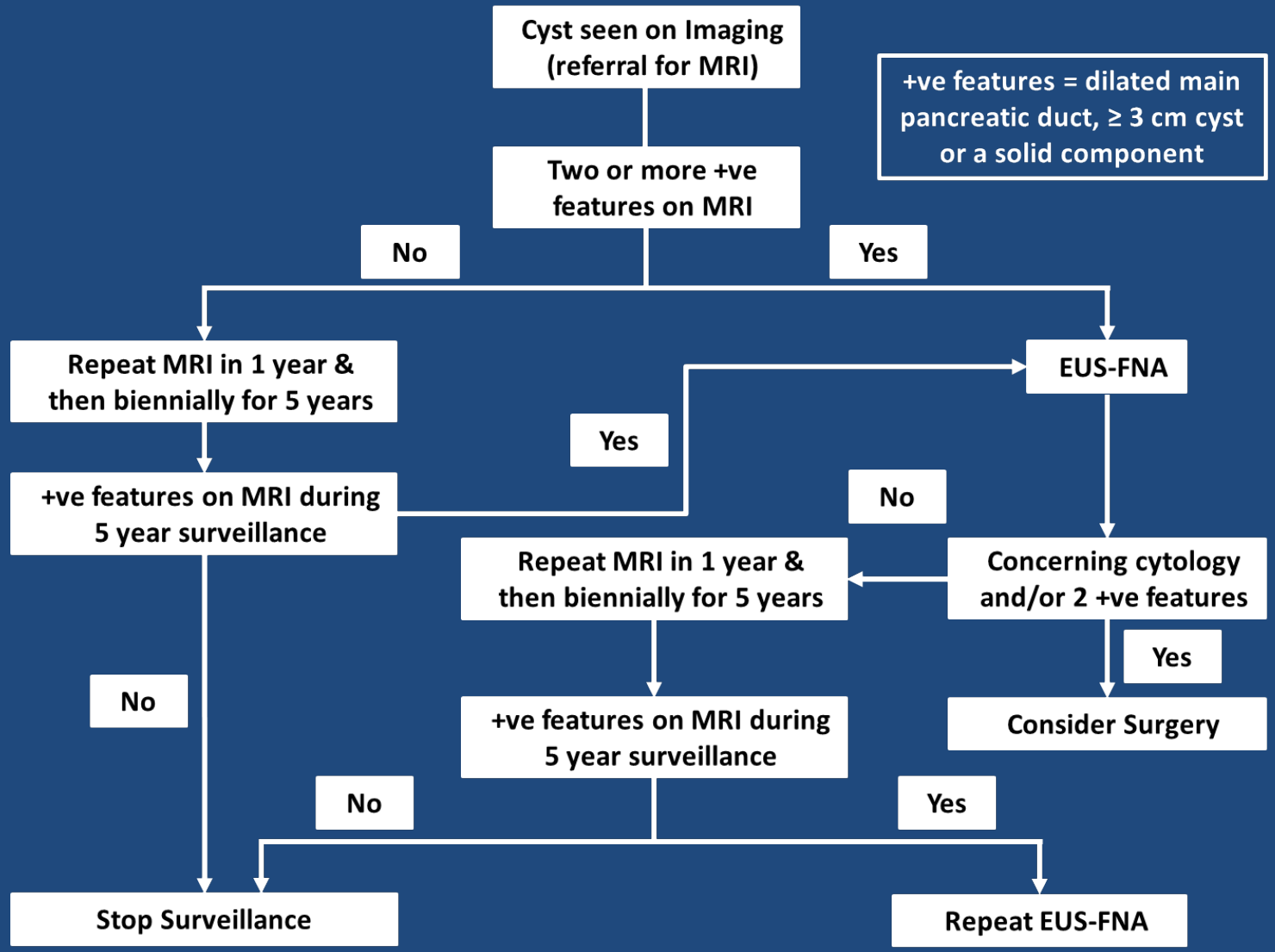


PancreaSeq: Pancreatic Cyst Fluid

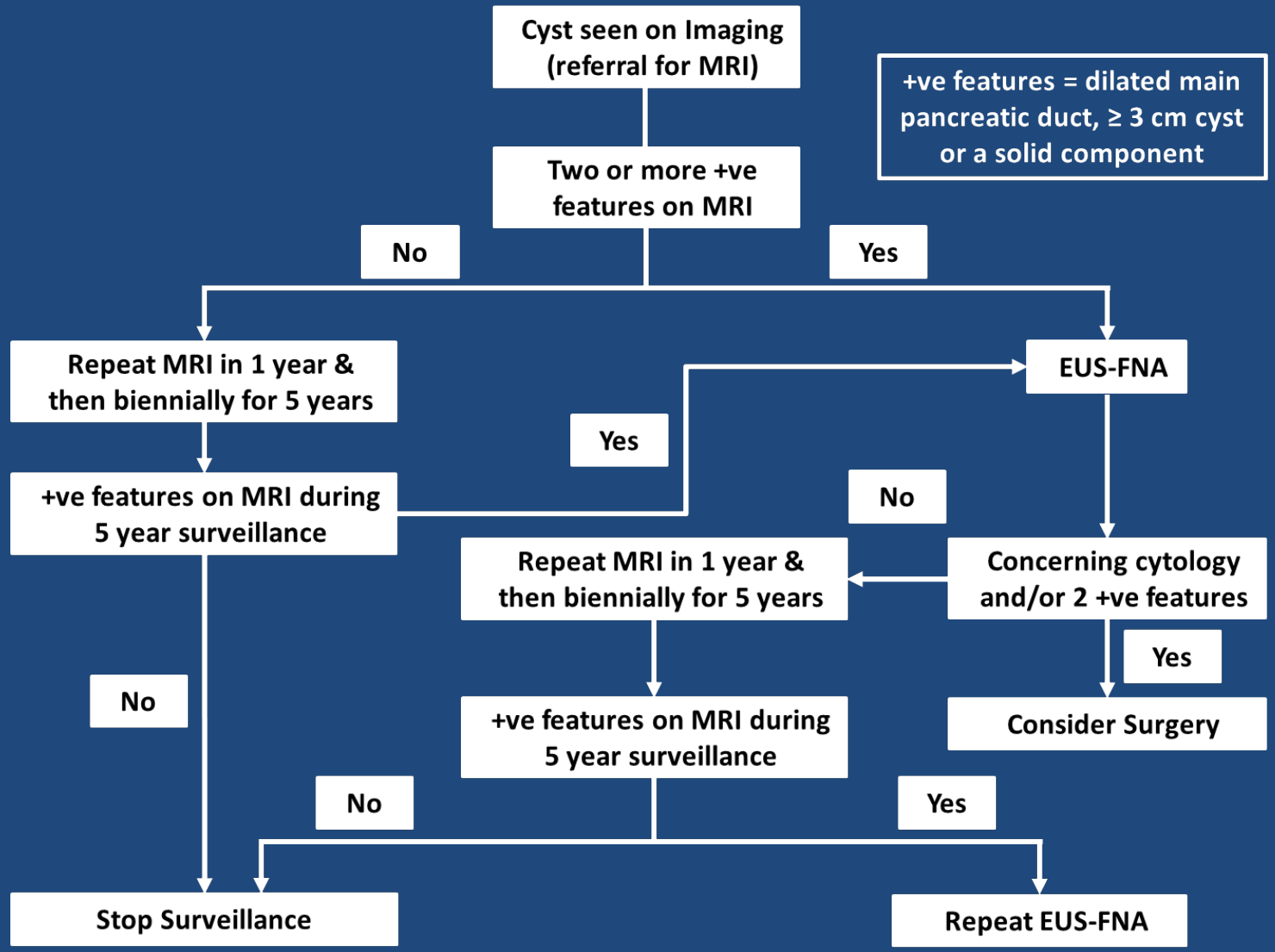


PancreaSeq versus AGA Guidelines



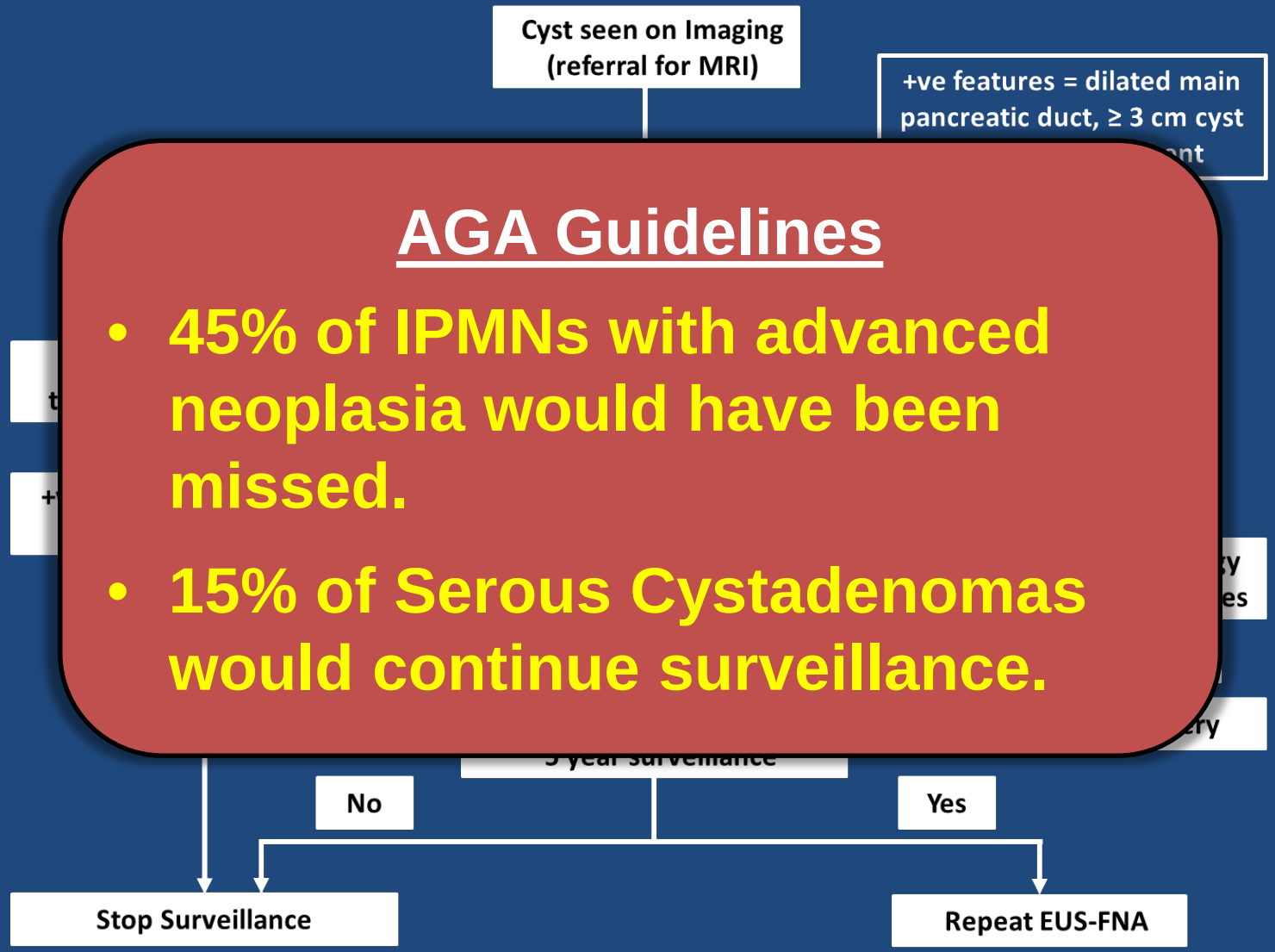
- **Study cohort:**
  - **225 patients with corresponding diagnostic pathology for 41 patients.**
  - **EUS-FNA with PancreaSeq testing.**

PancreaSeq versus AGA Guidelines



- Study cohort:
  - 225 patients with corresponding diagnostic pathology for 41 patients.
  - EUS-FNA with PancreaSeq testing.
- AGA Guidelines:
  - Sensitivity: 62%
  - Specificity: 79%
- Modified Fukuoka with PancreaSeq (UPMC):
  - Sensitivity: 100%
  - Specificity: 90%

PancreaSeq versus AGA Guidelines



AGA Guidelines

- 45% of IPMNs with advanced neoplasia would have been missed.
- 15% of Serous Cystadenomas would continue surveillance.

- Study cohort:
  - 225 patients with corresponding diagnostic pathology for 41 patients.
  - EUS-FNA with PancreaSeq testing.
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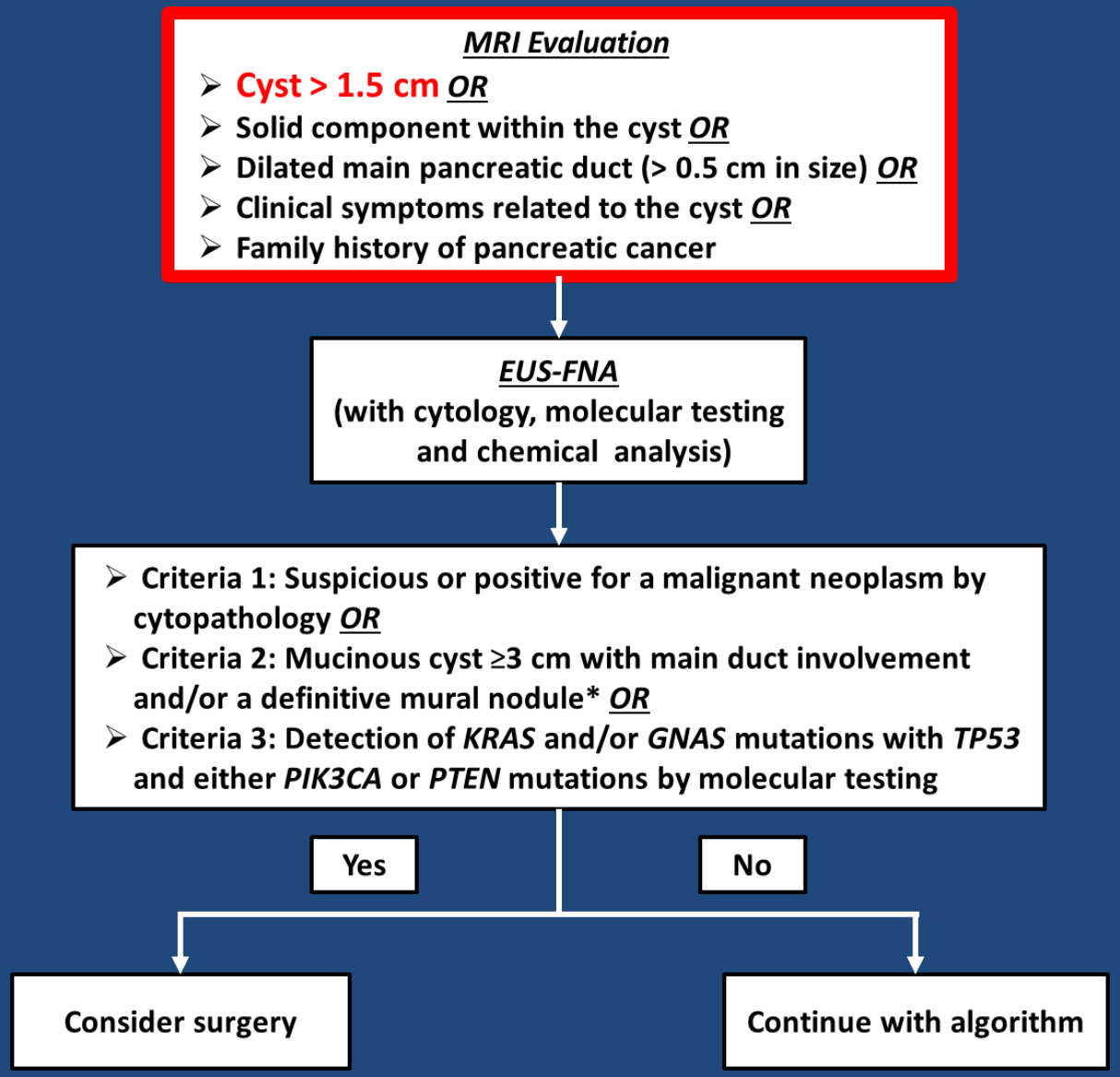
UPMC Pancreatic Cyst Workflow



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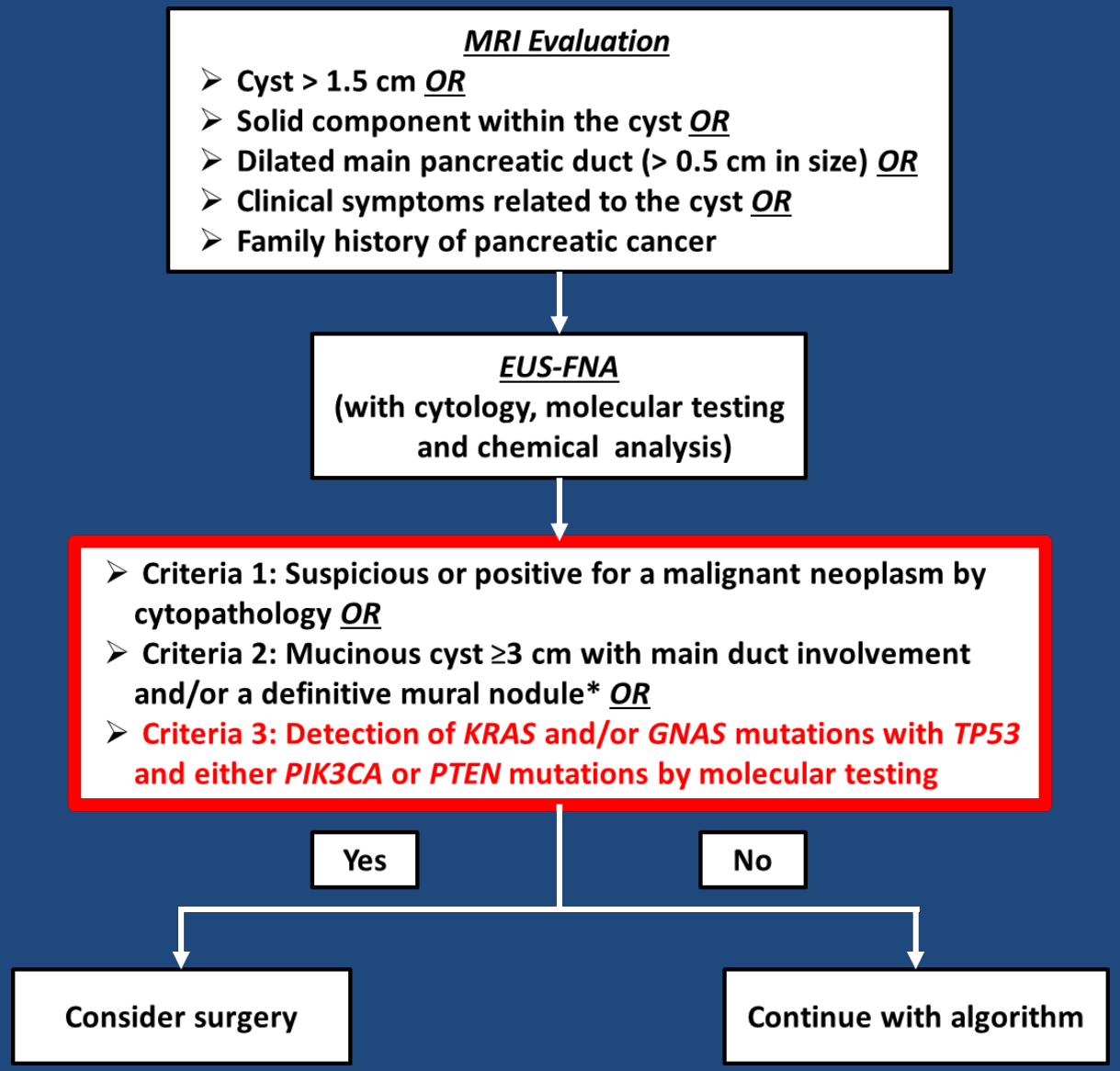


- Criteria 1: Mucinous cyst <3 cm with main duct involvement and/or a definitive mural nodule* ***OR***
- Criteria 2: Detection of *KRAS* and/or *GNAS* mutations with *TP53*, *PIK3CA* or *PTEN* mutations

→ ***Surveillance Plan A***
Alternating MRI and EUS-FNA every 6 to 12 months. Consider surgery in young fit patients.

- Demonstration of a mucinous cyst by positive cytopathology, elevated CEA or the presence of *KRAS* and/or *GNAS* mutations

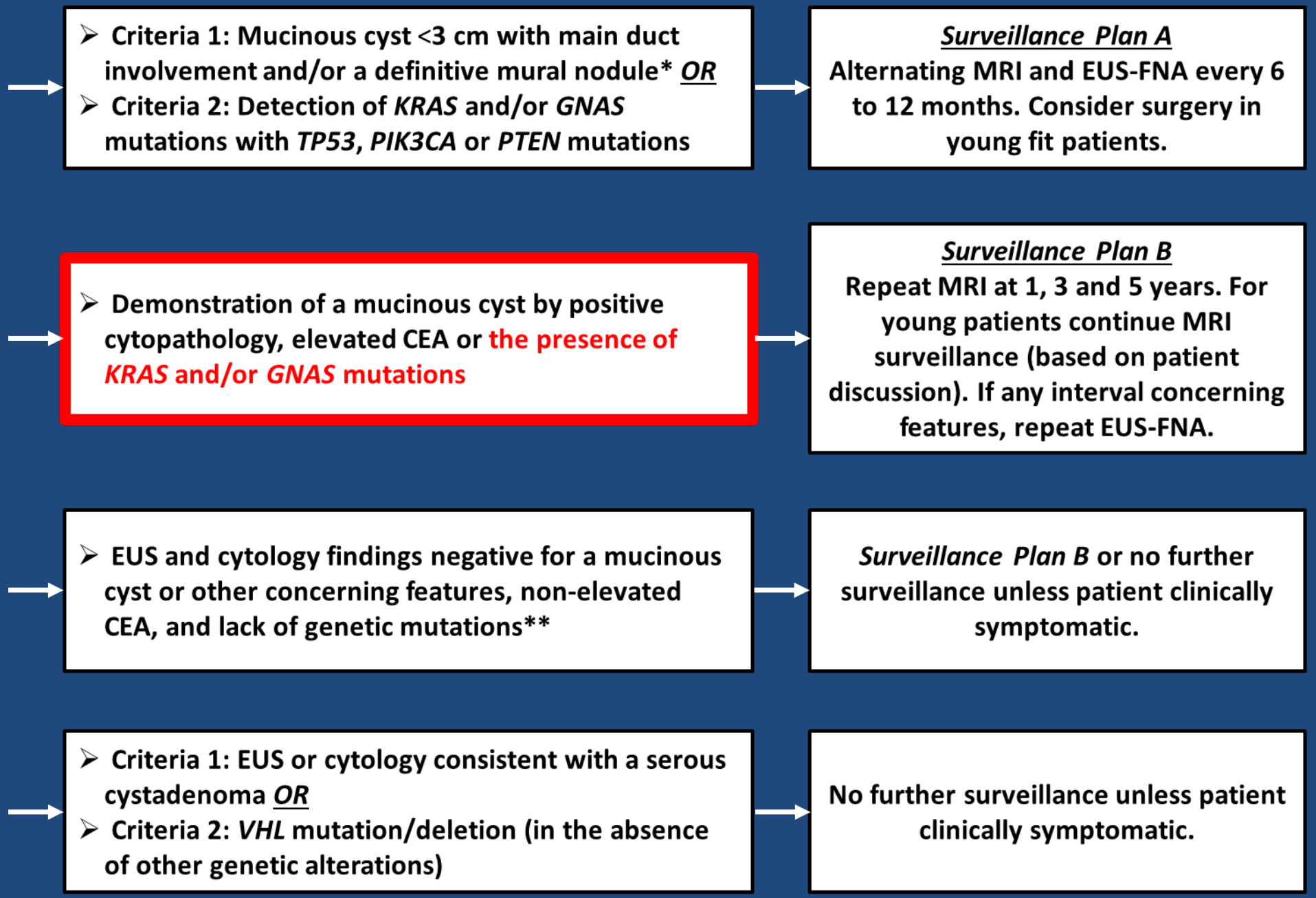
→ ***Surveillance Plan B***
Repeat MRI at 1, 3 and 5 years. For young patients continue MRI surveillance (based on patient discussion). If any interval concerning features, repeat EUS-FNA.

- EUS and cytology findings negative for a mucinous cyst or other concerning features, non-elevated CEA, and lack of genetic mutations**

→ *Surveillance Plan B* or no further surveillance unless patient clinically symptomatic.

- Criteria 1: EUS or cytology consistent with a serous cystadenoma ***OR***
- Criteria 2: *VHL* mutation/deletion (in the absence of other genetic alterations)

→ No further surveillance unless patient clinically symptomatic.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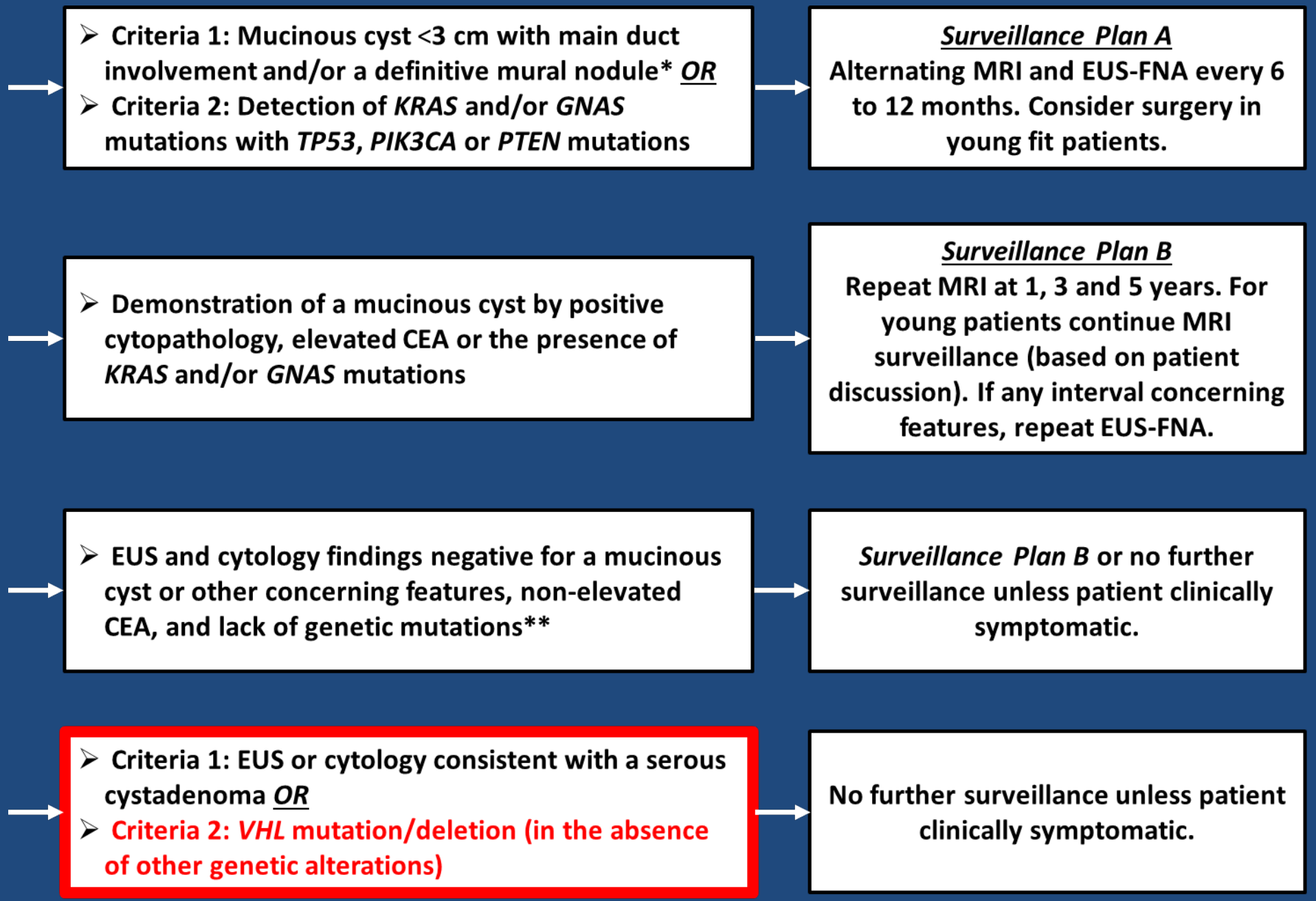
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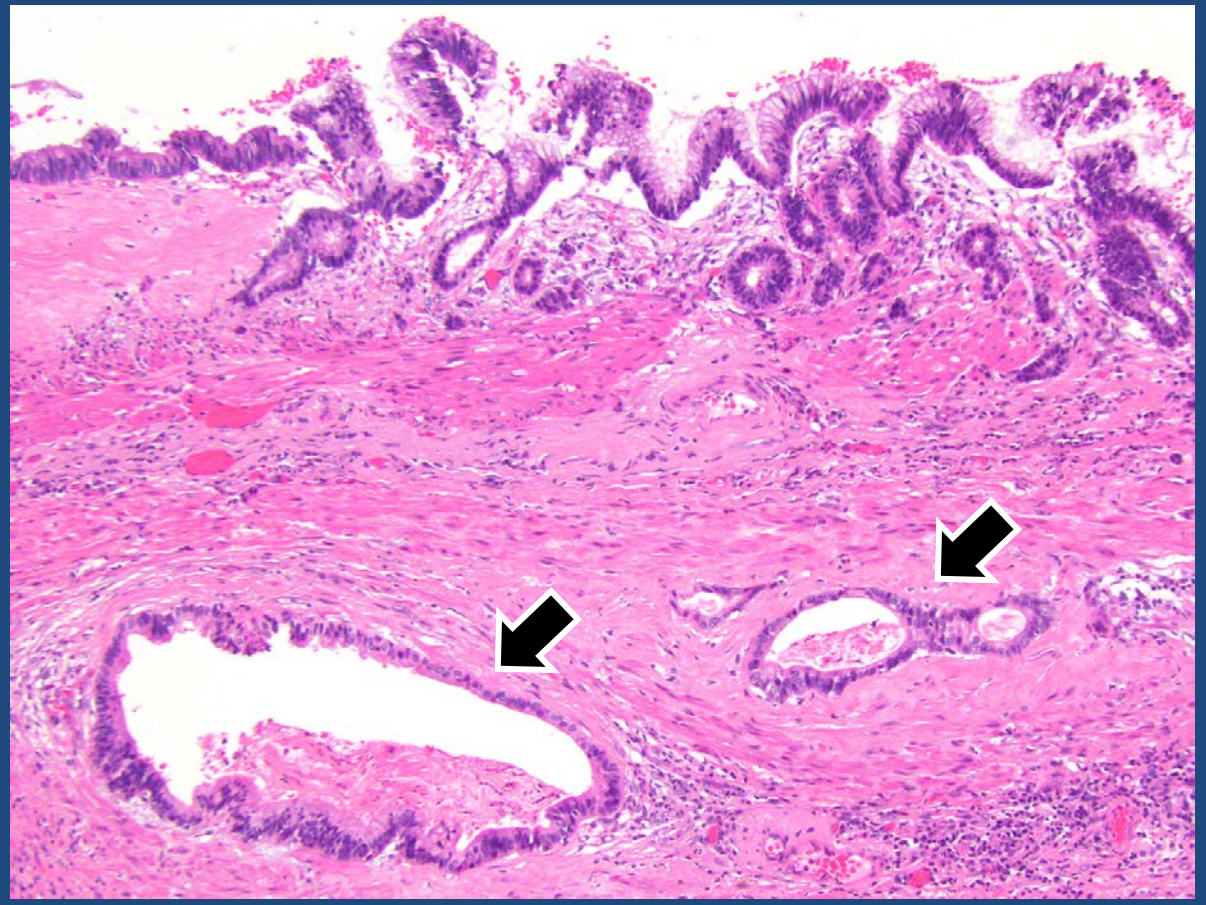
Clinical Case

Surgical Resection:

- Invasive moderately-differentiated adenocarcinoma, 0.9 cm (black arrow), arising in association with an IPMN.
- Pathologic stage (AJCC 8th edition): pT1a N0.



Summary

- **The application of molecular testing to pancreatic cyst fluid analysis can be a useful adjunct in the evaluation of pancreatic cysts.**
- **Cellular content and fluid volume of aspirated cysts are commonly suboptimal for routine ancillary studies (e.g. CEA and cytopathology).**
- **DNA from lysed or exfoliated pancreatic cyst epithelial lining shed into the cyst can be analyzed for genetic abnormalities.**

Summary

- **Mutations in *KRAS & GNAS* are highly specific for branch duct IPMNs, but not MCNs.**
- **The presence of high-risk alterations (e.g. *TP53*, *PIK3CA*, *PTEN*, high *GNAS*, etc.) can predict advanced neoplasia.**
- **Alterations in *VHL* can aid in classification of serous cystadenomas and decrease the number of patients undergoing surveillance.**

Take Away Message

	IPMN	MCN	SCA	SPN	Pseudocyst
Gender	M>F	F>>M	F>M	F>>M	M>F
Location	Head>Tail	Tail>>Head	Head>Tail	Tail>Head	Head=Tail
Viscosity	Increased	Increased	Low	Low	Low
CEA	>192 ng/mL	>192 ng/mL	<0.5 ng/mL	<192 ng/mL	<192 ng/mL
Amylase	High	Low	Low	Low	High
Cytology	Mucinous	Mucinous	Scant, Bland PAS+	Papillary & Vascular	Pigmented Histiocytes
Genetics	*KRAS,GNAS*	*KRAS*	*VHL*	*CTNNB1*	Absent

Challenges Ahead

- Continuing evolution of pancreatic cyst molecular profiling.
- **Additional biomarkers**: DNA, RNA, protein, carbohydrates and others.
- Refinements and optimization with other preoperative clinical, imaging and pathology metadata.
- Benefits versus costs: **insurance reimbursement**.
- **Multiple assays available**: academic versus industry.