Algorithmic approach to Pancreatic Cancer by EUS-FNA: A powerful diagnostic tool In The Era of Precision Medicine

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Goals and Objectives

1. Learn a simple algorithmic approach for the diagnosis of Pancreatic Cancer by EUS-FNA
2. Discuss the differential diagnosis for the suspected Pancreatic cancer/mass
3. Discuss the NCCN guidelines for the molecular testing of Pancreatic cancer and the importance of the same in the clinical practice
4. A case based approach making this session easy and fun for the learning, during which the ancillary tests including but not limited to IHC, Flow cytometry, Molecular testings will be discussed with the examples provided
5. At the end of the session, participants will be able to apply the most current knowledge in their day to day to practice leading to the better patient care for this challenging type of samples.

fnac
SOUND
TRAVEL
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Endoscopic Ultrasound–Guided Fine-Needle Aspiration

A Cytopathologist's Perspective

Am J Clin Pathol 2003;120:351-367
DOI: 10.1309/MFRFJ0XYJLN8NVDP

" Endosonographically obtained samples will soon become the standard of practice to obtain samples from deep seated organs"

JOP. J Pancreas (Online) 2004; 5(4):282-288.

ROUND TABLE

Pancreatic Fine Needle Aspiration: To Do or not To Do?

William R Brugge

GI Unit, Massachusetts General Hospital. Boston, MA, USA

Qian and Hecht suggested that US/CT-guided biopsies may be more accurate and sensitive for documenting malignancy than EUS, but noted
that EUS-guidance was used in more difficult lesions [41]. In contrast, in a small series, *Jhala et al. demonstrated that EUS-FNA was superior to CT-FNA in obtaining adequate cells from neuroendocrine tumors of the pancreas for the diagnosis and performing additional imunohistochemical stains [42].*

42. Jhala D, Eloubeidi M, Chhieng DC, Frost A, Eltoum IA, Roberson J, Jhala N. Fine needle aspiration biopsy of the islet cell tumor of pancreas: a comparison between computerized axial tomography and endoscopic ultrasound-guided fine needle aspiration biopsy. Ann Diagn Pathol 2002; 6:106-12. [PMID 12004358]

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB): past, present, and future

Kenji Yamao[1], Akira Sawaki[1], Nobumasa Mizuno[1], Yasuhiro Shimizu[2], Yasushi Yatabe[3], and Takashi Koshikawa[4]

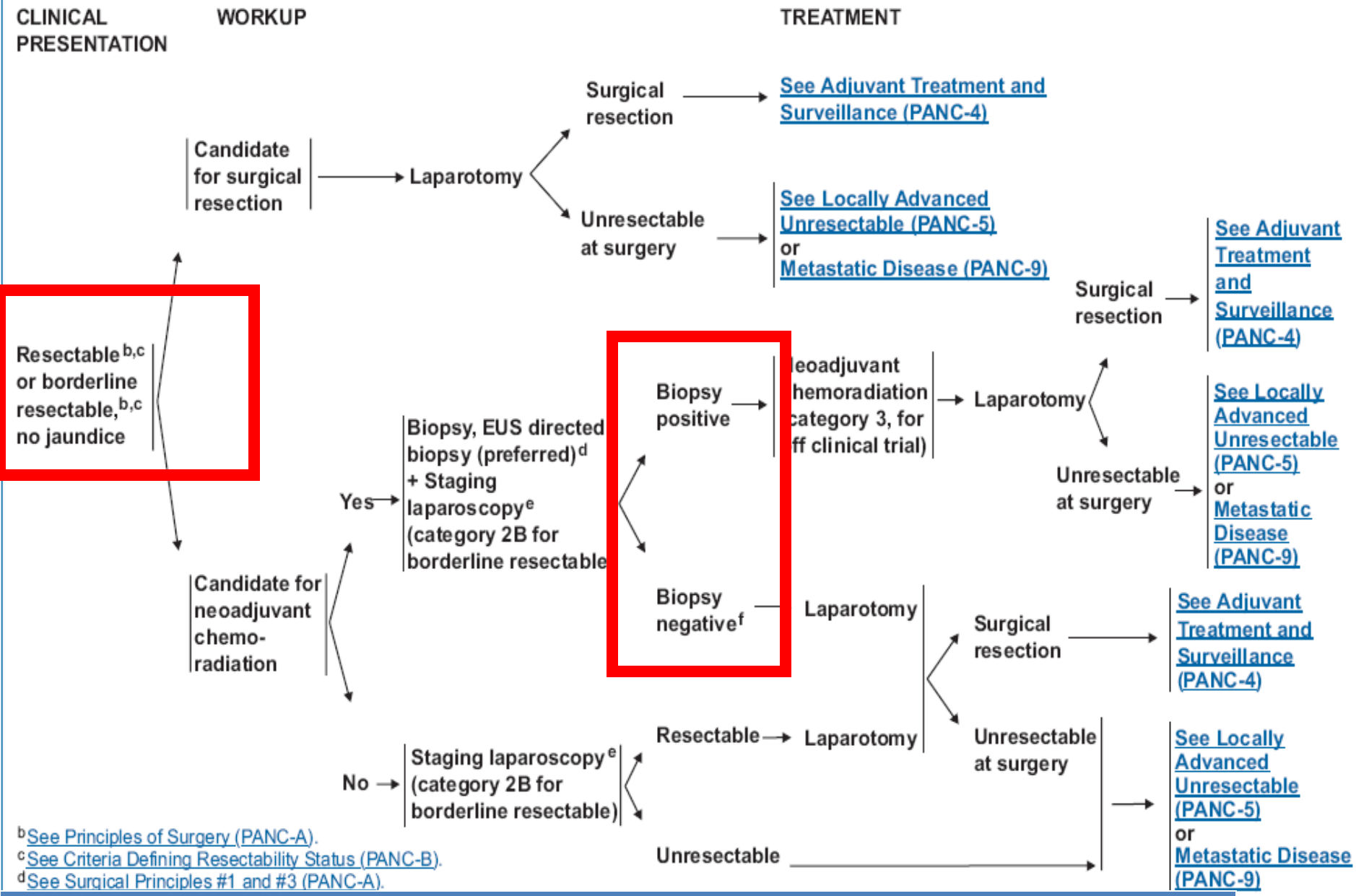
Table 1. History of EUS-FNAB

1980	DiMagno et al.[3]	Linear array echoendoscope
	Strohm et al.[4]	Mechanical radial echoendoscope
1984	Tio and Tytgat[5]	Possibility of EUS-FNAB
1989	Kouzu[a]	Possibility of EUS-FNAB
1991	Harada et al.[6]	Experimental study of EUS-FNAB
	Calletti et al.[7]	EUS-assisted FNA for gastric submucosal tumor using guillotine needle biopsy
1992	Vilmann et al.[2]	EUS-FNAB using convex linear array echoendoscope for pancreatic cancer
1993	Vilmann et al.[8]	Development of a new needle (steel needle with Teflon sheath) and EUS-FNAB for upper gastrointestinal tract lesion
	Wiersema et al.[9]	EUS-FNAB for mediastinal lymph node
	Tio et al.[10]	EUS-FNAB using mechanical radial echoendoscope for pancreatic cancer

J Gastroenterol 2005; 40:1013–1023
DOI 10.1007/s00535-005-1717-6

2002	Jhala et al.[30]	EUS-FNAB for pancreatic endocrine tumor
	Gress et al.[34]	EUS-FNT (tattooing)
	Wiersema et al.[35]	Development of a new needle (Trucut biopsy needle)
	Jacobson et al.[31]	EUS-FNAB for gallbladder
2003	Matsumoto et al.[32]	EUS-FNAB for autoimmune pancreatitis
	Fritscher-Ravens et al.[33]	EUS-FNAB for splenic lesion

Pancreatic Adenocarcinoma

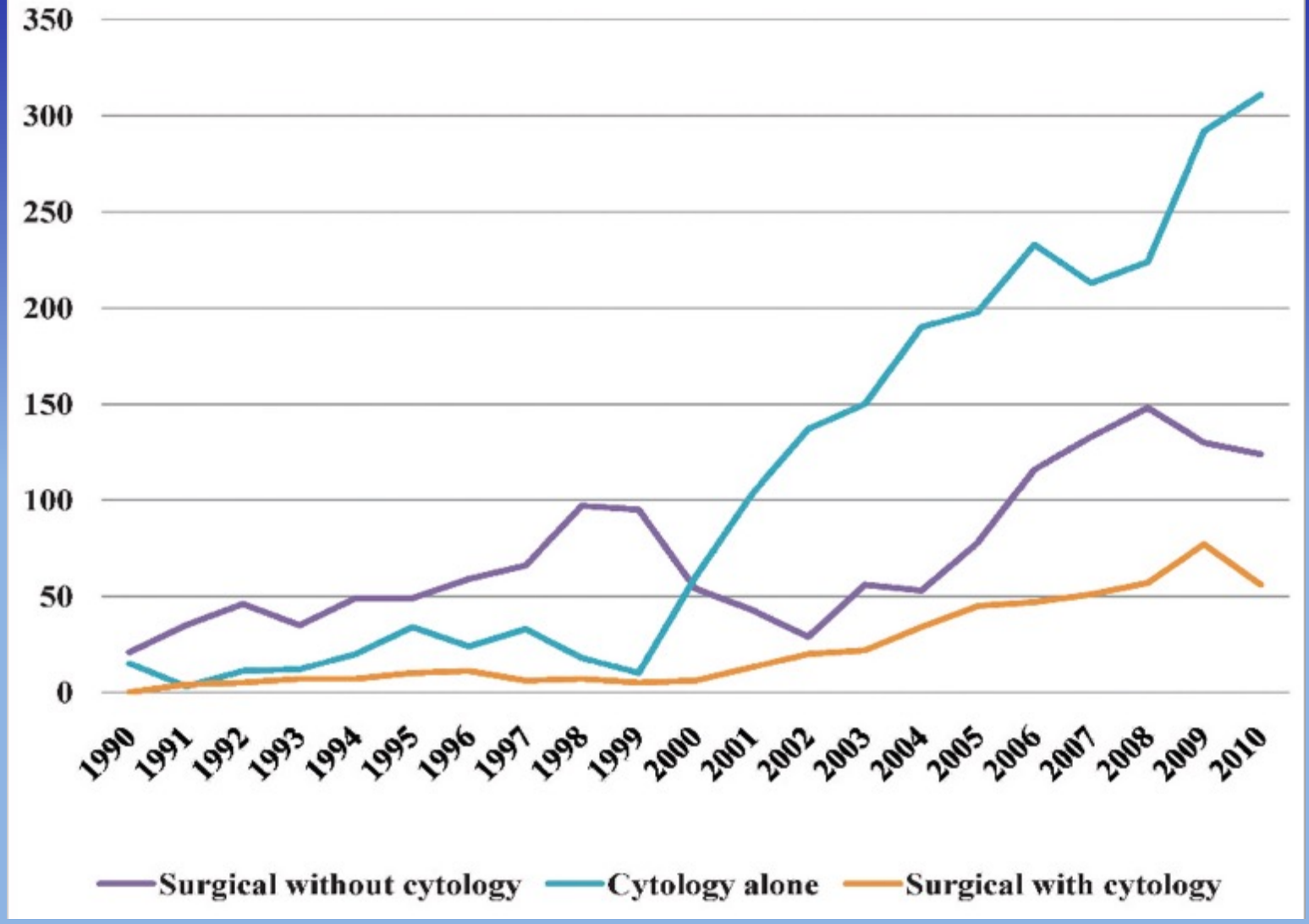


[b] See Principles of Surgery (PANC-A).
[c] See Criteria Defining Resectability Status (PANC-B).
[d] See Surgical Principles #1 and #3 (PANC-A).

F A negative biopsy should be confirmed by at least one repeat EUS biopsy

Trend Continues

Arch Pathol Lab Med. 2012;136(4):447-53.



How can we improve diagnostic performance of EUS-FNA for pancreatic lesions

- Experienced cytopathologist with interest in GI diseases[1].
- Good communication with the endosonographer.
- Onsite diagnosis/ specimen adequacy assessment[2,3].
- Understanding sample types obtained under EUS guidance could help avoid pitfalls in diagnosis[4].

1. Cytopathology 2007;18:143-50.
2. Cancer 2004; 110: 239-46;
3. Ann Diagn Pathol. 2007;11:176-81.
4. Am J Clin Pathol 2003; 102:351-67.

Trans GI Approach to Organs

- **Trans Esophageal** Mediastinum
  Celiac nodes
  Lung
- **Trans Gastric** Liver
  Gall Bladder
  Hilar Bile duct
  Body/ Tail of Pancreas
  Adrenal
  Spleen
  Celiac Node
  Left Kidney
- **Trans duodenal** Distal Bile Duct
  Head of pancreas
  Uncinate Process

- **Trans Colonic** Pericolonic tumors
  Urinary bladder lesions
  Pericolic Lymph node

FNA diagnosis and Pancreas

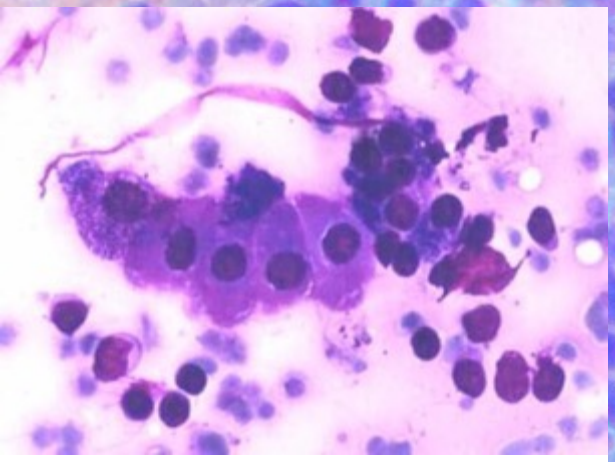
"There is a minefield that must be maneuvered to arrive at the accurate diagnosis. The material is often scant and bloody. The path the needle traverses may yield normal gastrointestinal tract epithelium, which may lead to false diagnoses. The diagnosis of pancreatic neoplasms is intrinsically difficult, including with EUS - FNA" **.

Editorial: Cancer. 2004;102:203-6.

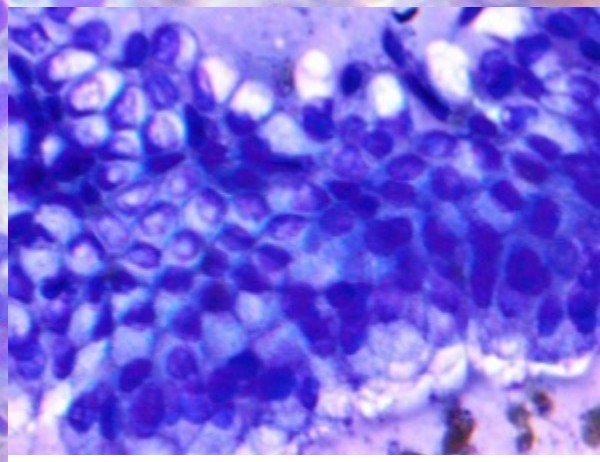
Acinar Cells

Cells from the pancreas

Ductal Cells



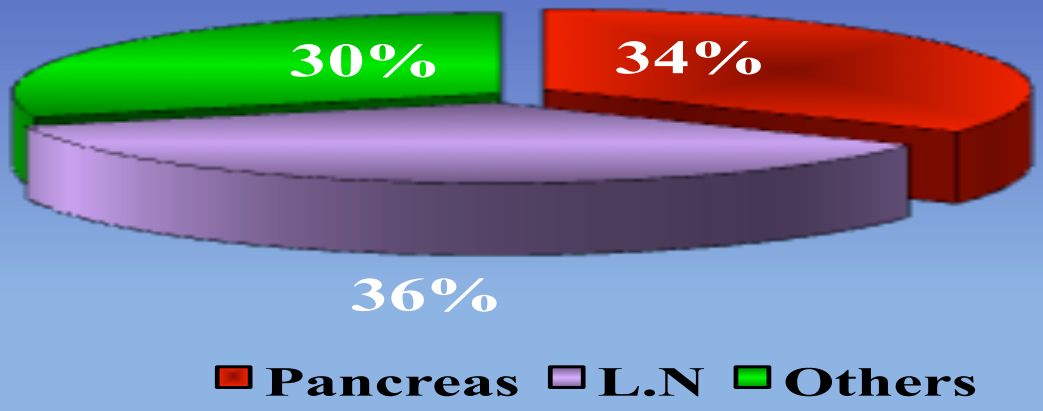
Parietal and Chief cells



Foveolar cells

EUS-FNAB: Site Distribution

N = 3,684

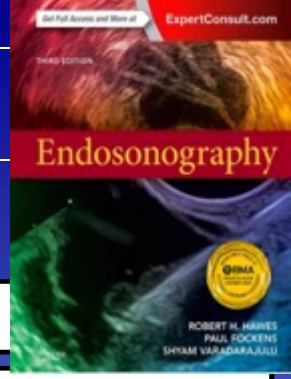


Others(30%): GI Tract, Hepatobiliary Tree, Adrenal gland, Spleen, Lung, Kidney, urinary bladder, peritoneum, primary mediastinal lesions

Nunez A .. Jhala D . Cytojournal 2012, 9: 14

Jhala Algorithm for Pancreas

Morphology Based Practical Algorithmic Approach to Pancreatic FNA



- Pancreatic FNA
  - Cellular Specimen
    - Groups of cells and +/- single cells (morphology consistent with Epithelial cells)
      - Predominantly ductal cells
        - Adenocarcinoma
      - Acinar cells with rare ductal cells
        - Presence of fibrosis and acute or chronic inflammatory cells
          - Acute or chronic pancreatitis
        - Presence of fibrosis and lymphoplasmacytic infiltrate
          - Autoimmune pancreatitis
      - Predominantly acinar cells
        - Acinar cell carcinoma
      - Groups of epithelial cells, but not ductal or acinar cells
        - Metastatic carcinoma (e.g. metastatic RCC or colon carcinoma)
    - Predominantly single cells
      - Single plasmacytoid cells
        - PEN
        - SPN
        - Others (Melanoma, lobular breast ca,myeloma)
      - Single monomorphous cells (Likely Lymphoma)
      - Single polymorphous cells (Lymphoid lesion)
  - Paucicellular Specimen
    - Not a neoplasm
    - Sampling Error
      - *-Anatomical Location (tail of the pancreas)*
      - *-Operator Dependent (new Endosonographer)*
      - *- Nature of the lesion (cystic lesion, presence of fibrosis*

Jhala D and Jhala N. Endosonography: A cytology primer for endosonographers . Chapter 22; 2019, 272-290

Jhala Algorithm

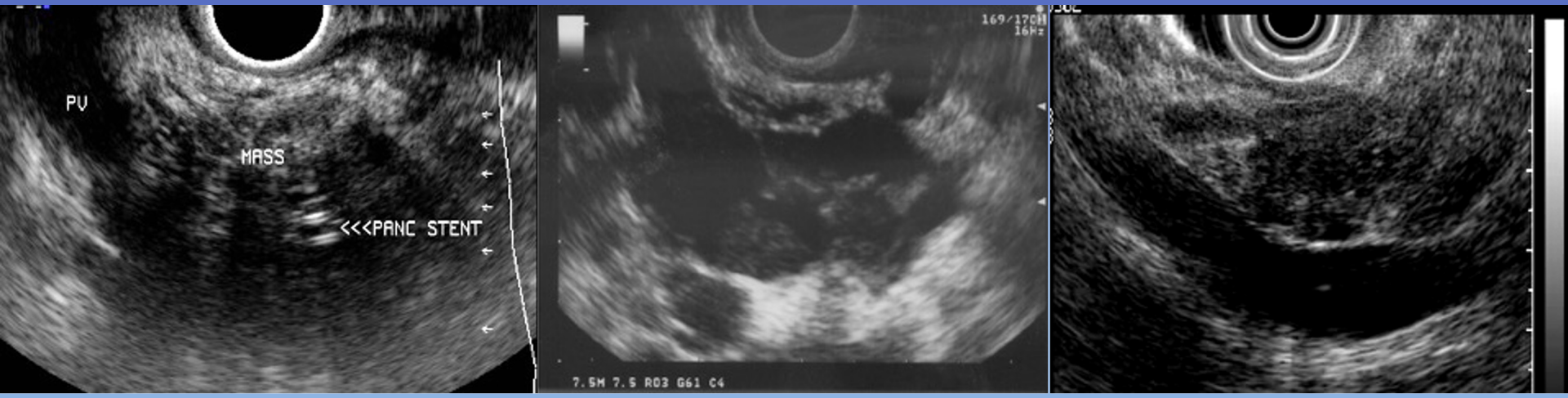
Algorithm distributed to over 1500 pathologists and 900 gastroenterologists in 27 countries

80% provided very positive feedback to arrive at conclusive diagnosis

Ancillary studies in our Arsenal (diagnosis, prognosis and predictive markers/personalized therapy)

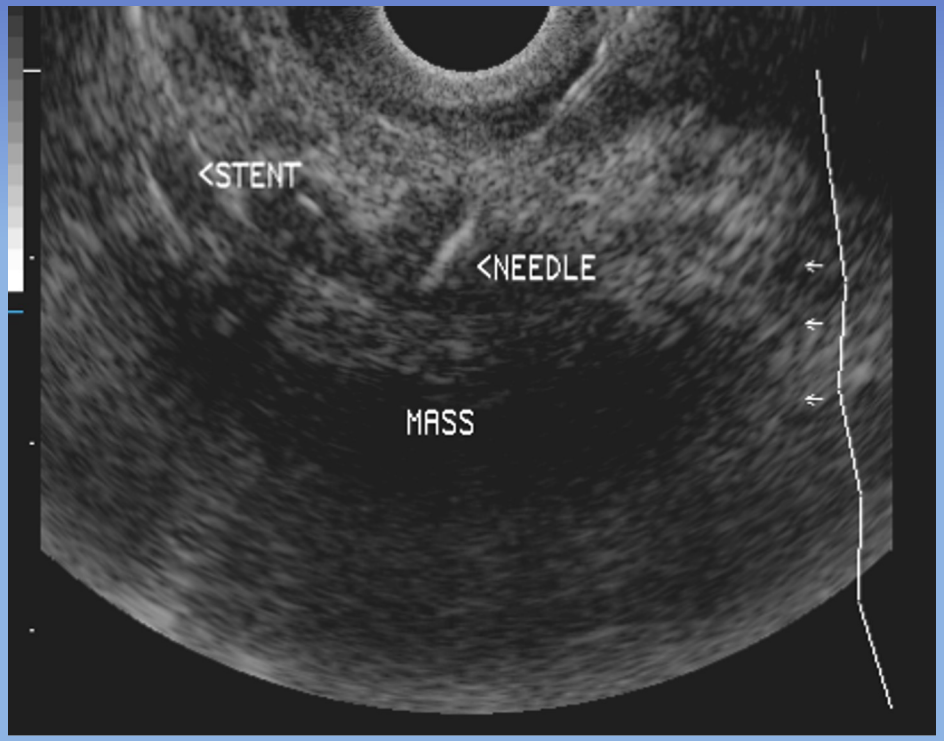
- Immunohistochemistry (Protein Expression)
- Flow Cytometry (Antigenic Epitopes)
- FISH
- Molecular techniques such as :
  - PCR
  - Next gen sequencing

What is the diagnosis?

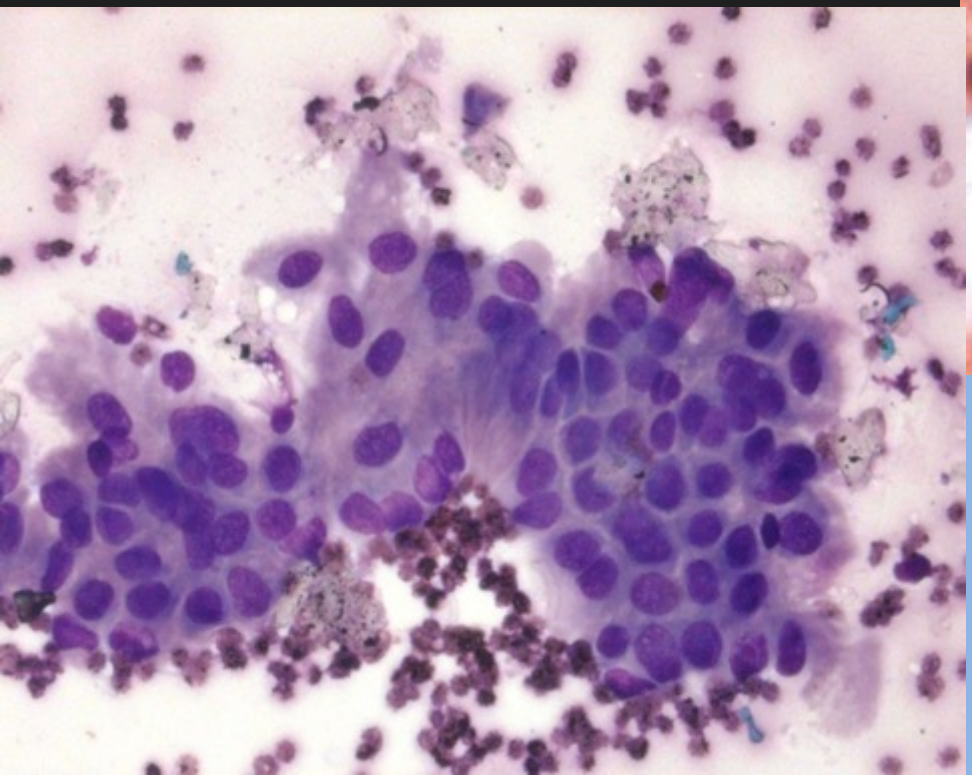


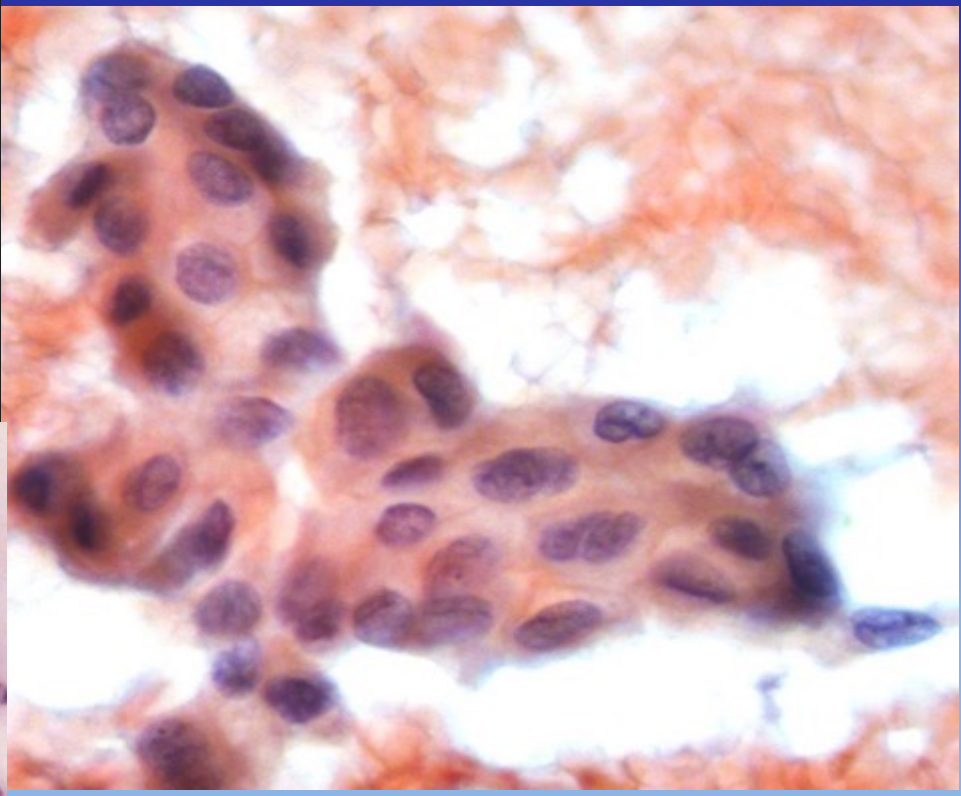
Clinical Cases

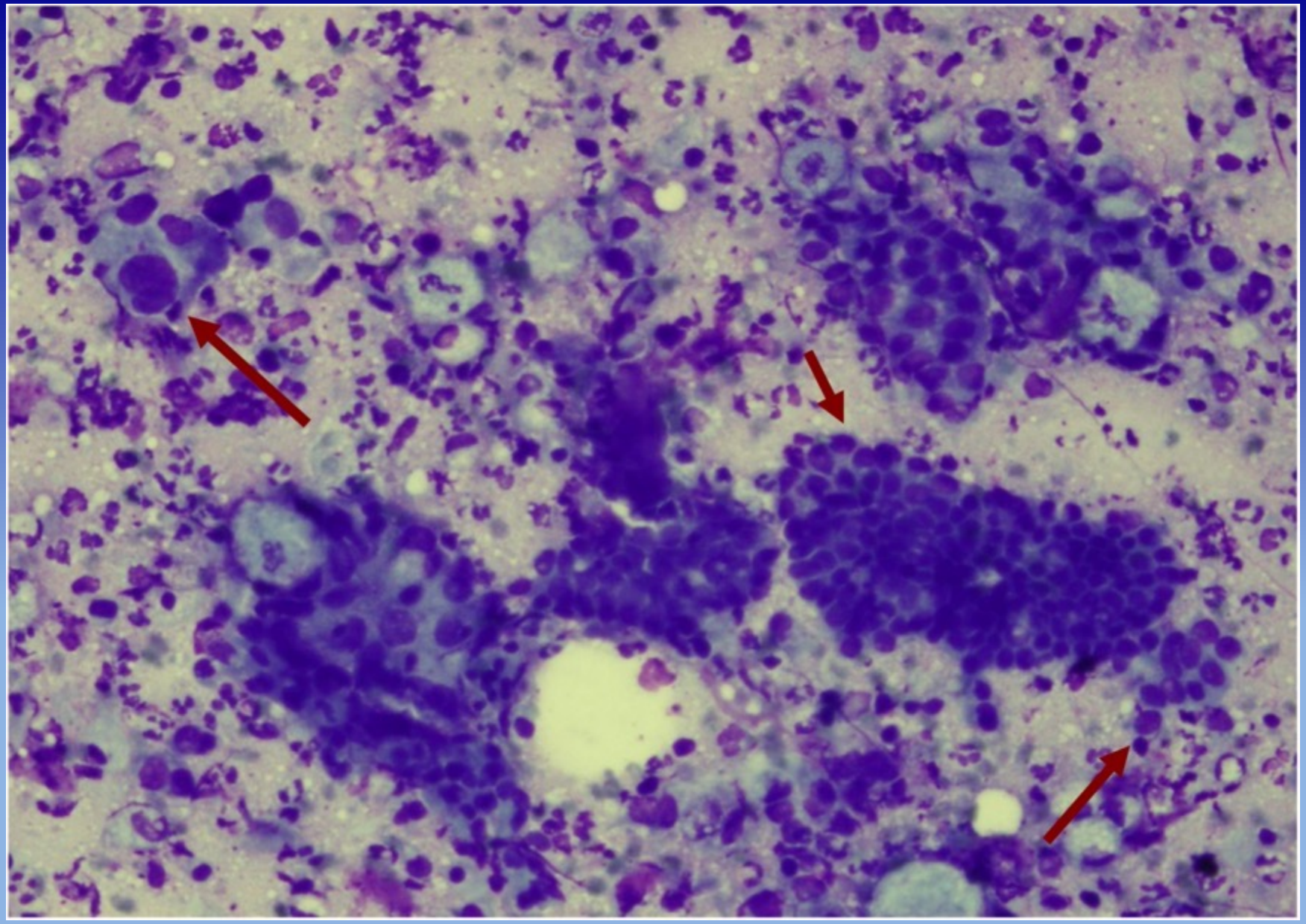
- **62 year old with mass in pancreas. R/O Carcinoma, EUS FNA is performed**



<STENT
<NEEDLE
MASS







Diagnosis :
Pancreas, Mass, EUS-FNA: ????

??Value of Molecular Analysis

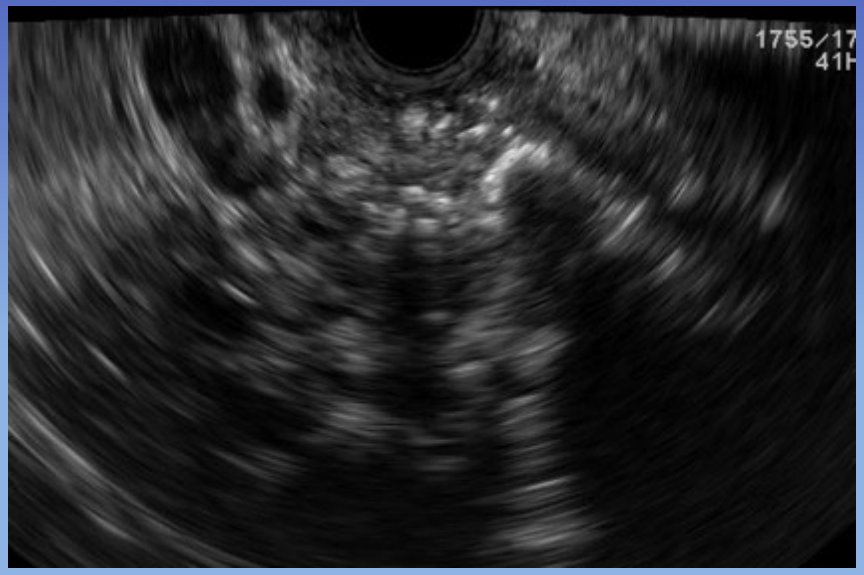
Yes or no?

If yes, possible findings on molecular Analysis

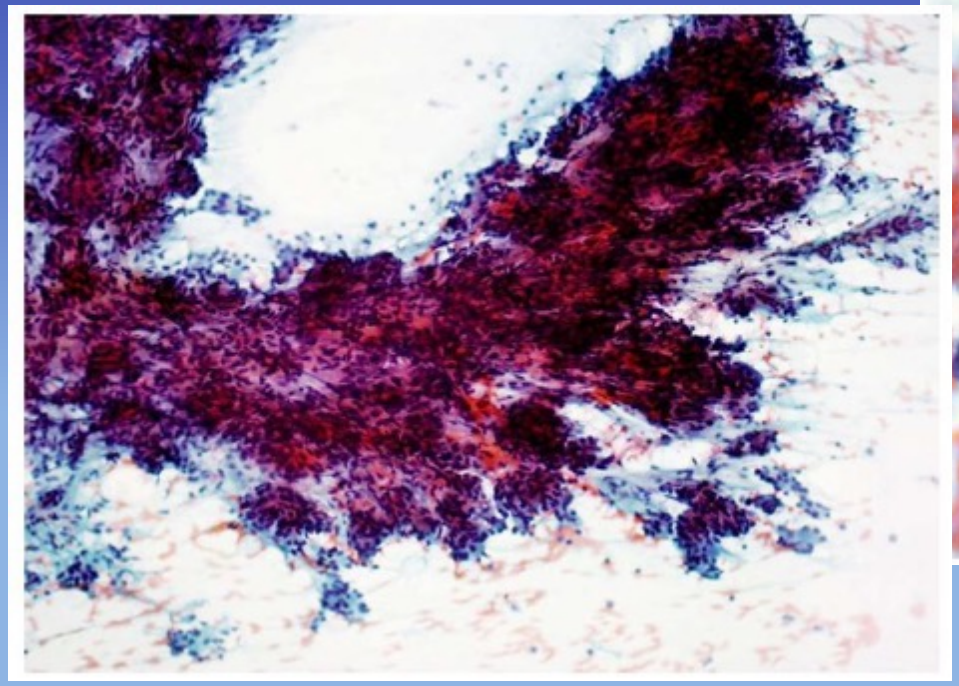
Any impact on personalized diagnosis and treatment?

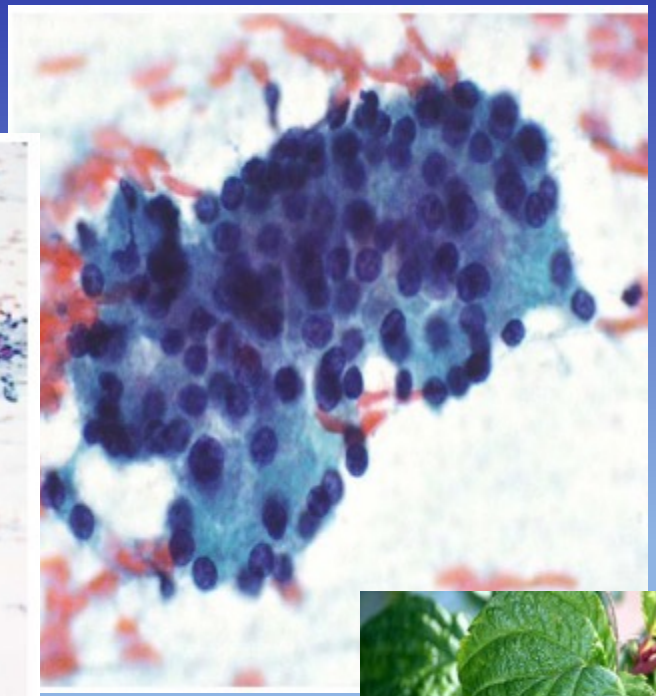
Clinical Case

64 WM presents with abdominal pain, weight loss and pancreatic mass



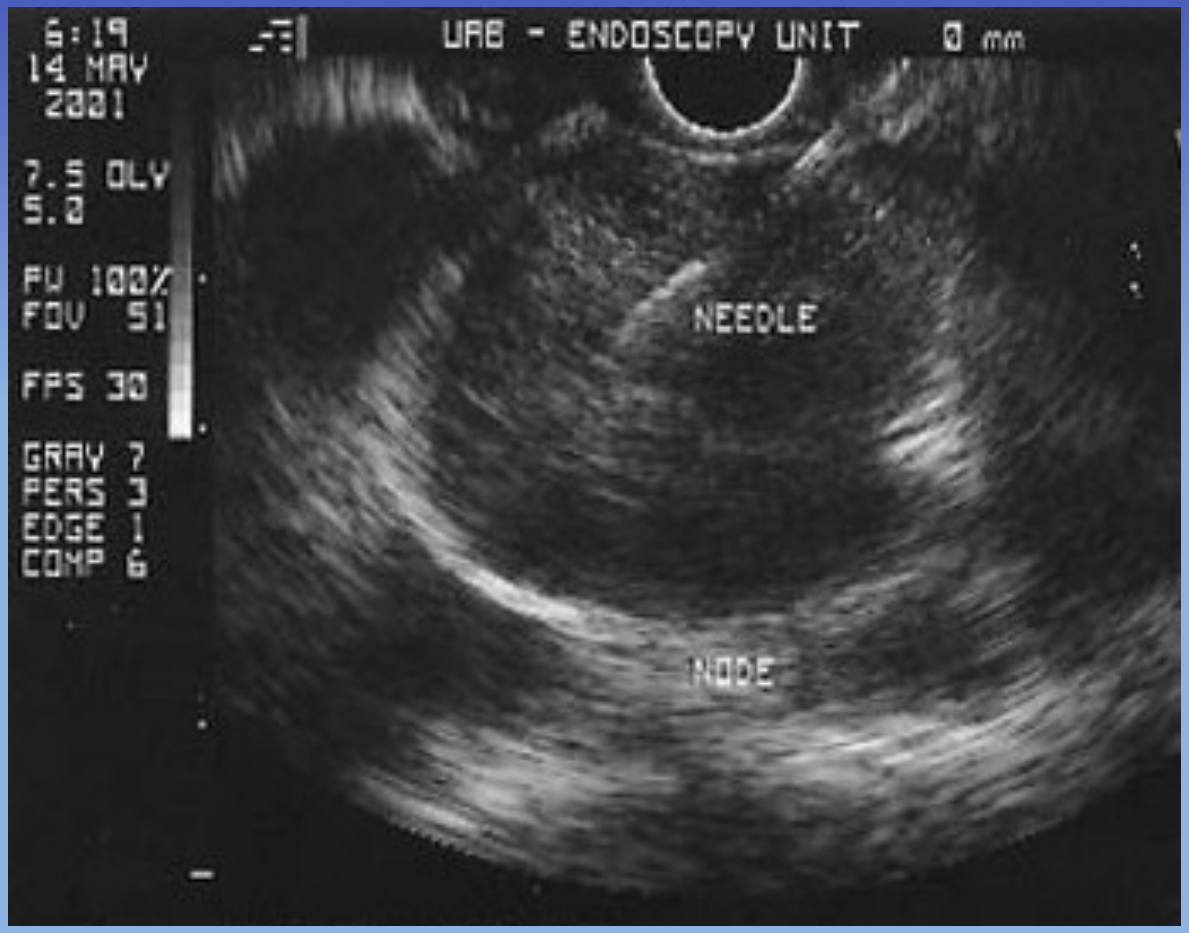
Diagnosis???



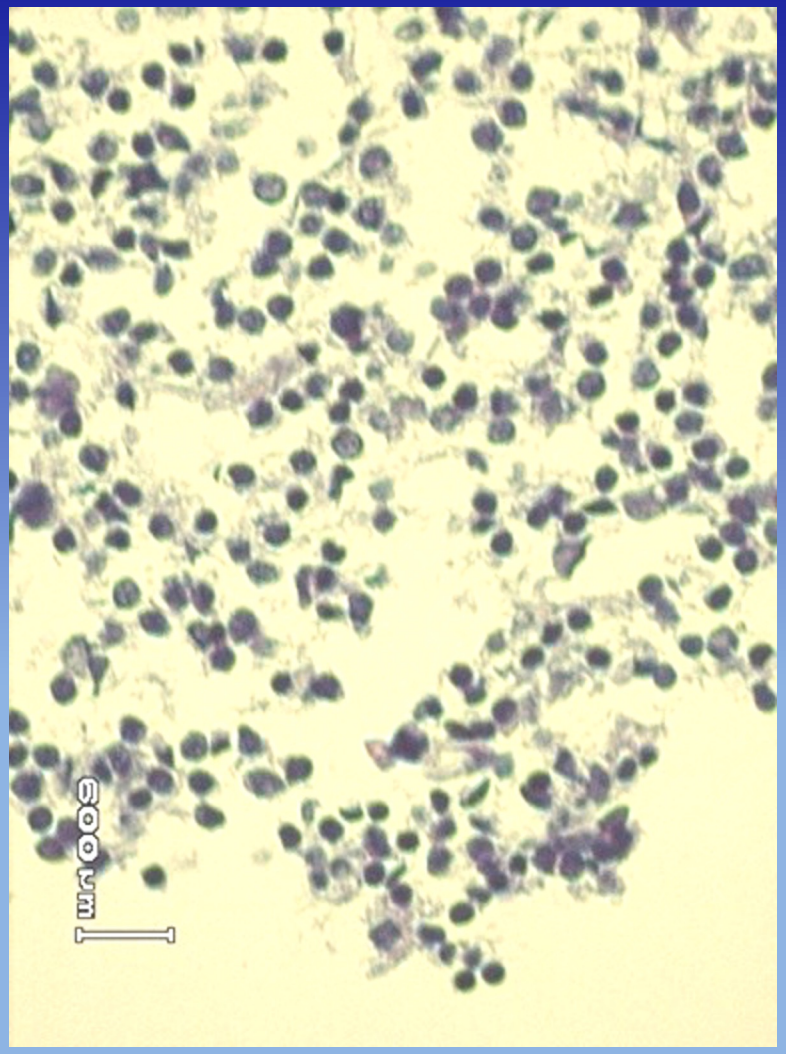


Clinical Case

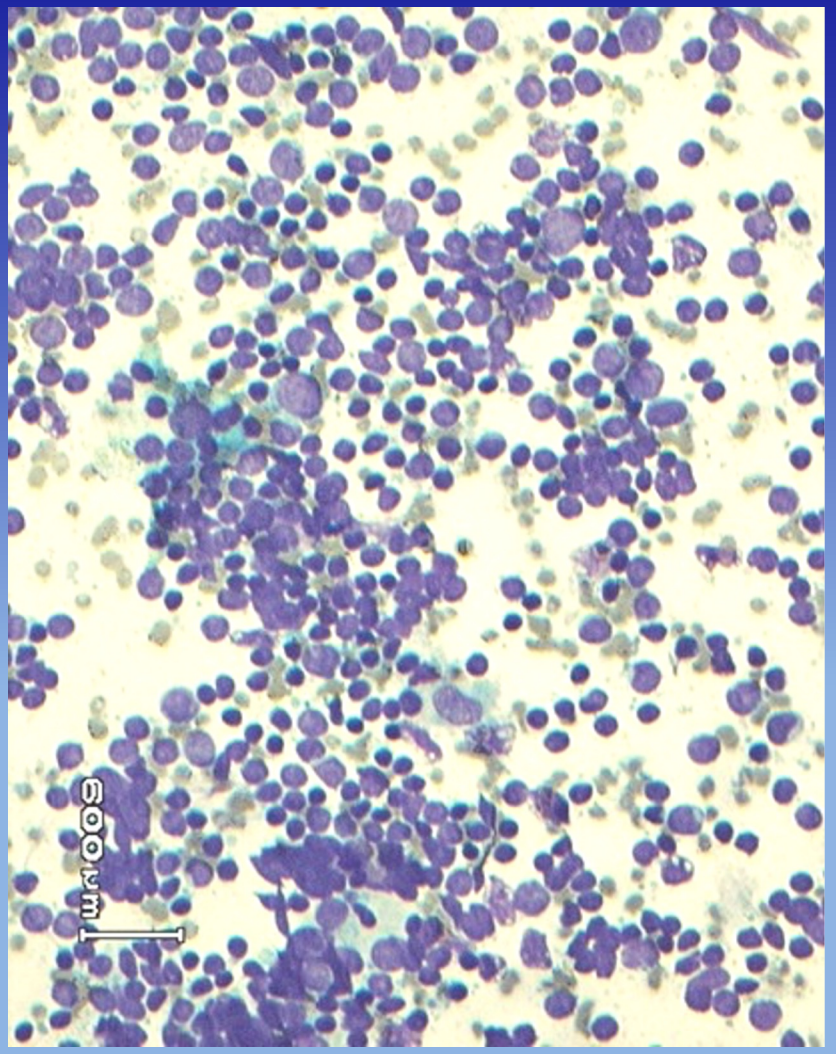
78 year old male with a history of abdominal /?Pancreatic mass. EUS FNA is performed.



Male 78 yrs With Pancreatic Mass



Papanicolaou



Diff-Quik

Diagnosis?

Differential diagnosis??

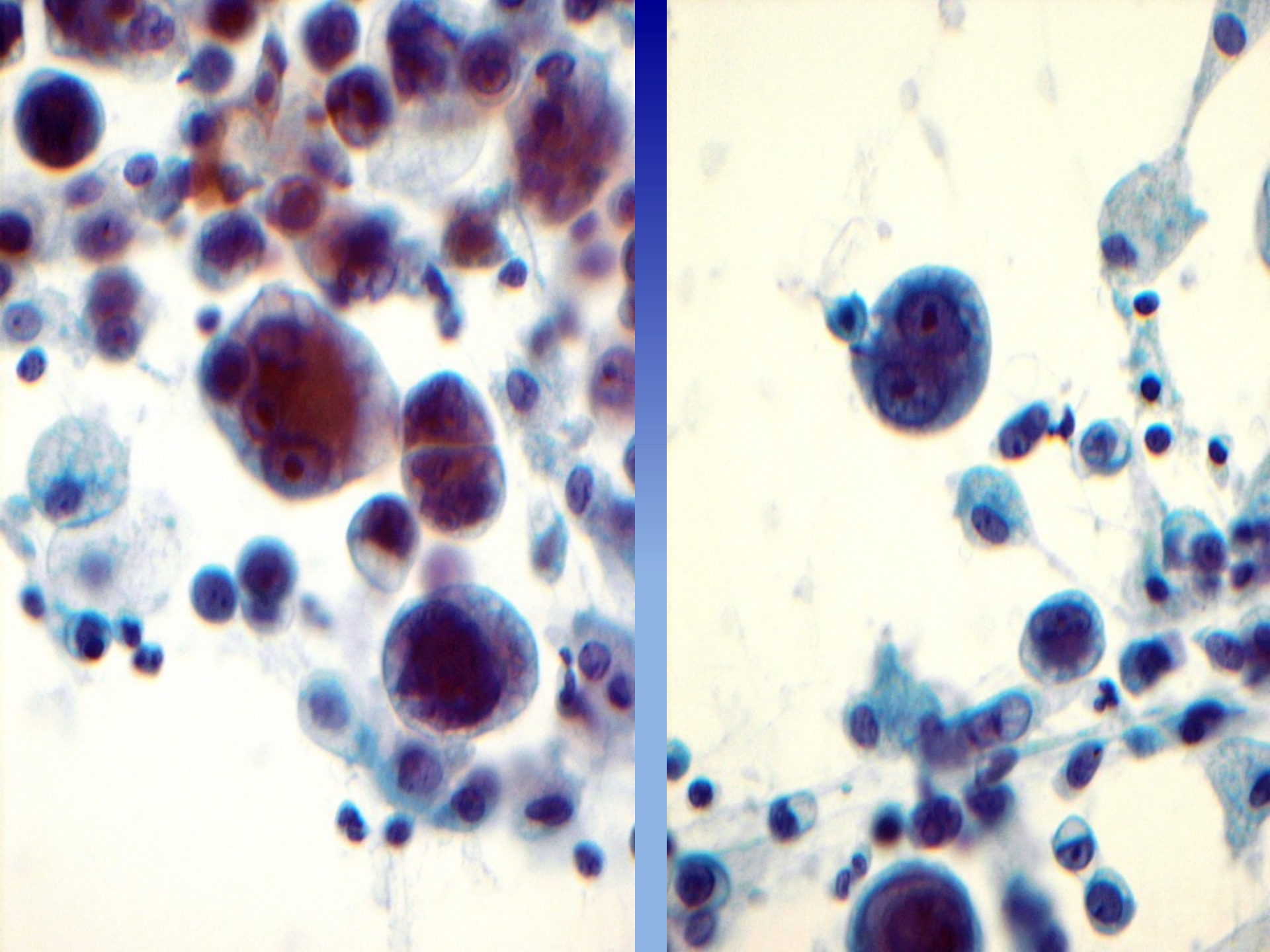
Any work up by the ancillary tests needed?? If yes, which tests?

Any role of a tru cut biopsy?

Clinical Case

- Male/70 yrs
- History of Jaundice
- Ultrasound- Peri-Pancreatic lymphnode
- EUS FNA is performed

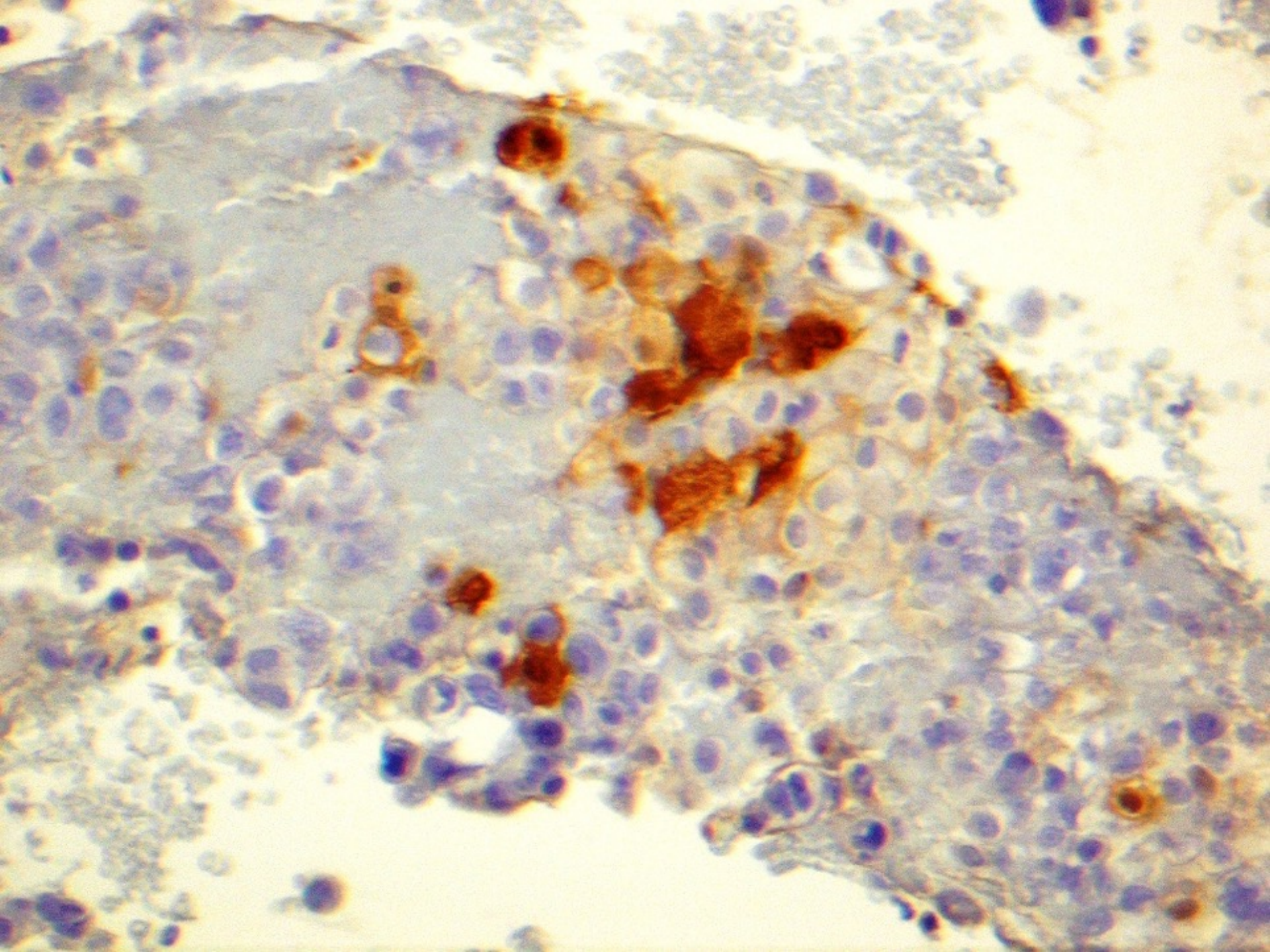
169/170
16Hz
7.5M 7.5 R03 G61 C4



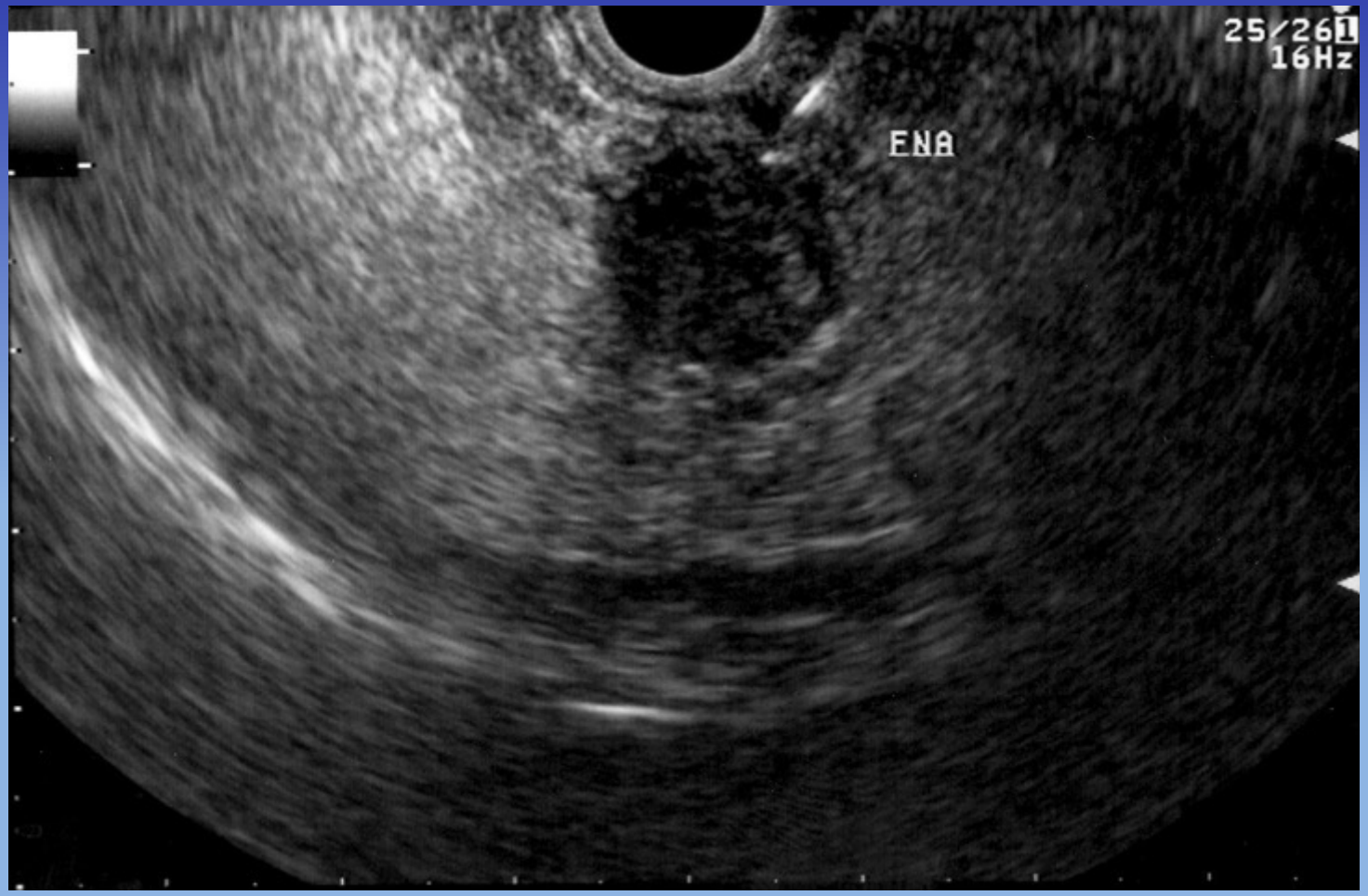
Diagnosis/Differential Diagnosis ??

Ancillary testing?

Molecular testing and personalized diagnostics??



Clinical Case
F/42 yrs with pancreatic mass



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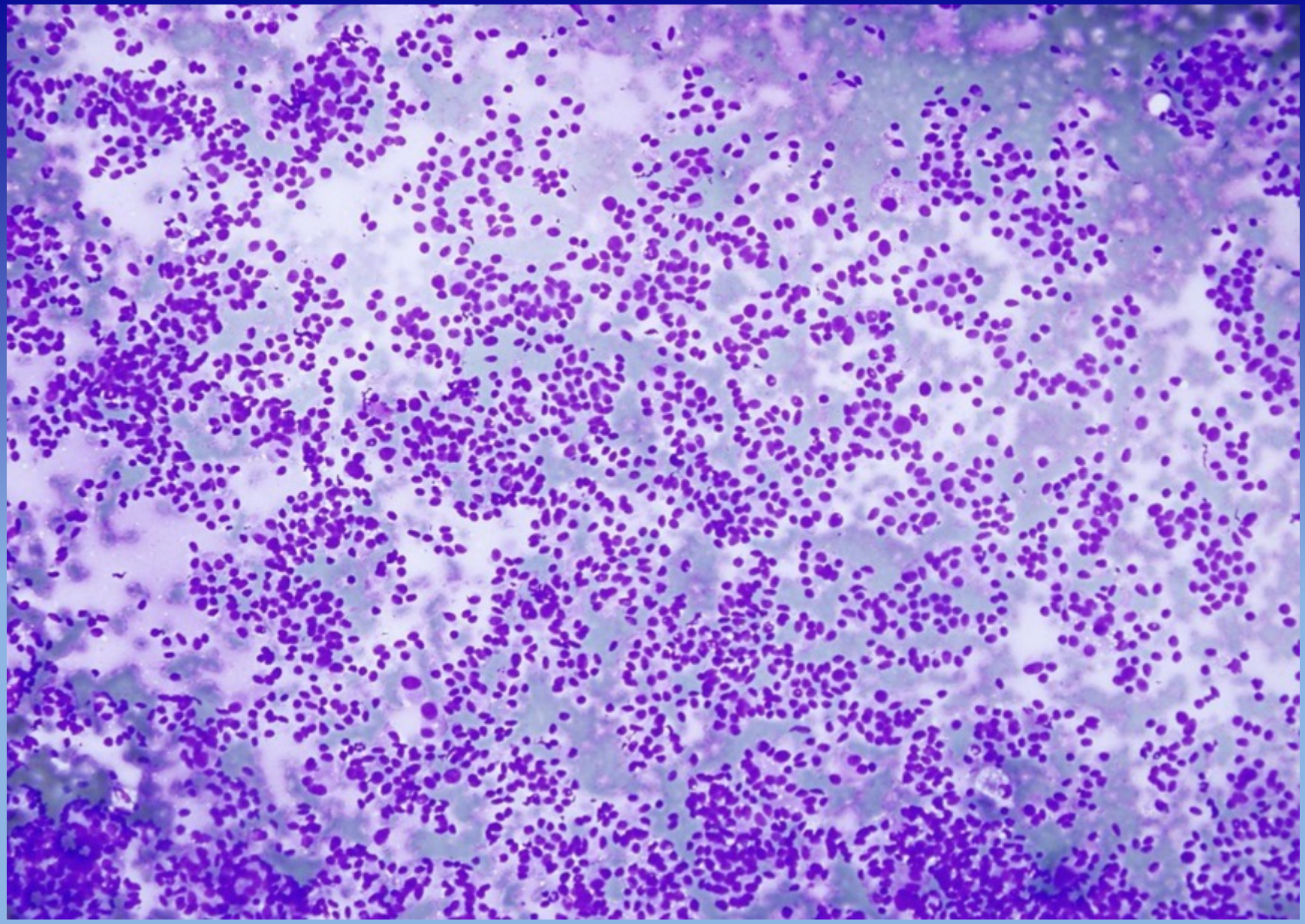
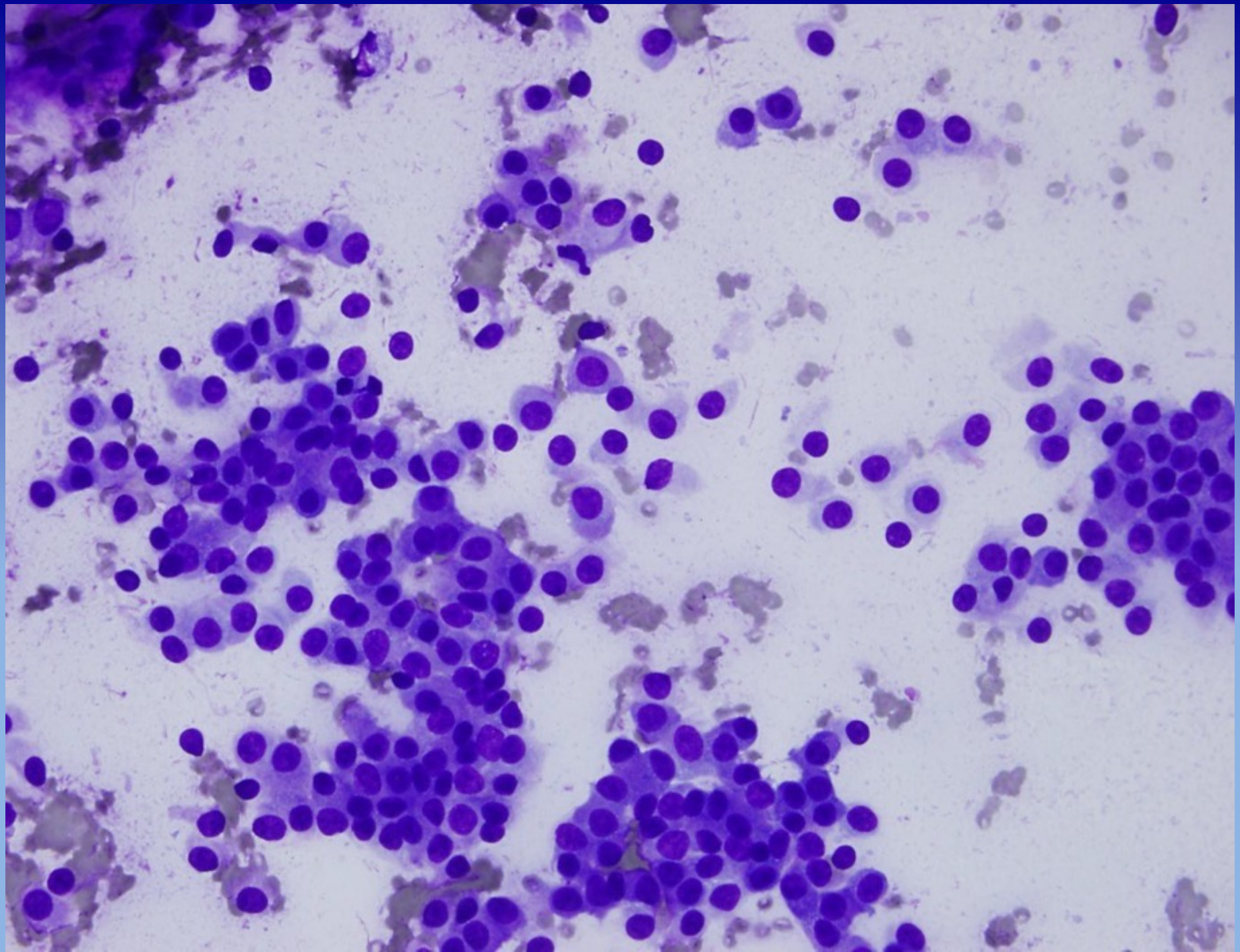
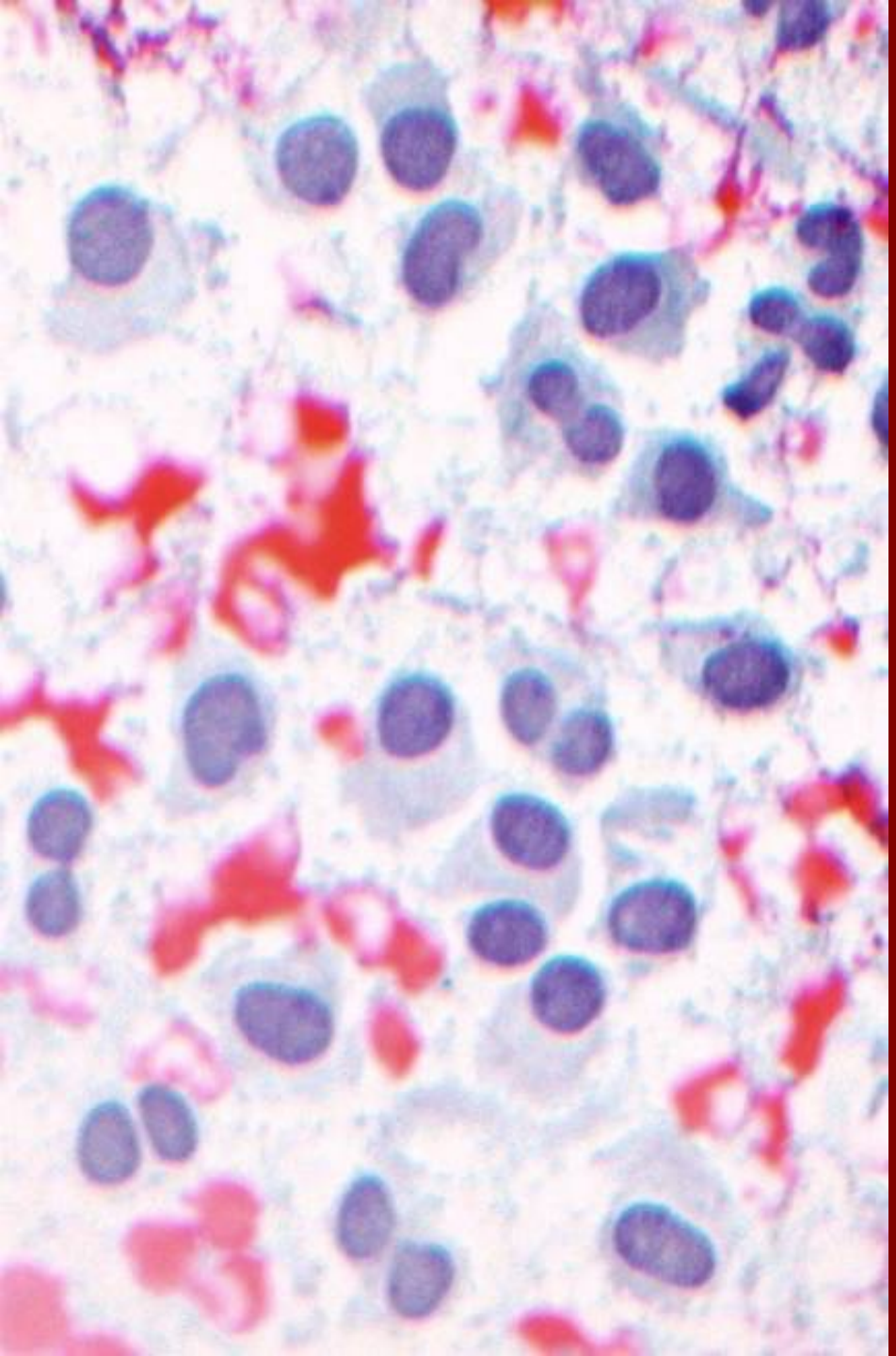
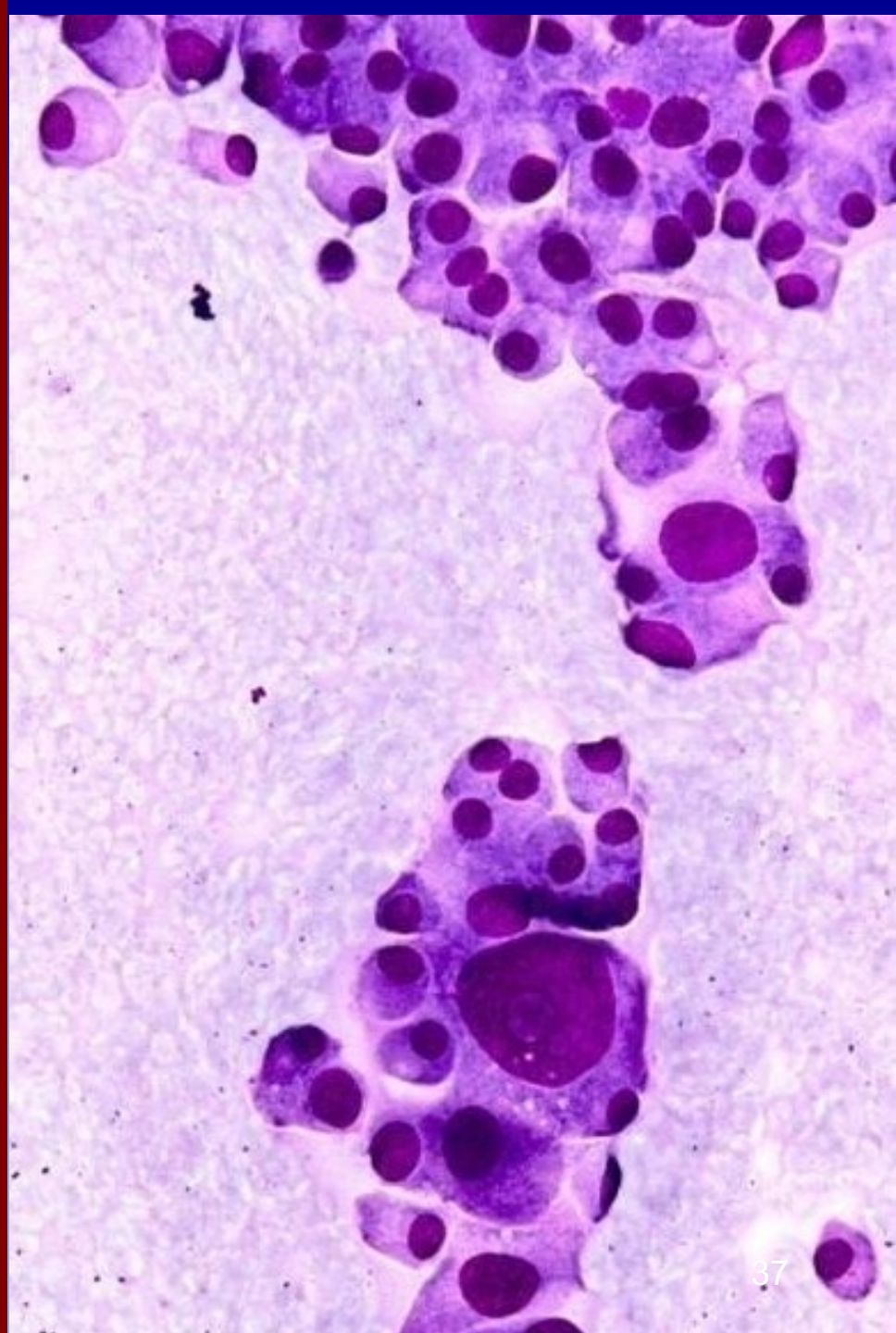






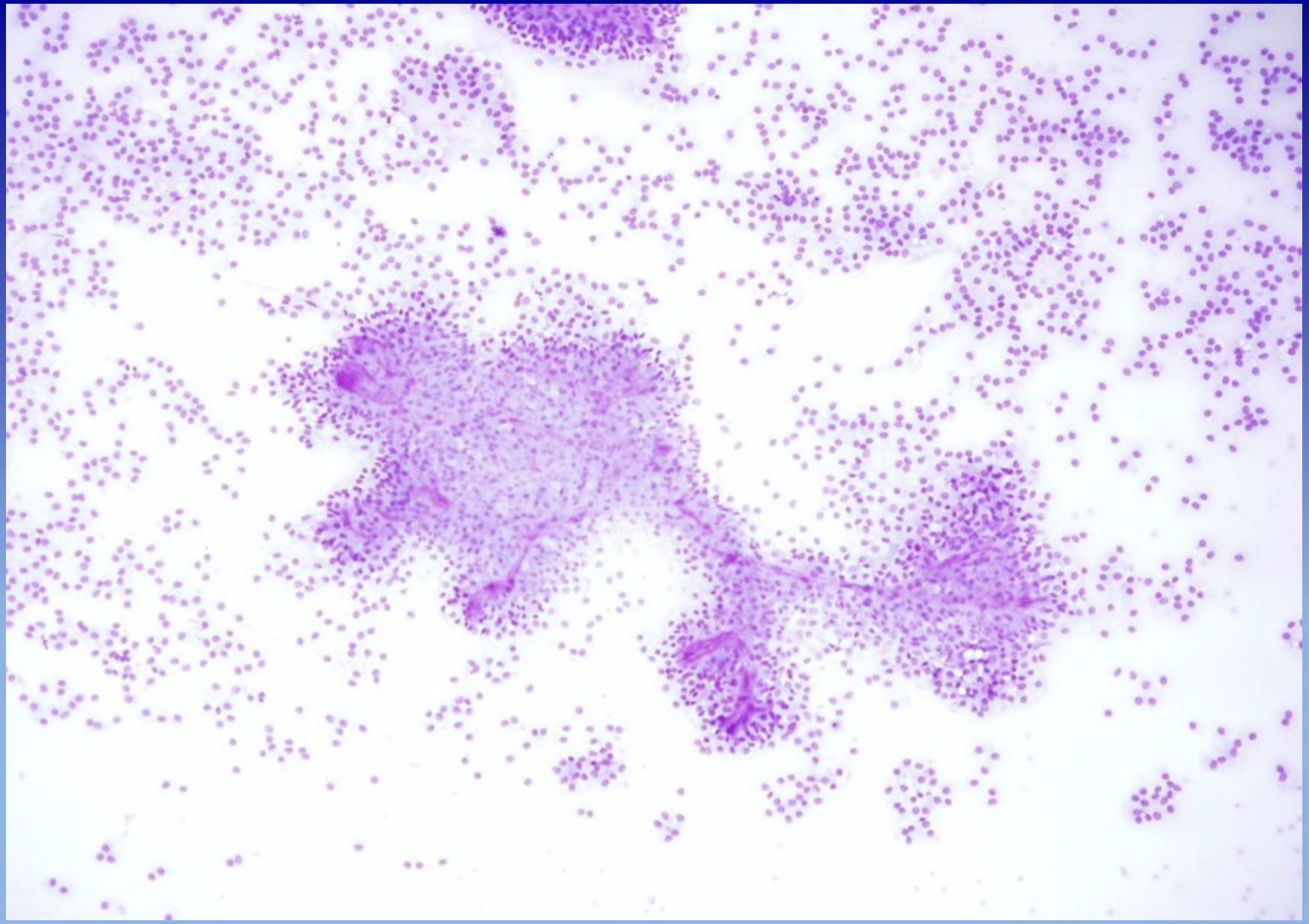


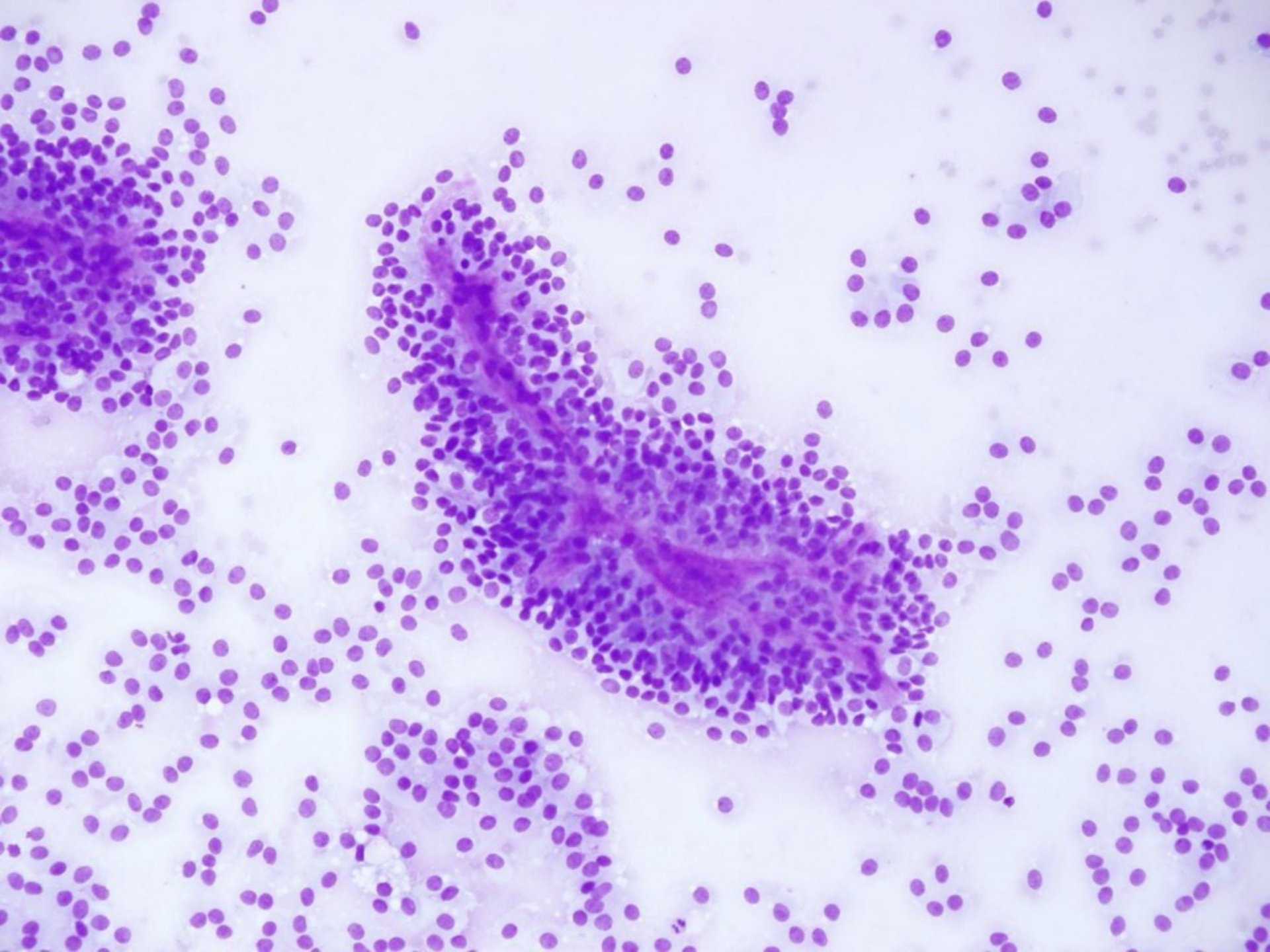
Diagnosis?

Differential diagnosis?

Ancillary studies?

M/34 YRS with abdominal pain and pancreatic tail mass





Diagnosis?

Differential diagnosis?

Ancillary studies?

Clinical Case

- Male 65 years
- Heterogeneous Pancreatic neck mass
- Mediastinal lymphadenopathy (PET +)
- ERCP : Distal bile duct stricture
- Prior FNA: Atypical Cells Present

Clinical Concern :

Pancreatic Carcinoma

Plan of Action :

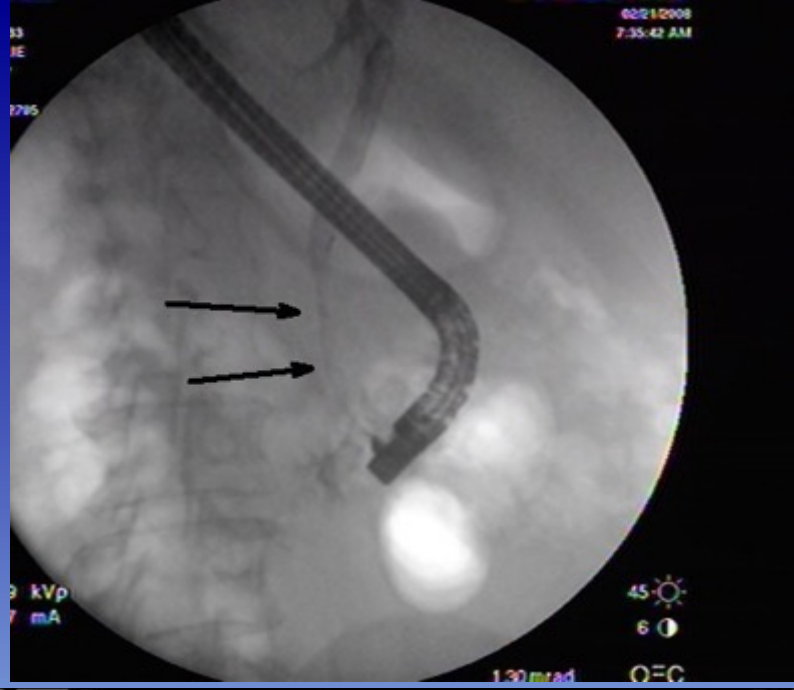
Need Endoscopic Ultrasound (EUS) and Guided Fine Needle Aspiration (FNA)

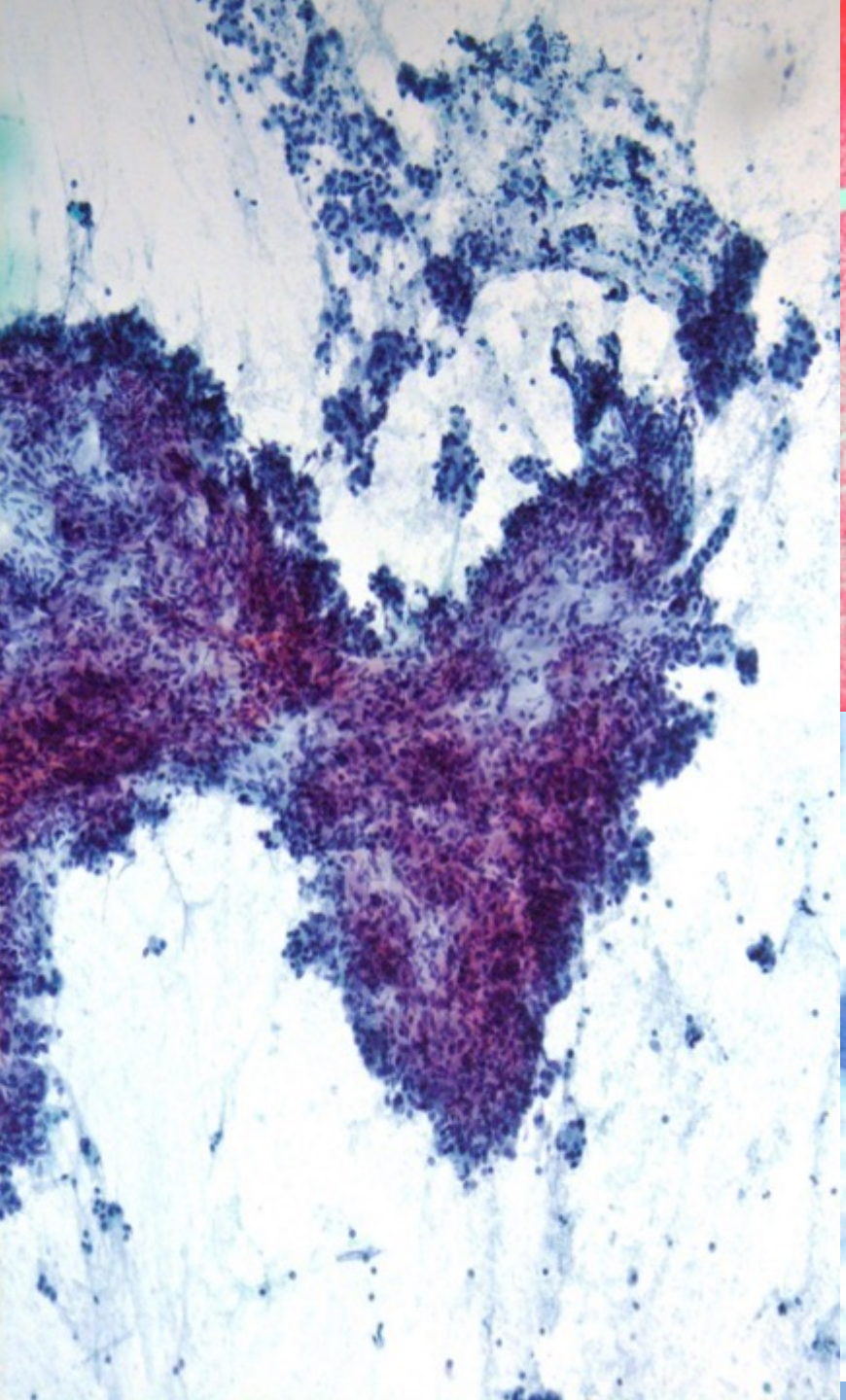
EUS Performed :

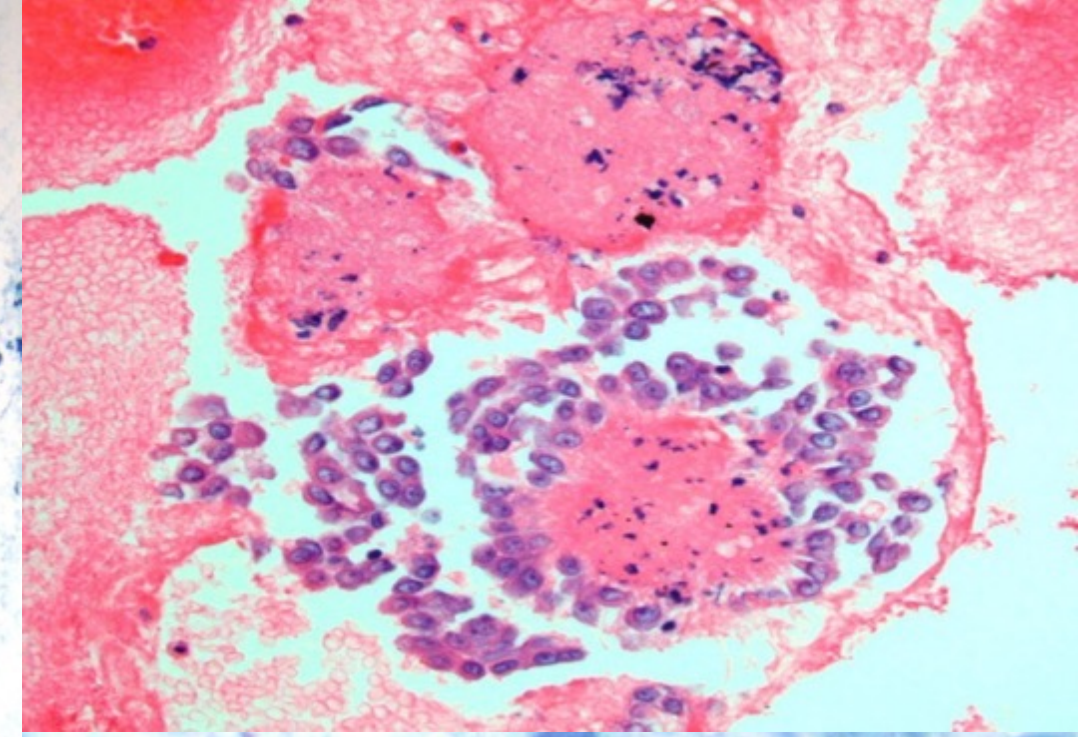
Pancreas: Global enlargement with 2.8 cm heterogeneous mass in the body of the pancreas

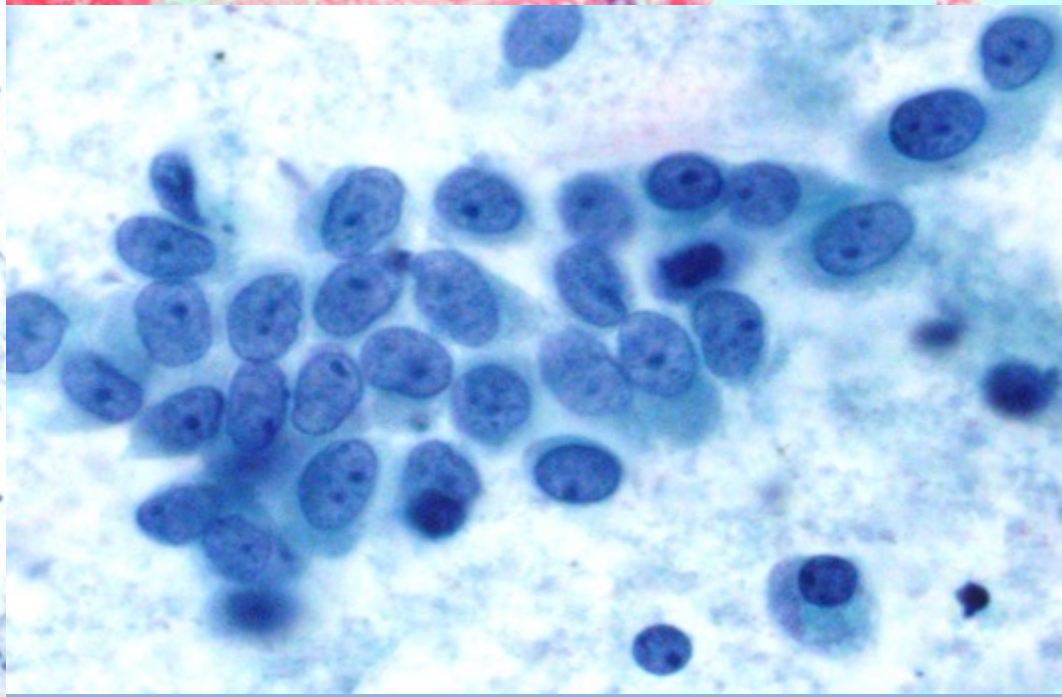
Mediastinum: Enlarged Irregular Lymph nodes – 2 CM

EUS- Impression: The pancreas lesion is concerning for a malignancy.









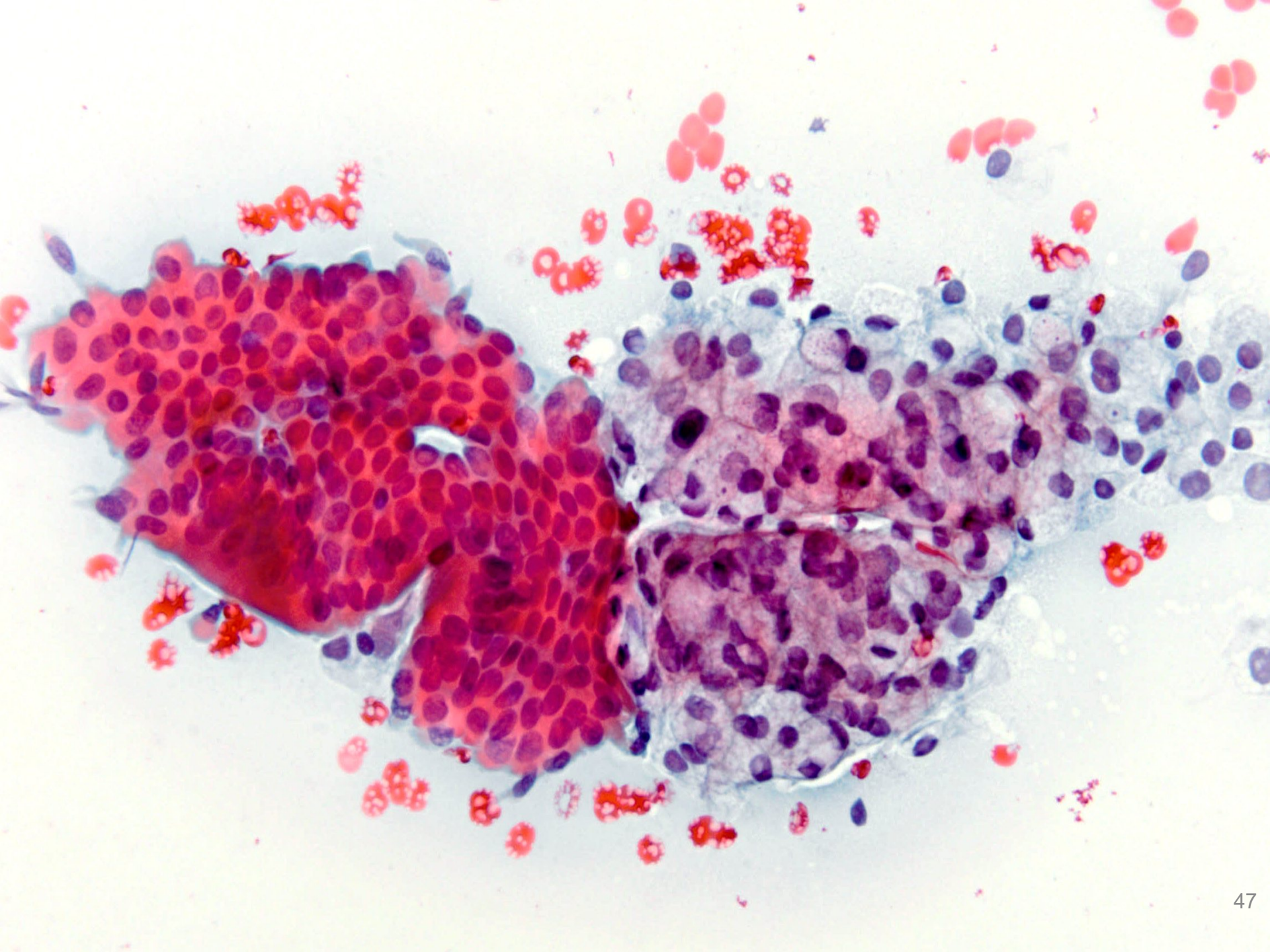
Diagnosis?

Differential diagnosis?

Ancillary studies?

2022: NCCN guidelines recommend molecular studies for all patients with pancreatic cancer

- Genetic testing for inherited mutations (Germline testing) – should be offered to all patients with pancreatic cancer
    - *Goal: Identify familial risk*
- Tumor molecular profiling (Tumor profiling) (NGS and MMR) offered to select patients:
    - Locally advanced (unresectable)
    - Metastatic
    - Recurrence after resection
    - Progression
        - Goal: Identify therapeutic targets



Our project

- Goals:
  - Determine how many patients with pancreatic cancer get appropriate molecular testing
  - Evaluate types of specimens used for molecular testing
  - Identify if testing is done in house or sent out and why
  - Evaluate the impact of sequencing studies on clinical management
- Design:
  - Retrospective review of surgical and cytological pancreatic cancer cases from 2019-2020

Cerner Database Search

Excluded cases with diagnosis other than pancreatic adenocarcinoma

2019
83 surgical specimens reviewed (of 122 total)

55 (66%) with molecular

Germline	41/55 (74%)
NGS	37/55 (67%)
MMR	31/55 (56%)
PDL1	11/55 (20%)

2019
32 cytology specimens reviewed (83 total)

20 (63%) with molecular

Germline	17/20 (85%)
NGS	9/20 (45%)
MMR	6/20 (30%)
PDL1	3/20 (15%)

2020
85 surgical specimens reviewed (of 85 total)

19 (22%) with molecular

Germline	14/19 (74%)
NGS	11/19 (58%)
MMR	6/19 (32%)
PDL1	2/19 (11%)

2020
105 cytology specimens reviewed (of 120 total)

Germline	27/39 (34%)
NGS	19/39 (48%)
MMR	12/39 (30%)
PDL1	5/39 (13%)

Combined:

Germline	99/134 (74%)
NGS	76/134 (57%)
MMR	56/134 (42%)
PDL1	21/134 (16%)

		# (%)
	Avg Age	
Male	76 (56%)	65.4
Female	58 (43%)	67.0
Combined		66.1

Variable amount of follow up information available, so we focused on cases with genetic results

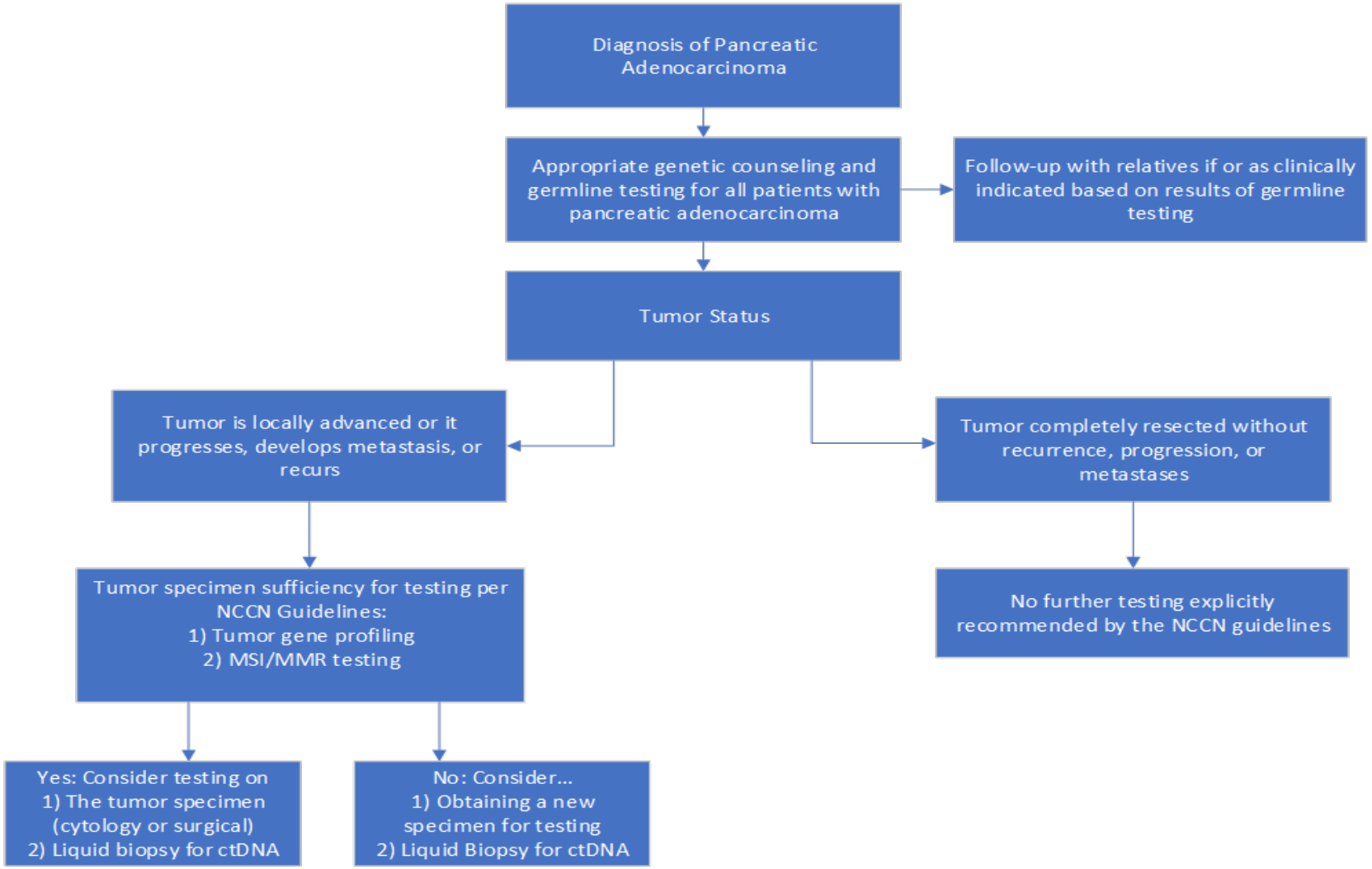
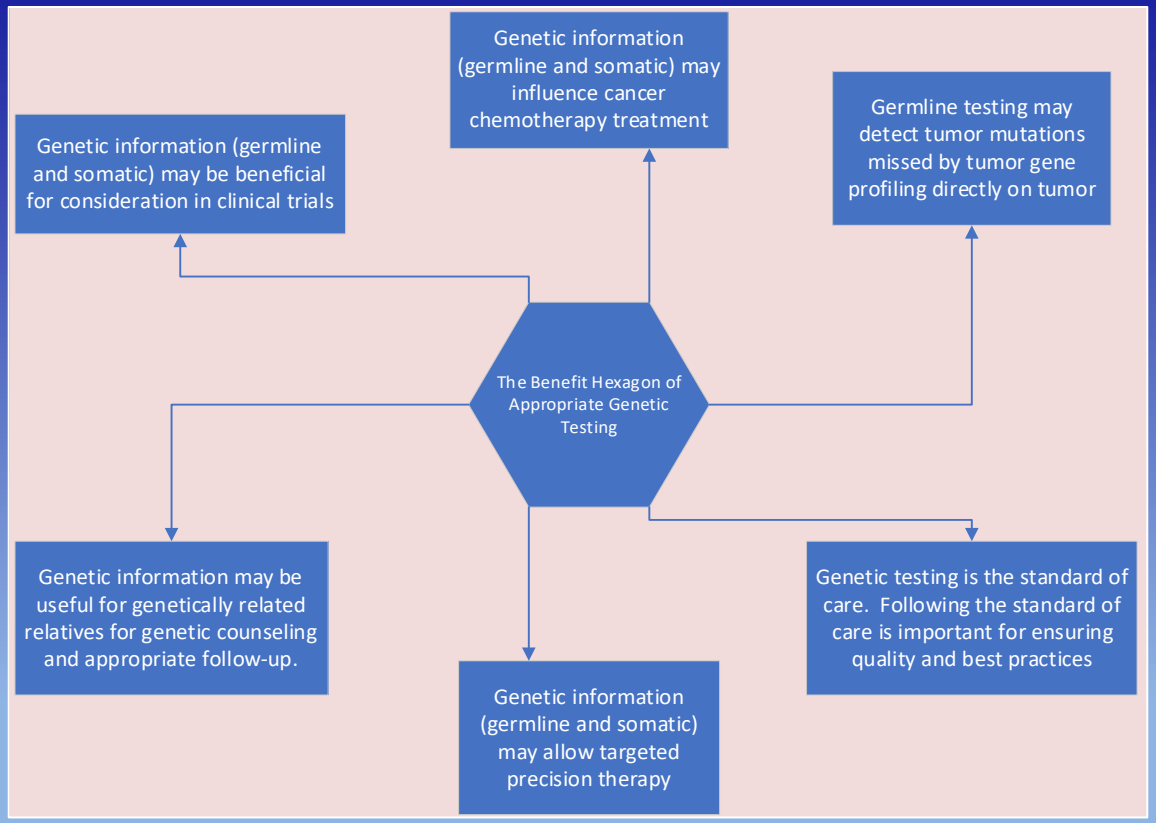


Figure 3: A Simplified Testing Algorithm for Pancreatic Adenocarcinoma to Comply with the Current NCCN Guidelines. All patients diagnosed with pancreatic adenocarcinoma should receive germline testing. Furthermore, for those who have tumor that cannot be resected, that progresses, that develops metastasis, or recurs would be recommended for tumor gene profiling and MSI/MMR testing. The presence of adequate tumor tissue or not would influence choice of specimen for testing, though in the presence of inadequate tumor tissue, options include either obtaining a new tumor specimen or attempting a liquid biopsy of circulating tumor DNA for this testing. If the pancreatic adenocarcinoma is resected and cured without recurrence, progression or metastases, no further testing is explicitly recommended by the NCCN guidelines. Abbreviations: NCCN = National Comprehensive Cancer Network, MSI/MMR = Microsatellite instability/mismatch repair, ctDNA = circulating tumor deoxyribonucleic acid.



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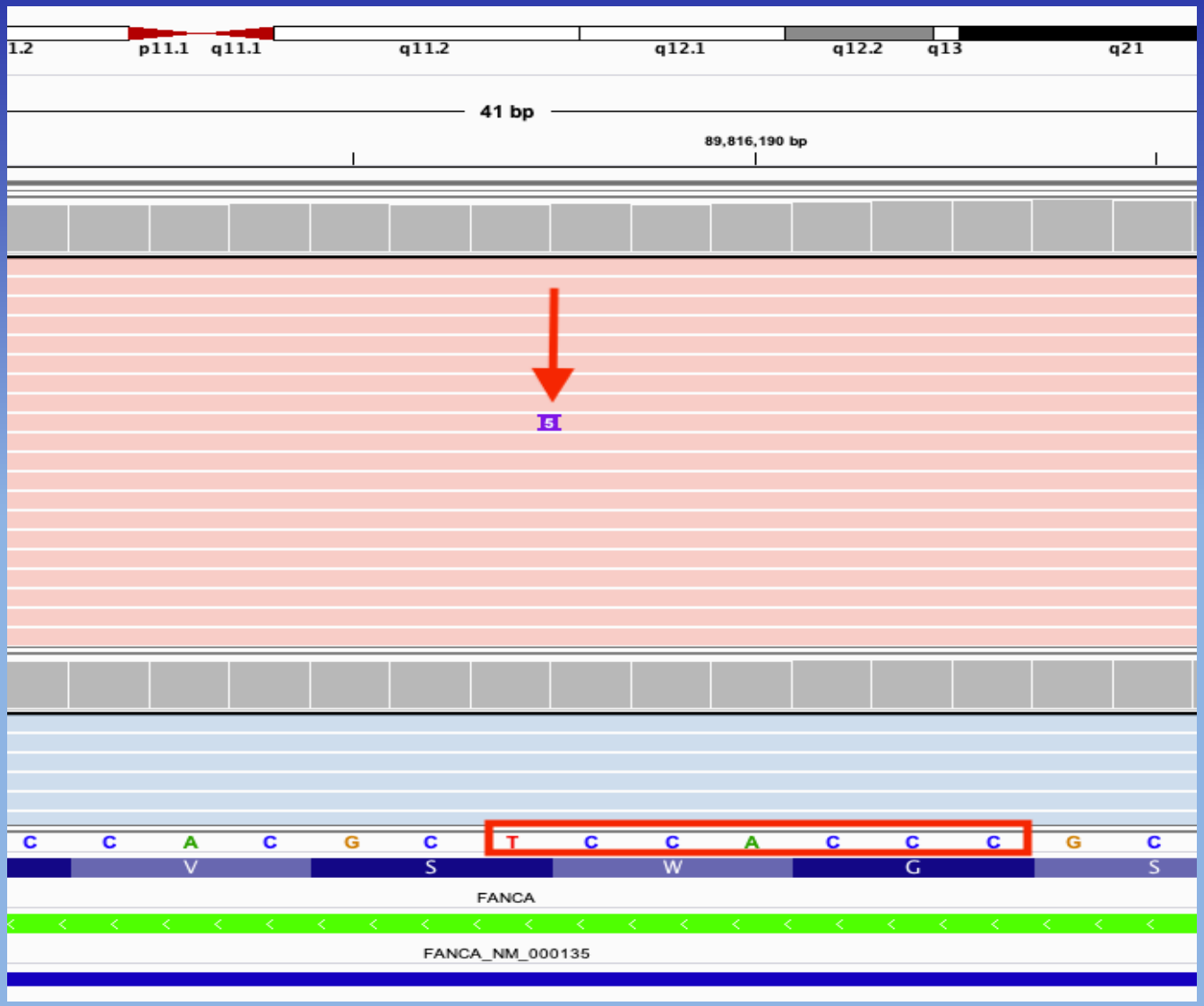
HRR Mutation #1: FANCA

c.3189_3190insGGTGG (shown as 5 bp insertion of CCACC in image below)



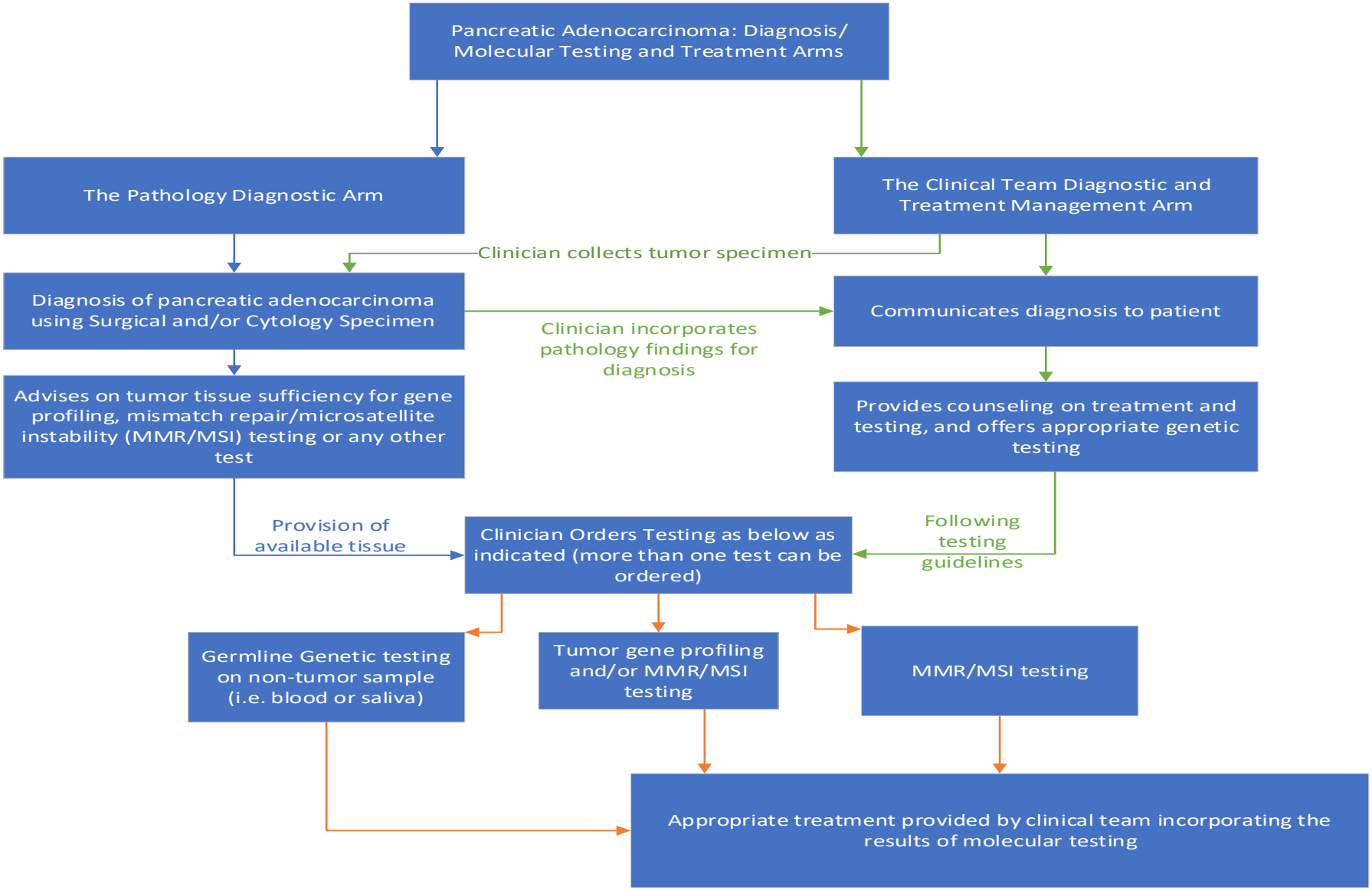


Figure 2: Schematic of the Pancreatic Adenocarcinoma Diagnosis/Molecular Testing and Treatment Arms. Pathology plays a critical role in diagnosing the adenocarcinoma, advising on tumor tissue sufficiency from the specimen, and providing the available tissue from the specimen for appropriate testing. The clinical team not only collects the tumor specimen and provides appropriate communication and counseling, but also decides on test ordering. As there are standard practice guidelines on what tests should generally be ordered, the monitoring of this test ordering represents a useful avenue for quality assurance. Blue arrows: pathology actions on pathology arm on left. Green arrows: Clinician actions on clinical arm on right. Red arrows: Actions related to genetic and ancillary studies recommended by standard of care NCCN guidelines.

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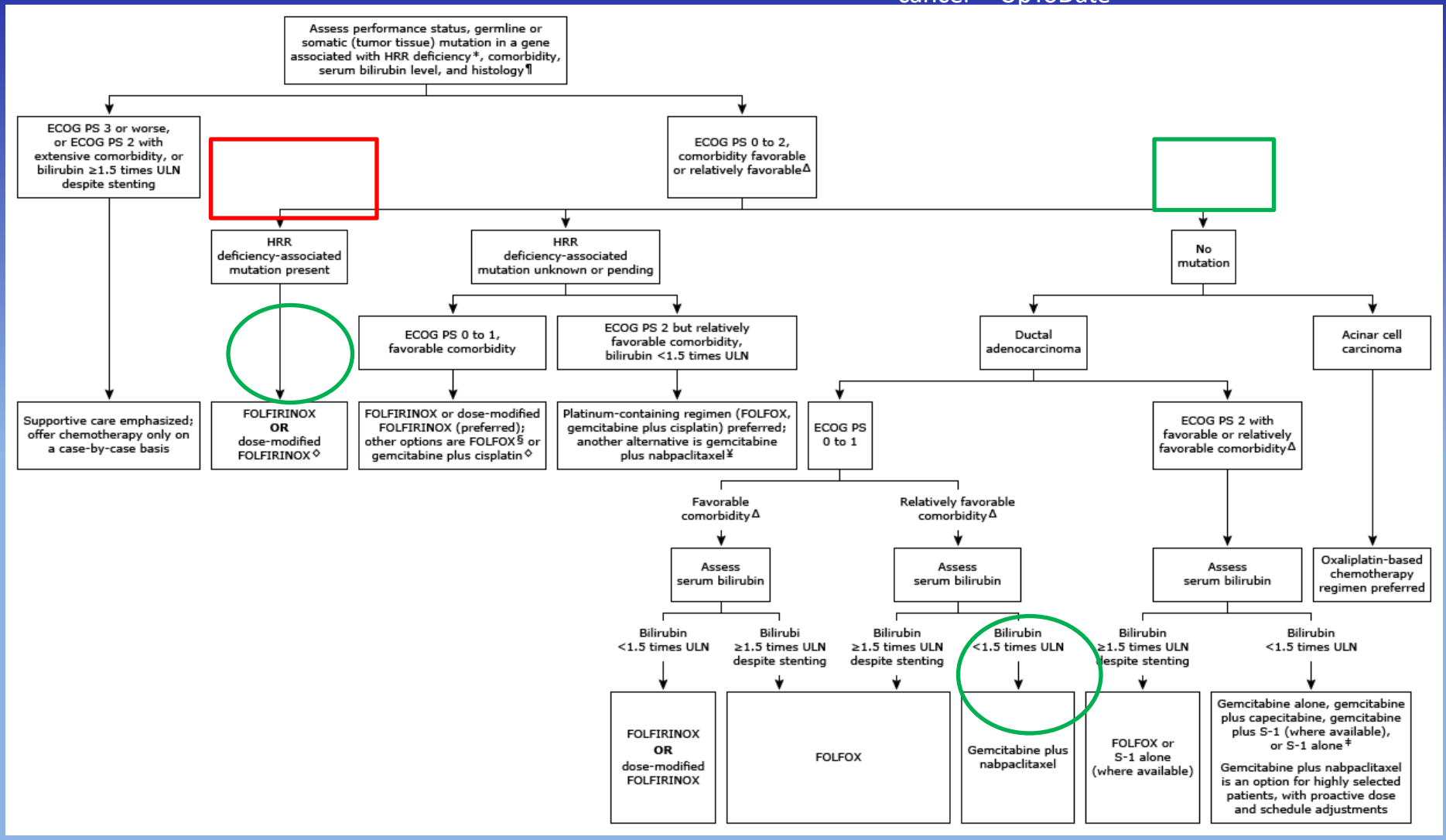
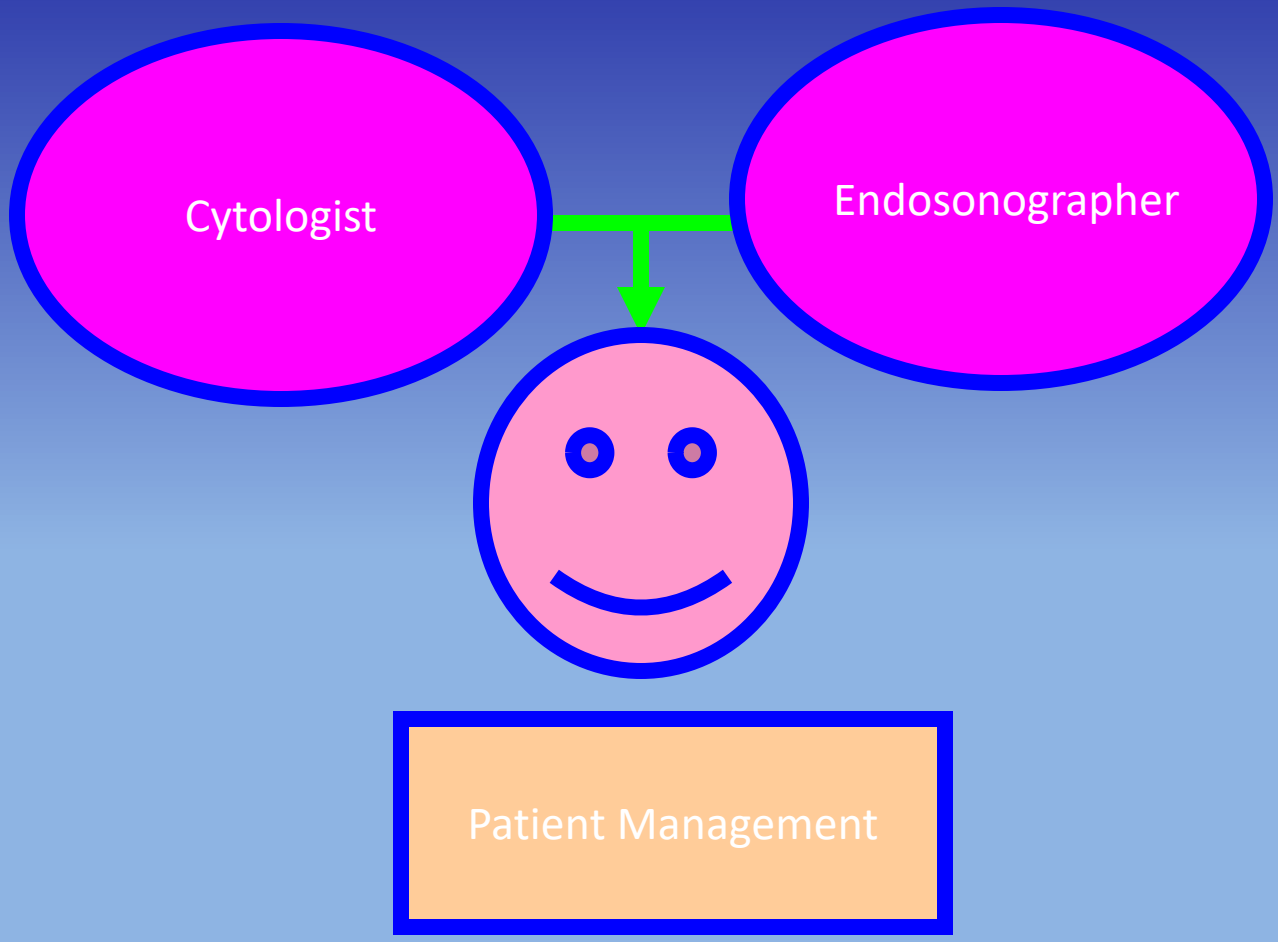
Treatment Algorithm for metastatic pancreatic cancer – UpToDate



Success of EUS program



911 reading references

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