Uniendo la Endoscopía de las Américas

BULLETIN OF THE ENDOSCOPIC ENDOSONOGRAPHY COMMITTEE

VOLUME V
FEBRUARY
2026

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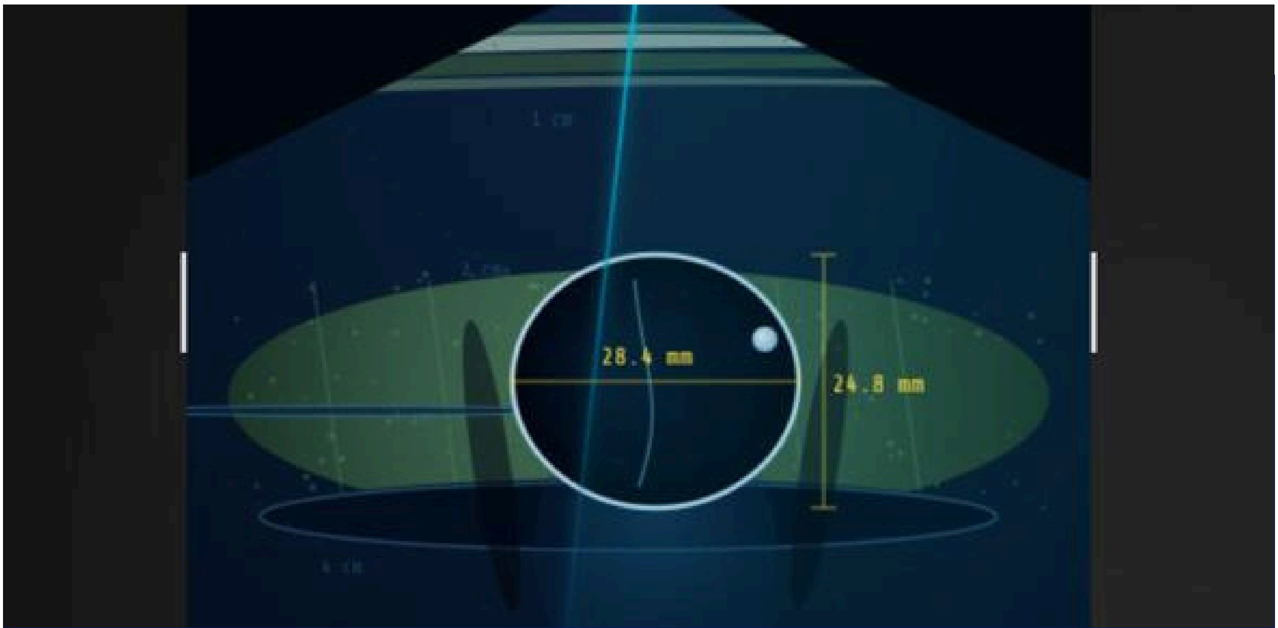
DIAGNOSIS OF PANCREATIC CYSTS

IMAGING, CYSTIC FLUID ANALYSIS, AND MOLECULAR MARKERS



Pancreatic cysts are among the most frequent incidental findings in clinical practice. With the increasing availability and quality of cross-sectional imaging, their prevalence in the general population ranges from 2.4% to 13.5%, reaching up to 40% in patients over 70 years of age undergoing magnetic resonance imaging (MRI) for non-pancreatic indications.[1,2]

According to the 2019 World Health Organization (WHO) classification, pancreatic cysts are grouped into: inflammatory pseudocysts, mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), serous cystic neoplasms (SCNs), and solid pseudopapillary neoplasms (SPNs), among other less frequent types.[3]

The diagnostic relevance lies in the fact that a subgroup of these cysts, primarily IPMNs and MCNs, has malignant potential. It is estimated that up to 20% of pancreatic ductal adenocarcinomas (PDACs) originate from mucinous cystic lesions, making accurate characterization of each lesion imperative. [2,4]

FIGURE 1 *It is very important to combine images and clinical presentation for the diagnosis of pancreatic cysts.*

CLASSIFICATION AND DIFFERENTIAL CHARACTERISTICS

The fundamental distinction is between mucinous cysts (with malignant potential) and non-mucinous cysts (benign). While being mucinous does not necessarily indicate malignancy, it merely suggests a tendency and a risk factor that should prompt further monitoring.

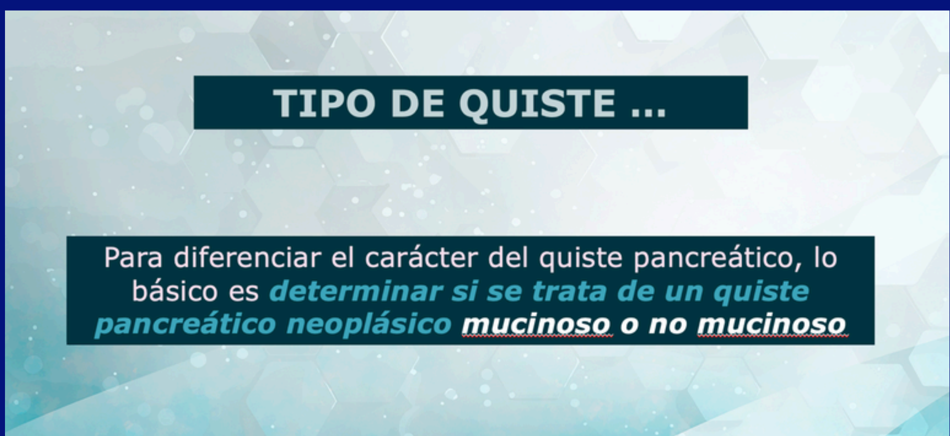


FIGURE 2

Table 1 summarizes the clinical, morphological, and histological characteristics of the main types.

Tipo de quiste	Prevalencia	Edad/Sexo	Localización	Comunicación con	Potencial maligno
Pseudoquiste	~40 % de PCL	Cualquier edad / M=F	Cuerpo/cola	Variable (amilasa	No
IPMN (BD)	Más común	> 60 años / M≥F	Cabeza/proceso	Sí (criterio dx)	Bajo-moderado
IPMN (MD)	< BD-IPMN	> 60 años / M>F	Difusa o segmentaria	Sí – dilatación	Alto (40 – 60 %)
NQM	Moderada	40-50 años / F>>>M	Cuerpo/cola	No	Bajo (< 5 %)
NQS	Moderada	> 60 años / F>M	Cabeza o difusa	No	Nulo (< 1 %)
NSPSE	Rara	Jóvenes / F>>M	Cuerpo/cola	No	Metastásico potencial

TABLE 1
Differential characteristics of the main pancreatic cysts (Source: Kyoto Guidelines 2024, Gastroenterology 2024). BD: BRANCH DUCT – MD: MAIN DUCT – NQM: MUCINOUS CYSTIC NEOPLASIA – NQS: SEROUS CYSTIC NEOPLASIA – NSPSE: PAPILLARY CYSTIC NEOPLASIA. [1,4.]

IMAGING MODALITIES

COMPUTED TOMOGRAPHY (CT)

CT with pancreatic protocol (arterial, portal, and equilibrium phases) has a detection rate of 1.2–2.6% for incidental cysts and is the first-line approach in emergency settings or when the patient cannot tolerate MRI. Its main strength lies in the identification of calcifications (especially the central 'sun-rising' calcification of the NQS) and in the assessment of vascular invasion. However, its overall diagnostic accuracy in differentiating benign from malignant cysts does not exceed 75–78%.[2,3]

FIGURE 3
Serous cystadenoma (SCN). Typical calcifications are seen on the CT scan.

IMAGING MODALITIES

MAGNETIC RESONANCE IMAGING WITH MRI (MRI/MRI)

Dynamic magnetic resonance cholangiopancreatography (MRCP) is the modality of choice for characterizing pancreatic cysts and evaluating high-risk signs or concerning features. Its high contrast resolution and sensitivity in T2-weighted sequences allow for:
(1) Identify communication with the main pancreatic duct (MPD), which is a definitive criterion for IPMN.
(2) detect mural nodules and septa.
(3) accurately measure the diameter of the CPP.

The diagnostic accuracy of MRI ranges from 73% to 81%.[2,5]

The Kyoto 2024 guidelines of the International Association of Pancreatology (IAP) incorporated as high-risk features (HRS) the presence of mural nodule >5 mm, obstructive jaundice with head injury and CPP dilation >10 mm.
Features of concern (WF) included: cystic growth ≥2.5 mm/year, elevated CA 19-9 in blood, de novo pancreatitis or new episodes of acute pancreatitis in an existing one, acute onset or exacerbation of diabetes mellitus and mural nodule ≤5 mm.[1,4,6]

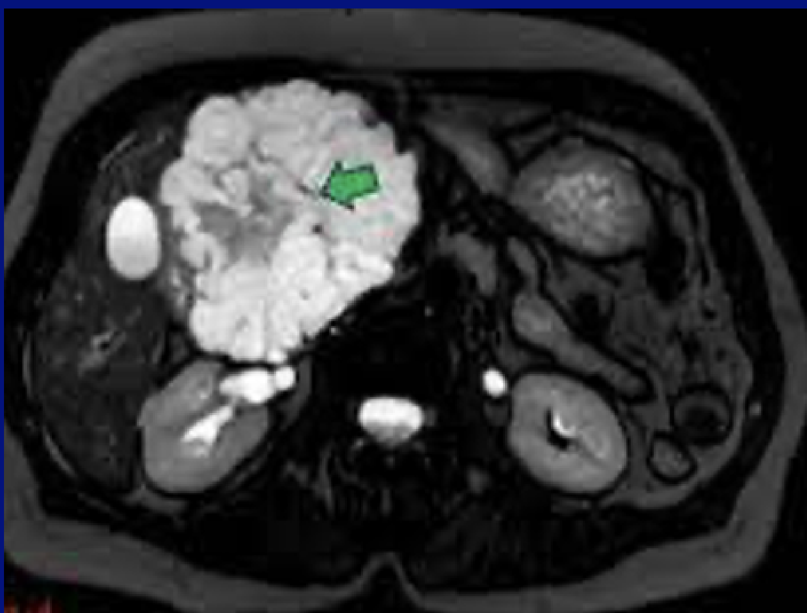


FIGURE 4 *MRI. Shows image of an NQM. Pattern of microcysts (honeycomb) plus central scar.*

ENDOSCOPIC ENDOSONOGRAPHY (EUS)

EUS offers superior morphological resolution for cysts ≤2 cm, detection of mural nodules, evaluation of thin septa, and ductal communication. Its accuracy in differentiating mucinous from non-mucinous cysts by morphology alone reaches only 51%, but this increases significantly when combined with aspiration and analysis of the cystic fluid.[3,7 VIDEOS 1,2]

SELECTION OF IMAGING STUDIO

• First choice for follow-up: MRI/MRCP (no ionizing radiation, superior for ductal communication).
• Complementary or urgent: CT with pancreatic protocol (best for calcifications).
• To guide puncture and evaluate lesions ≤2 cm: EUS ± FNA.
• If high risk is suspected: EUS + FNA with complete analysis of the cystic fluid.

ENDOSCOPIC ULTRASOUND WITH FINE-NEEDLE ASPIRATION (EUS-FNA)

EUS-FNA is indicated when analysis of the cystic fluid will alter clinical management. Experts recommend performing it in cases of cysts with indeterminate morphological characteristics, the presence of risk factors, or in the context of any risk factors. It is a technique with low complication rates, such as post-procedure pancreatitis (<1.1%), bleeding (<1%), and abdominal pain (<0.34%).[3,7]

Technically, a 19G needle is preferred (or 22G if the location is difficult), with a transgastric or transduodenal approach depending on the cyst's location. The maximum possible volume should be aspirated and the material distributed among the following studies in order of priority:

1- cytology
2- CEA
3- glucose
4- amylase
5- Molecular markers (KRAS/GNAS).[1,8]

ANALYSIS OF CYSTIC LIQUID: SAMPLES TO REQUEST

CYTOLOGY

Cytology of cystic fluid has high specificity (>93–100%) but limited sensitivity (<51%) due to the low cellularity of most aspirates. Identification of glycogen-rich cells (clear cuboidal cells) suggests neoplastic cysts (NCS), while the presence of mucin or mucinous columnar cells indicates a mucinous lesion. Malignant cells confirm adenocarcinoma but are uncommon. Cytology should be submitted in 10% formalin or liquid-based preservative solution.[3,7]

CEA IN CYSTIC FLUID

Intracystic carcinoembryonic antigen (CEA) is the most reliable marker for differentiating mucinous from non-mucinous cysts. With a cutoff point of 192 ng/mL, its sensitivity is 56–67% and its specificity is 80–96%. A recent meta-analysis by Pflüger et al. proposes that a cutoff point of 20 ng/mL optimizes diagnostic accuracy (sensitivity 91%, specificity 85%). With the 192 ng/mL cutoff, many true mucinous cysts were missed due to the high cutoff. Therefore, Pflüger proposes a positivity range between 20 and 192 ng/mL, which increases sensitivity and specificity. CEA is not useful for predicting malignancy or histological grade. It only indicates whether the cyst is mucinous or not.[8,9]

GLUCOSE IN CYSTIC FLUID

Intracystic glucose has emerged as a low-cost alternative to CEA. With a cutoff point <50 mg/dL, it has a sensitivity of 91% and a specificity of 75–86% for identifying mucinous cysts. Mucinous cysts actively metabolize glucose (low levels), while non-mucinous cysts exhibit glucose concentrations similar to serum glucose. It is measurable with a glucometer. Pseudocysts also exhibit low glucose levels, so CEA remains necessary for differential diagnosis.[9,10]

AMYLASE IN CYSTIC FLUID

Very high amylase levels (>250 U/L) suggest communication with the ductal system, with pseudocysts most consistently showing high values (mean 7,210 U/L). Elevated levels are also observed in IPMNs (due to ductal communication), but are low in NQS. Amylase testing is requested in all cases where pseudocysts or underlying pancreatitis are suspected.

Marcador	Muestra	Punto de corte	Sensibilidad	Especificidad	Interpretación
CEA	Líquido quístico	>192 ng/mL	56–67 %	80–96 %	Quiste mucinoso (IPMN / NQM)
CEA (óptimo)	Líquido quístico	>20 ng/mL	91%	85%	Mayor rendimiento dx (meta-análisis 2023)
Glucosa	Líquido quístico	<50 mg/dL	91%	75–86 %	Quiste mucinoso (bajo costo, glucómetro)
Amilasa	Líquido quístico	>250 U/L	Variable	Variable	Pseudoquiste / IPMN (comunicación ductal)
Citología	Líquido quístico	Células malignas	51%	93–100 %	Malignidad / mucina / glucógeno
CA 19-9 sérico	Sangre venosa	Elevado (> 37 U/mL)	Moderada	Moderada	Signos de alarma, no específico

Table 2. Markers in cystic fluid: samples to request and diagnostic thresholds.[8, 9, 10]

MOLECULAR MARKERS AND ADVANCED TECHNIQUES

CYST FLUID MUTATIONAL ANALYSIS (NGS)

Many of these technologies are still under development in Latin America. And not all centers have them.

Next-generation sequencing (NGS) of cyst fluid DNA represents the most significant advance in the molecular diagnosis of pancreatic cysts. A recent meta-analysis (Pflüger et al., Pancreatology 2023) evaluated DNA-based markers and reported the following findings:[8]

- KRAS mutations: sensitivity 59%, specificity 87% for mucinous cysts. The combination of KRAS + allele loss increases accuracy.
- GNAS mutations (codon 201): high specificity for IPMN (≈90%).
- VHL mutations: 99% specificity for NQS (56% sensitivity).
- CDKN2A, PIK3CA, SMAD4, TP53 mutations: 95–98% specificities for high-grade dysplasia or PDAC in mucinous cysts.

The Kyoto 2024 guidelines endorse the investigation of molecular markers in cystic fluid as part of multidisciplinary diagnostic work, especially in indeterminate cysts with sufficient volume (≥0.5 mL).[1, 6]

NEEDLE-BASED CONFOCAL ENDOMICROSCOPY (NCLE)

nCLE (needle-based Confocal Laser Endomicroscopy) integrates EUS with confocal laser microscopy, allowing real-time microscopic imaging of the cyst wall at submillimeter resolution through a 19G needle. Reported nCLE patterns: surface reticulation of vessels (NQS), epithelial band with papillary projections (IPMN), dark gray bands (NQM), and absence of epithelium with vascular structures (pseudocyst).[3,6]

A systematic review and meta-analysis (Clin Gastroenterol Hepatol, 2024) reported a sensitivity of 85%, specificity of 99%, and overall diagnostic accuracy of 99% (SROC) for nCLE. The post-procedure pancreatitis rate was 1%. Integration of nCLE with artificial intelligence (CNN) for high-grade dysplasia detection has achieved accuracies of 82.9% in recent studies.[3,6, FIGURE 5]

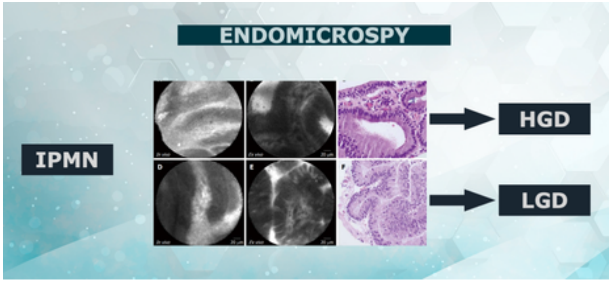


FIGURE 5 *Endomicroscopy showing IPMN and whether it is of low or high grade dysplasia.*

TRANSNEEDLE MICROFORCEPS BIOPSY

The microforceps device (Moray forceps) allows for the collection of histological fragments from the cyst wall using 19G needles. It offers greater cellularity than conventional aspiration. Its diagnostic performance is superior to that of cytology alone (specificity ~100% for malignancy). It is primarily indicated for nodules within cysts with concerning characteristics or when cytology and biomarkers are inconclusive.[3, VIDEO 4]

ALGORITHM

The Kyoto 2024 guidelines, the AGA 2024 guidelines, and a Hong Kong 2023 group propose a stepwise approach that integrates clinical evaluation, imaging, and cyst fluid analysis. A summary of the recommended diagnostic workflow is presented below.[1,2,4]

DIAGNOSTIC ALGORITHM — INCIDENTAL PANCREATIC CYST (Kyoto 2024 / AGA 2024)

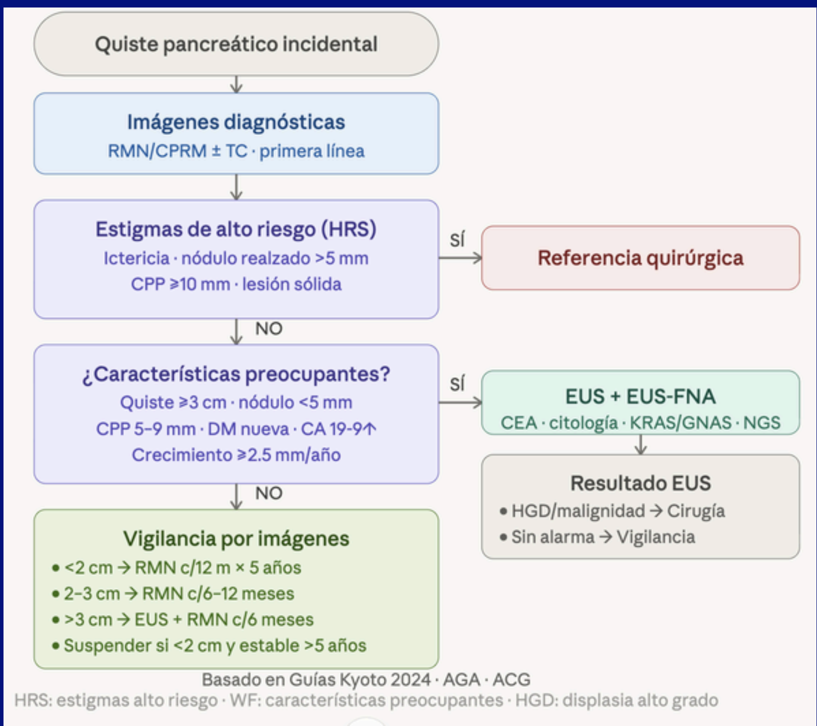
STEP 1 │ Initial assessment → Anamnesis: history of acute/chronic pancreatitis, jaundice, weight loss → Dynamic MRI/MRCP: first choice for any cyst ≥ 1 cm → CT if MRI is unavailable or urgent

STEP 2 │ High Risk (HRS) characteristics?
→ Mural nodule >5 mm | Obstructive jaundice | MPD ≥ 10 mm → YES: Refer to pancreatic surgery without delay

STEP 3 │ Worrying Characteristics (WF)?
→ Growth ≥2.5 mm/year | Nodule ≤5 mm | MPD 5–9 mm | Recent-onset DM → Elevated CA 19-9 | Recurrent acute pancreatitis → YES: EUS ± FNA + complete cystic fluid analysis

STEP 4 │ EUS-FNA — Apply (in order of priority):
→ [1] Cytology [2] CEA [3] Glucose [4] Amylase [5] NGS (KRAS/GNAS/VHL/TP53) → nCLE if indeterminate cyst with insufficient volume or diagnostic discordance

STEP 5 │ Final decision → Mucinous diagnosis with WF: resection vs. intensive surveillance (multidisciplinary) → NQS / pseudocyst / without WF: surveillance with MRI/MRCP every 1–2 years



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10. Lopes CV. Cyst fluid glucose: an alternative to carcinoembryonic antigen for pancreatic mucinous cysts. World J Gastroenterol. 2023;29(4):667-680.

VIDEOS OF THE MONTH

ELUXEO 8000 SYSTEM

VIDEO 1
NEOPLASIA QUÍSTICA SEROSA. VISIÓN DESDE LA EUS.

VIDEO 2
EUS EN IPMN MIXTO (DUCTO PRINCIPAL Y RAMAS SECUNDARIAS)

VIDEO 3
GLUCOMETRÍA EN LÍQUIDO DE QUISTE DE PÁNCREAS

VIDEO 4

LITERATURE

1. Ohtsuka T, Fernandez-del Castillo C, Furukawa T, Hijioka S, Hackert T, Hirono S, et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology. 2024;24(2):255-270.
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10. Lopes CV. Cyst fluid glucose: an alternative to carcinoembryonic antigen for pancreatic mucinous cysts. World J Gastroenterol. 2023;29(4):667-680.

ARTICLE OF THE MONTH

Diagnosis and Management of Pancreatic Cysts

Gardner TB, Park WG, Allen PJ. Diagnosis and management of pancreatic cysts. Gastroenterology. 2024 Aug;167(3):454–468. doi: 10.1053/j.gastro.2024.02.041. PMID: 38442782.

With the increasing incidence of pancreatic cysts, attributed primarily to the widespread use of cross-sectional imaging, their management presents a growing challenge for clinicians. Proper characterization of each cyst is essential, as therapeutic decisions depend on an accurate diagnosis. Diagnostic modalities such as cytology, biopsy, and biomarkers in cystic fluid allow for the definitive diagnosis of virtually all lesions.

Some cysts—such as papillary intraductal mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and cystic neuroendocrine tumors—have malignant potential and require monitoring. Others, such as serous cystadenomas and pancreatic fluid collections, do not have malignant potential.

Regarding diagnostic assessment, the authors highlight a step-by-step approach:

Imaging: CT and MRI are the first-line imaging modalities for characterizing morphology, size, and relationship to the main pancreatic duct. Maintaining a broad differential diagnosis is essential because an accurate diagnosis has significant management implications. Unfortunately, there is a lack of data on the ability of cross-sectional imaging to accurately diagnose small cysts (<10 mm) independently, without further evaluation such as EUS with FNA for cyst fluid analysis.

EUS and EUS-FNA: Even using EUS-FNA, a definitive diagnosis is sometimes not achieved in small cysts due to the limited sample volume available for analysis. The authors recommend EUS-FNA when high-risk characteristics are present or when diagnostic uncertainty necessitates a change in management.

Analysis of cystic fluid: Intracystic CEA with a cutoff point > 192 ng/mL has been used to define mucinous cyst positivity, although diagnostic criteria vary between studies. Amylase and cytology are also recommended for all fluid samples.

Molecular markers: Combining NGS (next-generation sequencing) findings with CEA levels increases sensitivity and specificity for detecting mucinous lesions to 78% and 87%, respectively. Advanced neoplasms showed 95% specificity for high-risk mutations, with the highest diagnostic accuracy observed for NGS mutations.

Advanced techniques: EUS with confocal laser endomicroscopy (EUS-nCLE) detects malignant IPMNs with a sensitivity of 90% and a specificity of 73%, although its availability is limited. Emerging biomarkers in cyst fluid or blood include mucins, miRNA panels (sensitivity 66.7–89%, specificity 89.7–100%), lipidomics, and cancer metabolite profiling, with a diagnostic accuracy reaching 89–91%.

Surveillance and Controversies: Surveillance strategies vary widely depending on the type and size of the cyst. The most controversial aspects include whether surveillance can be discontinued, how it should be conducted, and the significant economic burden that cyst management places on the healthcare system. Prospective studies are needed to definitively determine the rate of malignant transformation for each type of cyst.