

Clinical Data
Amylase
CEA
Imaging
Cytology
EUS

The image features a large iceberg floating in the ocean. The tip of the iceberg is above the water surface, while the much larger base is submerged. White lines with dots at the end point from text labels to various parts of the iceberg's surface. The labels include 'Clinical Data', 'Amylase', 'CEA', 'Imaging', 'Cytology', and 'EUS'. The background is a clear blue sky with some clouds and a calm sea.

Look Below the Surface

Molecular Testing
with
PancraGEN

DNA Quality/Quantity
GNAS
KRAS
LOH

BIOLOGICAL BEHAVIOR

The report categorizes patients into four groups according to their risk of cancer (Benign, Statistically Indolent, Statistically Higher Risk, or Aggressive) and provides either the probability of benign disease over 3 years or the probability of High Grade Dysplasia/carcinoma.

MOLECULAR & CLINICAL RESULTS

This section lists the molecular results generated and reported by Interpace Diagnostics.

This section also includes test and clinical information provided to Interpace Diagnostics by the submitting physician.

Patient Information			
Patient Name: Public, Jan Q	Accession #:	RPXX-XXXXX	
MRN: 00-0123456	Case Accessioned:	1/23/2019	
DOB: 01/01/1935 Age: 84 yrs Sex: Female	Specimen Received:	1/2/2019	
Ordering Physician: Smith, Mark M	External Accession #:	XXX-XXXXX	
Specimens Received:			
1. Buccal Brush (Ext Part 1; Collected 1/1/2019)			
2. Pancreatic Body Cyst Fluid (Ext Part 3; Collected 1/1/2019)			

Biological Behavior			
BENIGN	STATISTICALLY INDOLENT	STATISTICALLY HIGHER RISK	AGGRESSIVE
97% probability of benign disease over the next 3 years. Patient lacks significant molecular alterations ¹			

Molecular & Clinical Results (See detailed table of Molecular Alterations Tested)					
Fluid Chemistry	EUS Findings	Cytology Results	DNA Quantity & Quality	Oncogene Point Mutations	Tumor Suppressor Gene (LOH)
A CEA: 11,930 ng/mL Amylase: 103 U/L	Duct dilation ≥ 1cm	Acellular	Moderate quantity Good quality	KRAS: No mutation detected GNAS: No mutation detected	No LOH detected

Details

THE BIOLOGICAL BEHAVIOR OF THIS PATIENT'S LESION FALLS INTO THE CATEGORY OF "BENIGN."

Molecular characteristics favor benign biological behavior rather than aggressive disease. This is based on the lack of detectable mutational change. The greatly elevated cyst fluid CEA level and grossly dilated pancreatic duct (1.4cm) are noted, which raise a concern for potentially aggressive disease. However, molecular studies of the submitted fluid favor a benign process over aggressive disease. An available clinical indicator (cytology) also supports benign biological behavior.

Molecular criteria (KRAS/GNAS point mutations, two or more LOH mutations, greatly elevated amounts of DNA) for a mucinous process are not present. However, clinical criteria (dilation involving the pancreatic duct system, elevated cyst fluid CEA level) support a mucinous process. Lack of molecular evidence for a mucinous process tends to be found in benign, rather than aggressive, processes.

Please note that because pancreatic cyst lesions can be complex with multifocal areas of heterogeneous pathology, sampling variation may occasionally result in underdiagnosis of existing pathology. Clinical correlation and integration of the molecular results with clinical findings is required to minimize this possibility.

Notwithstanding the benign molecular features, close follow-up is recommended given the greatly elevated CEA level and the extent of duct dilation seen here. One approach to consider is to repeat the imaging and/or aspiration and perform both clinical and molecular analyses of this cystic process after an interval of time, if future clinical follow-up warrants additional studies. By comparing subsequent findings with the initial baseline studies, the stability, regression, or progression of mutational change can be determined.

DETAILS

This section includes an in-depth review of the findings: molecular data, an explanation of why a particular diagnostic category was selected, details on the integration of clinical information, and the pathologist's interpretation of the results.

Molecular Alterations Tested		
DNA quantity	Increased levels of DNA detected within a pancreatic cyst are indicative of cellular proliferation and rapid turnover of neoplastic or malignant processes, analogous to a proliferative index. The concentration of DNA predict pancreatic cyst type, ² discriminate benign/low grade from high grade and malignant mucinous cystic neoplasia, ³ and neuroendocrine tumor formation ⁴	
DNA quality	The integrity of cell-free cyst fluid DNA (short versus long lengths of DNA) correlates with the degree of cellular proliferation and turnover. Benign forms of cystic disease characterized by slow cellular turnover predictably yield poor quality (degraded) DNA. Conversely, states of high cellular proliferation (high grade dysplasia, carcinoma) deliver significant proportions of long length DNA fragments. Quantitative PCR is used to determine DNA quality, predicting cyst biological aggressiveness ⁵	
KRAS point mutation	KRAS oncogene point mutation is the most common molecular alteration in pancreatic precancer/cancer formation and is highly specific for mucinous processes. This alteration tends to occur early in mucinous lesions and by itself can be seen in benign states that do not necessarily progress to cancer ^{6,8}	
GNAS point mutation	Similar to KRAS oncogene point mutation, GNAS oncogene mutation is well recognized as an early event and specifically found only in intraductal papillary mucinous neoplasms. ⁹ GNAS mutation tends to be an early event which can exist in stable benign IPMNs ⁵	
TUMOR SUPPRESSOR GENE PANEL (LOSS OF HETEROZYGOSITY)		
Loci	Associated Genes	Clinical Relevance
1p	RUNX3, CUMM1, LMYC	RUNX3 1p36, 1p35 affects multiple growth regulatory pathways, manifesting as loss of heterozygosity in up to one third of pancreatic adenocarcinomas. Copy number imbalance of the LMYC oncogene is also detected at this loci. CMM1v - 1p36 loss is seen in cutaneous malignant melanoma and dy
3p	VHL, OGG1	VHL - 3p25.3, and loss of von Hippel-Lindau gene have been reported in 40% cystadenoma. Other TSGs such as OGG1 co-exist at this location. OGG1 function pathway and has been shown to contribute to cancers such as kidney and l
5q	MCC, APC	These TSGs are well established in many cancers including pancreatic carcin linked to APC gene and LOH is described in lung and esophageal cancers. AP adenomatous polyposis. LOH of APC is seen in sporadic colorectal and gastr
9p	CDKN2A, CDKN2B	CDKN2A - 9p21.3 regulates cell cycles by inhibiting cyclin D complexes and in 49% to 98% of pancreatic cancers. Both CDKN2A and CDKN2B situated on 9p contribute to carcinogenesis. ¹⁰⁻²²
10q	PTEN, MXI1	PTEN - 10q23.31 encodes tumor suppressors involved in PI3K and MAPK sign seen in 15% and loss of expression seen in 75% of pancreatic cancers. The 10 MXI1 -10q25.2, which antagonizes MYC function. ^{21,22}
17p	TP53	TP53 - 17p13.1 deregulates the cell cycle at the G1-S phase, with mutations reg cancers, seen in both ductal adenocarcinoma and neuroendocrine cancers. T many human cancers. ²³⁻²⁶
17q	RNF43, NME1	RNF43 - 17q22 tumor suppressor inhibits the Wnt/Beta catenin pathway. LOH 50% of MCNs, and up to 28% of invasive pancreatic cancers. NME1 - 17q21.33 independent pathways in development and progression of digestive cancer
18q	SMAD4, DCC	SMAD4 - 18q21.2 is a common mutation in pancreatic cancer associated with SMAD4 mutation is relatively specific and is found in 60% to 90% of pancreati such as DCC, are also found at this chromosomal locus. ^{30,33}
21q	TFF1	TFF1 - 21q22.3 is highly expressed on preneoplastic cells and also pancreatic 21q has been linked to both pancreatic ductal and endocrine tumors. ^{34,36}
22q	NF2	NF2 22q12.2 decreased expression is seen in pancreatic tumors, together wit Beta catenin pathway. Other TSGs are known to be located in this region. ^{27,40}

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PancreGEN RISK STRATIFICATION

Data from the National Pancreatic Cyst Registry study shows:

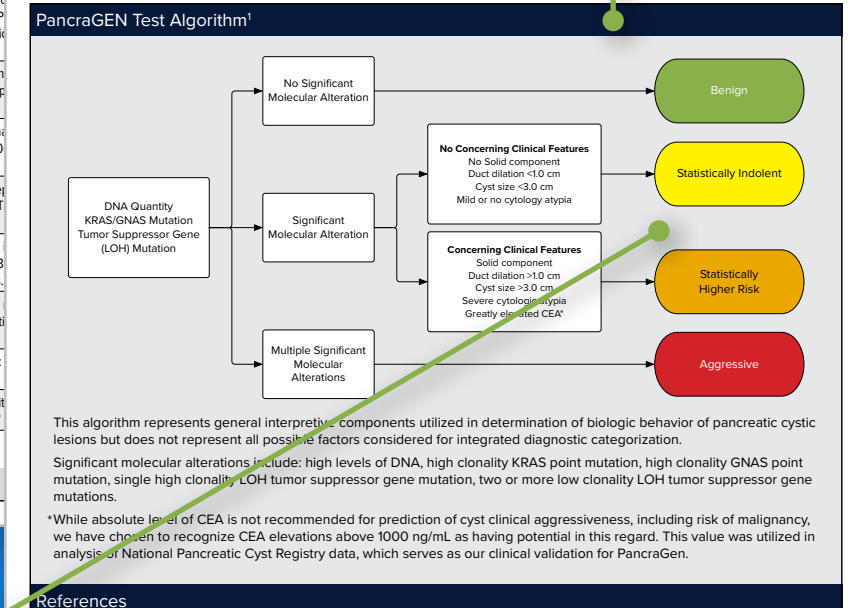
- ▶ "Benign" or "Statistically Indolent" patients have a 97% probability of benign disease over the next 3 years
- ▶ "Statistically Higher Risk" patients have a 65% probability of High Grade Dysplasia/carcinoma
- ▶ "Aggressive" patients have a 91% probability of High Grade Dysplasia/carcinoma

MOLECULAR ALTERATIONS TESTED

This section provides an explanation of the importance of DNA quality and quantity. A listing of the oncogenes and tumor suppressor genes tested, along with their implications for pancreatic cancer, is also provided within this section.

PancreGEN TEST ALGORITHM

This section provides an overview of the interpretive components used by the PancreGEN test in determining the biological behavior of pancreatic cysts.



References

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Report Guide

Limitations and Disclaimers:

Although PancraGEN is highly specific for malignancy, some malignant cysts may not be detected.¹ There may also be individuals who are falsely identified as having a malignant cyst.¹ Diagnosis and appropriate patient management are the responsibility of the referring physician or health care provider.

Reference

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