PancraGEN

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Introduction

PancraGEN testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
PancraGEN	81479

Criteria

Introduction

Requests for PancraGEN testing are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What are pancreatic cysts?

Definition

Pancreatic cysts are reported as incidental findings in 3 to 13% of individuals undergoing abdominal imaging procedures. Four of the most common types of pancreatic cysts are serous cystadenomas (SCA), solid-pseudopapillary neoplasms (SPN), mucinous cystic neoplasms (MCN), and intraductal papillary mucinous

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neoplasms (IPMN).[1]

- Overall, considering all types of pancreatic cysts, the risk of cancer is very low (<1% per year), but with different risks based on the histologic type of cyst and its clinical characteristics. Given that most cysts do not progress to cancer, and that pancreatic surgery has a high rate of morbidity and mortality, conservative management is recommended for the vast majority of individuals.[1,2]
- Clinicians typically rely on imaging, cytology, and fluid chemistry to assess the malignancy risk of pancreatic cysts.
- In cases where an individual's diagnosis based on conventional pathologic and imaging approaches is inconclusive, PancraGEN has been proposed as an adjunctive risk stratification tool to provide additional clarifying information to inconclusive results of standard diagnostic tools, including imaging, carcinoembryonic antigen (CEA), cytology, and clinical risk factors.[3-5]

Test information

Introduction

According to the test manufacturer, PancraGEN provides molecular results for DNA quantity and quality, specific oncogene point mutations (in codons 12 and 13 of KRAS and codon 201 of GNAS), and information on loss of heterozygosity at 10 loci [3p (VHL, OGG1), 10q (PTEN, MXI1), 17p (TP53), 18q (SMAD4, DCC), 9p (CDN2A/B), 17q (RNF43, NME1), 21q (PSEN2, TFF1), 1p (RUNX3, CMM1, LMYC), 5q (MCC, APC), and 22q (NF2)] in order to stratify individuals according to their risk for progression to malignancy.[6-10]

- The test requires specimens of pancreatobiliary fluid, pancreatic masses, or pancreatic tissue usually obtained by endoscopic ultrasound (EUS) guided fine needle aspiration (FNA).[6,11]
- The PancraGEN report categorizes individuals into one of four groups: low risk category that supports surveillance (a. benign; b. statistically indolent) or high risk category that supports treatment intervention decisions (c. statistically higher risk; d. aggressive).[6-10]
- This test is intended to determine an individual's risk of cancer progression and assess the best course of treatment. Based on test results, low-risk patients with benign cysts may benefit from early disease surveillance and avoidance of invasive surgical resection, while higher risk patients with aggressive cysts can receive proper surgical treatment for malignant lesions.[6-10]

Guidelines and evidence

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2018) published comprehensive guidelines for the diagnosis and management of pancreatic cysts. Although these guidelines did not include molecular analysis as part of the routine analysis of all pancreatic cysts, the authors stated: “A number of DNA, RNA, protein, and metabolomic markers have been evaluated in cyst fluid. The majority of these are still early in development and not yet ready for translation into clinical practice. However, analysis of DNA mutations in cyst fluid has shown promise in identifying IPMNs and MCNs.”[2]

National Institute of Health and Clinical Excellence

The National Institute for Health and Clinical Excellence (NICE, 2018) stated the following regarding evaluation of pancreatic cysts:[12]

- "Offer a pancreatic protocol CT scan or magnetic resonance cholangiopancreatography (MRI/MRCP) to people with pancreatic cysts. If more information is needed after one of these tests, offer the other one.
- Refer people with any of these high-risk features for resection:
    - obstructive jaundice with cystic lesions in the head of the pancreas
    - enhancing solid component in the cyst
    - a main pancreatic duct that is 10 mm diameter or larger
- Offer EUS after CT and MRI/MRCP if more information on the likelihood of malignancy is needed, or if it is not clear whether surgery is needed.
- Consider fine-needle aspiration during EUS if more information on the likelihood of malignancy is needed.
- When using fine-needle aspiration, perform carcinoembryonic antigen (CEA) assay in addition to cytology if there is sufficient sample.
- For people with cysts that are thought to be malignant, follow the recommendations on staging."

Selected Relevant Publications

A small base of evidence comprised of a few clinical studies evaluated the correlation between genetic testing using the PancraGEN test and histologic evaluation of pancreatic tissue samples (including cytology specimens).[13-25]

Overall, the quality of the evidence base is low, consisting primarily of retrospective studies comparing the diagnostic performance of PancraGEN with conventional testing methods. It is not clear if PancraGEN would perform well in a broad, general population of individuals with pancreatic cysts. Small sample sizes may lead to imprecise

estimates of test accuracy. The reported diagnostic performance values vary widely and were often not accompanied by confidence intervals. Included confidence intervals were wide, suggesting a lack of precision.

Additional well-designed clinical studies are needed to assess the clinical utility of PancraGEN testing in individuals with pancreatic cysts.

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for PancraGEN will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[26] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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