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.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
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<tbody>
<tr>
<td>PancraGEN</td>
<td>81479</td>
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</table>

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 neoplasm (SPN), mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasms (IPMN).

• Overall, considering all types of pancreatic cysts, the risk of cancer is very low (<1%), 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 patients.

• 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.

Test information

• 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 for approximately 15 tumor suppressor genes in order to stratify patients according to their risk of progression to malignancy.
• The test requires specimens of pancreatobiliary fluid, pancreatic masses, or pancreatic tissue usually obtained by endoscopic ultrasound (EUS) guided fine needle aspiration (FNA).\(^3,4\)

• The PancraGEN report categorizes patients 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).

• This test is intended to determine a patient’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.\(^3\)

### Guidelines and evidence

• The American College of Gastroenterology (2018) has published comprehensive guidelines for the diagnosis and management of pancreatic cysts. Although these guidelines do not include molecular analysis as part of the routine analysis of all pancreatic cysts, the authors state that: "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."\(^2\)

• A small base of evidence comprised of a few clinical studies have evaluated the correlation between genetic testing using the PancraGen test and histology, cytology and pathology of surgical or biopsy specimens of pancreatic tissue.\(^5-9\) Two of the most relevant studies, both published by the manufacturer and evaluating the same patient population, reported results of a retrospective analysis of the National Pancreatic Cyst Registry study (n=492).

  o In the study by Al-Haddad et al. (2015), patients underwent testing with PathFinderTG (now PancraGEN) and were followed to evaluate disease progression to malignancy.\(^5\) Diagnostic performance of PathFinder TG testing were compared with a set of international consensus guidelines, published in 2012, used for disease management in clinical practice.\(^6\) After a median follow-up of 35 months, negative predictive values and sensitivity values for PathFinderTG and consensus guidelines were comparable, although positive predictive value and positive likelihood ratios were significantly improved for PathFinder TG. Study authors concluded that the PathFinder TG test may improve disease management by supporting a surveillance decision established by the Sendai guideline criteria.

  o In the same study population from the National Pancreatic Cyst Registry described in by Al-Haddad et al. (n=491), Loren et al. (2016)\(^7\) compared the association between diagnoses made with PancraGEN and those made with the consensus guidelines by Sendai and Fukouka (2012), and also reported on the
subsequent clinical decisions made in the real world regarding choices made for either surveillance or surgical intervention. Study results suggest that testing with PancraGEN testing is significantly associated with real-world decisions, although it is not known if physician influence or patient preferences could have also impacted these decisions. Study results suggest that PancraGEN testing might properly reclassify some patients misclassified by consensus guidelines.

- Farrell and colleagues assessed the incremental value of DNA markers when applied against a clinically stratified patient population, rather than using the clinical information in aggregate as part of Integrated Molecular Pathology scoring. The absence of DNA abnormalities allowed a reduction in malignancy risk in patients with worrisome clinical findings (incremental relative risk of malignancy 0.4 (0.1-1.1 95% CI) to that of patients with no worrisome features or high risk stigmata.

- A retrospective assessment of the clinical utility of DNA biomarkers was performed by Arner and colleagues. Results of DNA marker testing changed management decisions (as made by each of 2 experts in a retrospective case review) in approximately 27% of cases.

- The performance DNA markers in assessing the malignant potential of intraductal papillary mucinous neoplasm, both independently and as part of the Integrated Molecular Pathology malignancy risk score was evaluated by two studies. The same study population, identified through retrospective chart-review, was used for both.

- Limitations of the evidence include retrospective study designs, limited follow-up times to adequately observe malignant progression, and a very small number of cases where results of PancraGEN and consensus guidelines do not agree.

- Given that the evidence base consists primarily of retrospective study designs, it is not clear if PancraGEN would perform well in a broad, general population of patients with pancreatic cysts. Small sample sizes may lead to imprecise estimates of test accuracy.

Criteria

- This test is considered investigational and/or experimental.
  - Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References


