# Select Health Medical Policies

## Pathology Policies

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Select Health

MEDICAL POLICY

# PANCRAGEN MOLECULAR DIAGNOSTIC TEST FOR EVALUATION OF PANCREATIC CYSTS

Policy # 603

Implementation Date:11/29/16

Review Dates: 12/21/17, 12/4/18, 12/16/19, 12/17/20, 12/6/21, 1/17/23, 12/11/23, 12/8/24

Revision Dates: 1/24/17, 12/23/24

**Disclaimer:**
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

## Description

Pancreatic cysts may be detected in over 2% of patients who undergo abdominal imaging for unrelated reasons, and this frequency increases with age.

Most pancreatic cystic neoplasms (PCNs) are detected incidentally when abdominal imaging is performed for other indications. PCNs account for more than 50% of pancreatic cysts, even in patients with a history of pancreatitis. The first step in evaluating a cyst is to obtain magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP). Cross-sectional imaging is obtained to determine if there are features present that can identify the specific cyst type and to determine if there are any findings that increase the risk of malignancy (large cyst > 3 cm, a solid component within the cyst, main pancreatic duct dilation). Endoscopic ultrasound with fine-needle aspiration (EUS-FNA) provides high-quality imaging of the pancreas and the opportunity to sample pancreatic lesions, which increases diagnostic accuracy. The addition of intraductal EUS may also increase diagnostic accuracy but is not part of the routine evaluation of pancreatic cysts.

Once a cyst has been aspirated, it undergoes analysis of any fluid obtained. This includes cytology, CEA level, and amylase, along with genetic testing for KRAS, GNAS, and sometimes other markers. In some instances, these markers are indeterminate and a decision to either monitor the cyst with periodic imaging based on established guidelines, or surgical intervention, must be undertaken with less certainty as to the true necessity of this invasive intervention.

PancraGEN (Interpace Diagnostics LLC, Parsippany, NJ), formerly Pathfinder TG (RedPath Diagnostics) is a laboratory test that integrates cytological, fluid chemistry (CEA, amylase), imaging, and DNA analysis into 4 diagnostic categories that works to help stratify the risk of malignancy, particularly in cysts with indeterminate features. On a DNA level, PancraGEN measures the quantity, quality, and level of DNA damage (specifically, the presence and clonality of loss of heterozygosity mutations (LOH) next to tumor suppressor genes and oncogene point mutations) that is causally responsible for pancreatic cancer. PancraGEN measures 15 genetic markers which are distributed across 10 chromosomal regions including KRAS and GNAS.

Cyst fluid chemistry (i.e., CEA, amylase), imaging, levels of atypia, and cellularity are abstracted from the patients' records provided by the managing physician. Parameters of these initial tests are used along with the results of DNA analysis to compute a malignancy risk estimate to help guide surgery.

## COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

**Select Health does NOT cover the PancraGEN molecular diagnostic test for routine evaluation of pancreatic cysts** as it is considered experimental/investigational.

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### SELECT HEALTH MEDICARE

**Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies.** For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

### SELECT HEALTH COMMUNITY CARE (MEDICAID)

**Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply.** For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

**Summary of Medical Information**

Two systematic reviews and 14 primary studies were identified that met inclusion criteria for this review. Data on > 1,500 samples have been reported in the literature since 2006. Most of the literature on PancraGEN or Pathfinder (as this test was previously known) was related to the clinical validity of the test, namely, the test's ability to accurately profile tissue samples versus cytology, cyst fluid, or other standard means of cyst assessment. All the studies that noted sensitivity and specificity showed that the test has higher of the latter than the former, with specificities ranging from 75% to 100%. Of the 14 primary studies, only 1 paper (Das et al.) discussed the health economics of the test, and identified the noteworthy number needed to treat as 56. Similarly, only 2 papers (Kowalski and Loren et al.) discussed the potential clinical utility of the study showing that use of the test may improve patient surveillance.

In general, the literature shows some measure of clinical validity but fails to prove the clinical utility of the test (e.g., altering treatment plans, improving morbidity and mortality, improving progression-free survival, etc.). Given that the test has an average specificity of 88%, the lack of clinical utility data, limited follow-up periods in the literature, and evidence of improved outcomes resulting from use of PancraGEN, the current body of evidence is not sufficient to draw meaningful conclusions regarding the clinical usefulness of the test.

According to the American College of Gastroenterology (ACG) clinical guideline: Diagnosis and Management of Pancreatic Cysts (Elta, 2018) Recent studies have shown that integrating molecular testing with cyst clinical features increases the sensitivity and specificity for identifying IPMNs or MCNs. Unfortunately, they are costly and have not helped determine cancer risk. Their use may be considered in cases in which the diagnosis is unclear, and the results are likely to change management (Conditional recommendation, very low quality of evidence).

In 2018 Arner and colleagues studied the addition of DNA molecular analysis in a retrospective review of 46 patients, they concluded that molecular analysis alters the clinical management of pancreatic cystic lesions most often when CEA levels are intermediate (45–800 ng/mL) or when no CEA concentration is available. Use of DNA molecular analysis can be considered in this cohort, and they concluded that further study of molecular markers in pancreatic cystic lesions is recommended.

In 2019, Farrell and colleagues reported results of a cohort study of 478 participants to determine the incremental predictive value of molecular analysis of pancreatic cyst fluid to assess for malignancy risk over the long term. A total of 209 participants had surgical pathology-derived outcomes and 269 had clinical follow-up of > 2 years. Cysts were classified based on (HRS) High risk stigmata (jaundice, main pancreatic duct >1 cm, solid pancreatic masses) and worrisome features (WFs) classified as (mural nodule, mucin or papillary projection; main pancreatic duct, .5-.9 cm; cyst size >3 cm; pancreatitis, abrupt changes in main pancreatic duct with distal atrophy and lymphadenopathy). Forty-two participants had high risk stigmata (HRS), 272 lacked both HRS and worrisome features (WFs), and 164 lacked HRS but had WFs. DNA abnormalities did not statistically change the long-term malignancy risk in participants with

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HRS nor in those individuals who were lacking both HRS and WFs. Although the presence of ≥ 2 DNA abnormalities in the cohort with worrisome (WF) significantly increased the malignancy risk (relative risk, 5.2; p=0.002) and the absence of all DNA abnormalities significantly decreased risk (relative risk, 0.4; p=0.040), this testing did not provide prospective evidence of impact on clinical outcomes.

In summary, the body of peer-reviewed literature concerning PancraGEN is insufficient to establish the analytic validity, clinical validity, and clinical utility of this test. There is insufficient literature and evidence to demonstrate that the topographic genotyping used in PancraGEN is an effective method to aid in the management of individuals with pancreatic cysts or solid pancreaticobiliary lesions when other testing methods are inconclusive or unsuccessful. There is also a lack of peer-reviewed evidence demonstrating that the use of topographic genotyping in the management of individuals with pancreatic cysts results in improved clinical outcomes.

### Billing/Coding Information

**CPT CODES**

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|---|---|
| **81479** | Unlisted molecular pathology procedure |
| **84999** | Unlisted chemistry procedure |

**HCPCS CODES**

No specific codes identified

**Key References**


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### Revision History

| Revision Date | Summary of Changes |
|---|---|
| 12/23/24 | For Commercial Plan Policy, modified exclusion as follows: “Select Health does NOT cover the PancraGEN molecular diagnostic test for ***routine evaluation*** of pancreatic cysts as it is considered experimental/investigational.” |







Select Health