Medical Policy

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Title: Molecular Testing for the Management of Pancreatic Cysts, Barrett's Esophagus, and Solid Pancreaticobiliary Lesions

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Populations	Interventions	Comparators	Outcomes
Individuals: • With pancreatic cysts who do not have a definitive diagnosis after first-line evaluation	Interventions of interest are: • Standard diagnostic and management practices plus topographic genotyping (PancraGEN molecular testing)	Comparators of interest are: • Standard diagnostic and management practices alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Change in disease status • Morbid events • Quality of life
Individuals: • With Barrett's esophagus	Interventions of interest are: • Standard prognostic techniques plus topographic genotyping (BarreGEN molecular testing)	Comparators of interest are: • Standard prognostic techniques alone	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Change in disease status • Morbid events • Quality of life

Populations	Interventions	Comparators	Outcomes
Individuals: • With solid pancreaticobiliary lesions who do not have a definitive diagnosis after first-line evaluation	Interventions of interest are: • Standard diagnostic and management practices plus topographic genotyping (PancraGEN molecular testing)	Comparators of interest are: • Standard diagnostic and management practices	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Change in disease status • Morbid events • Quality of life

DESCRIPTION

Tests that integrate microscopic analysis with molecular tissue analysis are generally called topographic genotyping. Interpace Diagnostics offers 2 such tests that use the PathFinderTG® platform (PancraGEN®). These molecular tests are intended to be used adjunctively when a definitive pathologic diagnosis cannot be made, because of the inadequate specimen or equivocal histologic or cytologic findings, to inform appropriate surveillance or surgical strategies.

OBJECTIVE

The objective of this evidence review is to determine whether testing using topographic genotyping in addition to standard diagnostic or prognostic practices improves the net health outcome in individuals with pancreatic cysts or solid pancreaticobiliary lesions.

BACKGROUND

Mucinous Neoplasms of the Pancreas

True pancreatic cysts are fluid-filled, cell-lined structures, which are most commonly mucinous cysts (intraductal papillary mucinous neoplasm [IPMN] and mucinous cystic neoplasm), which are associated with future development of pancreatic cancers. Incidence of IPMNs is generally equal between men and women, while mucinous cystic neoplasms occur almost exclusively in women (accounting for about 95% of cases).[1,] Pancreatic cancer arising from IPMNs and mucinous cystic neoplasms account for about 4% of pancreatic malignancies. Although mucinous neoplasms associated with cysts may cause symptoms (e.g. pain, pancreatitis), an important reason that such cysts are followed is the risk of malignancy, which is estimated to range from 0.01% at the time of diagnosis to 15% in resected lesions.[2,]

Management

Given the rare occurrence but the poor prognosis of pancreatic cancer, there is a need to balance potential early detection of malignancies while avoiding unnecessary surgical resection of cysts. Several guidelines address the management of pancreatic cysts, but high-quality evidence to support these guidelines is not generally available. Although recommendations vary, first-line evaluation usually includes an examination of cyst cytopathologic or radiographic findings and cyst fluid carcinoembryonic antigen. In 2012, an international consensus panel published statements on the management of IPMN and mucinous cystic neoplasm of the pancreas.[2,] These statements are referred to as the Fukuoka Consensus Guidelines and were based on a

symposium held in Japan in 2010, which updated a 2006 publication (Sendai Consensus Guidelines) by this same group.[3,] The panel recommended surgical resection for all surgically fit patients with main duct IPMN or mucinous cystic neoplasm. For branch duct IPMN, surgically fit patients with cytology suspicious or positive for malignancy are recommended for surgical resection, but patients without "high-risk stigmata" or "worrisome features" may be observed with surveillance. "High-risk stigmata" are obstructive jaundice in proximal lesions (head of the pancreas); the presence of an enhancing solid component within the cyst; or 10 mm or greater dilation of the main pancreatic duct. "Worrisome features" are pancreatitis; lymphadenopathy; cyst size 3 cm or greater; thickened or enhancing cyst walls on imaging; 5 to 10 mm dilation of the main pancreatic duct; or abrupt change in pancreatic duct caliber with distal atrophy of the pancreas.

The American Gastroenterological Association (2015) published guidelines on the evaluation and management of pancreatic cysts; it recommended patients undergo further evaluation with endoscopic ultrasound-guided fine-needle aspiration only if the cyst has 2 or more worrisome features (size ≥3 cm, a solid component, a dilated main pancreatic duct).[4,] The guidelines also recommended that patients with these "concerning features" confirmed on fine-needle aspiration undergo surgery.

Solid Pancreaticobiliary Lesions

Solid pancreaticobiliary lesions refer to lesions found on the pancreas, gallbladder, or biliary ducts. A solid lesion may be detected as an incidental finding on computed tomography scans performed for another reason, though this occurs rarely. The differential diagnosis of a solid pancreatic mass includes primary exocrine pancreatic cancer, pancreatic neuroendocrine tumor, lymphoma, metastatic cancer, chronic pancreatitis, or autoimmune pancreatitis.

Management

Currently, if a transabdominal ultrasound confirms the presence of a lesion, an abdominal computed tomography scan is performed to confirm the presence of the mass and determine disease extent. If the computed tomography provides enough information to recommend a resection and if the patient is able to undergo the procedure, no further testing is necessary. If the diagnosis remains unclear, additional procedures may be recommended. Symptomatic patients undergo cytology testing. If results from cytology testing are inconclusive, fluorescent in situ hybridization molecular testing of solid pancreaticobiliary lesions is recommended. PancraGEN topographic genotyping is being investigated as either an alternative to or as an adjunct to fluorescent in situ hybridization in the diagnostic confirmation process.

Topographic Genotyping

Topographic genotyping, also called molecular anatomic pathology, integrates microscopic analysis (anatomic pathology) with molecular tissue analysis. Under microscopic examination of tissue and other specimens, areas of interest may be identified and microdissected to increase tumor cell yield for subsequent molecular analysis. Topographic genotyping may permit pathologic diagnosis when first-line analyses are inconclusive.[5,]

RedPath Integrated Pathology (now Interpace Diagnostics) has patented a proprietary platform called PathFinderTG; it provides mutational analyses of patient specimens. The patented technology permits analysis of tissue specimens of any size, "including minute needle biopsy specimens," and any age, "including those stored in paraffin for over 30 years."[6,]

Interpace Diagnostics stopped the acceptance of PancraGEN specimens on February 7, 2025, following the Centers for Medicare & Medicaid Services (CMS) decision to discontinue reimbursement for the test.[7,] Consequently, no specimens or orders for PancraGEN were accepted after May 2, 2025.[8,]

Test	Description	Specimen Types
PathFinderTG Pancreas (now called PancraGEN)	Uses loss of heterozygosity markers, oncogene variants, and DNA content abnormalities to stratify patients according to their risk of progression to cancer	Pancreatobiliary fluid/ERCP brush, pancreatic masses, or pancreatic tissue

ERCP: endoscopic retrograde cholangiopancreatography.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Patented diagnostic tests (e.g. PancraGEN®) are available only through Interpace Diagnostics (formerly RedPath Integrated Pathology) under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

PancraGEN assesses the cumulative DNA mutations in key oncogenes and tumor suppressor genes associated with pancreatic cancer.[9,] Specifically, PancraGEN identifies:

- High levels of intact DNA are associated with actively dividing cells;
- Oncogenes: KRAS and GNAS point mutations;
- Tumor suppressor genes (in parentheses) in the following genomic loci: 3p (VHL, OGG1), 10q (PTEN, MXI1), 17p (TP53), 18q (SMAD4, DCC), 9p (CDKN2A, CDKN2B), 17q (RNF43, NME1), 21q (PSEN2, TFF1), 1p (RUNX3, CMM1, LMYC), 5q (MCC, APC), 22q (NF2).

POLICY

Molecular testing using the PathFinderTG system is considered **experimental / investigational** for all indications including the evaluation of pancreatic cyst fluid, Barrett's esophagus, and solid pancreaticobiliary lesions.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through May 21, 2025.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

When this evidence review was created, it evaluated representative applications of topographic genotyping-pancreatic cysts and gliomas. At present, Interpace Diagnostics offers tests using its technology to evaluate patients with pancreatic cysts and solid pancreaticobiliary lesions, which are the focus of the current review.

PANCREATIC CYSTS

Clinical Context and Test Purpose

The widespread use and increasing sensitivity of computed tomography and magnetic resonance imaging scans have been associated with a marked increase in the finding of incidental pancreatic cysts.[10,11,12,] In individuals without a history of symptoms of pancreatic disease undergoing computed tomography and magnetic resonance imaging, studies have estimated the prevalence of pancreatic cysts as being between 2% and 3%.[11,12,] Although data have suggested the malignant transformation of these cysts is very rare,[13,] due to the potential life-threatening prognosis of pancreatic cancer, an incidental finding can start an aggressive clinical workup.

Many cysts can be followed with imaging surveillance. Recommendations for which cysts should proceed for surgical resection vary. If imaging of the cyst is inconclusive, additional testing of cystic pancreatic lesions is usually performed by endoscopic ultrasound with fine-needle aspiration (EUS-FNA) sampling of the fluid and cyst wall for cytologic examination and analysis. Cytologic examination of these lesions can be difficult or indeterminate due to low cellularity, cellular degeneration, or procedural difficulties. Ancillary tests (e,g,, amylase, lipase,

carcinoembryonic antigen levels) often are performed on cyst fluid to aid in diagnosis and prognosis, but results still may be equivocal.

International consensus has recommended surgical resection for all surgically fit individuals with mucinous cystic neoplasm or main duct intraductal papillary mucinous neoplasm.[2,]This is due to the uncertainty of the natural history of mucinous cystic neoplasm and main duct intraductal papillary mucinous neoplasm and the presumed malignant potential of all types.[3,14,15,] Estimates of morbidity and mortality following resection vary. A technical review by Scheiman et al (2015), conducted for the American Gastroenterological Association, combined estimates into a pooled mortality rate of about 2% and serious complication rate of about 30%.[16,] Therefore, there is a need for more accurate prognosis to optimize detection of malignancy while minimizing unnecessary surgery and treatment.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals for whom there remains clinical uncertainty regarding the malignant potential of a pancreatic cyst after comprehensive first-line evaluation and who are being considered for surgery.

Interventions
The test being considered is PancraGEN topographic genotyping in addition to standard diagnostic or prognostic practices.

PathFinderTG (Interpace Diagnostics) gene variant profiles are intended to inform complex diagnostic dilemmas in patients at risk of cancer. The manufacturer's website states specifically that the PancraGEN technology is intended to be an adjunct to first line testing and suggests that the test is useful in assessing who will benefit most from surveillance and/or surgery.[17,] The clinical purpose of PancraGEN is to allow patients with low-risk cysts to avoid unnecessary surgery or to select patients with malignant lesions for surgery more accurately. PancraGEN would likely be used in conjunction with clinical and radiologic characteristics, along with cyst fluid analysis; therefore, one would expect an incremental benefit to using the test.

As shown in Table 1, the PathFinderTG Pancreas test (now called PancraGEN) combines measures of loss of heterozygosity (LOH) markers, oncogene variants, and DNA content abnormalities to stratify patients according to their risk of progression to cancer. According to Al-Haddad et al (2015), who reported results from a registry established with support from the manufacturer,[18,] the current diagnostic algorithm is as follows in Table 2.

Table 2. Diagnostic Algorithm for PancraGEN

Diagnostic Category	Molecular Criteria[a]	Coexisting Concerning Clinical Features[b]
Benign	DNA lacks molecular criteria	Not considered for this diagnosis
Statistically indolent	DNA meets 1 molecular criterion	None
Statistically higher risk	DNA meets 1 molecular criterion	1 or more
Aggressive	DNA meets at least 2 molecular criteria	Not considered for this diagnosis

Al-Haddad et al (2015).[18,]
[a] Molecular criteria: (1) a single high-clonality variant, (2) elevated level of high-quality DNA, (3) multiple low-clonality

variants; (4) a single low-clonality oncogene variant.
[b] Includes any of the following: cyst size >3 cm, growth rate >3 mm/y, duct dilation >1 cm, carcinoembryonic antigen level >1000 ng/mL, cytologic evidence of high-grade dysplasia.

Comparators
The following tests and practices are currently being used to diagnose pancreatic cysts: standard diagnostic and prognostic techniques, including imaging using magnetic resonance imaging with magnetic resonance cholangiopancreatography, multidetector computed tomography, or intraductal ultrasound, EUS-FNA, cytology, and amylase and carcinoembryonic antigen in cyst fluid. In the absence of definitive malignancy by first-line testing, indications for surgery are frequently based on morphologic features according to 2012 international consensus panel statements for a management of intraductal papillary mucinous neoplasm and mucinous cystic neoplasms.[2,]

Outcomes
The primary outcomes of interest are survival and complications of surgery. Beneficial outcomes resulting from a true-test result are the initiation of appropriate treatment or avoiding unnecessary surgery. Harmful outcomes resulting from a false test result are unnecessary surgery and failing to receive timely appropriate surgery or treatment. The American Gastroenterological Association has recommended surveillance of cysts that do not meet criteria for resection for 5 years.[4,]

Study Selection Criteria
For the evaluation of the clinical validity of the PancraGEN test (including the algorithm), studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the patented PathFinder Pancreas or PancraGEN technology for classifying patients into prognostic categories for malignancy;
- Included a suitable reference standard (long-term follow-up for malignancy; histopathology from surgically resected lesions);
- Patient and sample clinical characteristics were described;
- Patient and sample selection criteria were described.

Numerous studies were excluded from the evaluation of the clinical validity of the PancraGEN test for the following reasons: they assessed components of the test separately for the malignancy outcome, [19,20,21,22,23,24,25,26,27,28,29,30,31,32,] did not include information needed to calculate performance characteristics for the malignancy outcome, [33,] did not describe how the reference standard diagnoses were established,[34,] did not use a suitable reference standard,[35,36,] did not adequately describe the patient characteristics,[21,31,37,] or did not adequately describe patient selection criteria.[20,21,31,33,37,] The following paragraphs describe the selected studies, which included 3 retrospective studies.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Retrospective Studies

Three retrospective studies provide evidence on the clinical validity of topographic genotyping with Pathfinder TG (PancraGEN) tests (Table 3). The largest of these, conducted by Al-Haddad et al (2015)[18,] was an analysis of 492 patients enrolled in the National Pancreatic Cyst Registry (NPCR). Although study investigators reviewed the records of 1862 NPCR patients, the majority of these (n=1372) did not meet study inclusion criteria, primarily due to inadequate duration of follow-up. Investigators assessed the ability of the PathFinderTG and of the 2012 Sendai International Consensus Guideline classification to predict malignancy risk in patients with pancreatic cysts. At median follow-up of 35 months, for patients with benign and statistically indolent diagnoses (range, 23-92 months), 66 (35%) patients were diagnosed with a malignancy. Measures of diagnostic accuracy appear in Table 3. The authors noted that the PathFinderTG diagnostic criteria have evolved and older cases in the registry were recategorized using the new criteria. Of the 492 registry cases included, 468 (95%) had to be recategorized using the current diagnostic categories. A strength of the study was its inclusion of both surgery and surveillance groups. Limitations included the retrospective design, exclusion of 74% of all registry patients due primarily to insufficient follow-up; relatively short follow-up for observing the malignant transformation of benign lesions; and the exclusion of patients classified as malignant by international consensus criteria who would not have undergone PathFinderTG testing. The reclassification of the majority of the PathFinderTG diagnoses due to evolving criteria between 2011 and 2014 also make it questionable whether the older estimates of performance characteristics are relevant. Two other, single-center studies conducted by Winner et al (2015)[38,] and Malhotra et al (2014)[39,] retrospectively analyzed data from patients who were evaluated for pancreatic cysts between 2006 and 2012 and who had surgical resection and molecular analysis with PathFinderTG. Results of these studies are summarized in Table 3.

Table 3. Retrospective Studies of Clinical Validity of PancraGEN

Study	Population	N	Reference Standard	Performance Characteristics (95% CI), %	
				PancraGEN	International Consensus Guideline
Al-Haddad et al (2015)[18,]	• 69% female; race/ethnicity not reported • Patients who had undergone IMP testing prescribed by their physician and for whom clinical outcomes were available with 23-mo FU	492	Long-term FU, surgical pathology	• Sens: 83 (72 to 91) • Spec: 91 (87 to 93) • PPV: 58 (47 to 68) • NPV: 97 (95 to 99)	• Sens: 91 (81 to 97) • Spec: 46 (41 to 51) • PPV: 21 (16 to 26) • NPV: 97 (94 to 99)
Winner et al (2015)[38,]	• 60% female; 85% White (other race/ethnicity not reported)	36	Surgical pathology	• Sens: 67 (31 to 91) • Spec: 81 (61 to 93)	NA

Study	Population	N	Reference Standard	Performance Characteristics (95% CI), %	
	• Patients evaluated for pancreatic cysts, had surgical resection, cyst fluid, and molecular analysis			• PPV: 55 (25 to 82) • NPV: 88 (68 to 97)	
Malhotra et al (2014)[39,]	• Demographic characteristics not reported • Patients with pancreaticobiliary masses with cytologic diagnosis of atypical, negative, or indeterminate and minimum 3-mo FU	26	Surgical pathology or oncology FU report	• Sens: 47 (24 to 71) • Spec: 100 (63 to 100) • PPV: 100 (60 to 100) • NPV: 50 (27 to 73)	NA

CI: confidence interval; FU: follow-up; IMP: integrated molecular pathology; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Tables 4 and 5 display notable gaps identified in each study.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Winner et al (2015)[38,]	4. Patients in study were all scheduled for surgery, while not all patients with pancreatic cysts typically get surgical referrals		2. Comparisons to a reference standard were not made		
Al-Haddad et al (2015)[18,]		2. As the criteria for the test have evolved, older cases in the registry had to be recategorized based on new criteria			
Malhotra et al (2014)[39,]			2. Comparisons to a reference standard were not made	3. Key clinical validity outcomes not reported and calculated by BCBSA	1. Follow-up of 3 mo

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 5. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Winner et al (2015)[38,]		1. No discussion whether cytologists blinded to other test results				
Al-Haddad et al (2015)[18,]					1. High number of samples from registry excluded due to insufficient follow-up (74%)	
Malhotra et al (2014)[39,]		1. No discussion whether cytologists blinded to other test results				1. Small sample size did not allow for significance tests

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

REVIEW OF EVIDENCE

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Direct demonstration of clinical utility would require evidence that
PancraGEN produces incremental improvement in survival (by detecting malignant and potentially malignant cysts) or decreased morbidity of surgery (by avoiding surgery for cysts highly likely benign) when used adjunctively with the current diagnostic and prognostic standards.

No studies assessing clinical utility were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The publication by Al-Haddad et al (2015) from NPCR also assessed evidence of clinical utility by describing how the PancraGEN might provide incremental benefit over consensus guidelines.[18,] In the subset of 289 patients who met consensus criteria for surgery, 229 had a benign outcome. The PancraGEN algorithm correctly classified 193 (84%) of the 229 as benign or statistically indolent. The consensus guidelines classified 203 patients as appropriate for surveillance and 6 of them had a malignant outcome. The PancraGEN correctly categorized 4 of 6 as high risk (see Table 6). The complete cross-classification of the 2 classification strategies by outcomes was not provided.

Using the data from the same NPCR patients included by Al-Haddad et al (2015), Loren et al (2016) published results from 491 patients comparing the association between PancraGEN diagnoses and Sendai and Fukouka consensus guideline recommendations with clinical decisions regarding intervention and surveillance.[40,] Patients were categorized as (1) "low-risk" or "high-risk" using the PancraGEN diagnostic algorithm; (2) meeting "surveillance" criteria or "surgery" criteria using consensus guidelines; and (3) having "benign" or "malignant" outcomes during clinical follow-up as described previously. Additionally, the real-world management decision was categorized as "intervention" if there was a surgical report, surgical pathology, chemotherapy or positive cytology within 12 months of the index EUS-FNA, and as "surveillance" otherwise. Among patients who received surveillance as the real-world decision, 57% were also classified as needing surveillance according to consensus guidelines, and 96% were classified as low risk according to PancraGEN (calculated from data in Table 3). However, among patients who had an intervention as the real-world decision, 81% were classified as candidates for surgery by consensus guidelines, and 40% were classified as high risk by PancraGEN. In univariate logistic regression analyses, the odds ratio for the association between PancraGEN diagnoses and real-world decision was higher (odds ratio, 16.8; 95% CI, 9.0 to 34.4) than the odds for the association between the consensus guidelines recommendations and real-world decision (odds ratio, 5.6; 95% CI, 3.7 to 8.5). In 8 patients, the PancraGEN diagnosis was high risk, and the consensus guideline classification was low risk. In 7 of these cases, the patient received an intervention resulting in the discovery of an additional 4 malignancies that would have been missed using the consensus guideline classification alone, and in the remaining case the patient

underwent surveillance and did not develop a malignancy. In 202 patients, the PancraGEN diagnosis was low risk, and the consensus guideline classification was high risk. In 90 of these 202, patients had an intervention, and 8 additional malignancies were detected. In 112 of these 202, patients received surveillance, and 1 additional malignancy occurred in the surveillance group.[40,] The cross-tabulation of PancraGEN and international consensus classification by outcome was not shown in Loren et al (2016) but was derived by BCBSA from tables and text and is displayed in Table 6. This study demonstrated that results from PancraGEN testing are associated with real-world decisions, although other factors (e.g., physician judgment, patient preferences) could have affected these decisions.

Table 6. PancraGEN and International Consensus Classifications by Outcome (N=491)

Malignant Outcome			**Benign Outcome**		
Consensus Classification	PancraGEN Classification		Consensus Classification	PancraGEN Classification	
	Low Risk	High Risk		Low Risk	High Risk
Surveillance	2	4	Surveillance	193	4
Surgery	9	50	Surgery	193	36

Kowalski et al (2016) reported on an analysis of false-negatives from the same 492 records from the NPCR.[41,] Of the 6 cysts found false-negative using consensus classification, 5 cysts were 2 cm or less (the remaining case did not have data on cyst size) and 1 reported symptoms (obstructive jaundice). Of the 11 cases that were false-negative according to PancraGEN, 10 were reported to have EUS-FNA sampling limitations, 1 had a family history of pancreatic cancer, 4 reported symptoms (including pancreatitis, steatorrhea, nausea, bloating, and/or upper abdominal discomfort), and cysts sizes ranged from 0.7 to 6 cm for the 6 in which size was reported.

The best strategy for combining the results of PancraGEN with current diagnostic guidelines is not clear. There is some suggestion that PancraGEN might appropriately classify some cases misclassified by current consensus guidelines, but the sample sizes in the cases where the PancraGEN and consensus guidelines disagree are small, limiting confidence in these results.

Section Summary: Pancreatic Cysts

The evidence for the clinical validity of PancraGEN consists of several retrospective studies. Most evaluated performance characteristics of PancraGEN for classifying pancreatic cysts according to the risk of malignancy without comparison to current diagnostic algorithms. The best evidence regarding incremental clinical validity comes from the report from the NPCR, which compared PancraGEN performance characteristics with current international consensus guidelines and found that PancraGEN has slightly lower sensitivity (83% vs. 91%), similar NPV (97% vs. 97%), but better specificity (91% vs. 46%) and PPV (58% vs. 21%) than the consensus guidelines. The registry study included a very select group of patients, only a small fraction of all enrolled patients, and used a retrospective design. Longer follow-up including more of the registry patients is needed. The manufacturer has indicated the technology is meant as an adjunct to first-line testing, but no algorithm for combining PancraGEN with consensus guidelines for decision making has been proposed, and the data reporting outcomes in patients where the PancraGEN and consensus guideline diagnoses disagreed was limited. There are no prospective studies with concurrent control demonstrating that PancraGEN can affect patient-relevant outcomes (e.g., survival, time to tumor recurrence, reduction in unnecessary surgeries). The evidence reviewed does not demonstrate that PathFinderTG has incremental clinical value in the diagnosis or prognosis of pancreatic cysts and associated cancer.

SOLID PANCREATICOBILIARY LESIONS

Clinical Context and Test Purpose

Pancreatic cancer is usually diagnosed in advanced stages when effective treatment options are limited. Currently, symptomatic individuals with solid pancreaticobiliary lesions undergo cytology testing. If results from cytology testing are inconclusive, fluorescent in situ hybridization (FISH) molecular testing of solid pancreaticobiliary lesions is recommended. PancraGEN topographic genotyping is being investigated as either an alternative to or an adjunct to FISH in the diagnosis confirmation process.

The purpose of PancraGEN topographic genotyping in individuals who are symptomatic with high suspicion of cholangiocarcinoma or pancreatic cancer with inconclusive cytology testing results is to potentially confirm a diagnosis, which would inform patient management decisions.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is symptomatic individuals with high suspicion of cholangiocarcinoma or pancreatic cancer based on endoscopic imaging showing bile duct obstruction or solid mass who receive inconclusive cytology testing results.

Interventions

The test being considered is PancraGEN topographic genotyping, as either an alternative test or adjunct test to FISH molecular testing of solid pancreaticobiliary lesions. FISH is currently considered second-line to standard routine cytology testing.

Comparators

The following tests are currently being used to diagnose cholangiocarcinoma or pancreatic cancer: cytology testing with and without standard molecular FISH testing.

Outcomes

The primary outcome of interest is overall survival. Beneficial outcomes resulting from a true test result are the initiation of appropriate treatment or avoidance of unnecessary surgery. Harmful outcomes resulting from a false test result are unnecessary surgery or failing to receive timely appropriate surgery or chemotherapy. Cytology results with FISH and/or topographic genotyping may be available within a week. The long-term follow-up to monitor overall survival would require years.

Study Selection Criteria

For the evaluation of the clinical validity of the PancraGEN test (including the algorithm), studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the patented PathFinder Pancreas or PancraGEN technology for classifying patients into prognostic categories for malignancy;
- Included a suitable reference standard (long-term follow-up for malignancy; histopathology from surgically resected lesions);
- Patient and sample clinical characteristics were described;
- Patient and sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Prospective and Retrospective Studies

Three studies assessed the clinical validity of PancraGEN patients with biliary structures or solid pancreaticobiliary lesions (Table 7).[42,43,44,] The populations of 2 of the studies were patients being evaluated for biliary strictures. Biliary strictures may be caused by solid pancreaticobiliary lesions, but there are other potential causes such as trauma to the abdomen, pancreatitis, or bile duct stones. The authors did not specify what proportion of the population of patients with biliary strictures had solid pancreaticobiliary lesions.

Compared to cytology alone, the use of cytology plus fluorescence in situ hybridization (FISH) plus mutation profiling (MP) increased sensitivity significantly (Table 8). The incremental value of using cytology plus FISH plus MP over cytology plus FISH is unclear.

Table 7. Characteristics of Clinical Validity Studies Assessing PancraGEN

Study	Design	Population	N	Diagnostic Test	Comparator	Follow-Up, mo
Khosravi et al (2018)[42,]	Retrospective consecutive sample	• 56% female; race/ethnicity not reported • Patients who had EUS-FNA and/or ERCP for solid pancreatic lesions indeterminate by cytology	232	Cytology plus MP (PancraGEN)	Cytology alone	12
Kushnir et al (2018)[43,]	Prospective consecutive sample	• 32% female; 89% White, 10% Black, 1% Asian • Patients who underwent ERCP for evaluation of biliary strictures	100	Cytology plus MP (PancraGEN)	Cytology alone; cytology plus FISH; cytology plus FISH and MP	12
Gonda et al (2017)[44,]	Prospective consecutive sample	• 43% female; race/ethnicity not reported • Patients who underwent ERCP for evaluation of biliary strictures, with 2 brushings (1 for cytology, 1 for FISH)	100	Cytology plus MP (PathFinderTG-Biliary)	Cytology alone; cytology plus FISH; cytology plus FISH and MP	12

ERCP: endoscopic retrograde cholangiopancreatography; EUS-FNA: endoscopic ultrasound fine needle aspiration; FISH: fluorescence in situ hybridization; MP: mutation profiling.

Table 8. Diagnostic Accuracy Results of Clinical Validity Studies Assessing PancraGEN

Study	Diagnostic Test	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)
Khosravi et al (2018)[42,]	Cytology alone	41 (27 to 56)	97 (94 to 99)	80 (59 to 93)	86 (81 to 90)
	MP alone	46 (27 to 67)	94 (87 to 98)	71 (48 to 86)	85 (77 to 92)
	Cytology plus MP	67 (53 to 80)	95 (90 to 97)	81 (65 to 91)	92 (81 to 95)
Kushnir et al (2018)[43,]	Cytology alone	26 (NR)	100 (NR)	NR	NR
	Cytology plus FISH	44 (NR); p<.001	100 (NR)	NR	NR
	Cytology plus MP	56 (NR); p<.001	97 (NR)	NR	NR
	Cytology plus FISH plus MP	66 (NR); p<.001[a]	97 (NR)	NR	NR
Gonda et al (2017)[44,]	Cytology alone	32 (18 to 48)	100 (91 to 100)	NR	NR
	Cytology plus FISH	51 (35 to 67)	100 (91 to 100)	NR	NR
	Cytology plus MP	51 (35 to 67)	100 (91 to 100)	NR	NR
	Cytology plus FISH plus MP	73 (59 to 86)	100 (91 to 100)	NR	NR

[a] p-value compared to cytology alone
CI: confidence interval; FISH: fluorescence in situ hybridization; MP: mutation profiling; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.

Tables 9 and 10 display notable limitations identified in each study.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Khosravi et al (2018)[42,]					
Kushnir et al (2018)[43,]	4. Participants had "biliary strictures," which may include conditions other than solid pancreatic lesions			3. Positive and negative predictive values not calculated	

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Gonda et al (2017)[44,]	4. Participants had "biliary strictures," which may include conditions other than solid pancreatic lesions			3. Positive and negative predictive values not calculated	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 10. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Khosravi et al (2018)[42,]		1. No discussion whether cytologists blinded to other test results				
Kushnir et al (2018)[43,]		1. No discussion whether cytologists blinded to other test results				1. Confidence intervals not reported
Gonda et al (2017)[44,]		1. No discussion whether cytologists blinded to other test results				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

REVIEW OF EVIDENCE

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized controlled trials were identified that evaluated the clinical utility of PancraGEN for the classification of solid pancreaticobiliary lesions.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

An incremental benefit was seen in increased sensitivity when FISH plus MP were added to cytology alone. The sensitivity with cytology plus FISH plus MP averaged around 70%.

Whether the tradeoff between avoiding biopsies and the potential for missed cancers is worthwhile depends, in part, on patient and physician preferences. In the context of pancreaticobiliary cancers, overall survival depends on detection of these cancers at early, more treatable stages.

While there is indirect evidence that cytology plus FISH plus MP may predict more solid pancreaticobiliary lesions compared with cytology alone, the sensitivity is not sufficiently high enough to identify which patients can forego biopsy. Missing a solid pancreaticobiliary lesion diagnosis at a rate of 30%, is not inconsequential. A delay in diagnosis would delay potential treatment (surgery and/or chemotherapy).

Section Summary: Solid Pancreaticobiliary Lesions
The evidence for the clinical validity of using PancraGEN to evaluate solid pancreaticobiliary lesions consists of several retrospective studies. One study evaluated the performance characteristics of PancraGEN for classifying solid pancreatic lesions while the other 2 evaluated the classification of biliary strictures. Biliary strictures may be caused by solid pancreaticobiliary lesions but may have other causes. The authors of the studies did not specify what proportion of patients with biliary stricture had solid pancreaticobiliary lesions. Compared to cytology alone, the use of cytology plus FISH plus PancraGEN increased sensitivity significantly. The incremental value of using cytology plus FISH plus PancraGEN over cytology plus FISH is unclear. The manufacturer has indicated that the technology is meant as an adjunct to first-line testing, but no algorithm for combining PancraGEN with consensus guidelines for decision making has been proposed, nor has first-line testing been defined as cytology alone or cytology plus FISH. There are no prospective studies demonstrating that PancraGEN can affect patient-relevant outcomes (eg, survival, time to tumor recurrence, reduction in unnecessary surgeries). The

evidence reviewed does not demonstrate that PathFinderTG has incremental clinical value for the diagnosis of solid pancreatic lesions and associated cancer.

Whether the tradeoff between avoiding biopsies and the potential for missed cancers is worthwhile depends, in part, on patient and physician preferences. In the context of pancreaticobiliary cancers, overall survival depends on detection of these cancers at early, more treatable stages. While there is indirect evidence that cytology plus FISH plus MP may predict more solid pancreaticobiliary lesions compared with cytology alone, the sensitivity is not sufficiently high enough to identify which patients can forego biopsy. Missing a solid pancreaticobiliary lesion diagnosis at a rate of 30%, is not inconsequential. A delay in diagnosis would delay potential treatment (surgery and/or chemotherapy).

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology

In 2018, the American College of Gastroenterology published guidelines on the diagnosis and management of pancreatic cysts.[45,] The guidelines stated that the evidence for the use of molecular biomarkers for identifying high-grade dysplasia or pancreatic cancer is insufficient to recommend their routine use. However, molecular markers may help identify intraductal papillary mucinous neoplasms and mucinous cystic neoplasms in cases with an unclear diagnosis and if results are likely to change the management (conditional recommendation; very low quality evidence).

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma (v.2.2025) make the following recommendation: "Tumor/somatic molecular profiling, preferably using a next-generation sequencing (NGS) assay, is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify clinically actionable and/or emerging alterations. These alterations include, but are not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), amplifications (HER2), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) using comprehensive genomic profiling via an FDA-approved and/or validated NGS-based assay, and HER overexpression via IHC ± FISH. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible.".[46,]

National Comprehensive Cancer Network (NCCN) guidelines for biliary tract cancers (v.1.2025) does not make any specific recommendations regarding molecular testing for pancreaticobiliary cancers.[47,]

U.S. Preventative Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might impact this policy are listed in Table 11.

Table 11. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03855800	Molecular Detection of Advanced Neoplasia in Pancreatic Cysts (IN-CYST)	800	Dec 2030
NCT02110498	Early Detection of Pancreatic Cystic Neoplasms	3000	Mar 2025
Unpublished			
NCT01202136	The Clinical, Radiologic, Pathologic and Molecular Marker Characteristics of Pancreatic Cysts Study (PCyst)	450	Sept 2019 (completed)

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
84999	Unlisted chemistry procedure
89240	Unlisted miscellaneous pathology test

REVISIONS	
10-01-2015	Policy posted to the bcbsks.com web site on 09-01-2015.
08-17-2016	Updated Description section.
	In Policy section: ▪ Removed ", suspected or known gliomas," to read, "Molecular testing using the PathFinderTG® system is considered experimental / investigational for all indications including the evaluation of pancreatic cyst fluid and Barrett's esophagus." ▪ Added Policy Guidelines regarding genetic counseling.
	Updated Rationale section.
	Updated References section.
08-15-2017	Updated Description section.
	In Policy section: ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.
	Updated Appendix section.
10-25-2017	In Coding section: ▪ Added CPT code: 81479.
12-20-2018	Policy published to the bcbsks.com website on 11-20-2018 with an effective date of 12-20-2018.
	Policy title changed from "PathFinderTG Molecular Testing"
	Updated Description section.
	In Policy section: ▪ Added "solid pancreaticobiliary lesions" to read, "Molecular testing using the PathFinderTG system is considered experimental / investigational for all indications including the evaluation of pancreatic cyst fluid, Barrett's esophagus, or solid pancreaticobiliary lesions."
	Updated Rationale section.
	In Coding section: ▪ Added coding bullet.
	Updated References section.
	Removed Appendix section.
08-28-2019	Updated Description section.

REVISIONS	
	Updated Rationale section.
	Updated References section.
10-01-2019	In Coding section: ▪ Added PLA code: 0108U.
05-14-2021	Added "and Solid Pancreaticobiliary Lesions" to the Title
	Updated Description section.
	Updated Rationale section.
	In Coding section: • Removed CPT codes 84999 and 0108U
	Updated References section.
09-17-2021	Updated Rationale section.
	Updated References section.
09-13-2022	Updated Description Section
	Update Rationale Section
	Updated Coding Section ▪ Removed Coding Bullet o The suggested CPT code for this test is: 84999.
	Updated References Section
09-12-2023	Updated Description Section
	Update Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnoses Box
	Updated References Section
12-03-2024	Updated Description Section
	Update Rationale Section
	Updated References Section
08-26-2025	Updated Description Section
	Update Rationale Section
	Updated References Section

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