Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 5/1/22**
(See policy history boxes for previous effective dates)

Title: Genetic Testing- Molecular Testing for the Diagnosis and Management of Pancreatic Cysts, Barrett Esophagus, and Solid Pancreaticobiliary Lesions (e.g., PathFinderTG®, PancraGEN, BarreGEN)

Description/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 [MCN]), which are associated with future development of pancreatic cancers. 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.

Management

Given the rare occurrence but 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 examination of cyst cytopathologic or radiographic findings and cyst fluid carcinoembryonic antigen (CEA). In 2012, an international consensus panel published statements for the management of IPMN and MCN of the pancreas.[1] These statements are referred to as the Fukouka Consensus Guidelines and were based on a symposium held in Japan in 2010 and updated a 2006 publication (Sendai Consensus Guidelines) by this same group.[2] The panel recommended surgical resection for all surgically fit patients with main duct IPMN or MCN. 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); 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.

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

BARRETT ESOPHAGUS

Barrett esophagus refers to the replacement of normal esophageal epithelial layer with metaplastic columnar cells in response to chronic acid exposure from gastroesophageal reflux disease (GERD). The metaplastic columnar epithelium is a precursor to esophageal adenocarcinoma (EAC). These tumors frequently spread before symptoms are present so detection at an early stage might be beneficial.

Management

Surveillance for EAC is recommended for those diagnosed with Barrett esophagus.[4] However, there are few data to guide recommendations about management and surveillance, and many issues are controversial. In 2015 guidelines from the American College of Gastroenterology (ACG) and a consensus statement from an international group of experts (Benign Barrett's and CAncer Taskforce [BOB CAT]) regarding management of Barrett esophagus were published.[4] ACG recommendations for surveillance are stratified by presence of dysplasia. When no dysplasia is detected, ACG reports the estimated risk of progression to cancer for patients ranges from 0.2% to 0.5% per year and ACG recommends endoscopic surveillance every 3 to 5 years. For low-grade dysplasia, the estimated risk of progression is about 0.7% per year and ACG recommends endoscopic therapy or surveillance every 12 months. For high-grade dysplasia, the estimated risk of progression is about 7% per year and ACG recommends endoscopic therapy.[5] The BOB CAT consensus group did not endorse routine surveillance for people with no dysplasia and was unable to agree on surveillance intervals for low-grade dysplasia.[4]

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 (TG), 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. TG may permit pathologic diagnosis when first-line analyses are inconclusive.[6]

RedPath Integrated Pathology (now Interpace Diagnostics) has patented a proprietary platform, called PathFinderTG®, to provide 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."[7] RedPath currently offers 5 PathFinderTG® tests (listed and briefly described in Table 1). Interpace currently describes, in detail, one PathFinderTG test called PancraGEN on its website and describes another PathFinder test called BarreGEN™ as "in the pipeline" (listed and briefly described in Table 1).[8] As stated on the company website, PancraGEN integrates molecular analyses with first-line results (when these are inconclusive) and pathologist interpretation.[9] The manufacturer calls this technique integrated molecular pathology. Test performance information is not provided on the website.

Table 1. PathFinderTG Tests[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
PathFinderTG Barrett (now called BarreGen)	Measures the presence and extent of genomic instability and integrates those results with histology	Esophageal tissue

ERCP: endoscopic retrograde cholangiopancreatography

Regulatory Status:

These patented diagnostic tests are available only through RedPath Integrated Pathology (Pittsburgh, PA). The PathFinderTG® Molecular Test is not subject to review by the U.S. Food and Drug Administration (FDA) because it is a laboratory-developed test (LDT) conducted only at RedPath Integrated Pathology's licensed laboratory. Laboratories performing LDTs must be licensed for high complexity testing under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). RedPath is licensed under CLIA.

Medical Policy Statement

Molecular testing using the PathFinder TG® System (e.g., PancraGEN and BarreGEN) is experimental/investigational for all indications including the evaluation of pancreatic cyst fluid, Barrett esophagus, and solid pancreaticobiliary lesions. The impact of this technology on health outcomes compared with existing alternatives (i.e., incremental value) is not known.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

84999 89240

Rationale

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 3 representative applications of topographic genotyping—pancreatic cysts, gliomas, and Barrett esophagus. At present, Interpace Diagnostics offers tests using its technology to evaluate patients with pancreatic cysts, Barrett esophagus, 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 (CT) and magnetic resonance imaging scans have been associated with marked increase in the finding of incidental pancreatic cysts.[10-12] In patients without history of symptoms of pancreatic disease undergoing CT and magnetic resonance imaging, studies have estimated the prevalence of pancreatic cysts as being between 2% and 3%.[11-12] Although data have suggested that 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 patients with mucinous cystic neoplasm or main duct intraductal papillary mucinous neoplasm.[1] 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.[2,14,15] Estimates of morbidity and mortality following resection vary. The 2015 American Gastroenterological Association technical review 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 question addressed in this evidence review is: Does testing using PancraGEN topographic genotyping in addition to standard diagnostic or prognostic practices improve the net health outcome in individuals with pancreatic cysts?

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is patients 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 relevant intervention of interest is PancraGEN topographic genotyping in addition to standard diagnostic or prognostic practices.

PathFinderTG® (Interpace Diagnostics) mutational profiles in an attempt to help physicians resolve complex diagnostic dilemmas in patients who are 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 relevant comparators of interest are standard diagnostic and prognostic techniques, including imaging using magnetic resonance imaging with magnetic resonance cholangiopancreatography, multidetector CT, 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 the management of intraductal papillary mucinous neoplasm and mucinous cystic neoplasm.[1]

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.[3]

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; and
- Patient and sample selection criteria were described.

Several 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,[19-32] 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 1 systematic review and 3 retrospective studies.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Systematic Reviews

A systematic review of LOH-based topographic genotyping with PathFinder^{TG} was prepared by Trikalinos et al (2010) for the Agency for Healthcare Research and Quality technology assessment program.[6] Key questions addressed published evidence on analytic test performance, diagnostic ability, and clinical validity of the test, and what evidence compared the PathFinder^{TG} test with conventional pathology. Reviewers summarized 3 publications relating to diagnostic ability and clinical validity for pancreatic and biliary tree tumors,[20,21,38] but did not perform meta-analyses of performance characteristics. Reviewers concluded that eligible studies on the diagnostic and prognostic ability of the test were small in sample size and had overt methodologic limitations, including retrospective assessment. Reviewers pointed out that studies did not provide important information on patient selection, patient characteristics, treatments received, clinical end point definitions, justification of sample size, selection of test cut points, and selection among various statistical models. Additionally, reviewers noted that there were strong indications that the selection of certain test cut points was determined post hoc, in that cutoffs varied widely across studies and were not validated in an external population.

Table 3 describes the included retrospective studies on clinical validity. A summary paragraph of each study follows the table.

Table 3. Retrospective Studies of Clinical Validity of PancraGEN

Study	Population	Reference Standard	Performance Characteristics for PancraGEN (95% CI)	Performance Characteristics for Comparator (95% CI)
Malhotra et al (2014)[40]	26 patients with pancreaticobiliary masses with cytologic diagnosis of atypical, negative, or indeterminate and	Surgical pathology or oncology FU report	Sensitivity: 47 (24 to 71) Specificity: 100 (63 to 100) PPV: 100 (60 to 100) NPV: 50 (27 to 73)	NA

	minimum 3-mo FU			
Winner et al (2015)[39]	36 patients evaluated for pancreatic cysts, had surgical resection, cyst fluid, and molecular analysis	Surgical pathology	Sensitivity: 67 (31 to 91) Specificity: 81 (61 to 93) PPV: 55 (25 to 82) NPV: 88 (68 to 97)	NA
Al-Haddad et al (2015)[18]	492 patients who had undergone IMP testing prescribed by their physician and for whom clinical outcomes were available with 23-mo FU	Long-term FU, surgical pathology	**PancraGEN** Sensitivity: 83 (72 to 91) Specificity: 91 (87 to 93) PPV: 58 (47 to 68) NPV: 97 (95 to 99)	**Consensus Guidelines** Sensitivity: 91 (81 to 97) Specificity: 46 (41 to 51) PPV: 21 (16 to 26) NPV: 97 (94 to 99)

CI: confidence interval; FU: follow-up; IMP: integrated molecular pathology; N/A: not applicable; NPV: negative predictive value; PPV: positive predictive value.

In 2015, Winner et al published a retrospective analysis of prospectively collected data from 40 patients that were evaluated for pancreatic cysts between 2006 and 2012 who had surgical resection and cyst fluid molecular analysis with PathFinder.[39] The authors reported that the population tended to be low or intermediate risk according to Sendai international consensus criteria for surgical resection. Surgical pathology was the reference standard. The molecular results were classified as “favor benign” or “favor aggressive” based on “clinical impression, fluid cytology, CEA and amylase results as well as the molecular cyst fluid analysis and adjunct tests.” It is not clear whether these were the diagnosis classifications provided on the PathFinder reports. Results are reported for 36 cysts (the reasons for 4 exclusions are not given). PathFinder correctly classified 6 of the 9 malignant cysts as “favor aggressive” (sensitivity, 67%, 95% CI, 31%, 91%) and correctly classified 22 of 27 benign cysts as “favor benign” (specificity, 81%, 95% CI, 61% to 93%). The positive predictive value (PPV) was 55% (95% CI, 25% to 82%) and the negative predictive value (NPV) was 88% (95% CI, 68% to 97%). Confidence intervals were calculated from the data provided.

In 2011, RedPath Integrated Pathology established the National Pancreatic Cyst Registry,[41] and in 2015, published results of 492 (26%) of 1864 registered patients.[18] The registry website describes the registry as a prospective study “to evaluate the performance characteristics and clinical utility of integrated molecular pathology and determine the predictive value of both traditional first-line tests and integrated molecular pathology.” Ten academic medical centers and community-based practices registered patients who had pancreatic cysts, underwent PathFinder^{TG} testing, and were followed for development of malignancy. Benign outcomes included benign surgical pathology results, low- or intermediate-grade dysplasia, resolution of cyst, or clinical follow-up by imaging for a minimum of 23 months without evidence of malignant outcome; malignant outcomes were determined by surgical pathology diagnosis of high-grade dysplasia, carcinoma in situ, or adenocarcinoma, newly diagnosed malignant cytology results, clinically confirmed pancreatic cancer in patient records, or death attributed to pancreatic cancer. Investigators compared the diagnostic performance of PathFinder^{TG} to that of an international consensus classification scheme.[1] Both classification schemes categorize patients with pancreatic cysts as high or low risk for malignancy; those considered high risk undergo surgical resection and those considered low risk may elect observation with surveillance. 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 malignancy. Sensitivity, specificity, PPV, and NPV were 83% (95% CI, 72% to 91%), 91% (95% CI, 87% to 93%), 58% (95% CI, 47% to 68%), and 97% (95% CI, 95% to 99%) for

PathFinder^{TG} versus 91% (95% CI, 81% to 97%, p=0.17 PathFinder vs. consensus), 46% (95% CI, 41% to 51%, p<0.001), 21% (95% CI, 16% to 26%, p<0.001), and 97% (95% CI, 94% to 99%, p=0.88) for international consensus classification. Accuracy was 90% (95% CI, 87% to 92%) for PathFinder^{TG} versus 52% (95% CI, 48% to 57%) for the international consensus classification. The negative likelihood ratio was very similar for PancraGEN (0.2; 95% CI, 0.1 to 0.3) and the international consensus classification (0.2; 95% CI, 0.1 to 0.4). However, the positive likelihood ratio was much higher for PancraGEN (8.9; 95% CI, 6.5 to 12.2) than for the international consensus classification (1.7; 95% CI, 1.5 to 1.9). The authors noted that the PathFinder^{TG} diagnostic criteria have evolved over time 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 is the inclusion of both surgery and surveillance groups. Limitations include the retrospective design, resulting in the exclusion of 74% of all registry patients due primarily to insufficient follow-up; relatively short follow-up for observing malignant transformation of benign lesions; and the exclusion of patients classified as malignant by international consensus criteria who would not have undergone PathFinder^{TG} testing. The reclassification of the majority of the PathFinder^{TG} diagnoses due to evolving criteria between 2011 and 2014 also make it questionable whether the older estimates of performance characteristics are relevant. Because of these limitations, the evidence is not sufficient to draw conclusions on clinical validity.

Malhotra et al (2014) at RedPath retrospectively evaluated 30 patients who presented with pancreaticobiliary masses and had a minimum follow-up of 3 months.[40] Cytology correctly diagnosed 4 of 21 malignant cases (sensitivity, 19%), and identified 7 of 9 patients with nonaggressive disease (specificity, 78%). Only 26 patients with a cytologic diagnosis of atypical, negative, or indeterminate underwent PathFinder^{TG} mutational profiling, precluding assessment of diagnostic performance. PathFinder^{TG} correctly diagnosed 8 of 17 malignant cases (sensitivity, 47%) and identified all 9 patients with nonaggressive disease (specificity, 100%). Although the combination of positive cytology and positive PathFinder^{TG} results improved sensitivity to 57% (12/21), 9 malignant cases were missed by both tests.

The purpose of the limitations tables (see Tables 4 and 5) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 4. Relevance Study Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Winner et al (2015)[39]	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)[40]		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 evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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)[39]	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)[40]	1.No discussion whether cytologists blinded to other test results					1.Small sample size did not allow for significance tests

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., 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.

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.

The Agency for Healthcare Research and Quality systematic review conducted by Trikalinos et al (2010) concluded that there were no studies at that time directly measuring whether using LOH-based topographic genotyping with PathFinder^{TG} improved patient-relevant clinical outcomes.[6] No studies assessing clinical utility published since 2010 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.

Das et al published a simulation study in 2015 comparing 4 management strategies in a hypothetical cohort of 1000 asymptomatic patients with a 3-cm pancreatic cyst.[42] The first strategy (watch and wait) used cross-sectional imaging and surgical consultation for resection only if symptoms or high-risk morphologic features developed. The second strategy (resect if operable) referred all patients for surgical consultation for cyst resection, and operability was determined according to a surgical risk score. In the third strategy (standard of care), hypothetical patients had cross-sectional imaging and EUS- FNA; mucinous cysts were referred for surgical resection and non-mucinous cysts were followed with periodic imaging. The fourth strategy (standard of care plus integrated molecular pathology) was the same as strategy 3 but also included molecular testing using PathFinder^{TG}. The strategies were compared using a linear decision tree terminating in a Markov model. The estimates for the model variables were derived from published information or expert opinion. Specifically, the performance characteristics of the PathFinder^{TG} assay used in strategy 4 were estimated using data from a literature search covering the years 1977 to 2012. Strategy 4 resulted in the highest estimated quality-adjusted life years (QALYs) of the 4 strategies in the base case (10.36 in strategy 1; 9.95 in strategy 2; 11.22 in strategy 3; 12.33 in strategy 4) and for most of the sensitivity analyses. Confidence intervals were not reported for the QALY estimates. The quality of the data behind many of the model assumptions was low, including the assumptions about the PathFinder^{TG} performance characteristics. Given the uncertainty with the model assumptions, the relevance of the estimates from this simulation is unclear.

The 2015 publication by Al-Haddad et al from the National Pancreatic Cyst Registry also assessed evidence of clinical utility by describing how the PancraGEN might provide incremental benefit over consensus guidelines.[18] In 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 same subset of 491 patients described in the previous section from the National Pancreatic Cyst Registry, Loren et al published results in 2016 comparing the association between PancraGEN diagnoses and Sendai and Fukouka consensus guideline recommendations with clinical decisions regarding intervention and surveillance.[43] Patients were categorized as (1) "low-risk" or "high-risk" using the Interspace algorithm for PancraGEN diagnoses; (2) meeting "surveillance" criteria or "surgery" criteria using consensus guidelines; and (3) having "benign" or "malignant" outcomes during clinical follow-up as described previously. In addition, 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 actually 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 (OR) for the association between PancraGEN diagnoses and real-world decision was higher (OR=16.8; 95% CI, 9.0 to 34.4) than the OR for the association between the consensus guidelines recommendations versus real-world decision (OR=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 actually 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 1 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 actually 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.[43] 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.[44] 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 one reported symptoms (obstructive jaundice). Of the 11 cases that were false-negative according to PancraGEN, 10 were reported to have EUS-FNA sampling limitations, one 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 for 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 of incremental clinical validity comes from the report from the National Pancreatic Cyst Registry which compared PancraGEN performance characteristics to 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%) compared to the consensus guidelines. The registry study included a very select group of patients, only a small fraction of the enrolled patients, and used a retrospective design. Longer follow-up including more of the registry patients is needed. 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, and the data reporting outcomes in patients where the PancraGEN and consensus guideline diagnoses disagreed is limited. There are no prospective studies with a 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 PathFinder^{TG} has incremental clinical value for diagnosis or prognosis of pancreatic cysts and associated cancer.

BARRETT ESOPHAGUS

Clinical Context and Test Purpose
The American Gastroenterological Association (AGA) defines Barrett esophagus as replacement of normal epithelium at the distal esophagus by intestinal metaplasia, which predisposes to malignancy.[45] Although grading of dysplasia in mucosal biopsies is the current standard for assessing risk of malignant transformation, esophageal inflammation may mimic or mask dysplasia and interobserver variability may yield inconsistent risk classifications.[46] Additional prognostic information therefore may be potentially useful.

The Interpace website describes BarreGEN as a molecular diagnostic test to “determine the risk of progressing to esophageal cancer in patients with Barrett’s Esophagus.”[3]

The question addressed in this evidence review is: Does testing using BarreGEN topographic genotyping in addition to standard prognostic practices improve the net health outcome in individuals with Barrett esophagus?

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is patients with Barrett esophagus. It is unclear what other clinical characteristics would identify candidates for BarreGEN or what the previous testing is appropriate before BarreGEN.

Interventions
The relevant intervention of interest is BarreGEN topographic genotyping in addition to standard prognostic practices.

The Interpace website describes BarreGEN as a molecular diagnostic test to "determine the risk of progressing to esophageal cancer in patients with Barrett's Esophagus."[8]

Comparators
The relevant comparators of interest are standard prognostic techniques generally include grading of dysplasia from endoscopy with biopsy.

Outcomes
Outcomes of interest are survival and conversion to esophageal cancer. It is not clear how the test would fit into the diagnostic pathway and effect treatment or surveillance recommendations therefore complete specification of other important outcomes is not possible. Because it is not yet clear how this test would be used in practice, follow-up time for outcomes is unclear.

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

- Reported on the accuracy of the patented PathFinder Barrett Esophagus or BarreGEN 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; and
- Patient and sample selection criteria were described.

Two studies were excluded from the evaluation of the clinical validity of the BarreGEN test because it was not clear whether the authors used the marketed version of the BarreGEN test.[47,48]

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Systematic Reviews
The Agency for Healthcare Research and Quality review conducted by Trikalinos et al (2010), which assessed LOH-based topographic genotyping with PathFinder^{TG}, did not find any publications of the PathFinder^{TG} technology evaluating diagnostic ability, clinical validity or clinical utility for Barrett esophagus.[6]

Section Summary: Clinically Valid
Evidence for the clinical validity of BarreGEN is limited, consisting of a single systematic review that did not identify relevant studies. Two observational studies were excluded based on BCBSA selection criteria because it was unclear whether the specific test used was BarreGEN.

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.

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 studies assessing the clinical utility of BarreGEN in this population were found.

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.

Because evidence for the clinical validity of BarreGEN is lacking, a chain of evidence that would support clinical utility cannot be constructed.

Section Summary: Barrett Esophagus
There is limited evidence evaluating the clinical validity of the BarreGEN test for assessing Barrett esophagus. The evidence reviewed does not demonstrate that BarreGEN testing for prognosis of Barrett esophagus adds incremental value to current prognostic assessments.

SOLID PANCREATICOBILIARY LESIONS

Clinical Context and Test Purpose
Pancreatic cancer is usually diagnosed in advanced stages when effective treatment options are limited. Currently, symptomatic patients 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 patients 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 question addressed in this evidence review is: Does testing using PancraGEN topographic genotyping in addition to standard diagnostic practices improve the net health outcome in individuals with solid pancreaticobiliary lesions?

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is symptomatic patients 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.

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; and
- Patient and sample selection criteria were described.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Prospective and Retrospective Studies
Tables 7 and 8 summarize the characteristics and results of the 3 included studies on clinical validity. The populations of two 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. While sensitivity and specificity calculations showed

incremental improvements when molecular testing with PancraGEN was added to cytology results, not knowing what proportion of patients with biliary strictures had solid pancreaticobiliary lesions does not permit conclusions specific to patients with solid pancreaticobiliary lesions.

Table 7. Characteristics of Clinical Validity Studies Assessing PancraGEN

Study	Design	Population	N	Diagnostic Test	Comparator	Follow-Up, mo
Khosravi et al (2018)[49]	Retrospective, convenience sample	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)[50]	Prospective, convenience sample	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)[51]	Prospective; convenience sample	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)[49]	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)[50]	Cytology alone	26 (NR)	100 (NR)	NR	NR
	Cytology plus FISH	44 (NR)	100 (NR)	NR	NR
	Cytology plus MP	56 (NR)	97 (NR)	NR	NR
	Cytology plus FISH plus MP	66 (NR)	97 (NR)	NR	NR
Gonda et al (2017)[51]	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

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 gaps identified in each study.

Table 9. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Khosravi et al (2018)[49]					
Kushnir et al (2018)[50]	4. Participants had "biliary strictures," which may include conditions other than solid pancreatic lesions			3. Positive and negative predictive values not calculated	
Gonda et al (2017)[51]	4. Participants had "biliary strictures," which may include conditions other than solid pancreatic lesions			3. Positive and negative predictive values not calculated	

The evidence gaps 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 Gaps

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Khosravi et al (2018)[49]		1. No discussion whether cytologists blinded to other test results				
Kushnir et al (2018)[50]		1. No discussion whether cytologists blinded to other test results				1. Confidence intervals not reported
Gonda et al (2017)[51]		1. No discussion whether cytologists blinded to other test results				

The evidence gaps 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.

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 two 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. The studies reported sensitivities and specificities that were higher when PancraGEN testing was added to cytology alone; however, not knowing the causes of biliary strictures does not permit conclusions specific to patients with solid pancreaticobiliary lesions. 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. There are no prospective studies 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 PathFinder^{TG} 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).

SUMMARY OF EVIDENCE
For individuals who have pancreatic cysts who do not have a definitive diagnosis after first-line evaluation and who receive standard diagnostic and management practices plus topographic genotyping (PancraGEN molecular testing), the evidence includes retrospective studies of clinical validity and clinical utility. Relevant outcomes are overall survival, disease-

specific survival, test accuracy and validity, change in disease status, morbid events, and quality of life. The best evidence of incremental clinical validity comes from the National Pancreatic Cyst Registry report that compared PancraGEN performance characteristics to current international consensus guidelines and provided preliminary but inconclusive evidence of a small incremental benefit for PancraGEN. The analyses from the registry study included only a small proportion of enrolled patients, relatively short follow-up time for observing malignant transformation, and limited data on cases where the PancraGEN results are discordant with international consensus guidelines. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Barrett esophagus who receive standard prognostic techniques plus topographic genotyping (BarreGEN molecular testing), the evidence includes 2 observational studies evaluating the performance characteristics of a panel of genetic markers in Barrett esophagus. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, morbid events, and quality of life. The studies showed that high mutational load could distinguish less versus more severe histology and was a predictor of progression in Barrett esophagus. It is not clear if the test used was specifically BarreGEN or if the BarreGEN prognostic algorithm was applied for classification. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have solid pancreaticobiliary lesions who do not have a definitive diagnosis after first line evaluation and who receive standard diagnostic and management practices plus topographic genotyping (PancraGEN molecular testing), the evidence includes 3 observational studies of clinical validity. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, morbid events, and quality of life. Two of the 3 studies had populations with biliary strictures and the other had a population of patients with solid pancreaticobiliary lesions. The studies reported higher sensitivities and specificities when PancraGEN testing was added to cytology results compared with cytology alone. However, the inclusion of patients in the analysis who may not have solid pancreaticobiliary lesions (those with biliary strictures not caused by solid pancreaticobiliary lesions) limits the interpretation of the results. While preliminary results showed a potential incremental benefit for PancraGEN, further research focusing on patients with solid pancreaticobiliary lesions is warranted. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 2026
NCT02110498	Early detection of pancreatic cystic neoplasms	3000	Mar 2024
NCT02692898	Biomarker analysis of central nervous system tumors	500	Nov 2025
Unpublished			
NCT02000999	The diagnostic yield of malignancy comparing cytology, FISH and molecular analysis of cell free cytology brush supernatant in patients with biliary strictures undergoing endoscopic retrograde cholangiography (ERC): a prospective study	110	Jan 2019 (completed)
NCT02078544	Integrated molecular analysis of cancer in gynecologic oncology (IMAC-GO)	700	Aug 2018 (unknown)
NCT01202136	The clinical, radiologic, pathologic and molecular marker characteristics of pancreatic cysts study (PCyst)	450	Sep 2025 (ongoing)

NCT: national clinical trial

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Gastroenterological Association (AGA)

In 2015, the American Gastroenterological Association (AGA) published a guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts[3] based on findings from a technical review. The technical review states the following about molecular testing: "Case series have confirmed that malignant cysts have a greater number and quality of molecular alterations, but no study has been properly designed to identify how the test performs in predicting outcome with regard to need for surgery, surveillance, or predicting interventions leading to improved survival." The AGA guideline also states, "Molecular techniques to evaluate pancreatic cysts remain an emerging area of research, and the diagnostic utility of these tests is uncertain."

In 2011, AGA published a medical position statement on the management of Barrett esophagus.[45] Based on findings from a technical review,[52] AGA "suggest[s] against the use of molecular biomarkers to confirm the histological diagnosis of dysplasia or as a method of risk stratification for patients with Barrett's esophagus at this time (weak recommendation, low-quality evidence)."

American College of Gastroenterology (ACG)

The American College of Gastroenterology published guidelines on the diagnosis and management of Barrett esophagus in 2015.[5] The guidelines state "Given the complexity and diversity of alterations observed to date in the progression sequence, a panel of biomarkers may be required for risk stratification. At the present time, no biomarkers or panels of biomarkers are ready for clinical practice. In order to become part of the clinical armamentarium, biomarkers will have to be validated in large prospective cohorts."

The College (2018) published guidelines on the diagnosis and management of pancreatic cysts.[53] 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
Current National Comprehensive Cancer Network guidelines for pancreatic adenocarcinoma were updated in 2021 (v.2.2021) and recommend that clinicians consider molecular tumor analysis in patients with metastatic disease.

NCCN guidelines for central nervous system cancers (v.2.2021),[55] and esophageal and esophagogastric junction cancers (v.1.2022),[56] do not include recommendations for molecular anatomic pathology or integrated molecular pathology.

Network guidelines on hepatobiliary cancers (v.5.2021) state that molecular testing may be considered in the following situations[59]:

- Isolated intrahepatic mass (imaging characteristics consistent with malignancy but not consistent with hepatocellular carcinoma) that is unresectable or indicative of metastatic disease
- Extrahepatic cholangiocarcinoma that is unresectable or indicative of metastatic disease.

Government Regulations

National:

There is no national coverage determination.

Local:

There is no local coverage determination for Michigan (Medicare Jurisdiction 8).

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

1. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. May-Jun 2012;12(3):183-197. PMID 22687371

2. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. Dec 2006;6(1-2):17-32. PMID 16327281
3. Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. Apr 2015;148(4):819-822; quize812-813. PMID 25805375
4. Bennett C, Moayyedi P, Corley DA, et al. BOB CAT: a large-scale review and delphi consensus for management of Barrett's Esophagus with no dysplasia, indefinite for, or low-grade dysplasia. Am J Gastroenterol. May 2015;110(5):662-682; quiz 683. PMID 25869390
5. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. Jan 2016;111(1):30-50; quiz 51. PMID 26526079
6. Trikalinos T, Terasawa T, Raman G, et al. Technology Assessment: A systematic review of loss-ofheterozygosity based topographic genotyping with PathfinderTG®. Rockville, MD: Agency for Healthcare Research and Quality;2010.
7. U.S. Patent #7,014,999. Finkelstein et al. March 21, 2006. Topographic genotyping. http://patft.uspto.gov/netacgi/nphParser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearchadv.htm&r=16&f=G&l=50&d=PTXT&S1=(redpath+AND+specimen)&OS=redpath+AND+specimen&RS=(redpath+AND+specimen). Accessed August 30, 2018.
8. Interpace Diagnostics. Advancing patient care through molecular diagnostic testing. 2016; http://www.interpacediagnostics.com/. Accessed August 30, 2018.
9. Interpace Diagnostics. How PancraGEN works. 2016; http://www.interpacediagnostics.com/pancragen/how-itworks/. Accessed August 30, 2018.
10. de Oliveira PB, Puchnick A, Szejnfeld J, et al. Prevalence of incidental pancreatic cysts on 3 tesla magnetic resonance. PLoS One. Mar 23 2015;10(3):e0121317. PMID 25798910
11. Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT. AJR Am J Roentgenol. Sep 2008;191(3):802-807. PMID 18716113
12. de Jong K, Nio CY, Hermans JJ, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol. Sep 2010;8(9):806-811. PMID 20621679
13. Gardner TB, Glass LM, Smith KD, et al. Pancreatic cyst prevalence and the risk of mucin-producing adenocarcinoma in US adults. Am J Gastroenterol. Oct 2013;108(10):1546-1550. PMID 24091499
14. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. Oct 2007;102(10):2339-2349. PMID 17764489
15. Oh HC, Kim MH, Hwang CY, et al. Cystic lesions of the pancreas: challenging issues in clinical practice. Am J Gastroenterol. Jan 2008;103(1):229-239; quiz 228, 240. PMID 18076739
16. Scheiman JM, Hwang JH, Moayyedi P. American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. Apr 2015;148(4):824-848 e822. PMID 25805376
17. Interpace Diagnostics. Clinical utility. 2016; http://www.interpacediagnostics.com/pancragen/clinical-utility/. Accessed August 30, 2018.
18. Al-Haddad MA, Kowalski T, Siddiqui A, et al. Integrated molecular pathology accurately determines the malignant potential of pancreatic cysts. Endoscopy. Feb 2015;47(2):136-142. PMID 25314329
19. Khalid A, McGrath KM, Zahid M, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clin Gastroenterol Hepatol. Oct 2005;3(10):967-973. PMID 16234041

20. Khalid A, Nodit L, Zahid M, et al. Endoscopic ultrasound fine needle aspirate DNA analysis to differentiate malignant and benign pancreatic masses. Am J Gastroenterol. Nov 2006;101(11):2493-2500. PMID 17029619
21. Khalid A, Pal R, Sasatomi E, et al. Use of microsatellite marker loss of heterozygosity in accurate diagnosis of pancreaticobiliary malignancy from brush cytology samples. Gut. Dec 2004;53(12):1860-1865. PMID 15542529
22. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc. May 2009;69(6):1095-1102. PMID 19152896
23. Siddiqui AA, Kowalski TE, Kedika R, et al. EUS-guided pancreatic fluid aspiration for DNA analysis of KRAS and GNAS mutations for the evaluation of pancreatic cystic neoplasia: a pilot study. Gastrointest Endosc. Apr 2013;77(4):669-670. PMID 23498145
24. Schoedel KE, Finkelstein SD, Ohori NP. K-Ras and microsatellite marker analysis of fine-needle aspirates from intraductal papillary mucinous neoplasms of the pancreas. Diagn Cytopathol. Sep 2006;34(9):605-608. PMID16900481
25. Sawhney MS, Devarajan S, O'Farrel P, et al. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. Gastrointest Endosc. May 2009;69(6):1106-1110. PMID 19249035
26. Sreenarasimhaiah J, Lara LF, Jazrawi SF, et al. A comparative analysis of pancreas cyst fluid CEA and histology with DNA mutational analysis in the detection of mucin producing or malignant cysts. JOP. Mar 09, 2009;10(2):163-168. PMID 19287110
27. Mertz H. K-ras mutations correlate with atypical cytology and elevated CEA levels in pancreatic cystic neoplasms. Dig Dis Sci. Jul 2011;56(7):2197-2201. PMID 21264513
28. Talar-Wojnarowska R, Pazurek M, Durko L, et al. A comparative analysis of K-ras mutation and carcinoembryonic antigen in pancreatic cyst fluid. Pancreatology. Sep-Oct 2012;12(5):417-420. PMID 23127529
29. Chai SM, Herba K, Kumarasinghe MP, et al. Optimizing the multimodal approach to pancreatic cyst fluid diagnosis: developing a volume-based triage protocol. Cancer Cytopathol. Feb 2013;121(2):86-100. PMID 22961878
30. Nikiforova MN, Khalid A, Fasanella KE, et al. Integration of KRAS testing in the diagnosis of pancreatic cystic lesions: a clinical experience of 618 pancreatic cysts. Mod Pathol. Nov 2013;26(11):1478-1487. PMID 23743931
31. Lapkus O, Gologan O, Liu Y, et al. Determination of sequential mutation accumulation in pancreas and bile duct brushing cytology. Mod Pathol. Jul 2006;19(7):907-913. PMID 16648872
32. Tamura K, Ohtsuka T, Date K, et al. Distinction of invasive carcinoma derived from intraductal papillary mucinous neoplasms from concomitant ductal adenocarcinoma of the pancreas using molecular biomarkers. Pancreas. Jul 2016;45(6):826-835. PMID 26646266
33. Panarelli NC, Sela R, Schreiner AM, et al. Commercial molecular panels are of limited utility in the classification of pancreatic cystic lesions. Am J Surg Pathol. Oct 2012;36(10):1434-1443. PMID 22982886
34. Toll AD, Kowalski T, Loren D, et al. The added value of molecular testing in small pancreatic cysts. JOP. Nov 09, 2010;11(6):582-586. PMID 21068490
35. Kung JS, Lopez OA, McCoy EE, et al. Fluid genetic analyses predict the biological behavior of pancreatic cysts: three-year experience. JOP. Sep 2014;15(5):427-432. PMID 25262708
36. Shen J, Brugge WR, Dimaio CJ, et al. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. Cancer. Jun 25 2009;117(3):217-227. PMID 19415731

37. Deftereos G, Finkelstein SD, Jackson SA, et al. The value of mutational profiling of the cytocentrifugation supernatant fluid from fine-needle aspiration of pancreatic solid mass lesions. Mod Pathol. Apr 2014;27(4):594-601. PMID 24051700
38. Fasanella KE, McGrath KM, Sanders M, et al. Pancreatic endocrine tumor EUS-guided FNA DNA microsatellite loss and mortality. Gastrointest Endosc. May 2009;69(6):1074-1080. PMID 19152901
39. Winner M, Sethi A, Poneros JM, et al. The role of molecular analysis in the diagnosis and surveillance of pancreatic cystic neoplasms. JOP. Mar 20, 2015;16(2):143-149. PMID 25791547
40. Malhotra N, Jackson SA, Freed LL, et al. The added value of using mutational profiling in addition to cytology in diagnosing aggressive pancreaticobiliary disease: review of clinical cases at a single center. BMC Gastroenterol. Aug 01, 2014;14:135. PMID 25084836
41. Redpath Integrated Pathology. The National Pancreatic Cyst Registry. n.d.; http://www.npcnregistry.com/. Accessed August 30, 2018.
42. Das A, Brugge W, Mishra G, et al. Managing incidental pancreatic cystic neoplasms with integrated molecular pathology is a cost-effective strategy. Endosc Int Open. Oct 2015;3(5):E479-486. PMID 26528505
43. Loren D, Kowalski T, Siddiqui A, et al. Influence of integrated molecular pathology test results on real-world management decisions for patients with pancreatic cysts: analysis of data from a national registry cohort. Diagn Pathol. Jan 20, 2016;11(1):5. PMID 26790950
44. Kowalski T, Siddiqui A, Loren D, et al. Management of patients with pancreatic cysts: analysis of possible false negative cases of malignancy. J Clin Gastroenterol. Sep 2016;50(8):649-657. PMID 27332745
45. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. Mar 2011;140(3):1084-1091. PMID 21376940
46. Yantiss RK. Diagnostic challenges in the pathologic evaluation of Barrett esophagus. Arch Pathol Lab Med. Nov 2010;134(11):1589-1600. PMID 21043812
47. Khara HS, Jackson SA, Nair S, et al. Assessment of mutational load in biopsy tissue provides additional information about genomic instability to histological classifications of Barrett's esophagus. J Gastrointest Cancer. Jun 2014;45(2):137-145. PMID 24402860
48. Eluri S, Brugge WR, Daglilar ES, et al. The presence of genetic mutations at key loci predicts progression to esophageal adenocarcinoma in Barrett's esophagus. Am J Gastroenterol. Jun 2015;110(6):828-834. PMID 26010308
49. Khosravi F, Sachdev M, Alshati A, et al. Mutation profiling impacts clinical decision making and outcomes of patients with solid pancreatic lesions indeterminate by cytology. JOP (Online). 2018;19(1):6-11. PMID
50. Kushnir VM, Mullady DK, Das K, et al. The diagnostic yield of malignancy comparing cytology, fish, and molecular analysis of cell free cytology brush supernatant in patients with biliary strictures undergoing endoscopic retrograde cholangiography (ERC): a prospective study. J Clin Gastroenterol. Aug 13, 2018. PMID 30106834
51. Gonda TA, Viterbo D, Gausman V, et al. Mutation profile and fluorescence in situ hybridization analyses increase detection of malignancies in biliary strictures. Clin Gastroenterol Hepatol. Jun 2017;15(6):913-919 e911. PMID 28017843
52. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. Mar 2011;140(3):e18-52; quiz e13. PMID 21376939

53. Elta GH, Enestvedt BK, Sauer BG, et al. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. Am J Gastroenterol. Apr 2018;113(4):464-479. PMID 29485131
54. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: pancreatic adenocarcinoma. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 2022.
55. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: central nervous system cancers. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed January 2022.
56. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers. Version 5.2022. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed January 2022.
57. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: hepatobiliary cancers. Version 5.2021. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed January 2022.
58. Blue Cross Blue Shield Association. Molecular Testing for the Management of Pancreatic Cysts, Barrett Esophagus, and Solid Pancreatic Lesions. MPRM 2.04.52. Last reviewed August 2021.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/08	10/9/08	11/1/08	Joint policy established
3/1/10	12/8/09	12/8/09	Routine maintenance
11/1/11	8/16/11	8/16/11	Routine update of experimental and investigational service. Added additional rationale; refreshed references. Policy statement unchanged.
11/1/13	8/22/13	8/27/13	Routine maintenance
5/1/15	2/17/15	2/27/15	Routine maintenance Updated references and rationale; added information regarding Barrett's esophagus Added Medicare LCD from Novitas
5/1/16	2/16/16	2/16/16	Routine maintenance with reference update.
5/1/17	2/21/17	2/21/27	• Updated policy title throughout policy for consistency • Updated background section • Rationale section reformatted, study results summarized, individual studies displayed in chart format • Policy focus on Pancreatic Cysts and Barrett Esophagus, Glioma section removed since PathFinder^{TG} Glioma is not commercially available. • CMS section updated with coverage criteria
5/1/18	2/20/18	2/20/18	Updated rationale, added references # 33 & 46. Policy title changed. Added PancraGEN and BarreGEN to policy statement as exclusions.

5/1/19	2/19/19		Rationale updated; references 50-52 and 54 added. Policy revised with an additional indication – "Individuals with solid pancreaticobiliary lesions who do not have a definitive diagnosis after first line evaluation". Policy statements unchanged. The title of this policy was changed to "Molecular Testing for the Management of Pancreatic Cysts, Barrett Esophagus, and Solid Pancreaticobiliary Lesions."
5/1/19	2/18/20		Routine policy maintenance. No added references, no change in policy status.
5/1/21	2/16/21		Routine policy maintenance. No change in policy status.
5/1/22	2/15/22		Routine policy maintenance. No change in policy status.

Next Review Date: 1st Qtr. 2023

BLUE CARE NETWORK BENEFIT COVERAGE POLICY GENETIC TESTING- MOLECULAR TESTING FOR THE DIAGNOSIS AND MANAGEMENT OF PANCREATIC CYSTS, BARRETT ESOPHAGUS, AND SOLID PANCREATICOBILIARY LESIONS (E.G., PATHFINDERTG®, PANCRAGEN, BARREGEN)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.