Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers molecular testing using the PathFinderTG system for all indications including the evaluation of pancreatic cyst fluid and Barrett esophagus to be **investigational.***

Policy Guidelines

GENETICS NOMENCLATURE UPDATE
Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence

Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Background/Overview

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.

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." Interpace currently describes in detail 1 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). As stated on the company website, PancraGEN integrates molecular analyses with first-line results (when these are inconclusive) and pathologist interpretation. The manufacturer calls this technique integrated molecular pathology. Test performance information is not provided on the website.

Table 1. PathFinderTG Tests

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.

MANAGEMENT OF 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 (eg, 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.

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 for the management of IPMN and MCN of the pancreas. These statements are referred to as the Fukouka 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. 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); 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.

In 2015, the American Gastroenterological Association published guidelines on the evaluation and management of pancreatic cysts; it recommends 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). The guidelines recommended that patients with a solid component, dilated pancreatic duct, and/or "concerning features" on endoscopic ultrasound-guided fine-needle aspiration should undergo surgery.

MANAGEMENT OF 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. The metaplastic columnar epithelium is a precursor to esophageal adenocarcinoma. These tumors frequently spread before symptoms are present so detection at an early stage might be beneficial. Surveillance for esophageal adenocarcinoma is recommended for those diagnosed with Barrett esophagus. 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. ACG recommendations for surveillance are stratified by presence of dysplasia. When no dysplasia is detected, ACG has reported the estimated risk of progression to cancer for patients ranges from 0.2% to 0.5% per year and ACG has recommended endoscopic surveillance every 3 to 5 years. For low-grade dysplasia, the estimated risk of progression is about 0.7% per year, and ACG has recommended endoscopic therapy or surveillance every 12 months. For high-grade dysplasia, the estimated risk of progression is about 7% per year, and ACG has recommended endoscopic therapy. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 (CLIA). Patented diagnostic tests (eg, PancraGEN™)‡ are available only through Interpace Diagnostics (Pittsburgh, PA and New Haven, CT; formerly RedPath Integrated Pathology) under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers. The local coverage determination by Novatis Solutions is:

> "PathfinderTG®‡ will be considered medically reasonable and necessary when selectively used as an occasional second-line diagnostic supplement:
> - Only where there remains clinical uncertainty as to either the current malignancy or the possible malignant potential of the pancreatic cyst based upon a comprehensive first-line evaluation; AND
> - A decision regarding treatment (e.g. surgery) has NOT already been made based on existing information."

Rationale/Source

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 and Barrett esophagus, which are the focus of the current review.

The evaluation of a diagnostic or prognostic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test); (2) clinical validity (diagnostic or prognostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease or predicting course of disease); and (3) clinical utility (ie, a demonstration that the diagnostic or prognostic information can be used to improve patient health outcomes).

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. 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%. Although data have suggested that the malignant transformation of these cysts is very rare, 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 (eg, 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. 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. 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%. Therefore, there is a need for more accurate prognosis to optimize detection of malignancy while minimizing unnecessary surgery and treatment.

PathFinderTG (Interpace Diagnostics) mutation 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. 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.

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 PICOTS were used to select literature to inform this review.

Patients
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.

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.

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.

Time
The American Gastroenterological Association has recommended surveillance of cysts that do not meet criteria for resection for 5 years.

Setting
The National Comprehensive Cancer Network has recommended that decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with access to high-quality imaging. PancraGEN testing can be ordered from Interpace Diagnostics. The test may be used in the setting of gastroenterology or cytopathology.

Analytic Validity
No studies describing the technical performance or analytic validity of PancraGEN were found. The laboratory that performs the analyses for PancraGEN is certified under the Clinical Laboratory Improvement Amendments.

Clinical Validity
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 a 2015 publication of results from a registry established with support from the manufacturer, 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

[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.

Several studies have reported on the diagnostic and prognostic characteristics of individual molecular components of this test (eg, *KRAS* variant or LOH markers) with mixed results. Gillis et al (2015) in Ireland conducted a systematic review of the literature on molecular analysis including assessment for *KRAS* variants, DNA quantification, and LOH in the diagnosis of pancreatic cystic lesions compared with surgical pathology as the reference standard. They included 9 studies that reported performance characteristics for *KRAS* variants. The sensitivities of selected studies ranged from 12% to 75%, with a pooled estimate of 39% (95% confidence interval [CI], 28% to 51%). The specificities ranged from 67% to 100% with a pooled estimate of 95% (95% CI, 83% to 99%). Evidence for LOH and DNA quantification was insufficient to form conclusions.

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: assessed components of the test separately for the malignancy outcome, did not include information needed to calculate performance characteristics for the malignancy outcome, did not describe how the reference standard diagnoses was established, did not use a suitable reference standard, did not adequately describe the patient characteristics, or did not adequately describe patient selection criteria. The following paragraphs describe the selected studies, which included 1 systematic review and 3 retrospective studies.

In 2010, a systematic review of LOH-based topographic genotyping with PathFinderTG was prepared for the Agency for Healthcare Research and Quality technology assessment program. Key questions addressed published evidence on analytic test performance, diagnostic ability, and clinical validity of the test, and what evidence compared the PathFinderTG test with conventional pathology. Reviewers summarized 3 publications relating to diagnostic ability and clinical validity for pancreatic and biliary tree tumors, 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 (Year)	Population	Reference Standard	Performance Characteristics for PancraGEN (95% CI), %	Performance Characteristics for Comparator (95% CI), %
Malhotra et al (2014)	26 patients with pancreaticobiliary masses with cytologic diagnosis of atypical, negative, or indeterminate and minimum 3-mo FU	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
Winner et al (2015)	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)	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; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value.

Malhotra et al (2014) at RedPath retrospectively evaluated 30 patients who presented with pancreaticobiliary masses and had a minimum follow-up of 3 months. 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 PathFinderTG mutation profiling, precluding assessment of diagnostic performance. PathFinderTG 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 PathFinderTG results improved sensitivity to 57% (12/21), 9 malignant cases were missed by both tests.

In 2015, Winner et al retrospectively analyzed 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 PathFinderTG. 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 [carcinoembryonic antigen] and amylase results as well as the molecular cyst fluid analysis and adjunct tests.” It is unclear whether these were the diagnosis classifications provided on the PathFinderTG reports. Results are reported for 36 cysts (the reasons for 4 exclusions were not given). PathFinderTG 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 (NPCR) and, in 2015, published results of 492 (26%) of 1864 registered patients. 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 PathFinderTG 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 PathFinderTG with that of an international consensus classification scheme. 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 might 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 PathFinderTG and 91% (95% CI, 81% to 97%, p=0.17 PathFinderTG 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 PathFinderTG and 52% (95% CI, 48% to 57%) for the international consensus classification, all respectively. 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 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, 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 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. Because of these limitations, the evidence is not sufficient to draw conclusions on clinical validity.

Clinical Utility

Direct demonstration of clinical utility would require evidence that PancraGEN can produce 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. Indirect demonstration of clinical utility would require a demonstration

that the clinical validity of PancraGEN is such that if results were used to change management decisions, the resulting change in management would lead to improved outcomes.

The 2010 Agency for Healthcare Research and Quality systematic review concluded that there were no studies at that time directly measuring whether using LOH-based topographic genotyping with PathFinderTG improved patient-relevant clinical outcomes.

Das et al (2015) published a simulation study comparing 4 management strategies in a hypothetical cohort of 1000 asymptomatic patients with a 3-cm pancreatic cyst. 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 nonmucinous 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 PathFinderTG. 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 PathFinderTG 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 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 quality-adjusted life year estimates. The quality of the data behind many of the model assumptions was low, including the assumptions about the PathFinderTG performance characteristics. Given the uncertainty with the model assumptions, the relevance of the estimates from this simulation is unclear.

The 2015 publication from the NPCR Registry also assessed evidence of clinical utility by describing how the PancraGEN might provide incremental benefit over consensus guidelines. 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 six of them had a malignant outcome. The PancraGEN correctly categorized 4 of 6 as high risk (see Table 4). The complete cross-classification of the 2 classification strategies by outcomes was not provided.

Using the same subset of patients described in the previous section from the NPCR (n=491), 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. 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. 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 2). 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 odds for the association between the consensus guidelines recommendations and 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 seven 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. The cross-tabulation of PancraGEN and international consensus classification by outcome was not shown in Loren et al but was derived from tables and text and is displayed in Table 4. This study demonstrated that results from PancraGEN testing are associated with real-world decisions, although other factors (eg, physician judgment, patient preferences) could affect these decisions.

Table 4. 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. 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.

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Section Summary: Pancreatic Cysts
There are no studies describing the analytic validity of this technology. The evidence for the clinical validity of PancraGEN consists of several retrospective studies. Most studies 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%) compared with 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 was limited. There are no prospective studies with a concurrent control 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 diagnosis or prognosis of pancreatic cysts and associated cancer.

BARRETT ESOPHAGUS

Clinical Context and Test Purpose

The American Gastroenterological Association has defined Barrett esophagus as replacement of normal epithelium at the distal esophagus by intestinal metaplasia, which predisposes to malignancy. Although grading of dysplasia in mucosal biopsies is the current standard for assessing the risk of malignant transformation, esophageal inflammation may mimic or mask dysplasia, and interobserver variability may yield inconsistent risk classifications. 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.”

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 PICOTS were used to select literature to inform this review.

Patients
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

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.

Time
Because it is not yet clear how this test would be used in practice, follow-up time for outcomes is unclear.

Setting
It is not clear how BarreGEN would be used. The Interpace Diagnostics website indicates that the test development is in the pipeline. Once available, the test might be used in the setting of gastroenterology or pathology.

Analytic Validity
No studies describing the analytic validity or technical performance of BarreGEN were found. The laboratory that performs the analyses for BarreGEN is Clinical Laboratory Improvement Amendments–certified.

Clinical Validity
The 2010 Agency for Healthcare Research and Quality a systematic review of LOH-based topographic genotyping with PathFinderTG did not find any publications of the PathFinderTG technology evaluating test performance, diagnostic ability, clinical validity or clinical utility for Barrett esophagus.

Khara et al (2014) examined LOH in microsatellite regions of the *TP53* and *CDKN2A* tumor suppressor genes and in 8 other tumor suppressor genes (total 10 loci) as prognostic markers in Barrett esophagus. Formalin-fixed paraffin-embedded tissues from 415 patients from 3 study sites who had histologically diagnosed Barrett esophagus were microdissected to yield 877 specimens. Each was histologically classified as normal squamous epithelium, columnar mucosa, intestinal metaplasia, indefinite for dysplasia (applied when cellular atypia is present but criteria for dysplasia are not met), low-grade dysplasia, high-grade dysplasia, or esophageal adenocarcinoma. At 1 study site, consensus diagnosis required agreement among 2 of 3 pathologists. All pathologists were blinded to molecular results, but it is unclear whether those conducting molecular analyses were blinded to pathology results. In the molecular analysis, thresholds for defining significant LOH were determined using normal specimens; a standard deviation greater than 2 was defined as “LOH present.” High clonality was defined as LOH variant in more than 75% of DNA. Mutational

load (ML) for each genomic locus was calculated by summing the proportional value of LOH and microsatellite instability (eg, 0.5 for low-clonality, 1 for high clonality, 0.75 for microsatellite instability at a single locus, 0.5 for microsatellite stability at each additional locus). Mean ML increased with increasingly severe histology. Categories of ML (none, low [lower 95th percentile], high [upper 5th percentile]) appeared to discriminate less severe and more severe histology, but there was considerable overlap between no and low ML and between low and high ML.

Eluri et al (2015) published a case-control study evaluating ML as a predictor of progression to high-grade dysplasia or esophageal adenocarcinoma in Barrett esophagus. Twenty-three patients had Barrett esophagus with no or low-grade dysplasia at baseline who developed high-grade dysplasia or esophageal adenocarcinoma during follow-up. Forty-six controls also had no dysplasia or low-grade dysplasia but no progression during follow-up. Controls were matched in a 2:1 ratio to cases by age, sex, index biopsy histology, and length of follow-up. The ML assessments were made using the method described above in Khara (2014). ML ranged from 0 to 10. Mean follow-up was 4 years and patients were mostly men, with mean age of 63 years. Mean ML in baseline biopsies was higher in cases (2.21) than in controls (0.42; $p<0.0001$). The performance characteristics of the ML test for predicting progression were evaluated with different ML cutoffs, ranging from 0.5 to 1.5. The sensitivity of the test was 100% at an ML of 0.5 or more while the specificity was 96% at an ML of 1.5 of more. Accuracy was highest (90%) for an ML of 1 or more. All 10 genetic loci included in the ML score showed a higher rate of mutation in cases compared with controls.

Section Summary: Clinical Validity
The evidence for the clinical validity of BarreGEN consists of 2 observational studies evaluating the performance characteristics of a panel of genetic markers in Barrett esophagus. The studies showed that high ML could distinguish less from more severe histology and was a predictor of progression in Barrett esophagus. How these findings might be applied in clinical practice is unclear. Although the manufacturer of BarreGEN helped to fund the studies, it is not clear whether the specific test used was BarreGEN.

Clinical Utility
No studies describing the clinical utility of BarreGEN were found.

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.

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 regarding incremental clinical validity comes

from the National Pancreatic Cyst Registry report that compared PancraGEN performance characteristics with 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 were 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 from more severe histology and was a predictor of progression in Barrett esophagus. It is not clear whether the test used was specifically BarreGEN or whether the BarreGEN prognostic algorithm was applied for classification. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 01/09/2013
Current Effective Date: 01/17/2018

01/03/2013	Medical Policy Committee review
01/09/2013	Medical Policy Implementation Committee approval. New policy.
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. No change to coverage.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. Added Barrett esophagus to list of investigational indications.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.

Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus

Policy # 00334
Original Effective Date: 01/09/2013
Current Effective Date: 01/17/2018

01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. Gliomas removed from policy and policy statement (PathFinderTG® Glioma not commercially available).
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. Title changed.

Next Scheduled Review Date: 01/2019

Coding

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Code Type	Code
CPT	81402, 84999, 89240
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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