Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus

Policy Number: 2.04.52  Last Review: 8/2017
Origination: 5/2008  Next Review: 8/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for PathFinderTG® molecular testing. This is considered investigational.

Note: This is a type of genetic testing that may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Molecular testing using the PathFinderTG® system is considered investigational for all indications including the evaluation of pancreatic cyst fluid and Barrett esophagus.

Considerations
This test has multiple potential uses including use in diagnosis, determining prognosis, and predicting response to therapies. All uses are considered investigational.

Information regarding coding and individual consideration of Medicare claims for this test was released in a provider bulletin from Highmark Medicare Services in June 2007 (available at: https://secure.highmark.com/ldap/medicalpolicy/wpa-highmark/printerfriendly/L-83-001.html). Because the RedPath laboratory is located in Pennsylvania, all Medicare claims for this test would be processed by Highmark Medicare Services. The CPT code suggested by Highmark Medicare Services for this test is code 84999 – unlisted chemistry procedure.
Tests that integrate microscopic analysis with molecular tissue analysis are generally called topographic genotyping. Interpace Diagnostics offers 2 such tests that use the PathFinderTG platform (eg, PancraGEN, BarreGEN). These molecular tests are intended to be used adjunctively when a definitive pathologic diagnosis cannot be made, because of inadequate specimen or equivocal histologic or cytologic findings, to inform appropriate surveillance or surgical strategies.

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

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

**Background**

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.\(^1\)

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.”\(^2\) 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).\(^3\) As stated on the company website, PancraGEN integrates molecular analyses with first-line results (when these are inconclusive) and pathologist interpretation.\(^4\) The manufacturer calls this technique integrated molecular pathology. Test performance information is not provided on the website.

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Specimen Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>PathFinderTG Pancreas (now called</td>
<td>Uses loss of heterozygosity markers, oncogene mutations, and DNA content</td>
<td>Pancreatobiliary fluid/ERCP</td>
</tr>
<tr>
<td>PancraGEN)</td>
<td>abnormalities to stratify patients according to their risk of progression to cancer</td>
<td>brush, pancreatic masses, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pancreatic tissue</td>
</tr>
<tr>
<td>PathFinderTG Barrett (now called</td>
<td>Measures the presence and extent of genomic instability and integrates those results with</td>
<td>Esophageal tissue</td>
</tr>
<tr>
<td>BarreGEN)</td>
<td>histology</td>
<td></td>
</tr>
</tbody>
</table>

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.
There is no single standardized approach to evaluating and managing pancreatic cysts. 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. 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. 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). The guideline recommends that patients with a solid component, dilated pancreatic duct and/or “concerning features” on EUS-FNA 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 (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. Surveillance for EAC 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 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. 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.

REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) 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 LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale
This evidence review was created in April 2008 and has been updated annually with literature search of the MEDLINE database. The most recent update with literature review covered the period through June 14, 2016 (see Appendix Table 1 for genetic testing categories).

PathFinderTG (Interpace Diagnostics) mutational profiles are intended to inform 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.

When this evidence review was originally 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.

Molecular tests using the RedPathTG platform are best evaluated within the framework of a diagnostic or prognostic test, because such frameworks provide diagnostic and prognostic information that assists in treatment decisions. Assessment of a diagnostic or prognostic tool typically focuses on 3 categories of evidence: (1) analytic validity; (2) clinical validity (ie, statistically significant association between the test result and health outcomes); and (3) clinical utility (ie, demonstration that use of the diagnostic or prognostic information clinically can improve health outcomes compared with patient management without use of the tool). Because the test is an adjunct to the usual diagnostic workup, it is important to evaluate whether the test provides incremental information above the standard workup to determine if the test has utility in clinical practice.
Pancreatic Cysts

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 (CLIA).

Clinical Validity
The diagnosis of cystic pancreatic lesions is usually performed by endoscopic, ultrasound-guided fine-needle aspiration 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, procedural difficulties, etc. Ancillary tests (eg, amylase, lipase, carcinoembryonic antigen [CEA] levels) often are performed on cyst fluid to aid in diagnosis and prognosis, but results still may be equivocal. Information provided by additional testing modalities would, therefore, be potentially useful. The clinical purpose of PancraGEN is to allow patients with low-risk cysts to avoid unnecessary surgery or to more accurately select patients with malignant lesions for surgery. 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 mutations, and DNA content abnormalities to stratify patients according to their risk of progression to cancer.(5) According to a 2015 publication of results from a registry established with support from the manufacturer,(12) the current diagnostic algorithm is as follows in Table 2.

### Table 2. Diagnostic Algorithm for PancraGEN$^{12}$

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Molecular Criteria$^a$</th>
<th>Coexisting Concerning Clinical Features$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>DNA lacks molecular criteria</td>
<td>Not considered for this diagnosis</td>
</tr>
<tr>
<td>Statistically indolent</td>
<td>DNA meets 1 molecular criterion</td>
<td>None</td>
</tr>
<tr>
<td>Statistically higher risk</td>
<td>DNA meets 1 molecular criterion</td>
<td>1 or more</td>
</tr>
<tr>
<td>Aggressive</td>
<td>DNA meets at least 2 molecular criteria</td>
<td>Not considered for this diagnosis</td>
</tr>
</tbody>
</table>

$^a$ Molecular criteria: (1) a single high-clonality mutation, (2) elevated level of high-quality DNA, (3) multiple low-clonality mutations; (4) a single low-clonality oncogene mutation.

$^b$ 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 mutation or LOH markers) with mixed results.(13-25) Gillis et al (2015) in Ireland conducted a systematic review of the literature on molecular analysis including assessment for KRAS mutations, DNA quantification, and LOH in the diagnosis of pancreatic cystic lesions compared to surgical pathology as the reference standard. They included 9 studies that reported performance characteristics for KRAS mutations.(16,18-
The sensitivities of selected studies ranged from 0.12 to 0.75, with a pooled estimate of 0.39 (95% confidence interval [CI], 0.28 to 0.51). The specificities ranged from 0.67 to 1.00 with a pooled estimate of 0.95 (95% CI, 0.83 to 0.99) Evidence for LOH and DNA quantification was insufficient to form conclusions.

For the evaluation of clinical validity of the PancraGEN test (including the algorithm), studies that meet 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/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Several studies were excluded from the evaluation of the clinical validity of the PancraGEN test because they evaluated components of the test separately for the malignancy outcome,(13-25) did not include information needed to calculate performance characteristics for the malignancy outcome,(26) did not describe how the reference standard diagnoses was established,(28) did not use a suitable reference standard,(29,30) did not adequately describe the patient characteristics,(15,25,31) or patient selection criteria.(14,15,26,31) The following paragraphs describe the included studies which consist of 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.(1) 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. The review summarized 3 publications relating to diagnostic ability and clinical validity for pancreatic and biliary tree tumors,(14,15,32) but did not perform meta-analyses of performance characteristics. The review concluded that eligible studies on diagnostic and prognostic ability of the test were small in sample size and had overt methodologic limitations, including retrospective assessment. The review 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. In addition, 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>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Standard</th>
<th>Performance Characteristics for PancraGEN (95% CI)</th>
<th>Performance Characteristics for Comparator (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malhotra, et al (2014)</td>
<td>26 patients with pancreaticobiliary masses with cytologic diagnosis of atypical, negative, or indeterminate and minimum 3-mo FU</td>
<td>Surgical pathology or oncology FU report</td>
<td>Sensitivity: 47% (24% to 71%) Specificity: 100% (63% to 100%) PPV: 100% (60% to 100%) NPV: 50% (27% to 73%)</td>
<td>NA</td>
</tr>
<tr>
<td>Winner, et al (2015)</td>
<td>36 patients evaluated for pancreatic cysts, had surgical resection, cyst fluid, and molecular analysis</td>
<td>Surgical pathology</td>
<td>Sensitivity: 67% (31% to 91%) Specificity: 81% (61% to 93%) PPV: 55% (25% to 82%) NPV: 88% (68% to 97%)</td>
<td>NA</td>
</tr>
<tr>
<td>Al-Haddad, et al (2015)</td>
<td>492 patients who had undergone IMP testing prescribed by their physician and for whom clinical outcomes were available with 23-mo FU</td>
<td>Long-term FU, surgical pathology</td>
<td><strong>PancraGEN</strong> Sensitivity: 83% (72% to 91%) Specificity: 91% (87% to 93%) PPV: 58% (47% to 68%) NPV: 97% (95% to 99%)</td>
<td>International consensus guidelines Sensitivity: 91% (81% to 97%) Specificity: 46% (41% to 51%) PPV: 21% (16% to 26%) NPV: 97% (94% to 99%)</td>
</tr>
</tbody>
</table>

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.(33) 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 mutational 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 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.(34) 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,(35) and in 2015, published results of 492 (26%) of 1864 registered patients.(12) 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 to that of an international consensus classification scheme.(6) 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 PathFinderTG 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 PathFinderTG 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 PathFinderTG 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 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**
The widespread use and increasing sensitivity of computed tomography and magnetic resonance imaging scans have been associated with marked increase in the finding of incidental pancreatic cysts.(36-38) Although data have suggested that the malignant transformation of these cysts is very rare,(39) due to the potential life-threatening prognosis of pancreatic cancer, an incidental finding can start an aggressive clinical workup. International consensus recommends surgical resection for all surgically fit patients with mucinous cystic neoplasm (MCN) or main duct intraductal papillary mucinous neoplasm (IPMN).(6) This is due to the uncertainty of the natural history of MCN and main duct IPMN and the presumed malignant potential of all types.(7,40,41) Estimates of morbidity and mortality following resection vary. The 2015 American Gastroenterological Association (AGA) technical review combined estimates into a pooled mortality rate of about 2% and serious complication rate of about 30%.(42) Therefore, there is a need for more accurate prognosis to optimize detection of malignancy while minimizing unnecessary surgery and treatment. Direct demonstration of clinical utility would require evidence that PancraGEN can produce incremental improvement in survival (by detecting malignant and potentially malignant cysts) and decreased morbidity of surgery (by avoiding surgery for cysts that are highly likely benign) when used adjuntively with the current diagnostic and prognostic standards. Indirect demonstration of clinical utility would require 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 (AHRQ) systematic review concluded that there were that no studies at that time directly measuring whether using LOH-based topographic genotyping with PathFinderTG improved patient-relevant clinical outcomes.(1)

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.(43) 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 (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 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 National Pancreatic Cyst 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 6 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 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. 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. (44) Table 4 shows the cross-tabulation of PancraGEN and international consensus classification by outcome. 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. 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.

Table 4. PancraGEN and International Consensus Classifications by Outcome (N=491)

<table>
<thead>
<tr>
<th>Malignant Outcome</th>
<th>Benign Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consensus Classification</strong></td>
<td><strong>PancraGEN Classification</strong></td>
</tr>
<tr>
<td>Surveillance</td>
<td>Low Risk</td>
</tr>
<tr>
<td>Surgery</td>
<td>Low Risk</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Low Risk</td>
</tr>
<tr>
<td>Surgery</td>
<td>Low Risk</td>
</tr>
</tbody>
</table>

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 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 (eg, survival, time to tumor recurrence, reduction in unnecessary surgeries).
evidence reviewed does not demonstrate that PathFinderTG has incremental clinical value for diagnosis or prognosis of pancreatic cysts and associated cancer.

**Barrett Esophagus**

AGA has defined 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)

**Analytic Validity**

No studies describing the analytic validity or technical performance of BarreGEN were found. The laboratory that performs the analyses for BarreGEN is CLIA-certified.

**Clinical Validity**

The 2010 AHRQ 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.(1)

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.(47) 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 between 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 molecular analysis, thresholds for defining significant LOH were determined using normal specimens; standard deviation greater than 2 was defined as “LOH present.” High clonality was defined as LOH mutation in more than 75% of DNA. Mutational load 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 mutational load (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.(48) 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 male with mean age around 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. Sensitivity of the test was 100% at an ML of 0.5 or more while specificity was 96% at an ML of 1.5 or 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 versus more severe histology and was a predictor of progression in Barrett esophagus. How these findings may be applied in clinical practice is unclear. Although the manufacturer of BarreGEN helped to fund the studies, it is not clear if 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 evaluating Barrett esophagus. The evidence reviewed does not demonstrate that PathFinderTG testing for prognosis of Barrett esophagus adds incremental value to current prognostic assessments.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might impact this policy are listed in Table 5.

**Table 5. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01202136</td>
<td>The Clinical, Radiologic, Pathologic and Molecular Marker Characteristics of Pancreatic</td>
<td>450</td>
<td>Sep 2016</td>
</tr>
</tbody>
</table>
### 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.

### SUPPLEMENTAL INFORMATION

#### Practice Guidelines and Position Statements

**American Gastroenterological Association**

In 2015, the American Gastroenterological Association (AGA) published a guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts.
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. Based on findings from a technical review, 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**
The American College of Gastroenterology published guidelines on the diagnosis and management of Barrett esophagus in 2015. 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.”

**National Comprehensive Cancer Network**
Current National Comprehensive Cancer Network guidelines for pancreatic adenocarcinoma, central nervous system cancers, esophageal and esophagogastric junction cancers, and hepatobiliary cancers do not include recommendations for molecular anatomic pathology or integrated molecular pathology.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination (NCD). In the absence of an NCD, 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.”

References:


34. Winner M, Sethi A, Poneros JM, et al. The role of molecular analysis in the diagnosis and surveillance of pancreatic cystic neoplasms. JOP. 2015;16(2):143-149. PMID 25791547


Billing Coding/Physician Documentation Information

84999 Unlisted chemistry procedure
89240 Unlisted miscellaneous pathology test

Additional Policy Key Words
PathFinder

Policy Implementation/Update Information
5/1/08 New policy; considered investigational.
5/1/09 No policy statement changes.
5/1/10 No policy statement changes.
5/1/11 Policy statement clarified that this is considered investigational for all indications.
5/1/13 No policy statement changes.
8/1/13 No policy statement changes.
8/1/14 Added Barrett's esophagus to investigational policy statement.
8/1/15 No policy statement changes.
8/1/16 No policy statement changes.
8/1/17 Tests not commercially available (PathFinderTG® Glioma) removed from policy.

Appendix

Appendix Table 1. Categories of Genetic Testing Addressed in Policy No. 2.04.52

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td>X</td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td>a,b,c</td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td>X</td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td>X</td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td>X</td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td>X</td>
</tr>
<tr>
<td>5d. In utero testing: mutations</td>
<td>X</td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td>X</td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

*PathFinderTG® Pancreas tests for gene mutations in pancreatic cyst fluid and tissue (potentially precancerous cells).

PathFinderTG® Glioma tests for gene mutations in patients with suspected glioma.

PathFinderTG® Barrett tests for gene mutations in dysplastic esophageal cells (potentially precancerous cells) in patients with Barrett esophagus.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.