This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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

DESCRIPTION

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

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),...
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 two 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.

POLICY

Molecular testing using the PathFinderTG® system is considered investigational for all indications including the evaluation of pancreatic cyst fluid, and Barrett esophagus.

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 protocol 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
</tbody>
</table>
**Variant Classification** | **Definition**
--- | ---
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

**MEDICARE ADVANTAGE**
For Medicare Advantage PATHFINDERTG® will be considered **medically necessary** when selectively used as an occasional second-line diagnostic supplement (see Medicare Advantage Policy Guidelines):

- 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.

All PATHFINDERTG® indications other than pancreatic cyst fluid evaluation are considered **investigational**.

**MEDICARE ADVANTAGE POLICY GUIDELINES**
The specific requirements for medical necessity involve:

1. Highly-concise affirmation, documented in the medical record, that a decision regarding treatment has not already been made and that the results of the molecular evaluation will assist in determining if more aggressive treatment than what is being considered is necessary.

2. Previous first-line diagnostics, such as, but not restricted to, the following have demonstrated:
   a. A pancreatic cyst fluid carcinoembryonic antigen (CEA), which is greater than or equal to 200 ng/ml, suggesting a mucinous cyst, but is not diagnostic.
   b. Cyst cytopathologic or radiographic findings, which raise the index of malignancy suspicion, but where second-line molecular diagnostics is expected to be more compelling in the context of a surgical vs. nonsurgical care plan.

**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

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 one PathFinderTG test called PancraGEN on its website and describes another PathFinder test called BarreGEN as “in the pipeline” (listed and briefly described in Table 1).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 1. PathFinderTG Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Specimen Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>PancraGEN</td>
<td>Uses loss of heterozygosity markers, oncogene variants, and DNA content abnormalities to stratify patients according to their risk of progression to cancer</td>
<td>Pancreatobiliary fluid/ERCP brush, pancreatic masses, or pancreatic tissue</td>
</tr>
<tr>
<td>PathFinderTG Barrett (now called BarreGEN)</td>
<td>Measures the presence and extent of genomic instability and integrates those results with histology</td>
<td>Esophageal tissue</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 (e.g., pain, pancreatitis), an important reason that such cysts are followed is the risk of malignancy, which is estimated to range from 0.01% at the time of diagnosis to 15% in resected lesions.

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.7 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 three cm or greater; thickened or enhancing cyst walls on imaging; five 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 two or more worrisome features (size three cm or larger, a solid component, a dilated main pancreatic duct).8 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.9 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 publish-
ed. 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 three to five 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.

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 (e.g., 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


42. Winner M, Sethi A, Poneros JM, et al. The role of molecular analysis in the diagnosis and surveillance of pancreatic cystic neoplasms. JOP. Mar 20 2015;16(2):143-149. PMID 25791547


56. Novitas Solutions, Inc. (Primary Geographic Jurisdiction - Arkansas, Louisiana, Mississippi, Colorado, New Mexico, Oklahoma, Texas, Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania) Local Coverage Determination (LCD): Loss-of-Heterozygosity Based Topographic Genotyping with PATHFINDERTG® (L34864), Revision Effective Date for services performed on or after 01/04/2016.