Medical Policy
Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus

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Policy Number: 566
BCBSA Reference Number: 2.04.52
NCD/LCD: N/A

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

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

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
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<tr>
<td>Medicare HMO Blue℠</td>
<td>This is not a covered service.</td>
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<tr>
<td>Medicare PPO Blue℠</td>
<td>This is not a covered service.</td>
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**CPT Codes**
There is no specific CPT code for this service.

**Description**
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 1. PathFinderTG Tests⁵**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Specimen Types</th>
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<tbody>
<tr>
<td>PathFinderTG Pancreas (now called PancraGEN)</td>
<td>Uses loss of heterozygosity markers, oncogene mutations, 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>
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<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>
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</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.6 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.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); 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).8 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.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 published.9,10 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.10 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.9

**Summary**

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 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.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>9/2017</td>
<td>BCBSA National medical policy review. The policy title was changed. Policy statements unchanged. 9/2017</td>
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<tr>
<td>9/2016</td>
<td>BCBSA National medical policy review. Tests not commercially available (PathFinderTG® Glioma) removed from policy. References added. 9/1/2016</td>
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<tr>
<td>2/2016</td>
<td>BCBSA National medical policy review. Updated laboratory information and new test names added to policy. Policy statement unchanged. 2/1/2016</td>
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<tr>
<td>7/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>10/20/2010</td>
<td>New policy effective 10/20/10 describing ongoing non-coverage.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References


35. 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


