Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus

Description

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 (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.

OBJECTIVE

The objective of this evidence review is to determine whether testing using topographic genotyping in addition to standard diagnostic or prognostic practices improve the net health outcome in individuals with pancreatic cysts, Barrett esophagus, or solid pancreaticobiliary lesions.
POLICY STATEMENT

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

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society 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). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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>
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</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA</td>
<td>sequence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated</td>
<td>variant identified in a proband for use in subsequent targeted genetic</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td>testing in first-degree relatives</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</td>
</tr>
<tr>
<td></td>
<td>sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the</td>
</tr>
<tr>
<td></td>
<td>DNA sequence</td>
</tr>
</tbody>
</table>

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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

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

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

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. Patented diagnostic test (e.g. PancreaGEN™) are available only through Interpace Diagnostics (formerly RedPath Integrated Pathology) under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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**

*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 (PancreaGEN molecular testing), the evidence includes retrospective studies of clinical validity and clinical utility. Relevant outcomes are overall survival, disease-specific survival, test 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 PancreaGEN performance characteristics with current international consensus guidelines and provided preliminary but inconclusive evidence of a small incremental benefit for PancreaGEN. 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 PancreaGEN 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 a systematic review. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, morbid events, and quality of life. The systematic review identified no studies relevant to this evidence review. Two observational studies were excluded based on BCBSA selection criteria because it was unclear 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.

For individuals who have solid pancreaticobiliary lesions who do not have a definitive diagnosis after first-line evaluation and who receive standard diagnostic and management practices plus topographic genotyping (PancraGEN molecular testing), the evidence includes 3 observational studies of clinical validity. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, morbid events, and quality of life. Two of the 3 studies had populations with biliary strictures and the other had a population of patients with solid pancreaticobiliary lesions. The studies reported higher sensitivities when PancraGEN and FISH testing was added to cytology results compared with cytology alone. However, the inclusion of patients in the analysis who may not have solid pancreaticobiliary lesions (those with biliary strictures not caused by solid pancreaticobiliary lesions) limits the interpretation of the results. While preliminary results showed a potential incremental benefit for PancraGEN plus FISH plus cytology, further research focusing on patients with solid pancreaticobiliary lesions is warranted. Whether the tradeoff between avoiding biopsies and the potential for missed cancers is worthwhile depends, in part, on patient and physician preferences. In the context of pancreaticobiliary cancers, overall survival depends on detection of these cancers at early, more treatable stages. While there is indirect evidence that cytology plus FISH plus MP may predict more solid pancreaticobiliary lesions compared with cytology alone, the sensitivity is not sufficiently high enough to identify which patients can forego biopsy. Missing a solid pancreaticobiliary lesion diagnosis at a rate of 30%, is not inconsequential. A delay in diagnosis would delay potential treatment (surgery and/or chemotherapy). The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Gastroenterological Association

The American Gastroenterological Association (AGA; 2015) published guidelines on the diagnosis and management of asymptomatic neoplastic pancreatic cysts, based on findings from a technical review. The technical review stated 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 guidelines also stated: "Molecular techniques to evaluate pancreatic cysts remain an emerging area of research, and the diagnostic utility of these tests is uncertain."

AGA (2011) published a medical position statement on the management of Barrett esophagus. Based on findings from a technical review, AGA recommended: "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 guidelines stated: "Given the complexity and diversity of alterations observed to date in the progression sequence, a panel of biomarkers may be required for risk stratification. At the present time, no biomarkers or panels of biomarkers are ready for clinical practice. In order to become part of the clinical armamentarium, biomarkers will have to be validated in large prospective cohorts."

The guidelines stated that the evidence for the use of molecular biomarkers for identifying high-grade dysplasia or pancreatic cancer is insufficient to recommend their routine use. However, molecular markers may help identify intraductal papillary mucinous neoplasms and mucinous cystic neoplasms in cases with an unclear diagnosis and if results are likely to change the management (conditional recommendation; very low quality evidence).

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**National Comprehensive Cancer Network**

Current National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma were updated in 2019 and recommend that clinicians consider molecular tumor analysis in patients with metastatic disease.\(^{54}\).

NCCN guidelines for central nervous system cancers (v.1.2018)\(^{55}\), and esophageal and esophagogastric junction cancers (v.2.2018)\(^{56}\), do not include recommendations for molecular anatomic pathology or integrated molecular pathology.

Network guidelines on hepatobiliary cancers (v.2.2019) state that molecular testing may be considered in the following situations\(^{57}\):

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

**U.S. Preventative Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

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."

**REFERENCES**


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FEP 2.04.52 Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus

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**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2012</td>
<td>New policy</td>
<td>Policy updated with literature search; references 4-13, 16 and 17 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>September 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review; References 2-4, 19-23, 30-37 added. Barrett esophagus added to policy statement, which is otherwise unchanged.</td>
</tr>
<tr>
<td>September 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review; references 5, 23, and 26-29 added; reference 21 deleted. The policy statement was revised from not medically necessary to investigational as a correction to align with FDA regulatory status.</td>
</tr>
<tr>
<td>September 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review; references 3-4, 8-9, 11, 34, 36-38, 42-44, and 48 added. Tests not commercially available (PathFinderTG® Glioma) removed from policy.</td>
</tr>
<tr>
<td>December 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 16, 2018; references 50-52 and 54 added. Policy revised with an additional indication – &quot;Individuals with solid pancreaticobiliary lesions who do not have a definitive diagnosis after first line evaluation&quot;. Policy statements unchanged. The title of this policy was changed to &quot;Molecular Testing for the Management of Pancreatic Cysts, Barrett Esophagus, and Solid Pancreaticobiliary Lesions.&quot;</td>
</tr>
<tr>
<td>December 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 29, 2019; references for NCCN updated. Policy statement unchanged.</td>
</tr>
</tbody>
</table>

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