MEDICAL POLICY – 12.04.52
Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus

Effective Date: Sept. 1, 2017
Last Revised: Aug. 22, 2017
Replaces: 2.04.52

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Introduction

Looking at tissue samples is one way to diagnose cancer. In some cases, though, tissue tests alone don’t give clear enough information to make a diagnosis. This is when other types of tests can be used to diagnose cancer. In recent years, tests known as topographic genotyping have been tried. First, certain cells are taken from a tissue sample, and then the DNA is removed and analyzed. Then the information from the tissue test and the DNA test is combined to try to make a firm diagnosis of cancer. At this time, there are not enough published medical studies to show if diagnosing cancer this way leads to better health outcomes compared to other ways of diagnosing cancer.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

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

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
</tbody>
</table>

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### Related Information

N/A

### Evidence Review

### 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 (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.
Background

Topographic genotyping (TG), 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. TG may permit pathologic diagnosis when first-line analyses are inconclusive.¹

RedPath Integrated Pathology (now Interpace Diagnostics) has patented a proprietary platform called PathFinderTG that 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 on its website one PathFinderTG test called PancraGEN. It also describes another PathFinderTG test called BarreGEN™ as being “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>
</tr>
</thead>
<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>
</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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might impact this policy are listed in Table 2.
### Table 2. 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 Cysts Study (PCyst)</td>
<td>450</td>
<td>Sep 2017</td>
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<tr>
<td>NCT02078544</td>
<td>Integrated Molecular Analysis of Cancer in Gynaecologic Oncology (IMAC-GO)</td>
<td>700</td>
<td>Aug 2018</td>
</tr>
<tr>
<td>NCT02692898</td>
<td>Biomarker Analysis of Central Nervous System Tumors</td>
<td>500</td>
<td>Nov 2025</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02000999</td>
<td>The Diagnostic Yield of Malignancy Comparing Cytology, FISH and Molecular Analysis of Cell Free Cytology Brush Supernatant in Patients With Biliary Strictures Undergoing Endoscopic Retrograde Cholangiography (ERC): A Prospective Study</td>
<td>110</td>
<td>Jan 2017</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

### Summary of Evidence

For individuals who have pancreatic cysts who do not have a definitive diagnosis after first-line evaluation and who receive standard diagnostic and management practices plus topographic genotyping (PancraGEN molecular testing), the evidence includes retrospective studies of clinical validity and clinical utility. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, morbid events, and quality of life. The best evidence regarding incremental clinical validity comes from the National Pancreatic Cyst Registry report that compared PancraGEN performance characteristics 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 from 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.

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 stated “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 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 American College of Gastroenterology published guidelines on the diagnosis and management of Barrett esophagus in 2015. 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.”
National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines for pancreatic adenocarcinoma,\textsuperscript{52} central nervous system cancers,\textsuperscript{53} esophageal and esophagogastric junction cancers,\textsuperscript{54} and hepatobiliary cancers\textsuperscript{55} do not include recommendations for molecular anatomic pathology or integrated molecular pathology.

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 (eg, surgery) has NOT already been made based on existing information.”

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.
References


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
<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/09/11</td>
<td>New Policy – Add to Pathology/Laboratory section.</td>
</tr>
<tr>
<td>08/20/12</td>
<td>Replace policy. A literature review through May 2012 found no new studies; no references added. Policy statement unchanged. Policy moved to genetic testing section and renumbered from 2.04.52 to 12.04.52.</td>
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<tr>
<td>01/11/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>07/31/14</td>
<td>Annual Review. Policy updated with literature review through April 16, 2014; 2-4, 19-23, 30-37 added; reference 1 updated. Barrett esophagus added to policy statement, which is otherwise unchanged.</td>
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<tr>
<td>07/14/15</td>
<td>Annual Review. Policy updated with literature review through April 29, 2015; references 5, 23, and 26-29 added; reference 21 deleted. Policy statements unchanged.</td>
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<tr>
<td>10/01/16</td>
<td>Annual Review, approved September 13, 2016. Policy updated with literature review through June 14, 2016; 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>02/10/17</td>
<td>Policy moved into new format; no change to policy statements.</td>
</tr>
<tr>
<td>09/01/17</td>
<td>Annual Review, approved August 22, 2017. Policy updated with literature review through June 20, 2017; references 33 and 46 added. Policy statements unchanged. During the editorial review phase, the title of this policy was changed to “Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus.”</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

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من دقيقة الإشارة. يجب أن يكون متوفرًا في ترجمة معينة للعربية على متعلقات الصحافة والمساعدة
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037338 (07-2016)
Do not hallucinate.

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