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.
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>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### 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® Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Specimen Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>PathFinderTG Pancreas</td>
<td>Uses loss of heterozygosity markers, oncogene mutations, and DNA content</td>
<td>Pancreatobiliary fluid/ERCP brush, pancreatic masses, or pancreatic tissue</td>
</tr>
<tr>
<td>(now called PancraGEN)</td>
<td>abnormalities to stratify patients according to their risk of progression to cancer</td>
<td></td>
</tr>
<tr>
<td>PathFinderTG Barrett</td>
<td>Measures the presence and extent of genomic instability and integrates those results with histology</td>
<td>Esophageal tissue</td>
</tr>
<tr>
<td>(now called BarreGEN)</td>
<td></td>
<td></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</td>
<td>450</td>
<td>Sep 2017</td>
</tr>
<tr>
<td></td>
<td>of Pancreatic Cysts Study (PCyst)</td>
<td></td>
<td></td>
</tr>
<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</td>
<td>110</td>
<td>Jan 2017 (unknown)</td>
</tr>
<tr>
<td></td>
<td>Analysis of Cell Free Cytology Brush Supernatant in Patients With Biliary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strictures Undergoing Endoscopic Retrograde Cholangiography (ERC): A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prospective Study</td>
<td></td>
<td></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 (PancreaGEN 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,\(^5\) central nervous system cancers,\(^5\) esophageal and esophagogastric junction cancers,\(^4\) and hepatobiliary cancers\(^5\) 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.


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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination Is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon yon law osa konèsan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan av si sila a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la osa pou yo ka ede w av ekips yo. Se dwa w pou resewa enfòmasyon ya a ak assitans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaak ket naglaon iti Napateg nga Impomarsion. Daytoy a pakdaak mabalini nga adda ket naglaon iti napateg nga impomarsion maipanggep iti aplikasyonono wenno coverage babena Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelta iti daytoy a pakdaak. Mabalini nga adda rumbeng nga aramideny na nga addang sakkab dagiti partikular a naituding nga aldaw tapno mapagtalainedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impomarsion ken tulong ti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

037338 (07-2016)
Premera Blue Cross. It is possible that you need to take some action before certain dates.

To view this notification, please call 800-722-1471 (TTY: 800-842-5357).

Información importante. Este aviso contiene información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas críticas en este aviso. Es posible que deba tomar alguna medida antes de ciertas fechas para mantener su cobertura médica o ayuda con los costos. Usted debe tomar acción si desea recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Esta notificación puede contener información importante privada que permitiría la identificación de la persona y cuya protección debe ser garantizada. Si desea obtener una copia impresa de este aviso, llame al 800-722-1471 (TTY: 800-842-5357).

Jak (Czech): 

Polski (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje, takie jak wydanie pożyczki lub zakup zamienników, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utraty polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwonienie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):

Română (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении и страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощи на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas críticas en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay magagaling na nag airam hagupot sa pagpakawala ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring may magailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na may itanong ka na magsagawa ng hakbang sa ilang mga itinakdang panahon. Umiyak na ka na makakaya ng galing impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้อาจมีข้อมูลที่สําคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross. โปรดส่งเรื่องของคุณภายในกําหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่า โดยต้องเตรียมคําใช้ภาษาของคุณได้ในกรณีที่มีการเปลี่ยนแปลงในการประกันสุขภาพของคุณ.

倘有疑问，请拨打800-722-1471 (TTY: 800-842-5357)及向客服部门询问。