

# Corporate Medical Policy

## PathFinderTG® Molecular Testing

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<b>Origination:</b>	1/2009
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<b>Last Review:</b>	3/2018

### Description of Procedure or Service

The patented PathFinderTG® test is a molecular test intended to be used adjunctively when a definitive pathologic diagnosis cannot be made, because of inadequate specimen or equivocal histologic or cytologic findings. RedPath Integrated Pathology (Pittsburgh, PA), the test provider, states that PathFinderTG® produces mutational profiles to help physicians resolve complex diagnostic dilemmas in patients who are at risk of cancer.

#### 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.

RedPath Integrated Pathology (now Interspace Diagnostics) has patented a proprietary platform, called PathFinderTG®, to provide 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.” Interspace currently describes in detail one PathFinderTG® tests called PancaGEN™ on its website and describes one other PathFinder test called BarreGEN™ as “in the pipeline” (listed and briefly described in Table 1). As stated on the company website, PancaGEN™ integrates molecular analyses with first-line results (when these are inconclusive) and pathologist interpretation. The manufacturer calls this technique integrated molecular pathology. Test performance information is not provided on the website.

**Table 1. PathFinderTG® Tests**

Test	Description	Specimen Type(s)
PathFinderTG® Pancreas (now called PancaGEN™)	Uses loss of heterozygosity markers, oncogene mutations, and DNA content abnormalities to stratify patients according to their risk of progression to cancer	Pancreatobiliary fluid/ERCP <sup>a</sup> brush, pancreatic masses, or pancreatic tissue
PathFinderTG® Barrett (now called BarreGEN™)	Measures the presence and extent of genomic instability and integrates those results with histology	Esophageal tissue

<sup>a</sup>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 because of 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 consensus statements for the management of IPMN and mucinous cystic neoplasm (MCN) of the pancreas. These statements are referred to as the Fukouka Consensus Guidelines and were based on a consensus symposium held in Japan in 2010 and updated a 2006 publication (Sendai Consensus Guidelines) by this same group. 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 that is 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 (AGA) published a guideline on the evaluation and management of pancreatic cysts which recommends patients undergo further evaluation with EUS-FNA only if the cyst has 2 or more worrisome features (size  $\geq 3$  cm, a solid component, or a dilated main pancreatic duct). 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. However, there are little 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 (BOB CAT; Benign Barrett’s and Cancer Taskforce) regarding management of Barrett esophagus were published. The ACG recommendations for surveillance are stratified by presence of dysplasia. When no dysplasia is detected, the ACG reports the estimated risk of progression to cancer for patients range 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. The BOB CAT consensus group did not endorse routine surveillance for people with no dysplasia and was not able to come to agreement on surveillance intervals for low-grade dysplasia.

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***\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

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**PathFinderTG® Molecular Testing is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When PathFinderTG Molecular Testing is covered

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Not applicable.

## When PathFinderTG Molecular Testing is not covered

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

## Policy Guidelines

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Tests that integrate microscopic analysis with molecular tissue analysis are generally called topographic genotyping. Interpace Diagnostics (Pittsburgh, PA and New Haven, CT) offers 2 such tests that use the patented PathFinder TG® platform (eg. PancaGEN™, 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. The manufacturer states that the purpose of the test is to choose appropriate surveillance or surgical strategies.

Evidence reviewed for representative uses of PathFinderTG has limitations, as discussed. Demonstrating the utility of a test for diagnostic and prognostic purposes or to predict therapeutic response requires that results accurately inform clinical decision making in a manner leading to a net health benefit defined by clinical outcomes. Results must also be clearly reproducible, as shown by applying the test (with prior-defined cutoff points) to independent samples for validation.

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 (PancaGEN™ 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 report from the National Pancreatic Cyst Registry which compares the PancaGEN performance characteristics to current international consensus guidelines and provides preliminary but inconclusive evidence of a small incremental benefit for PancaGEN. 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 PancaGEN results are discordant with international consensus guidelines. The evidence is insufficient to determine the effects of the technology on health outcomes.

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For individuals who have Barrett esophagus and 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.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: There is no specific HCPCS or CPT code for this technology. The unlisted code 84999 may be used.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.52, 4/9/2008

Senior Medical Director Review - 12/10/2008

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.52, 4/24/2009

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National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: pancreatic adenocarcinoma, version 1.2014 (discussion update in progress). [http://www.nccn.org/professionals/physician\\_gls/pdf/pancreatic.pdf](http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf).

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.52, 5/21/15

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.52, 7/14/16

Specialty Matched Consultant Advisory Panel- 3/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.52, 7/13/17

Specialty Matched Consultant Advisory Panel- 3/2018

## Policy Implementation/Update Information

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- 2/16/09 New policy implemented. "Molecular testing using the PathFinderTG® system is considered **investigational** for all indications including but not limited to the evaluation of pancreatic cyst fluid and of suspected or known gliomas." Reviewed with the Senior Medical Director 12/10/2008. Notification given 2/16/2009. Policy effective 5/18/2009. (btw)
- 6/22/10 Policy Number(s) removed. (amw)
- 7/6/10 Specialty Matched Consultant Advisory Panel review 5/24/2010. Updated "Description" section. No change to policy intent. References added. btw
- 4/26/11 Specialty Matched Consultant Advisory Panel Review March 30, 2011. No change to policy intent. References added. (btw)
- 8/16/11 Reference added. (btw)
- 4/17/12 Specialty Matched Consultant Advisory Panel 3/21/2012. No change to policy. (btw)
- 8/7/12 Reference added. (btw)
- 4/16/13 Specialty Matched Consultant Advisory Panel review 3/20/2013. No change to policy statement. (btw)
- 7/16/13 Reference added. (btw)
- 4/15/14 Specialty Matched Consultant Advisory Panel review 3/25/2014. No change to policy statement. (btw)
- 7/15/14 Description section extensively revised to include individual PathFinder tests. "When not Covered" policy statement revised as follows: "Molecular testing using the PathFinderTG® system is considered investigational for all indications including the evaluation of pancreatic cyst fluid, suspected or known gliomas, and Barrett esophagus." Policy Guidelines updated. Unlisted code 84999 added to Billing/Coding section. References updated. Medical Director review 7/2014. (mco)

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- 4/28/15 Specialty matched consultant advisory panel review meeting 3/25/2015. No change to policy. (lpr)
- 7/28/15 Reference added. No change to policy statement.(lpr)
- 4/29/16 Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)
- 8/30/16 Updated Description and Policy Guidelines sections. Removed reference to PathFinder TG Glioma test which is not commercially available. Reference added. No change to policy statement. (lpr)
- 4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)
- 8/25/17 Reference added. No change to policy statement. (lpr)
- 4/27/18 Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. (lpr)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.