Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus, and Solid Pancreaticobiliary Lesions

Policy # 00334
Original Effective Date: 01/09/2013
Current Effective Date: 12/01/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider PathfinderTG®‡ (i.e., PancraGEN) for pancreatic cyst fluid evaluation when selectively used as an occasional second-line diagnostic supplement to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be considered when all of the following criteria are met:

- Remaining clinical uncertainty regarding possible malignant potential of the pancreatic cyst after comprehensive first-line evaluation (i.e., pancreatic cyst fluid carcinoembryonic antigen (CEA) is greater than or equal to 200 ng/mL and cytology does not demonstrate definitive diagnosis of malignancy); AND
- A decision regarding treatment (e.g., surgery) has not already been made based on existing information and the results of the molecular evaluation will be used in treatment planning; AND
- Pancreatic cyst findings do not meet AGA guidelines to reach a definitive diagnosis of benign disease:
    - Cyst is under 1 cm;
    - Lack a solid component;
    - Lack concerning cytology features;
    - Lack main pancreatic duct dilatation of > 1cm in diameter with absence of abrupt change in duct diameter;

  - Have fluid CEA level not exceeding 5 ng/ml; AND
- PathfinderTG®‡ was not used before for pancreatic cyst evaluation.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers molecular testing using the PathFinderTG ®‡ system for all other indications, including but not limited for the evaluation of pancreatic cyst fluid when selection criteria are not met, repeat testing for pancreatic cyst evaluation, Barrett esophagus, and solid pancreaticobiliary lesions to be **investigational.***

Background/Overview

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), which are associated with future development of pancreatic cancers. Incidence of IPMNs is generally equal between men and women, while mucinous cystic neoplasms occur almost exclusively in women (accounting for about 95% of cases). Pancreatic cancer arising from IPMNs and mucinous cystic neoplasms account for about 4% of pancreatic malignancies. Although mucinous neoplasms associated with cysts may cause symptoms (e.g. 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.

Management

Given the rare occurrence but the 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 an examination of cyst cytopathologic or radiographic findings and cyst fluid carcinoembryonic antigen. In 2012, an international consensus panel published statements on the management of IPMN and mucinous cystic neoplasm of the pancreas. These statements are referred

to as the Fukuoka Consensus Guidelines and were based on a symposium held in Japan in 2010, which updated a 2006 publication (Sendai Consensus Guidelines) by this same group. The panel recommended surgical resection for all surgically fit individuals with main duct IPMN or mucinous cystic neoplasm. For branch duct IPMN, surgically fit individuals with cytology suspicious or positive for malignancy are recommended for surgical resection, but individuals 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); the 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.

The American Gastroenterological Association (2015) published guidelines on the evaluation and management of pancreatic cysts; it recommended individuals undergo further evaluation with endoscopic ultrasound-guided fine-needle aspiration only if the cyst has 2 or more worrisome features (size ≥3 cm, a solid component, a dilated main pancreatic duct). The guidelines also recommended that individuals with these "concerning features" confirmed on fine-needle aspiration undergo surgery.

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. The metaplastic columnar epithelium is a precursor to esophageal adenocarcinoma. These tumors frequently spread before symptoms are present so detection at an early stage might be beneficial. The prevalence of Barrett esophagus in the United States is estimated to be about 6 percent, although prevalence estimates vary according to study populations. Barrett esophagus is more prevalent in male than female individuals, and is more prevalent in White race individuals relative to Black race or Hispanic ethnicity.

Management

Surveillance for esophageal adenocarcinoma is recommended for those diagnosed with Barrett esophagus. 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]) on the management of Barrett esophagus were published. ACG recommendations for surveillance are stratified by the presence of dysplasia. When no dysplasia is detected, ACG has reported the estimated risk of progression to cancer for individuals ranges from 0.2% to 0.5% per year and ACG has recommended endoscopic surveillance every 3 to 5 years. For low-grade dysplasia, the estimated risk of progression is about 0.7% per year, and ACG has recommended endoscopic therapy or surveillance every 12 months. For high-grade dysplasia, the estimated risk of progression is about 7% per year, and ACG has recommended endoscopic therapy. 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.

Solid Pancreaticobiliary Lesions
Solid pancreaticobiliary lesions refer to lesions found on the pancreas, gallbladder, or biliary ducts. A solid lesion may be detected as an incidental finding on computed tomography scans performed for another reason, though this occurs rarely. The differential diagnosis of a solid pancreatic mass includes primary exocrine pancreatic cancer, pancreatic neuroendocrine tumor, lymphoma, metastatic cancer, chronic pancreatitis, or autoimmune pancreatitis.

Management
Currently, if a transabdominal ultrasound confirms the presence of a lesion, an abdominal computed tomography scan is performed to confirm the presence of the mass and determine disease extent. If the computed tomography provides enough information to recommend a resection and if the patient is able to undergo the procedure, no further testing is necessary. If the diagnosis remains unclear, additional procedures may be recommended. Symptomatic individuals undergo cytology testing. If results from cytology testing are inconclusive, fluorescent in situ hybridization molecular testing of solid pancreaticobiliary lesions is recommended. PancraGEN topographic genotyping is being investigated as either an alternative to or as an adjunct to fluorescent in situ hybridization in the diagnostic confirmation process.

Topographic Genotyping
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.

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."

Table 1. PathFinderTG Tests

Test	Description	Specimen Types
PathFinderTG Pancreas (now called PancraGEN)	Uses loss of heterozygosity markers, oncogene variants, and DNA content abnormalities to stratify individuals according to their risk of progression to cancer	Pancreatobiliary fluid/ERCP 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

ERCP: endoscopic retrograde cholangiopancreatography.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. PancraGEN®)‡ 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. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

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 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 with 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 individuals, relatively short follow-up time for observing malignant transformation, and limited data on cases where the PancraGEN results were discordant with international consensus guidelines. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

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 individuals with solid pancreaticobiliary lesions. The studies reported higher sensitivities and specificities when PancraGEN testing was added to cytology results compared with cytology alone. However, the inclusion of individuals 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, further research focusing on individuals with solid pancreaticobiliary lesions is warranted. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Gastroenterological Association

Two (now retired) American Gastroenterological Association (AGA) guidelines previously indicated that "molecular techniques to evaluate pancreatic cysts remain an emerging area of research, and the diagnostic utility of these tests is uncertain" and recommended "against the use of

molecular biomarkers to confirm the histological diagnosis of dysplasia or as a method of risk stratification for individuals with Barrett's esophagus." As of May 2022, the AGA recommendation on the management of Barrett esophagus is in the process of being updated.

American College of Gastroenterology
In 2022, the American College of Gastroenterology released guidelines on the diagnosis and management of Barrett esophagus. The guidelines stated: "We could not make a recommendation on the use of predictive tools (p53 staining and TissueCypher) in addition to standard histopathology in individuals undergoing endoscopic surveillance of BE." The BarreGEN test was not specifically addressed in the guidelines.

In 2018, the American College of Gastroenterology published guidelines on the diagnosis and management of pancreatic cysts. 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).

National Comprehensive Cancer Network
National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma (v. 2.2023) recommend that clinicians consider molecular tumor analysis in individuals with metastatic disease who are candidates for anti-cancer therapy.

NCCN guidelines for esophageal and esophagogastric junction cancers (v. 2.2023) do not include recommendations for molecular anatomic pathology or integrated molecular pathology.

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."

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03855800	Molecular Detection of Advanced Neoplasia in Pancreatic Cysts (IN-CYST)	800	Dec 2026
NCT02110498	Early Detection of Pancreatic Cystic Neoplasms	3000	Mar 2024
Unpublished			
NCT01202136	The Clinical, Radiologic, Pathologic and Molecular Marker Characteristics of Pancreatic Cysts Study (PCyst)	450	Sept 2019 (completed)
NCT02000999	The Diagnostic Yield of Malignancy Comparing Cytology, FISH and Molecular Analysis of Cell Free Cytology Brush Supernatant in Individuals With Biliary Strictures Undergoing Endoscopic Retrograde Cholangiography (ERC): A Prospective Study	110	Jan 2019 (completed)

NCT: national clinical trial.

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54. LCD - Loss-of-Heterozygosity Based Topographic Genotyping with PathfinderTG ® (L34864) (cms.gov)

Policy History

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01/03/2013	Medical Policy Committee review
01/09/2013	Medical Policy Implementation Committee approval. New policy.
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. No change to coverage.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. Added Barrett esophagus to list of investigational indications.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.

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01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. Gliomas removed from policy and policy statement (PathFinderTG® Glioma not commercially available).
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. Title changed.
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. Solid pancreaticobiliary lesions was added to the investigational statement. Title was changed to "Molecular Testing for the Management of Pancreatic Cysts, Barrett Esophagus, and Solid Pancreaticobiliary Lesions."
09/09/2019	Coding update
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. No change to coverage.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. No change to coverage. Title changed to "Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus, and Solid Pancreaticobiliary Lesions"
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. No change to coverage. NCCN guideline access dates updated and central nervous system and hepatobiliary cancer guidelines removed.
09/01/2022	Medical Policy Committee review
09/14/2022	Medical Policy Implementation Committee approval. Senate bill update. Coverage changed from investigational to eligible with criteria.
10/11/2022	Coding update
09/07/2023	Medical Policy Committee review
09/13/2023	Medical Policy Implementation Committee approval. PathfinderTG®‡ was not used before for pancreatic cyst evaluation added as eligible. Repeat testing for pancreatic cyst evaluation added as investigational.

Next Scheduled Review Date: 09/2024

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0108U, 0114U, 0313U, 81479, 84999, 89240 Delete code effective 1/1/2023: 81402
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses K86.2, K86.3

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.