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

Policy # 00334
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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.

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 indications including the evaluation of pancreatic cyst fluid, Barrett esophagus, and solid pancreaticobiliary lesions to be **investigational.***

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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
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.

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. 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 Fukouka 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 patients with main duct IPMN or mucinous cystic neoplasm. For branch duct IPMN, surgically fit patients with cytology 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); 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 patients 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 patients 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.

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) 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 patients 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 Benign Barrett's and CAncer Taskforce 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 patients 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."[7] Interpace currently describes in detail 1 PathFinderTG test called PancraGEN on its website and describes another PathFinder test called BarreGEN as in a "soft launch" (listed and briefly described in Table 1). As stated on the company website, PancraGEN integrates molecular analyses with first-line results (when they 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 Types
PathFinderTG Pancreas (now called PancraGEN)	Uses loss of heterozygosity markers, oncogene variants, and DNA content abnormalities to stratify patients 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. PancraGENTM) 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

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 patients, 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 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 and specificities when PancraGEN 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, further research focusing on patients with solid pancreaticobiliary lesions is warranted. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

American Gastroenterological Association

In 2015, the American Gastroenterological Association (AGA) 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."

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
In 2015, the American College of Gastroenterology released guidelines on the diagnosis and management of Barrett esophagus. 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."

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
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.

NCCN guidelines for central nervous system cancers (v.1.2018) and esophageal and esophagogastric junction cancers (v.2.2018) 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:

- 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."

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
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 Patients With Biliary Strictures Undergoing Endoscopic Retrograde Cholangiography (ERC): A Prospective StudyThe 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 StudyThe 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	110	Jan 2019 (completed)
NCT02078544	Integrated Molecular Analysis of Cancer in Gynaecologic Oncology (IMAC-GO)	700	Aug 2018 (unknown)

NCT: national clinical trial.

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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.
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"

Next Scheduled Review Date: 12/2021

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 2019 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, 81402, 84999, 89240
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.