

Protocol

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

(20452)

Medical Benefit		Effective Date: 10/01/20	Next Review Date: 07/21
Preauthorization	No	Review Dates: 09/09, 09/10, 07/11, 07/12, 07/13, 07/14, 07/15, 07/16, 07/17, 07/18, 07/19, 07/20	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With pancreatic cysts who do not have a definitive diagnosis after first-line evaluation 	Interventions of interest are: <ul style="list-style-type: none"> Standard diagnostic and management practices plus topographic genotyping (PancreGEN molecular testing) 	Comparators of interest are: <ul style="list-style-type: none"> Standard diagnostic and management practices alone 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test validity Change in disease status Morbid events Quality of life
Individuals: <ul style="list-style-type: none"> With Barrett esophagus 	Interventions of interest are: <ul style="list-style-type: none"> Standard prognostic techniques plus topographic genotyping (BarreGEN molecular testing) 	Comparators of interest are: <ul style="list-style-type: none"> Standard prognostic techniques alone 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test validity Change in disease status Morbid events Quality of life
Individuals: <ul style="list-style-type: none"> With solid pancreaticobiliary lesions who do not have a definitive diagnosis after first-line evaluation 	Interventions of interest are: <ul style="list-style-type: none"> Standard diagnostic and management practices plus topographic genotyping (PancreGEN molecular testing) 	Comparators of interest are: <ul style="list-style-type: none"> Standard prognostic techniques alone 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test validity Change in disease status Morbid events Quality of life

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 (e.g., PancreGEN, 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 (PancreGEN molecular testing), the evidence includes retrospective studies of clinical validity and clinical utility. Relevant outcomes are overall survival, disease-specific survival, test validity, changes 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 PancreGEN performance characteristics with current international consensus guidelines and provided preliminary but inconclusive evidence of a small incremental benefit for PancreGEN. 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 PancreGEN 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, changes 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 (PancreGEN molecular testing), the evidence includes three observational studies of clinical validity. Relevant outcomes are overall survival, disease-specific survival, test validity, changes in disease status, morbid events, and quality of life. Two of the three 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 PancreGEN 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 PancreGEN, 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.

POLICY

Molecular testing using the PathFinderTG[®] system is considered **investigational** for all indications including the evaluation of pancreatic cyst fluid, Barrett esophagus, and solid pancreaticobiliary lesions.

POLICY GUIDELINES

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) 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 protocol updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUMAN Genome Organization (HUGO). The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of se-

quence variants represent expert opinion from ACMG, AMP, and 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

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

MEDICARE ADVANTAGE

For Medicare Advantage PATHFINDERTG® will be considered **medically necessary** when selectively used as an occasional second-line diagnostic supplement (see Medicare Advantage Policy Guidelines):

- 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.

All PATHFINDERTG® indications other than pancreatic cyst fluid evaluation are considered **not medically necessary**.

MEDICARE ADVANTAGE POLICY GUIDELINES

The specific requirements for medical necessity involve:

1. Highly-concise affirmation, documented in the medical record, that a decision regarding treatment has not already been made and that the results of the molecular evaluation will assist in determining if more aggressive treatment than what is being considered is necessary.
2. Previous first-line diagnostics, such as, but not restricted to, the following have demonstrated:
 - a. A pancreatic cyst fluid carcinoembryonic antigen (CEA), which is greater than or equal to 200 ng/ml, suggesting a mucinous cyst, but is not diagnostic.
 - b. Cyst cytopathologic or radiographic findings, which raise the index of malignancy suspicion, but where second-line molecular diagnostics is expected to be more compelling in the context of a surgical vs. non-surgical care plan.

BACKGROUND

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.¹

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.¹ 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.² 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 mm 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 two or more worrisome features (size ≥ 3 cm, a solid component, a dilated main pancreatic duct).³ 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.⁴ 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)⁵ and a consensus statement from an international group of experts (Benign Barrett’s and Cancer Taskforce) on the management of Barrett esophagus were published.⁴ 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 three to five 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.⁵ 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.⁴

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. PancaGEN 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.⁶

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 one PathFinderTG test called PancaGEN on its website and describes another PathFinder test called BarreGEN as in a "soft launch" (listed and briefly described in Table 1).⁸ As stated on the company website, PancaGEN integrates molecular analyses with first-line results (when they are inconclusive) and pathologist interpretation.⁹ The manufacturer calls this technique integrated molecular pathology. Test performance information is not provided on the website.

Table 1. PathFinderTG Tests⁸

Test	Description	Specimen Types
PathFinderTG Pancreas (now called PancaGEN)	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.

REGULATORY STATUS

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

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