MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Predictive Testing for Pancreatic Cancer**
Policy Number	**2.02.39**
Category	**Technology Assessment**
Original Effective Date	**07/17/08**
Committee Approval Date	**03/19/09, 03/18/10, 03/17/11**
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Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, predictive molecular testing, utilizing pancreatic tissue, masses or cyst fluid to determine the risk or early detection of pancreatic cancer have not been medically proven to be effective and, therefore, the following tests are considered **investigational**, including but not limited to:
   A. PancraGen (Pathfinder TG);
   B. BT-Reveal;
   C. PancreaSeq.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services.

POLICY GUIDELINES

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

DESCRIPTION

PancraGEN (Pathfinder TG)

The patented PancraGEN pancreatic risk classifier is a proprietary integrated molecular pathology test that assesses the cumulative DNA mutations in key oncogenes and tumor suppressor genes associated with pancreatic cancer. PancraGEN can help assess risk of malignancy in patients with pancreatic cysts or pancreatic masses and enhance diagnostic tools such as endoscopic ultrasound (EUS) imaging, CEA, cytology and other risk factors by providing more information for use in management decisions.

This test is intended to determine a patient's risk of cancer progression and to assess the best course of treatment. The PancraGEN report categorizes patients into one of four groups: benign, statistically indolent, statistically higher risk, or aggressive. A patient with a benign (low risk) test result may opt for disease surveillance while a patient with an aggressive (high-risk) disease may undergo surgery.

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 at any age, "including those stored in paraffin for over 30 years." As stated on the company website, PancraGEN is a personalized molecular pathology test, that interrogates cumulative oncogene and tumor suppressor gene damage, reporting results in the context of each patient's clinical history, imaging, fluid chemistry, and cytology test results. The manufacturer calls this technique integrated molecular pathology.

BT-Reveal

BT-Reveal was granted breakthrough device designation by the U.S Food and Drug Administration (FDA). It is a blood-based test that looks at 59 clinically validated DNA methylation regions that originate from cell-free tumor DNA molecules that circulate in the blood. This test is meant to be used as a regular screening tool in individuals at high risk for pancreatic cancer. The three categories of clinical use for this test are: known genetic risks and family history of pancreatic or other cancers, known pancreatic cysts and inconclusive CT-scans, MRIs, or endoscopic ultrasound (EUS) results, and informing non-specific gastrointestinal conditions and new onset diabetes.

PancreaSeq

PancreaSeq genomic classifier is a comprehensive molecular test that utilizes pancreatic genetic tumor genetics and sequencing to distinguish major types of pancreatic cystic lesions and predict their malignant potential to try to allow for optional patient management.

RATIONALE

For individuals with 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 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, which 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, 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.

A prospective, multi-institutional study conducted by Paniccia (2023) was conducted using a 22-gene next-generation sequencing (NGS) panel (PancreaSeq) in patients with pancreatic cysts. 1832 patients underwent PancreaSeq testing, follow-up was available for 1216 patients. Genomic alterations detected in 1220 specimens. Genomic alterations in KRAS, BRAF, NRAS, and HRAS were seen in 917 (49%), 91 (5%), 2 (<1%) and 1 (<1%) cysts, respectively. A diverse number of genomic alterations were identified in intraductal papillary mucinous neoplasms (eg, BRAF), serous cystadenomas (eg, TP53 and TERT), and pancreatic neuroendocrine tumors (eg, loss of heterozygosity of multiple genes) and are of associated clinical significance. Clinopathologic data was available for 1216 or 1832 patients, that includes 1253 EUS-FNA obtained pancreatic cyst fluid specimens with genomic alterations detected in 851 specimens, whereas

the remaining 402 specimens were negative for detectable mutations. While pancreaSeq was sensitive and specific for various pancreatic cyst types and advanced neoplasia originating from mucinous cysts, additional studies are required.

In a retrospective study conducted by Nikiforova (2023), they are reporting the results of a combined DNA/RNA next-generation (NGS) platform to improve the evaluation of pancreatic cysts. This study reviewed the updated 74-gene DNA/RNA-targeted NGS panel (PancreaSeq Genomic Classifier). This panel was created to evaluate five classes of genomic alterations to include gene mutations, fusions and expression, including CEA mRNA (CEACAM5) and was trained with 108 preoperative EUS-FNA pancreatic cyst fluid specimens that correspond to 72 cystic precursor neoplasms and 36 other neoplastic and non-neoplastic cysts. All 108 specimens were sufficient for targeted DNA/RNA-based NGS and identified genomic alterations. PancresSeq GC yielded a 95% sensitivity and 100% specificity for cystic precursor neoplasm, for advanced neoplasia it was 82% sensitivity and 100% specificity, respectively. Associated symptoms, cyst size, duct dilatation, a mural nodule, increasing cyst size, and malignant cytopathology had lower sensitivities (41–59%) and lower specificities (56–96%) for advanced neoplasia. Limitations of the study include surgical selection bias, testing selection bias as specimens used within the study were previously deemed satisfactory for molecular analysis. Prospective studies is needed to determine true diagnostic performance. Additional studies are needed to determine the optimal approach for PancreaSeq GC and how it can be incorporated into the current and future guidelines for pancreatic cysts.

The National Comprehensive Cancer Network (NCCN) guidelines Version 3.2024 for pancreatic adenocarcinoma recommend:

- For patients with evidence of metastatic disease, the Panel recommends a biopsy confirmation from preferably a metastatic site followed by genetic testing for inherited mutations, molecular profiling of tumor tissues, and complete staging with chest and pelvis CT.

The 2018 American Journal of Gastroenterology clinical guidelines for the Diagnosis and Management of Pancreatic Cysts recommend:

- Patients with intraductal papillary mucinous neoplasm (IPMNs) or mucinous cystic neoplasms (MCNs) with new onset or worsening diabetes mellitus, or a rapid increase in cyst size (of >3 mm/year) during surveillance, may have an increased risk of malignancy so should undergo a short-interval MRI or Endoscopic Ultrasound (EUS)±(Fine Needle Aspirate) FNA. (Conditional recommendation, very low quality of evidence).
- EUS-FNA and cyst fluid analysis should be considered in cysts in which the diagnosis is unclear, and where the results are likely to alter management. Analysis of cyst fluid CEA may be considered to differentiate IPMNs and MCNs from other cyst types but cannot be used to identify IPMNs and MCNs with high-grade dysplasia or pancreatic cancer (Conditional recommendation, very low quality of evidence).
- Cyst fluid cytology should be sent to assess for the presence of high-grade dysplasia or pancreatic cancer when the imaging features alone are insufficient to warrant surgery (Conditional recommendation, very low quality of evidence).
- Molecular markers can help identify IPMNs or MCNs. Their use may be considered in cases in which the diagnosis is unclear, and the results are likely to change management (Conditional recommendation, very low quality of evidence).

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81479	Unlisted molecular pathology procedure
0313U **(E/I)**	Oncology (pancreas), DNA and mRNA next generation sequencing analysis or 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (i.e., negative, low probability of neoplasia or positive, high probability of neoplasia) (Includes PancreaSeq Genomic Classifier, Molecular and Genomic Pathology Laboratory, University of Pittsburgh Medical Center)
0405U **(E/I)**	Oncology (pancreatic), 59 methylation haplotype block markers, next-generation sequencing, plasma, reported as cancer signal detected or not detected (Includes BTG Early Detection of Pancreatic Cancer (BT-Reveal), Breakthrough Genomics)
0573U **(E/I)**	Oncology (pancreas), 3 biomarkers (glucose, carcinoembryonic antigen, and gastricsin), pancreatic cyst lesion fluid, algorithm reported as categorical mucinous or non-mucinous *(effective 07/01/25)*

HCPCS Codes

Code	Description
No specific code	

ICD10 Codes

Code	Description
Investigational for all diagnosis codes	

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*Key Article

KEY WORDS

Molecular anatomic pathology, PathFinder, RedPath, Topographic genotyping, PancreGEN, PancraSEQ, BT-Reveal

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based upon our review, PathfinderTG is not addressed in National or Regional Medicare coverage determinations or policies.

However, please refer to the Medicare Managed Care Manual/Chapter 4: Benefits and Beneficiary Protections (Rev.121, Issued: 04-22-16)/Section 90 National and Local Coverage Determinations/Subsection 90.4.1 MAC with Exclusive Jurisdiction over a Medicare Item or Service:

In some instances, one Medicare A/B MAC processes all of the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one provider of a particular item or service (for example, certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage policy reflected in an LCD issued by the A/B MAC that enrolled the provider and processes all the Medicare claims for that item or service. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019326 accessed 11/01/24.