

Corporate Medical Policy

Pancreatic Cancer Risk Testing Using Molecular Classifier in Pancreatic Cyst Fluid AHS-M2114

File Name:	pancreatic_cancer_risk_testing_using_molecular_classifier_in_pancreatic_cyst_fluid
Origination:	1/2019
Last CAP Review:	3/2021
Next CAP Review:	3/2022
Last Review:	3/2021

Description of Procedure or Service

Pancreatic cancer is the fourth leading cause of death among cancers in the United States, and neoplasms frequently arise from pancreatic cysts that require investigation to differentiate benign neoplasms from malignant ones (Longnecker, 2019).

Integrated molecular pathology (IMP) testing combines molecular analysis with first-line test results (cytology, imaging, and fluid chemistry) to assess malignant potential (Al-Haddad et al., 2015). It is currently most commonly a second line testing strategy used adjunctively when a definitive pathologic diagnosis cannot be made, because of inadequate specimen or equivocal histologic or cytologic findings.

Related policies:

AHS-G2124 Serum Tumor Markers for Malignancies

AHS-G2153 Pancreatic Enzyme Testing for Acute Pancreatitis

AHS-M2066 Genetic Cancer Susceptibility Using Next Generation Sequencing

AHS-M2079 Genetic Testing for Hereditary Pancreatitis

AHS-M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy

******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

Pancreatic cancer risk testing using molecular classifier in pancreatic cyst fluid is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

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 Pancreatic Cancer Risk Testing Using Molecular Classifier is covered

Not applicable.

When Pancreatic Cancer Risk Testing Using Molecular Classifier is not covered

Molecular classifier testing using the PathFinderTG® system (eg PancaGEN) is considered investigational.

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Policy Guidelines

Discovery of pancreatic cysts is becoming more and more common as imaging technologies improve. Classifying these cysts is crucial as these cysts may be neoplastic with malignant potential, whereas non-neoplastic cysts only require treatment if they are symptomatic. However, these non-neoplastic cysts are often only identified after a surgical resection (McGrath, 2017). Proprietary tests are available that propose that they can estimate the chances of pancreatic cancer with pancreatic cyst fluid.

RedPath Integrated Pathology developed and patented a proprietary platform, PathFinderTG®, based on topographic genotyping (TG), also called molecular anatomic pathology, which integrates microscopic analysis (anatomic pathology) with molecular tissue analysis and claims that TG may permit pathologic diagnosis when first-line analyses are inconclusive (Finkelstein & Finkelstein, 2001). RedPath developed 5 different Pathfinder GT test (Pancreas, biliary, Barrett, Glioma, and Metastasis versus Primary Tumors (MvP)) before the company was purchased by Interpace Diagnostics. Interpace Diagnostics has continued development of these molecular pathology panels and markets them separately as PancaGen (Diagnostics, 2017).

The PancaGen is a DNA-based, integrated molecular pathology test that helps to assess the cancer risk in aspirated pancreatic cyst fluid. This test uses extracted DNA from aspirated pancreatic cyst fluid for testing tumor suppressor genes (Loss of Heterozygosity) in a panel of microsatellite markers using PCR/capillary electrophoresis, and oncogene point mutations using Sanger sequencing and capillary electrophoresis. PancaGen formerly known as PathFinderTG has claimed molecular diagnostic sensitivity of 95% and is performed in CLIA certified laboratory.

- PancaGen is a second-line, multi-variate assay that combines molecular analysis with first line test results (cytology, fluid chemistry, and imaging) to assess the malignant potential of pancreatic cysts. PancaGen is not indicated for cases where the cytology is positive for malignancy. PanDNA is the molecular technology that drives PancaGEN. The DNA abnormalities identified by this technology include tumor suppressor gene panel (Loss of Heterozygosity) analysis of VHL, OGG1; PTEN, MXI1; TP53; SMAD4, DCC; CDKN2A; RNF43, NME1; PSEN2, TFF1; CMM1v; MCC, APC; NF2. Oncogene point mutations provided by this test are those in KRAS (codons 12, 13) and GNAS (codon 201). The report provides summary of molecular results, specific molecular results and details of each result with the possible clinical meanings of those results (Interpace Diagnostics, 2018).

Clinical Validity and Utility

Malhotra et al evaluated the supporting role that mutational profiling of DNA may play in the diagnosis of malignancy in fine-needle aspirates (FNA) and biliary brushing specimens from patients with pancreaticobiliary masses. 30 patients who presented with pancreaticobiliary masses were evaluated and had minimum follow-up of 3 months. PathFinderTG® mutational profiling was done and analyzed in 26 patients with atypical, negative or indeterminate cytology. Cytology correctly diagnosed 4 of 21 malignant cases (sensitivity, 19%), and identified 7 of 9 patients with non-aggressive disease (specificity, 78%). PathFinderTG® correctly diagnosed 8 of 17 malignant cases (sensitivity, 47%) and identified all 9 patients with non-aggressive disease (specificity, 100%). When first-line malignant cytology results were combined with positive second-line mutational profiling results, sensitivity improved to 57% (12/21 cases of aggressive disease were identified). The investigators concluded that mutational profiling provided additional information regarding the presence of aggressive disease. When used in conjunction with first-line cytology, mutational profiling increased detection of aggressive disease without compromising specificity in patients that were difficult to diagnose by cytology alone (Malhotra et al., 2014).

Al-Haddad et al (2015) published a study that found “IMP more accurately determined the malignant potential of pancreatic cysts than a Sendai 2012 guideline management criteria model. IMP may improve patient management by justifying more relaxed observation in patients meeting Sendai surveillance criteria. IMP can more accurately differentiate between the need for surveillance or surgery in patients meeting Sendai surgical criteria.”

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Loren et al (2016) also found that “DNA-based IMP diagnoses were predictive of real-world management decisions. Importantly, when International Consensus Guidelines and IMP were discordant, IMP influence benefitted patients by increasing confidence in surveillance and surgery decisions and reducing the number of unnecessary surgeries in patients with benign disease.”

Springer and colleagues evaluated “whether a combination of molecular markers and clinical information could improve the classification of pancreatic cysts and management of patients”. 130 patients with resected pancreatic cystic neoplasms were enrolled. The cyst fluid was evaluated for the following genetic alterations: “BRAF, CDKN2A, CTNNB1, GNAS, KRAS, NRAS, PIK3CA, RNF43, SMAD4, TP53 and VHL); loss of heterozygosity at CDKN2A, RNF43, SMAD4, TP53, and VHL tumor suppressor loci; and aneuploidy”. The authors found this panel to identify 67 of the 74 patients who did not require surgery and estimated the sensitivity to be 90-100% and the specificity to be 92-98% (Springer et al., 2015)

Singhi et al (2016) assessed the accuracy of the AGA guidelines in detecting advanced neoplasia and present an alternative approach to pancreatic cysts. The clinical findings, EUS features, cytopathology results, carcinoembryonic antigen analysis, and molecular testing of pancreatic cyst fluid of 225 patients who underwent EUS-guided FNA for pancreatic cysts were reviewed. “Diagnostic pathology results were available for 41 patients (18%), with 13 (6%) harboring advanced neoplasia. Among these cases, the AGA guidelines identified advanced neoplasia with 62% sensitivity, 79% specificity, 57% positive predictive value, and 82% negative predictive value. Moreover, the AGA guidelines missed 45% of intraductal papillary mucinous neoplasms with adenocarcinoma or high-grade dysplasia. For cases without confirmatory pathology, 27 of 184 patients (15%) with serous cystadenomas (SCAs) based on EUS findings and/or VHL alterations would continue magnetic resonance imaging (MRI) surveillance. In comparison, a novel algorithmic pathway using molecular testing of pancreatic cyst fluid detected advanced neoplasias with 100% sensitivity, 90% specificity, 79% positive predictive value, and 100% negative predictive value (Singhi et al., 2016).

Singhi et al also evaluated the accuracy of pancreatic cyst fluid (PCF) DNA testing. A total of 626 PCF samples were taken from 595 patients. KRAS/GNAS mutations were identified in 308 samples (49%), and PIK3CA/PTEN/TP53 mutations were identified in 35 samples (6%). 102 patients had a surgical follow-up, and KRAS/GNAS mutations were detected in 56 intraductal papillary mucinous neoplasms (IPMNs) and 3 mucinous cystic neoplasms (MCNs), which corresponded to an 89% sensitivity and 100% specificity for a mucinous pancreatic cyst. Next generation sequencing identified the combination of KRAS/GNAS mutations and TP53/PTEN/PIK3CA alterations at an 89% sensitivity and 100% specificity. The authors concluded, “In contrast to Sanger sequencing, preoperative NGS of PCF for KRAS/GNAS mutations is highly sensitive for IPMNs and specific for mucinous PCs. In addition, the combination of TP53/PIK3CA/PTEN alterations is a useful preoperative marker for advanced neoplasia (Singhi et al., 2018).”

Das and colleagues investigated the cost efficiency of IMP in a “third-party-payer perspective Markov decision model” of a hypothetical cohort of 1000 asymptomatic patients with a 3 cm solitary pancreatic cyst. They used four different strategies to evaluate the cost efficiency in terms of quality-adjusted life-years (QALY): “Strategy I used cross-sectional imaging, recommended surgery only if symptoms or risk factors emerged. Strategy II considered patients for resection without initial EUS. Strategy III (EUS+CEA+Cytology) referred only those with mucinous cysts (CEA > 192 ng/mL) for resection. Strategy IV implemented IMP; a commercially available panel provided a ‘Benign,’ ‘Mucinous,’ or ‘Aggressive’ classification based on the level of mutational change in cyst fluid. ‘Benign’ and ‘Mucinous’ patients were followed with surveillance; ‘Aggressive’ patients were referred for resection.” The authors report that the IMP-based Strategy IV provided the greatest increase in QALY at approximately the same cost as the “cheapest approach”, concluding that “use of IMP was the most cost-effective strategy, supporting its routine clinical use (Das et al., 2015).” It should be noted, however, that two of the authors listed on the study were employed by RedPath Integrated Pathology, the developer of the IMP test.

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Applicable Federal Regulations

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements

American Gastroenterological Association (AGA)

In 2015, the AGA published guidelines on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. These guidelines only state, "Molecular techniques to evaluate pancreatic cysts remain an emerging area of research, and the diagnostic utility of these tests is uncertain (Vege, Ziring, Jain, & Moayyedi, 2015)."

In 2018, the AGA updated its recommendations (Elta, Enestvedt, Sauer, & Lennon, 2018) on the diagnosis and management of pancreatic cysts to state: "Molecular markers may help identify IPMNs and 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)."

The ACG also acknowledges the cost of cyst analysis, noting: "The cost of cyst analysis and cyst surveillance is high, and the benefit in terms of cancer prevention is unproven. There have been no dedicated cost effectiveness analyses about surveillance of incidental pancreatic cysts (Elta et al., 2018)."

American Society for Gastrointestinal Endoscopy (ASGE, 2016)

The ASGE states that "additional research is needed to determine the precise role molecular analysis of cyst fluid will play in evaluating pancreatic cystic lesions". However, the ASGE suggests that "molecular testing of the cyst be considered when initial ancillary testing of cytology and CEA is inconclusive and when test results may alter management (Muthusamy et al., 2016)."

National Comprehensive Cancer Network (NCCN)

Current NCCN clinical practice guidelines for pancreatic adenocarcinoma, central nervous system cancers, esophageal and esophagogastric junction cancers and hepatobiliary cancers do not include recommendations for molecular anatomic pathology or integrated molecular pathology (NCCN, 2018 and 2019).

International Consensus Fukuoka Guidelines

The International Association of Pancreatology (Tanaka et al., 2017) held a consensus symposium to examine the guidelines regarding prediction of invasive carcinoma and high-grade dysplasia, surveillance, and postoperative follow-up of IPMN. They found that "At present, EUS-FNA with cytological and molecular analyses is still considered investigational and should be performed only in centers with expertise in performing EUS-FNA and interpreting the results. More data are needed to accurately determine the sensitivity, specificity, and safety of this procedure and if results can be generalized."

Billing/Coding/Physician Documentation Information

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. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81479, 84999, 89240

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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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Medical Director review 8/2019

Specialty Matched Consultant Advisory Panel 3/2020

Medical Director review 3/2020

Medical Director review 4/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel 3/2021

Medical Director review 3/2021

Policy Implementation/Update Information

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| 1/1/2019 | New policy developed. Pancreatic cancer risk testing using the molecular classifier such as PancaGEN test is considered investigational for all indications, including the evaluation of pancreatic cyst fluid and of suspected or known gliomas and Barrett esophagus. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr) |
| 10/1/19 | Reviewed by Avalon 2 nd Quarter 2019 CAB. Deleted coding table from Billing/Coding section. Medical Director review 8/2019. (lpr) |
| 3/31/20 | Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (lpr) |
| 5/12/20 | Off cycle review. Medical Director review 4/2020. Updated Description, Policy Guidelines, References. Added PathFinderTG (PancaGEN) testing is considered investigational in When Not Covered section. (lpr) |
| 7/28/20 | Reviewed by Avalon 2 nd Quarter 2020 CAB. Added CPT code 81479 to “Billing/Coding” section. (lpr) |
| 4/6/21 | Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr) |

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

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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.