

MEDICAL POLICY

POLICY TITLE	MOLECULAR TESTING FOR THE MANAGEMENT OF PANCREATIC CYSTS, BARRETT ESOPHAGUS, AND SOLID PANCREATICOBILIARY LESIONS
POLICY NUMBER	MP 2.266

CLINICAL BENEFIT	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	1/1/2025

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I. 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. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

III. DESCRIPTION/BACKGROUND

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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 (PancraGEN[®] and 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.

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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 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 resections 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.

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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 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 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 patients undergo cytology testing. If results from cytology testing are inconclusive, fluorescent in situ hybridization molecular testing of solid pancreaticobiliary lesions is recommended. PancreGEN 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

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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 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 Amendments. Patented diagnostic tests (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. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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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

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

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members

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and providers should consult the member’s health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross’ medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member’s plan of benefits, please contact Capital Blue Cross’ Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
81479	84999	89240	0313U					

IX. REFERENCES

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1. Scholten L, van Huijgevoort NCM, van Hooft JE, et al. Pancreatic Cystic Neoplasms: Different Types, Different Management, New Guidelines. *Visc Med.* Jul 2018; 34(3): 173-177. PMID 30182024
2. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology.* May-Jun 2012;12(3):183-197. PMID 22687371
3. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology.* Dec 2006;6(1-2):17-32. PMID 16327281
4. Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology.* Apr 2015;148(4):819-822; quiz812-813. PMID 25805375

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5. Abrams JA, Fields S, Lightdale CJ, et al. Racial and ethnic disparities in the prevalence of Barrett's esophagus among patients who undergo upper endoscopy. *Clin Gastroenterol Hepatol.* Jan 2008; 6(1): 30-4. PMID 18063419
6. Bennett C, Moayyedi P, Corley DA, et al. BOB CAT: a large-scale review and delphi consensus for management of Barrett's Esophagus with no dysplasia, indefinite for, or low-grade dysplasia. *Am J Gastroenterol.* May 2015;110(5):662-682; quiz 683. PMID 25869390
7. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol.* Jan 2016;111(1):30-50; quiz 51. PMID 26526079
8. Trikalinos T, Terasawa T, Raman G, et al. Technology Assessment: A systematic review of loss-of- heterozygosity based topographic genotyping with PathfinderTG. Rockville, MD: Agency for Healthcare Research and Quality; 2010
9. U.S. Patent #7,014,999. Finkelstein et al. March 21, 2006. Topographic genotyping
10. Interpace Diagnostics. *Advancing patient care through molecular diagnostic testing.* 2016
11. de Oliveira PB, Puchnick A, Szejnfeld J, et al. Prevalence of incidental pancreatic cysts on 3 tesla magnetic resonance. *PLoS One.* Mar 23 2015;10(3):e0121317. PMID 25798910
12. Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol.* Sep 2008;191(3):802-807. PMID 18716113
13. de Jong K, Nio CY, Hermans JJ, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. *Clin Gastroenterol Hepatol.* Sep 2010;8(9):806-811. PMID 20621679
14. Gardner TB, Glass LM, Smith KD, et al. Pancreatic cyst prevalence and the risk of mucin-producing adenocarcinoma in US adults. *Am J Gastroenterol.* Oct 2013;108(10):1546-1550. PMID 24091499
15. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. *Am J Gastroenterol.* Oct 2007;102(10):2339-2349. PMID 17764489
16. Oh HC, Kim MH, Hwang CY, et al. Cystic lesions of the pancreas: challenging issues in clinical practice. *Am J Gastroenterol.* Jan 2008;103(1):229-239; quiz 228, 240. PMID 18076739
17. Scheiman JM, Hwang JH, Moayyedi P. American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology.* Apr 2015;148(4):824-848 e822. PMID 25805376
18. Interpace Diagnostics. *Clinical utility.* 2022
19. Al-Haddad MA, Kowalski T, Siddiqui A, et al. Integrated molecular pathology accurately determines the malignant potential of pancreatic cysts. *Endoscopy.* Feb 2015;47(2):136-142. PMID 25314329
20. Khalid A, McGrath KM, Zahid M, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. *Clin Gastroenterol Hepatol.* Oct 2005;3(10):967-973. PMID 16234041

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21. Khalid A, Nodit L, Zahid M, et al. Endoscopic ultrasound fine needle aspirate DNA analysis to differentiate malignant and benign pancreatic masses. *Am J Gastroenterol.* Nov 2006;101(11):2493-2500. PMID 17029619
22. Khalid A, Pal R, Sasatomi E, et al. Use of microsatellite marker loss of heterozygosity in accurate diagnosis of pancreaticobiliary malignancy from brush cytology samples. *Gut.* Dec 2004;53(12):1860-1865. PMID 15542529
23. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc.* May 2009;69(6):1095-1102. PMID 19152896
24. Siddiqui AA, Kowalski TE, Kedika R, et al. EUS-guided pancreatic fluid aspiration for DNA analysis of KRAS and GNAS mutations for the evaluation of pancreatic cystic neoplasia: a pilot study. *Gastrointest Endosc.* Apr 2013;77(4):669-670. PMID 23498145
25. Schoedel KE, Finkelstein SD, Ohori NP. K-Ras and microsatellite marker analysis of fine-needle aspirates from intraductal papillary mucinous neoplasms of the pancreas. *Diagn Cytopathol.* Sep 2006;34(9):605-608. PMID 16900481
26. Sawhney MS, Devarajan S, O'Farrel P, et al. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. *Gastrointest Endosc.* May 2009;69(6):1106-1110. PMID 19249035
27. Sreenarasimhaiah J, Lara LF, Jazrawi SF, et al. A comparative analysis of pancreas cyst fluid CEA and histology with DNA mutational analysis in the detection of mucin producing or malignant cysts. *JOP.* Mar 09 2009;10(2):163-168. PMID 19287110
28. Mertz H. K-ras mutations correlate with atypical cytology and elevated CEA levels in pancreatic cystic neoplasms. *Dig Dis Sci.* Jul 2011;56(7):2197-2201. PMID 21264513
29. Talar-Wojnarowska R, Pazurek M, Durko L, et al. A comparative analysis of K-ras mutation and carcinoembryonic antigen in pancreatic cyst fluid. *Pancreatology.* Sep-Oct 2012;12(5):417-420. PMID 23127529
30. Chai SM, Herba K, Kumarasinghe MP, et al. Optimizing the multimodal approach to pancreatic cyst fluid diagnosis: developing a volume-based triage protocol. *Cancer Cytopathol.* Feb 2013;121(2):86-100. PMID 22961878
31. Nikiforova MN, Khalid A, Fasanella KE, et al. Integration of KRAS testing in the diagnosis of pancreatic cystic lesions: a clinical experience of 618 pancreatic cysts. *Mod Pathol.* Nov 2013;26(11):1478-1487. PMID 23743931
32. Lapkus O, Gologan O, Liu Y, et al. Determination of sequential mutation accumulation in pancreas and bile duct brushing cytology. *Mod Pathol.* Jul 2006;19(7):907-913. PMID 16648872
33. Tamura K, Ohtsuka T, Date K, et al. Distinction of invasive carcinoma derived from intraductal papillary mucinous neoplasms from concomitant ductal adenocarcinoma of the pancreas using molecular biomarkers. *Pancreas.* Jul 2016;45(6):826-835. PMID 26646266
34. Panarelli NC, Sela R, Schreiner AM, et al. Commercial molecular panels are of limited utility in the classification of pancreatic cystic lesions. *Am J Surg Pathol.* Oct 2012;36(10):1434-1443. PMID 22982886
35. Toll AD, Kowalski T, Loren D, et al. The added value of molecular testing in small pancreatic cysts. *JOP.* Nov 09 2010;11(6):582-586. PMID 21068490

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36. Kung JS, Lopez OA, McCoy EE, et al. Fluid genetic analyses predict the biological behavior of pancreatic cysts: three-year experience. *JOP*. Sep 2014;15(5):427-432. PMID 25262708
37. Shen J, Brugge WR, Dimaio CJ, et al. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. *Cancer*. Jun 25 2009;117(3):217-227. PMID 19415731
38. Deftereos G, Finkelstein SD, Jackson SA, et al. The value of mutational profiling of the cytocentrifugation supernatant fluid from fine-needle aspiration of pancreatic solid mass lesions. *Mod Pathol*. Apr 2014;27(4):594- 601. PMID 24051700
39. Winner M, Sethi A, Poneris JM, et al. The role of molecular analysis in the diagnosis and surveillance of pancreatic cystic neoplasms. *JOP*. Mar 20 2015;16(2):143-149. PMID 25791547
40. Malhotra N, Jackson SA, Freed LL, et al. The added value of using mutational profiling in addition to cytology in diagnosing aggressive pancreaticobiliary disease: review of clinical cases at a single center. *BMC Gastroenterol*. Aug 01 2014;14:135. PMID 25084836
41. Loren D, Kowalski T, Siddiqui A, et al. Influence of integrated molecular pathology test results on real-world management decisions for patients with pancreatic cysts: analysis of data from a national registry cohort. *Diagn Pathol*. Jan 20 2016;11(1):5. PMID 26790950
42. Kowalski T, Siddiqui A, Loren D, et al. Management of patients with pancreatic cysts: analysis of possible false- negative cases of malignancy. *J Clin Gastroenterol*. Sep 2016;50(8):649-657. PMID 27332745
43. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology*. Mar 2011;140(3):1084-1091. PMID 21376940
44. Yantiss RK. Diagnostic challenges in the pathologic evaluation of Barrett esophagus. *Arch Pathol Lab Med*. Nov 2010;134(11):1589-1600. PMID 21043812
45. Khara HS, Jackson SA, Nair S, et al. Assessment of mutational load in biopsy tissue provides additional information about genomic instability to histological classifications of Barrett's esophagus. *J Gastrointest Cancer*. Jun 2014;45(2):137-145. PMID 24402860
46. Eluri S, Brugge WR, Daglilar ES, et al. The presence of genetic mutations at key loci predicts progression to esophageal adenocarcinoma in Barrett's esophagus. *Am J Gastroenterol*. Jun 2015;110(6):828-834. PMID 26010308
47. Khosravi F, Sachdev M, Alshati A, et al. Mutation profiling impacts clinical decision making and outcomes of patients with solid pancreatic lesions indeterminate by cytology. *JOP (Online)*. 2018;19(1):6-11
48. Kushnir VM, Mullady DK, Das K, et al. 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 study. *J Clin Gastroenterol*. Aug 13 2018. PMID 30106834
49. Gonda TA, Viterbo D, Gausman V, et al. Mutation profile and fluorescence in situ hybridization analyses increase detection of malignancies in biliary strictures. *Clin Gastroenterol Hepatol*. Jun 2017;15(6):913-919 e911. PMID 28017843

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- 50. Shaheen NJ, Falk GW, Iyer PG, et al. *Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. Am J Gastroenterol. Apr 01 2022; 117(4): 559-587. PMID 35354777*
- 51. Elta GH, Enestvedt BK, Sauer BG, et al. *ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. Am J Gastroenterol. Apr 2018; 113(4): 464-479. PMID 29485131*
- 52. *National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: pancreatic adenocarcinoma. Version 2.2024*
- 53. *National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers. Version 3.2024*
- 54. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.52 Molecular Testing for the Management of Pancreatic Cysts or Barrett Esophagus, August 2023*

X. POLICY HISTORY

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MP 2.266	01/03/2020 Consensus Review. No changes to policy statements. References updated, background and rationale reviewed. Code review completed. No changes.
	11/10/2020 Consensus Review. No change to policy statement. Background, Rationale and References updated.
	10/22/2021 Consensus Review. No change to policy statement. References reviewed and updated.
	03/11/2022 Administrative Update. New code 0313U added to policy. Effective 4/1/2022.
	08/31/2022 Consensus Review. Policy statement unchanged. NCCN language added. Background, Rationale and References updated.
	08/14/2023 Consensus Review. No change to policy statement. Policy guidelines removed. References updated.
	01/19/2024 Administrative Update. Clinical benefit added.
	05/09/2024 Consensus Review. No change to policy statement. References updated. Coding reviewed, no changes.
	11/19/2024 Administrative Update. Removed NCCN statement.

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