Pancreatic Cancer Risk Testing Using Pancreatic Cyst Fluid

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I. Policy Description

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. Up to 10% of pancreatic adenocarcinoma instances are "familial," in nature. Pathogenic germline variants in specific genes play a role in a 4%-40% risk of developing pancreatic cancer over a lifetime. In such patients who are determined to be at risk, screening and meaningful intervention can make the difference in detecting pancreatic neoplasms early, but the risk of unnecessary and invasive intervention is also high.

First-line tests for pathologic diagnosis of a pancreatic cyst include cytology, imaging, and fluid chemistry. Integrated molecular pathology (IMP) testing combines molecular analysis with first-line test results (cytology, imaging, and fluid chemistry) to assess malignant potential. 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.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

1) As a first step analysis of pancreatic cyst fluid, the following tests **MEET COVERAGE CRITERIA:**
   a) Carcinoembryonic antigen (CEA)
   b) Amylase
   c) Cytology

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness. The

2) Pancreatic cancer risk testing using molecular classifiers to evaluate pancreatic cyst fluid, such as the PancraGEN test, **DOES NOT MEET COVERAGE CRITERIA** for all indications.

III. Table of Terminology

Term	Definition
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association

ASGE	American Society for Gastrointestinal Endoscopy
CA 19-9	Carbohydrate antigen 19-9
CAPS	International Cancer of The Pancreas Screening
CEA	Carcinoembryonic antigen
CF	Cystic fluid
CLIA ’88	Clinical Laboratory Improvement Amendments Of 1988
CMS	Centers For Medicare and Medicaid
CTNNB1	*Catenin beta 1* gene
DNA	Deoxyribonucleic acid
ESG	European Study Group on Cystic Tumours Of The Pancreas
EUS	Endoscopic ultrasound
EUS-FNA	Endoscopic ultrasound fine-needle aspiration
FDA	Food And Drug Administration
FNA	Fine-Needle Aspirates
GNAS	*Guanine nucleotide binding protein, alpha stimulating* gene
IAP	International Association of Pancreatology
ICG	International Consensus Guideline
IMP	Integrated Molecular Pathology
indels	Insertions/deletions
IPMNs	Intraductal papillary mucinous neoplasms
KRAS	*Kirsten rat sarcoma viral oncogene homolog* gene
LDTs	Laboratory-developed tests
MCNs	Mucinous cystic neoplasms
MRI	Magnetic resonance imaging
MvP	Metastasis versus primary tumors
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NT	Neoplastic tissue
PCF	Pancreatic cyst fluid
PCN	Pancreatic cystic neoplasm
POLD1	*DNA polymerase delta 1, catalytic subunit* gene
PTPRD	*Protein tyrosine phosphatase receptor type d* gene
QALY	Quality-adjusted life-years
RAF	*Rapidly accelerated fibrosarcoma* gene
RNF43	*Ring finger protein 4* gene
SCAs	Serous cystadenomas
SNVs	Single nucleotide variants
SPNs	Solid pseudopapillary neoplasms (SPNs)
TG	Topographic genotyping
TP53	Tumor protein p53
WGO	World Gastroenterology Organization

IV. Scientific Background

Discovery of pancreatic cysts is becoming more and more common as imaging technologies such as computed tomography and magnetic resonance imaging scans have become widespread in use. Though data suggests that malignant transformation of cysts is rare, due to the overall poor prognosis of pancreatic cancer, an incidental finding of a cyst can lead to an aggressive clinical workup. Cysts may be neoplastic with malignant potential, whereas non-neoplastic cysts only require treatment if they are symptomatic. Pancreatic cysts are divided pathologically into three different categories: inflammatory fluid collections, non-neoplastic pancreatic cysts and pancreatic cystic neoplasms (PCNs). Non-neoplastic cysts are often only identified after a surgical resection.

PCNs are further categorized into four subtypes with varying degrees of potential towards malignancy:

- Serous neoplasms
- Mucinous cystic neoplasms (MCNs)
- Intraductal papillary mucinous neoplasms (IPMNs)
- Solid pseudopapillary neoplasms (SPNs)

Evaluating tissues samples pathologically is a critical component of diagnosing patients with malignancy. Many cysts are first surveilled by imaging technology. The management of PCNs focuses on preventing progression of malignancy, while also avoiding unnecessary and invasive surgical intervention. If imaging is inconclusive, an evaluation is usually performed by endoscopic, ultra-sound guided fine needle aspiration sampling of fluid and the cyst wall using cytologic examination and analysis. Generally, before a diagnosis is made, the patient may have undergone any or all of the following diagnostic procedures: computed tomography, magnetic resonance imaging/magnetic resonance cholangiopancreatography, and/or endoscopic ultrasound (with or without fine needle aspiration). Additional tests may include amylase, lipase, and carcinoembryonic antigen (CEA) levels on cyst fluid, but these may still leave uncertainty as to a diagnosis.

Combining pathological study with molecular analysis and/or serum biomarkers is proposed to enhance the ability for greater diagnostic confirmation. One method used to ascertain subtypes of PCN and to identify malignancy is the use of biomarkers in peripheral blood such as serum carbohydrate antigen (CA) 19-9. Serum CA 19-9 levels that exceed 37 U/ml, may provide information on potential malignancy or invasive IPMN.

Cystic fluid analysis is also purported as useful to further analyze PCN by subtype. Analyses of pancreatic cystic fluid for this purpose may include CEA, CA 19-9, amylase and lipase, viscosity, mucin stain, and cytology.

DNA molecular analysis has been suggested as another way to gather important diagnostic information on pancreatic cysts. DNA markers such as *GNAS* and *KRAS* have evidenced specificity and sensitivity for diagnosis of whether a cyst is an IPMN.

Proprietary tests are available that propose that they can estimate the chances of pancreatic cancer with pancreatic cyst fluid and integrated molecular pathology or molecular anatomic pathology.

Proprietary Testing

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. RedPath developed 5 different Pathfinder GT tests (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 PancraGen.

PancraGen 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 to test tumor suppressor genes (such as *PTEN* and *TP53*) and oncogenes (such as *KRAS* and *NRAS*). PancraGen is intended as a supplement to other diagnostic tools such as cytology and imaging, and is proposed to enhance assessments of malignancy risk. 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 and GNAS. The report provides summary of specific molecular results and details of each result with the possible clinical meanings of those results. Interpace also offers PanDNA, which provides molecular-only results to enhance risk stratification of pancreatic cysts. DNA abnormalities are identified by PanDNA technology from aspirated pancreatic cyst fluid without the integration with first-line testing results.

Another test revolving around pancreatic cyst fluid testing is PancraSeq, from UPMC. This test "detects single nucleotide variants (SNVs) and insertions/deletions (indels) in targeted regions of 20 pancreatic cancer-related genes (which are as follows: *AKT1, APC, BRAF, CTNNB1, GNAS, HRAS, IDH1, IDH2, KRAS, MEN1, MET, NF2, NRAS, PIK3CA, PTEN, STK11, TERT, TP53, TSC2,* and *VHL*), and copy number alterations in 4 genes (*RNF43, SMAD4, TP53,* and *VHL)*" and is intended to aid in diagnosis of several categories of pancreatic cyst, such as pseudocysts and mucinous cystic neoplasms (MCNs). The test reports alterations in any of its genes, its allele frequency, and whether the variant is of clinical or "potential" clinical significance.

Clinical Utility and Validity

Malhotra et al. (2014) 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.

Al-Haddad et al. (2015) published a study that examined the diagnostic accuracy of IMP for pancreatic adenocarcinoma. 492 samples were assessed, and out of the benign or indolent IMP diagnoses, 97% had a benign follow-up for up to 7 years, 8 months after IMP testing. Statistically higher risk and aggressive

diagnoses had hazard ratios for malignancy of 30.8 and 76.3, respectively. The Sendai surveillance criteria had identical chances of benign follow-up over the same timeframe, but the Sendai surgical criteria only had a hazard ratio of 9.0. The authors concluded, "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."

Loren et al. (2016) performed a study evaluating the impact of IMP testing on clinical management decisions. 491 patients were examined, and 66 had a malignant outcome (425 benign). The IMP testing was compared to the 2012 International Consensus Guideline (ICG) recommendations. When the two methods agreed, surveillance and surgery was undertaken in 83% and 88% of the cases, respectively. However, when the methods disagreed, the clinicians tended to agree with the IMP method. 88% of patients had an intervention when ICG recommended surveillance but IMP indicated "high-risk", and 55% of patients underwent surveillance when ICG recommended surgery but IMP indicated low risk. The authors concluded 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 et al. (2015) 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%.

Singhi et al. (2016) assessed the accuracy of the AGA guidelines in detecting advanced neoplasia and presented an alternative approach to pancreatic cysts. The clinical findings 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 with 13 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. (2018) 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/GNA*S 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."

Das et al. (2015) 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." 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.

Laquiere et al. (2019) investigated the concordance of mutation analysis between pancreatic cyst fluid and neoplastic tissue. The authors used next-generation sequencing to compare DNA collected from both cystic fluid (CF) and neoplastic tissue (NT). 17 patients were included, and concordant CF-NT genotypes were found in 15 of 17 patients. A higher proportion of mutated alleles were found in CF compared to NT. The authors also noted that "the sensitivity and specificity of *KRAS/GNAS* mutations in CF to predict an appropriate indication for surgical resection were 0.78 and 0.62, respectively. The sensitivity and specificity of *RAF/PTPRD/CTNNB1 /RNF43/POLD1/TP53* mutations in CF were 0.55 and 1.0, respectively." Although the authors remarked that mutational analysis between both media were highly concordant, they also stated that the results "need to be confirmed on a larger scale."

Volckmar et al. (2019) published preliminary results from the "prospective ZYSTEUS biomarker study." This study is intended to investigate "(i) whether detection of driver mutations in IPMN [intraductal papillary mucinous neoplasm] by liquid biopsy is technically feasible, (ii) which compartment of IPMN is most suitable for analysis, and (iii) implications for clinical diagnostics." 15 patients with pancreatic cysts larger than 10 mm were included, 12 of which had an IPMN and 3 acute pancreatitis controls. All 12 IPMN cases were found to harbor at least one mutation in either KRAS (n = 11) or GNAS (n = 4), with 3 cases harboring both mutations. In 3 cases with "pseudocysts", no alterations were identified. The authors also found that DNA yields were higher and showed higher mutation diversity in the cellular fraction and concluded that "mutation detection in pancreatic cyst fluid is technically feasible with more robust results in the cellular than in the liquid fraction." The authors also suggested that their results, "targeted sequencing supports discrimination of IPMN from pseudocysts" when combined with imaging.

Herranz Pérez et al. (2021) studied the impact of molecular analysis on the detection of mucinous cysts and malignancy. Currently, recommendations suggest endoscopic ultrasound fine-needle aspiration (EUS-FNA) with molecular analysis to improve the diagnosis of pancreatic cysts. EUS-FNA and next-generation sequencing was performed in 36 pancreatic cysts, which were classified as mucinous, non-mucinous, and malignant. Of the 36 lesions, 28 (82.4%) were classified as mucinous, 6 (17.6%) were classified as non-mucinous, and 5 (13.9%) were classified as malignant lesions. *KRAS* and *GNAS* genes were analyzed for mutations. Analysis of *KRAS* and *GNAS* showed 83.33% sensitivity, 60% specificity, 88.24% positive predictive value, and 50% negative predictive value for the diagnosis of mucinous cystic

lesions. Mutations in *KRAS* and *GNAS* were found in 2/5 (40%) of the lesions classified as non-mucinous, so they were recategorized as mucinous neoplasms. These led to a modification of the follow up plan in 8% of the cysts. Additionally, 1 indeterminate cyst showed a mutation in both *KRAS* and *GNAS*, so it could also be classified as mucinous. Therefore, performing molecular analysis in cases of uncertain diagnosis improved categorization of the cyst. 100% of the malignant cysts had mutations in *KRAS* and/or *GNAS*. However, the presence of a mutation was not related to malignancy. Overall, the authors conclude that "molecular analysis can improve the classification of pancreatic cysts as mucinous or non-mucinous. This is important as mucinous cysts are premalignant lesions and have a higher risk of concomitant pancreatic adenocarcinoma, thus implying long-term follow-up."

Buerlein and Shami (2021) published an overview of current guidelines for gastroenterologists as part of recommendations for pancreatic cysts. The prevalence of pancreatic cysts has increased as technology has improved. However, incidental identification of asymptomatic pancreatic cysts causes patient concern as malignancy varies greatly and surgical resection is an invasive technique. Pancreatic cystic neoplasms (PCNs) fall into one of two categories: mucinous PCNs, which create mucus and have a greater potential for malignancy, as compared to non-mucinous PCNs. In regard to biomarker identification, EUS-guided fluid samples taken from PCNs combined with ways of acquiring tissue to analyze PCN malignancy “could improve our ability to accurately diagnose PCNs and understand their risk of malignant transformation.” However, “these are not currently recommended for usage by any of the guidelines.” The authors briefly discussed several methods of risk-stratifying pancreatic cysts through identifying mucinous versus non-mucinous cysts: (1) next-generation sequencing of PCN fluid (2) cyst fluid glucose level (3) microbiopsy, and (4) confocal laser endomicroscopy. All four methods were described as requiring further clinical validation.

Nagula et al. (2010) evaluated the use of cyst fluid CEA analysis in the diagnosis of mucinous cysts of the pancreas. A group of 267 patients was identified by pathological diagnosis. Mucinous cysts were identified in 66 of 97 patient cases (68%) by CEA value. A CEA greater than 192 ng/mL had a sensitivity of 73% and specificity of 65% when it came to identifying mucinous cysts. However, cyst fluid CEA was not found to be associated with malignancy. A non-surgical strategy was used to manage the 178 patients identified to have mucinous cysts. Eight of these patients later had radiographic developments that required surgery. Results from pathology indicated seven benign mucinous cysts and one retention cyst. The conclusion of the study was that “cyst fluid CEA is a useful test for identifying mucinous cysts, including MCN and IPMN. In mucinous cysts, cyst fluid CEA is not associated with malignancy or radiographic progression.”

Oh et al. (2014) used a pancreatic cyst database containing the profiles of 78 patients with histologically proven cysts to study the differential diagnosis of pancreatic cysts using cyst fluid amylase and CEA. Of 78 patients, 32 were male and the median age was 60.4 years. Cyst fluid amylase levels showed a significant difference between pseudocysts (PP) and mucinous cystic neoplasms (MCNs) but did not aid in distinguishing between MCNs and IPMN. The cyst fluid CEA showed a significant difference between pseudocysts and mucinous cystic neoplasms (median: 26.00 versus 627.50 ng/mL respectively, $p< 0.001$) and between pseudocysts (26.00 ng/mL) and IPMN (356.50 ng/mL). Overall, the established optimal cut-off values from the study were 6,800 U/mL for amylase and 50 ng/mL for CEA. These correlated with the “crossover of the sensitivity and specificity curves for differentiating PP and mucinous neoplasms. The overall accuracies of cyst fluid amylase and CEA were 69% and 85%, respectively.”

Smith et al. (2016) performed a retrospective study on cytology, amylase, and CEA in the preoperative diagnosis of pancreatic cysts. The goal of the study was to reclassify and analyze malignancy risk in cysts

that were already histologically proven to be pancreatic neoplastic mucinous cysts using Pap Center guidelines, ancillary testing through amylase and CEA values, and cytology. First, a database search was conducted. Pancreatic neoplastic mucinous cyst resections using EUS-FNA technique in the prior year were identified. One hundred and thirty-eight cases of pancreatic neoplastic mucinous cysts were retrieved. Eleven cases were excluded for missing slides. Of the remaining 127 cases, there were 81 IPMNs and 86 MCNs. Cysts that were atypical, suspicious, or positive were re-reviewed, blinded to the previous diagnosis and categorization. The authors concluded that the sensitivity of cytology for diagnosis of neoplastic mucinous cysts (with ancillary information from amylase and CEA values) was 76.4%. Diagnosis of malignancy using cytology had a sensitivity of 48.3%, specificity of 94.9% and accuracy of 84.3%. The authors concluded that a "purely cytologic approach is inferior to an integrated approach of cytology with ancillary testing in diagnosing a neoplastic mucinous cyst of the pancreas."

V. Guidelines and Recommendations

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."

American College of Gastroenterology (ACG)

In 2018, the ACG updated its recommendations 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."

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."

American Society for Gastrointestinal Endoscopy (ASGE)

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."

National Comprehensive Cancer Network (NCCN)

The current NCCN clinical practice guidelines for pancreatic adenocarcinoma does not include recommendations for assessment of pancreatic cyst fluid.

International Consensus Fukuoka Guidelines

The International Association of Pancreatology (IAP) 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." Overall, the guideline remarked that molecular analysis of cyst fluid is "still evolving."

European Study Group on Cystic Tumours of the Pancreas

This guideline is considered "a joint initiative of the European Study Group on Cystic Tumors of the Pancreas, United European Gastroenterology, European Pancreatic Club, European-African Hepato-Pancreato-Biliary Association, European Digestive Surgery, and the European Society of Gastrointestinal Endoscopy."

The guidelines state that "DNA markers, in particular, mutations in *GNAS* and *KRAS*, have shown promise in identifying mucin-producing cysts. In cases in which the diagnosis is unclear, and a change in diagnosis will alter management, analysis of these mutations using highly sensitive techniques, such as next-generation sequencing (NGS), may be considered." This recommendation was given a grade of "2C." The guidelines also remarked that there is "insufficient evidence" to support the use of RNA or non-carcinoembryonic antigen protein markers in pancreatic cysts. This recommendation was given a grade of "1B."

International Cancer of the Pancreas Screening (CAPS) Consortium

The CAPS Consortium was convened to update the consensus recommendations for "management of individuals with increased risk of pancreatic cancer based on family history or germline mutation status (high-risk individuals)." In this Consortium, the authors state that "In some cases, evidence of pancreatic neoplasia can be inferred by the presence of mutations detected in secretin-stimulated pancreatic fluid samples…but further investigation is needed to determine the value of these tests for patients under pancreatic surveillance."

World Gastroenterology Organization (WGO)

THE WGO Global Guidelines provided key guidelines in diagnosis and management of pancreatic cystic lesions. The following recommendations were made:

1. "At the initial cyst fluid aspiration: carry out carcinoembryonic antigen (CEA), amylase, and cytology testing.
2. Molecular testing is not routinely done because of limited data and the expense, but it does hold promise for the future.
3. When fluid is aspirated, the following tests are recommended in the sequence described, depending on the volume of the aspirate:
   - Cytology: glycogen-rich cells (SCNs) or mucin-containing cells (MCNs and IPMNs), but the sensitivity is low.
   - Tumor markers: CEA level, an accurate tumor marker for diagnosing a mucinous PCN (the accuracy and cut-off level vary among laboratories).
   - Diagnostic molecular markers: KRAS, GNAS, VHL, CTNNB1.
   - Prognostic molecular markers: TP53, PIK3CA, PTEN.
   - Mucins: assessment of cyst mucin is complementary to cyst CEA levels and cytology
   - Viscosity: the "string sign" concept is an indirect, inexpensive, but subjective measurement of viscosity, assessed by placing a sample of aspirated fluid between the thumb and index finger and measuring the length of stretch prior to disruption.
   - Amylase (or lipase)."

The guidelines also state: “molecular testing is not routinely done because of limited data and the expense, but it does hold promise for the future.”

American College of Radiology

The Expert Panel on Gastrointestinal Imaging of the American College of Radiology created guidelines to determine the appropriate initial imaging study to further evaluate a pancreatic cyst that was incidentally detected on a nondedicated imaging study. ACR mentions that molecular assays for markers such as *K-ras, GNAS, PTEN, VHL, TP53*, and *PIK3CA* “may also assist in differentiating neoplastic cystic lesions and predicting cyst behavior. When performed in centers with expertise in EUS-FNA, cytological evaluation can identify atypia, dysplasia, or neoplasia.”

American Society of Clinical Oncology (ASCO)

In 2019, ASCO published a guideline on the susceptibility to pancreatic cancer. The authors note the importance of emerging data despite very few clinical trials. In a disclaimer, they note: “This PCO should be read with the understanding that randomized clinical trial data are not available for these guidance statements, but it is the opinion of the Expert Panel that the statements made represent the state of the data available**.”** Generally, they note that there are “currently no approved biomarkers for screening or surveillance.”

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST Integration members under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Policy History

Policy approved by Medical Directors	9/20/2022
Policy approved at UMC	12/16/2022
Policy effective	6/1/2023
Updated Lines of Business	12/18/2023