Topographic Genotyping

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DESCRIPTION

Topographic genotyping is also referred to as integrated molecular pathology, is a type of quantitative genetic mutational analysis. Interspace Diagnostics has created two topographic tests, PancraGEN® and BarreGEN® which combines genetic testing with pathology services, such as sample preparation, genetic testing, and interpretation of the results by a pathologist. These tests are proposed as adjunctive tools when a definitive pathologic diagnosis or prognosis is inconclusive.

The PathFinderTG® is a patented topographic genotyping test platform that combines anatomic pathology (microscopic analysis) with quantitative genetic mutational analysis (molecular tissue analysis). Under microscopic examination of tissue and other specimens, areas of interest may be identified and microdissected to increase tumor cell yield for subsequent molecular analysis. Topographic genotyping may permit pathologic diagnosis when first-line analyses are inconclusive.

Interpace Diagnostics acquired RedPath Integrated Pathology and has since cultivated and developed the PancraGEN® and BarreGEN® molecular pathology panels on the

PathFinderTG® platform. 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."

BarreGEN®
BarreGEN® (esophageal cancer risk classifier) is a molecular based assay that helps resolve the risk of progression of Barrett's Esophagus (BE) to esophageal cancer.

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 (GERD). Barrett's esophagus (BE) is a precancerous condition typically caused by gastroesophageal reflux disease (GERD) and is a major risk for esophageal cancer. These tumors frequently spread before symptoms are present so detection at an early stage might be beneficial. Other risks for Barrett's esophagus (BE) include age, male sex, white race, obesity, tobacco use, and family history of GERD, BE or esophageal cancer. While individuals with BE are at higher risk of esophageal cancer, progression to cancer is uncommon. Roughly, only 0.5% people with BE develop cancer each year. While uncommon there is a potential for the progression of cellular changes that can lead to esophageal cancer. BarreGEN® is utilized to help identify Barrett's esophagus (BE) individuals at higher risk of esophageal cancer.

Triaging individuals according to their risk of future progression to esophageal cancer would help to limit unnecessary repeat endoscopies in individuals with low risk and justify more aggressive management in individuals with higher risk, perhaps even supporting early means of cancer prevention such as ablation. However, differentiating the presence and stage of dysplasia remains a challenge for pathologists, resulting in high inter-observer variability in diagnosing the level of dysplasia and the associated risk of esophageal cancer.

BarreGEN® is a molecular based assay conducted using tissue biopsy sample that quantifies the mutational load (ML) in esophageal specimens obtained from individuals with BE. ML provides a measure of cumulative genomic instability (DNA damage). In looking at key genomic loci 1p (CMM1, L-myc), 3p (VHL, HoGG1), 5q (MCC, APC), 9p (CDKN2A), 10q (PTEN, MXI1), 17p (TP53), 17q (RNF43, NME1), 18q (SMAD4, DCC), 21q (TFF1, PSEN2) and 22q (NF2) in individuals with BE and assessing DNA damage in tumor suppressor genes associated with progression to HGD and esophageal cancer, the risk of more advanced disease can be determined. The use of BarreGEN® purports this testing assists the physicians understanding if dysplasia is present or if there is a risk for developing dysplasia or cancer in the future, which assists in treatment management decisions for cancer preventative treatments such as ablation or provide justification for when such treatments may not be necessary.

Clinical Context and Test Purpose
The American Gastroenterological Association has defined Barrett esophagus as replacement of normal epithelium at the distal esophagus by intestinal metaplasia, which

predisposes to malignancy. Although grading of dysplasia in mucosal biopsies is the current standard for assessing the risk of malignant transformation, esophageal inflammation may mimic or mask dysplasia, and interobserver variability may yield inconsistent risk classifications. Additional prognostic information, therefore, may be potentially useful.

Populations
The relevant population of interest is individuals with Barrett esophagus. It is unclear what other clinical characteristics would identify candidates for BarreGEN® or what previous testing is appropriate before BarreGEN®.

Interventions
The test being considered is BarreGEN® topographic genotyping in addition to standard prognostic practices.

The Interpace website describes BarreGEN® as a molecular diagnostic test to "determine the risk of progressing to esophageal cancer in individuals with Barrett's Esophagus.",

Comparators
The following tests and practices are currently being used to predict developing Barrett esophagus: standard prognostic techniques generally include grading of dysplasia from endoscopy with biopsy.

Outcomes
Outcomes of interest are survival and conversion to esophageal cancer. It is not clear how the test would fit into the diagnostic pathway and effect treatment or surveillance recommendations, therefore, complete specification of other important outcomes is not possible. Because it is not yet clear how this test would be used in practice, follow-up time for outcomes is unclear.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Section Summary: BarreGEN®
There is limited evidence evaluating the clinical validity of the BarreGEN® test for assessing Barrett esophagus. The evidence reviewed does not demonstrate that BarreGEN® testing for prognosis of Barrett esophagus adds incremental value to current prognostic assessments.

PancraGEN®
PancraGEN® 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 individuals with pancreatic cysts and solid pancreaticobiliary lesions and enhance diagnostic tools by providing more information for use in management decisions for surveillance versus surgical intervention.

The specimen type utilized is cytologic testing and PancraGEN® identifies the following:

- Oncogene Mutations
    - KRAS and GNAS; and
- The following tumor suppressor gene mutations:

Tumor Suppressor Gene Mutations	
VHL, OGG1	3p
PTEN, MXI1	10q
TP53	17p
SMAD4, DCC	18q
CDKN2A	9p
RNF43, NME1	17q
PSEN2, TFF1	21q
CMM1, LMYC	1p
MCC, APC	5q
NF2	22q

The PancraGEN® molecular panel using PathFinderTG® also provides risk stratification of an individual's pancreaticobiliary sample by integrating clinical features and the following test components:

- Oncogene point mutations (KRAS and GNAS)
- Tumor suppressor gene mutations (loss of heterozygosity through fragment analysis)

The PacraGEN® report categorizes individuals into four group according to their risk (benign, statistically indolent, statistically higher- risk or aggressive) and provides either the probability of benign disease over three years or the probability of high-grade dysplasia/carcinoma.

Low Risk Supports Surveillance

- Benign: 97% probability of benign disease over the next three years. An individual lacks significant molecular alterations.

- Statistically Indolent (SI): 97% probability of benign disease over the next three years. The individual has significant molecular alteration but lacks concerning clinical features.

High-Risk Supports Intervention

- Statistically Higher Risk (SHR): 65% probability of HDG/carcinoma. The individual has significant molecular alteration accompanied by concerning clinical features.
- Aggressive: 91% probability of HGD/carcinoma. The individual has multiple significant DNA abnormalities.

Pancreatic Cysts

The widespread use and increasing sensitivity of computed tomography and magnetic resonance imaging scans have been associated with a marked increase in the finding of incidental pancreatic cysts. In individuals without a history of symptoms of pancreatic disease undergoing computed tomography and magnetic resonance imaging, studies have estimated the prevalence of pancreatic cysts as being between 2% and 3%. Although data have suggested the malignant transformation of these cysts is very rare, due to the potential life-threatening prognosis of pancreatic cancer, an incidental finding can start an aggressive clinical workup.

Many cysts can be followed with imaging surveillance. Recommendations for which cysts should proceed for surgical resection vary. If imaging of the cyst is inconclusive, additional testing of cystic pancreatic lesions is usually performed by endoscopic ultrasound with fine-needle aspiration (EUS-FNA) sampling of the fluid and cyst wall for cytologic examination and analysis. Cytologic examination of these lesions can be difficult or indeterminate due to low cellularity, cellular degeneration, or procedural difficulties. Ancillary tests (e.g., amylase, lipase, carcinoembryonic antigen levels) often are performed on cyst fluid to aid in diagnosis and prognosis but results still may be equivocal.

International consensus has recommended surgical resection for all surgically fit individuals with mucinous cystic neoplasm or main duct intraductal papillary mucinous neoplasm. This is due to the uncertainty of the natural history of mucinous cystic neoplasm and main duct intraductal papillary mucinous neoplasm and the presumed malignant potential of all types. Estimates of morbidity and mortality following resection vary. A technical review by Scheiman et al. (2015), conducted for the American Gastroenterological Association, combined estimates into a pooled mortality rate of about 2% and serious complication rate of about 30%. Therefore, there is a need for more accurate prognosis to optimize detection of malignancy while minimizing unnecessary surgery and treatment.

The question addressed in this evidence review is: Does testing using PancraGEN® topographic genotyping in addition to standard diagnostic or prognostic practices improve the net health outcome in individuals with pancreatic cysts?

Populations
The relevant population of interest is patients for whom there remains clinical uncertainty regarding the malignant potential of a pancreatic cyst after comprehensive first-line evaluation and who are being considered for surgery.

Interventions
The test being considered is PancraGEN® topographic genotyping in addition to standard diagnostic or prognostic practices.

PathFinderTG® (Interpace Diagnostics) gene variant profiles are intended to inform complex diagnostic dilemmas in patients at risk of cancer. The manufacturer's website states the PancraGEN® technology is "intended to be an adjunct to first line testing" and suggests the test is useful in assessing who will benefit most from surveillance and/or surgery. The clinical purpose of PancraGEN® is to allow patients with low-risk cysts to avoid unnecessary surgery or to select patients with malignant lesions for surgery more accurately. PancraGEN® would likely be used in conjunction with clinical and radiologic characteristics, along with cyst fluid analysis; therefore, one would expect an incremental benefit to using the test.

Diagnostic Algorithm for PancraGEN®		
Diagnostic Category	**Molecular Criteria**	**Coexisting Concerning Clinical Features**
Benign	DNA lacks molecular criteria	Not considered for this diagnosis
Statistically indolent	DNA meets 1 molecular criterion	None
Statistically higher risk	DNA meets 1 molecular criterion	1 or more
Aggressive	DNA meets at least 2 molecular criteria	Not considered for this diagnosis

Comparators
The following tests and practices are currently being used to diagnose pancreatic cysts: standard diagnostic and prognostic techniques, including imaging using magnetic resonance imaging with magnetic resonance cholangiopancreatography, multidetector computed tomography, or intraductal ultrasound, EUS-FNA, cytology, and amylase and carcinoembryonic antigen in cyst fluid. In the absence of definitive malignancy by first-line testing, indications for surgery are frequently based on morphologic features according to 2012 international consensus panel statements for a management of intraductal papillary mucinous neoplasm and mucinous cystic neoplasms.

Outcomes
The primary outcomes of interest are survival and complications of surgery. Beneficial outcomes resulting from a true-test result are the initiation of appropriate treatment or avoiding unnecessary surgery. Harmful outcomes resulting from a false test result are unnecessary surgery and failing to receive timely appropriate surgery or treatment. The American Gastroenterological Association has recommended surveillance of cysts that do not meet criteria for resection for five years.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

(2019) Farrell et al. determined the incremental predictive value of pancreatic cyst fluid molecular analysis to assessing malignancy risk over long-term follow-up of a well-characterized cohort, given the underlying predictive value of imaging parameters routinely used to triage such patients. They identified patients who lacked initial cytologic malignancy in cyst fluid and had final pathology or a follow-up period of more than 2 years were included. Patient outcomes determined the malignancy-free survival of patients with high-risk stigmata (HRS), worrisome features (WFs), and DNA abnormalities. DNA analysis included 3 abnormalities: loss of heterozygosity mutations among a panel of tumor suppressor genes, Kras mutation, and elevated DNA quantity. The study included were 478 patients; 209 had surgical pathology-derived outcomes and 269 had clinical follow-up of >2 years. Eleven percent had malignant outcome. Forty-two patients had HRS, 272 lacked both HRS and WFs, and 164 lacked HRS but had WFs. DNA abnormalities did not statistically change long-term malignancy risk in patients with HRS or in patients lacking both HRS and WFs. Among patients with WFs, the presence of ≥2 DNA abnormalities significantly increased malignancy risk (relative risk, 5.2; P = .002) and the absence of all DNA abnormalities significantly decreased risk (relative risk, .4; P = .040). Sensitivity analysis confirmed results of survival analysis over differing baseline malignancy probabilities. The authors concluded the study defines the clinical characteristic of patients in which DNA abnormality testing has the greatest impact on patient outcomes. Use of DNA abnormality testing is supported in a carefully selected patient population limited to cysts with WFs.

(2016) Kowalski et al. reported on an analysis of false negatives from the same 492 records from the NPCR. Of the 6 cysts found false negative using consensus classification, 5 cysts were 2 cm or less (the remaining case did not have data on cyst size) and 1 reported symptom (obstructive jaundice). Of the 11 cases that were false-negative according to PancraGEN, 10 were reported to have EUS-FNA sampling

limitations, 1 had a family history of pancreatic cancer, 4 reported symptoms (including pancreatitis, steatorrhea, nausea, bloating, and/or upper abdominal discomfort), and cysts sizes ranged from 0.7 to 6 cm for the 6 in which size was reported. The authors concluded, adjunct use of IMP can provide evidence for relaxed surveillance of patients with benign cysts that meet Fukuoka criteria for closer observation or surgery. Although infrequent, FN results with IMP can be associated with EUS-FNA sampling limitations or high-risk clinical circumstances.

(2016) Loren et al. published results comparing the association between PancraGEN diagnoses and Sendai and Fukouka consensus guideline recommendations with clinical decisions regarding intervention and surveillance. Patients were categorized as (1) "low-risk" or "high-risk" using the Interpace algorithm for PancraGEN diagnoses; (2) meeting "surveillance" criteria or "surgery" criteria using consensus guidelines; and (3) having "benign" or "malignant" outcomes during clinical follow-up as described previously. Additionally, the real-world management decision was categorized as "intervention" if there was a surgical report, surgical pathology, chemotherapy, or positive cytology within 12 months of the index EUS-FNA, and as "surveillance" otherwise. Among patients who received surveillance as the real-world decision, 57% were also classified as needing surveillance according to consensus guidelines, and 96% were classified as low risk according to PancraGEN. However, among patients who had an intervention as the real-world decision, 81% were classified as candidates for surgery by consensus guidelines, and 40% were classified as high risk by PancraGEN. In univariate logistic regression analyses, the odds ratio for the association between PancraGEN diagnoses and real-world decision was higher (odds ratio, 16.8; 95% CI, 9.0 to 34.4) than the odds for the association between the consensus guidelines recommendations and real-world decision (odds ratio, 5.6; 95% CI, 3.7 to 8.5). In 8 patients, the PancraGEN diagnosis was high risk, and the consensus guideline classification was low risk. In seven of these cases, the patient received an intervention resulting in the discovery of an additional four malignancies that would have been missed using the consensus guideline classification alone, and in the remaining case the patient underwent surveillance and did not develop a malignancy. In 202 patients, the PancraGEN diagnosis was low risk, and the consensus guideline classification was high risk. In 90 of these 202, patients had an intervention, and 8 additional malignancies were detected. In 112 of these 202, patients received surveillance, and 1 additional malignancy occurred in the surveillance group. This study demonstrated that results from PancraGEN testing are associated with real-world decisions, although other factors (e.g., physician judgment, patient preferences) could have affected these decisions.

Section Summary: Pancreatic Cysts

The evidence for the clinical validity of PancraGEN consists of several retrospective studies. Most evaluated performance characteristics of PancraGEN for classifying pancreatic cysts according to the risk of malignancy without comparison to current diagnostic algorithms. The best evidence regarding incremental clinical validity comes from the report from the NPCR, which compared PancraGEN® performance characteristics with current international consensus guidelines and found that

PancraGEN® has slightly lower sensitivity (83% vs 91%), similar NPV (97% vs 97%), but better specificity (91% vs 46%) and PPV (58% vs 21%) than the consensus guidelines. The registry study included a very select group of patients, only a small fraction of all enrolled patients, and used a retrospective design. Longer follow-up including more of the registry individuals is needed. The manufacturer has indicated the technology is meant as an adjunct to first-line testing, but no algorithm for combining PancraGEN® with consensus guidelines for decision making has been proposed, and the data reporting outcomes in individuals where the PancraGEN® and consensus guideline diagnoses disagreed was limited. The best strategy for combining the results of PancraGEN® with current diagnostic guidelines is not clear. There is some suggestion that PancraGEN® might appropriately classify some cases misclassified by current consensus guidelines, but the sample sizes in the cases where the PancraGEN® and consensus guidelines disagree are small, limiting confidence in these results. The evidence reviewed does not demonstrate that PathFinderTG® has incremental clinical value in the diagnosis or prognosis of pancreatic cysts and associated cancer.

Solid Pancreaticobiliary Lesions

Clinical Context and Test Purpose
Pancreatic cancer is usually diagnosed in advanced stages when effective treatment options are limited. Currently, symptomatic individuals with solid pancreaticobiliary lesions undergo cytology testing. If results from cytology testing are inconclusive, fluorescent in situ hybridization (FISH) molecular testing of solid pancreaticobiliary lesions is recommended. PancraGEN® topographic genotyping is being investigated as either an alternative to or an adjunct to FISH in the diagnosis confirmation process.

The purpose of PancraGEN® topographic genotyping in individuals who are symptomatic with high suspicion of cholangiocarcinoma or pancreatic cancer with inconclusive cytology testing results is to potentially confirm a diagnosis, which would inform individual management decisions.

Populations
The relevant population of interest is symptomatic individuals with high suspicion of cholangiocarcinoma or pancreatic cancer based on endoscopic imaging showing bile duct obstruction or solid mass who receive inconclusive cytology testing results.

Interventions
The test being considered is PancraGEN® topographic genotyping, as either an alternative test or adjunct test to FISH molecular testing of solid pancreaticobiliary lesions. Fluorescence in situ hybridization (FISH) is currently considered second-line to standard routine cytology testing.

Comparators
The following tests are currently being used to diagnose cholangiocarcinoma or pancreatic cancer: cytology testing with and without standard molecular fluorescence in situ hybridization (FISH) testing.

Outcomes
The primary outcome of interest is overall survival. Beneficial outcomes resulting from a true test result are the initiation of appropriate treatment or avoidance of unnecessary surgery. Harmful outcomes resulting from a false test result are unnecessary surgery or failing to receive timely appropriate surgery or chemotherapy. Cytology results with FISH and/or topographic genotyping may be available within a week. The long-term follow-up to monitor overall survival would require years.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

(2019) Kushnir et al. noted routine cytology of biliary stricture brushings obtained during ERCP has suboptimal sensitivity for malignancy. They compared the individual and combined ability of cytology, FISH analysis and PCR-based MP to detect malignancy in standard biliary brushings. They performed a prospective study of patients undergoing ERCP using histology or 1 year follow-up to determine patient outcomes; MP was performed on free-DNA from biliary brushing specimens using normally discarded supernatant fluid. MP examined KRAS point mutations and tumor suppressor gene associated LOH mutations at 10 genomic loci; FISH examined chromosome specific gains or losses. A total of 101 patients were included in final analysis and 69 % had malignancy. Cytology had 26 % sensitivity and 100 % specificity for malignancy. Using either FISH or MP in combination with cytology increased sensitivity to 44 % and 56 %, respectively. The combination of all 3 tests (cytology, FISH, and MP) had the highest sensitivity for malignancy (66 %). There was no difference in the specificity of cytology, FISH or MP testing when examined alone or in combination; MP improved diagnostic yield of each procedure from 22 % to 100 %; FISH improved yield to 90 %; MP detected 21 malignancies beyond that identified by cytology; FISH detected an additional 13. The combination of FISH and MP testing detected an additional 28 malignancies. The authors concluded that both MP and FISH are complimentary molecular tests that could significantly increase detection of biliary malignancies when used in combination with routine cytology of standard biliary brush specimens.

(2018) Khosravi et al. reported indeterminate cytology occurs in a significant number of patients with solid pancreaticobiliary lesion that undergo EUS-FNA or endoscopic retrograde cholangiopancreatography (ERCP) and can incur further expensive testing and inappropriate surgical intervention. Mutation profiling improves diagnostic accuracy and yield but the impact on clinical management is uncertain. These researchers determined

the performance of MP in clinical practice and its impact on management in solid pancreaticobiliary patients with indeterminate cytology. Solid pancreaticobiliary patients with non-diagnostic, benign, atypical, or suspicious cytology who had past MP testing were included. Mutation profiling examined KRAS mutation, and a tumor suppressor gene associated loss of heterozygosity mutation panel covering 10 genomic loci. Two endo-sonographers made management recommendations without and then with MP results, indicating their level of confidence. Mutation profiling improved diagnostic accuracy in 232 patients with indeterminate cytology. Among patients with non-diagnostic cytology, low-risk MP provided high specificity and negative predictive value (NPV) for the absence of malignancy while high-risk MP identified malignancies otherwise undetected. Mutation profiling increased clinician confidence in management recommendations and resulted in more conservative management in 10 % of patients. Mutation profiling increased the rate of benign disease in patients recommended for conservative management (84 % to 92 %, $p < 0.05$) and the rate of malignant disease in patients recommended for aggressive treatment (53 % to 71 %, $p < 0.05$). The authors concluded that MP improved diagnostic accuracy and significantly impacted management decisions. Low-risk MP results increased recommendations for conservative management and increased the rate of benign outcomes those patients, helping to avoid unnecessary aggressive interventions and improve patient outcomes. These researchers stated that their study was limited by its retrospective nature. Moreover, they noted that although high-risk MP results were able to help confirm the presence of malignancy in cases in which cytology indicated a high suspicion of malignancy, low-risk results could not effectively exclude the possibility of malignancy in such cases.

(2017) Gonda et al. reported it is a challenge to detect malignancies in biliary strictures. Various sampling methods are available to increase diagnostic yield, but these require additional procedure time and expertise. They evaluated the combined accuracy of fluorescence in situ hybridization (FISH) and PCR-based DNA MP of specimens collected using standard brush techniques. Thw researchers performed a prospective study of 107 consecutive patients treated for biliary strictures by endoscopic retrograde cholangiopancreatography from June 2012 through June 2014. They carried out routine cytology and FISH analyses on cells collected by standard brush techniques and analyzed supernatants for point mutations in KRAS and LOH mutations in tumor-suppressor genes at 10 loci (MP analysis was performed at Interpace Diagnostics). Strictures were determined to be non-malignant based on repeat image analysis or laboratory test results 12 months after the procedure. Malignant strictures were identified based on subsequent biopsy or cytology analyses, pathology analyses of samples collected during surgery, or death from biliary malignancy. These researchers determined the sensitivity and specificity with which FISH and MP analyses detected malignancies using the exact binomial test. The final analysis included 100 patients; 41 % had biliary malignancies. Cytology analysis identified patients with malignancies with 32 % sensitivity and 100 % specificity. Addition of FISH or MP results to cytology results increased the sensitivity of detection to 51 % ($p < 0.01$) without reducing specificity. The combination of cytology, MP, and FISH analyses detected malignancies with 73 % sensitivity ($p <$

0.001); FISH identified an additional 9 of the 28 malignancies not detected by cytology analysis, and MP identified an additional 8 malignancies; FISH and MP together identified 17 of the 28 malignancies not detected by cytology analysis. The authors concluded that these findings supported the use of both FISH testing and PCR-based MP of tumor-suppressor gene LOH and KRAS in evaluation of cytology-negative or indeterminate biliary strictures; MP allowed for increased diagnostic yield from each individual brush, given that normally discarded, cell-free supernatant material that contains DNA can be analyzed. Based on these findings, these researchers suggested using either FISH or MP as a 2nd-line diagnostic modality to 1st-line cytology. They stated that MP may be best prioritized to scenarios of low cellularity. Any case that is negative or indeterminate by 2 testing modalities should undergo a 3rd to increase the probability of detecting possible malignancy. To do so, normally discarded supernatant fluid should be retained for MP testing during the standard cytology cytocentrifugation preparation of cells for cytology. These researchers stated that additional studies may help to better understand the reflex order of sequential testing and the impact of this reflex on health economics. The authors stated that this study had several limitations which may have impacted generalized conclusions. A somewhat higher benign stricture rate was noted in their cases than in other prior series. There also were relatively few primary sclerosing cholangitis (PSC) patients included in this study. Prior studies have shown that there is a significant aneuploidy rate associated with pre-malignant lesions seen in PSC. Because of this, specificity of FISH for malignancy was expected to be lower in a cohort of PSC patients than the authors reported in their cohort. Less was known about detection of KRAS mutations in the progression of PSC to cholangiocarcinoma. However, based on this study cohort and prior studies, these findings likely were not generalizable to the PSC population.

Section Summary: Solid Pancreaticobiliary Lesions

The evidence for the clinical validity of using PancraGEN® to evaluate solid pancreaticobiliary lesions consists of several retrospective studies. One study evaluated the performance characteristics of PancraGEN® for classifying solid pancreatic lesions while the other others evaluated the classification of biliary strictures. Biliary strictures may be caused by solid pancreaticobiliary lesions but may have other causes. The authors of the studies did not specify what proportion of individuals with biliary stricture had solid pancreaticobiliary lesions. Compared to cytology alone, the use of cytology plus FISH plus PancraGEN® increased sensitivity significantly. The incremental value of using cytology plus FISH plus PancraGEN® over cytology plus FISH is unclear. The manufacturer has indicated that the technology is meant as an adjunct to first-line testing, but no algorithm for combining PancraGEN® with consensus guidelines for decision making has been proposed, nor has first-line testing been defined as cytology alone or cytology plus FISH. The evidence reviewed does not demonstrate that PathFinderTG ® has incremental clinical value for the diagnosis of solid pancreatic lesions and associated cancer.

Summary of Evidence: PancraGEN® and BarreGEN®
Currently, there is insufficient evidence in the published, peer-reviewed, scientific literature to demonstrate that topographic genotyping using PancraGEN® or BarreGEN® is an effective method to aid in the diagnosis or management of individuals with pancreatic cysts, solid pancreaticobiliary lesions, or Barrett's esophagus (BE) when other testing methods, such as endoscopic ultrasound, microscopic analysis, and staining, fail or are inconclusive. There is a lack of peer-reviewed evidence demonstrating that the use of topographic genotyping in the diagnosis and management of individuals with pancreatic cysts or Barrett's esophagus (BE) results in improved clinical outcomes. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Practice Guidelines and Position Statements

American College of Gastroenterology (ACG)

- **Barrett Esophagus**
  - (2022) The ACG released guidelines on the diagnosis and management of *Barrett esophagus*. The guidelines stated: We suggest that a swallowable, nonendoscopic capsule sponge device combined with a biomarker is an acceptable alternative to endoscopy for screening for BE in those with chronic reflux symptoms and other risk factors (strength of recommendation: conditional; quality of evidence: very low).
    - The summary of evidence further describes the following information:…trials to assess the performance methylated DNA markers (MDMs) in screening populations are ongoing to determine their performance characteristics in this setting.
  - We recommend endoscopic eradication therapy for patients with BE and high-grade dysplasia and those with BE and low-grade dysplasia. We propose structured surveillance intervals for patients with dysplastic BE after successful ablation based on the baseline degree of dysplasia. We could not make recommendations regarding chemoprevention or use of biomarkers in routine practice due to insufficient data.
    (*Accessed June 2022*)

- **Pancreatic Cysts**
  - (2018) The ACG published guidelines on the diagnosis and management of *pancreatic cysts*. The guidelines stated the evidence for the use of molecular biomarkers for identifying high-grade dysplasia or pancreatic cancer is insufficient to recommend their routine use. However, molecular markers may help identify intraductal papillary mucinous neoplasms and mucinous cystic neoplasms in cases with an unclear diagnosis and if results are likely to change the management (conditional recommendation; very low-quality evidence). (*Accessed June 2022*)

American Gastroenterological Association (AGA)

- **Asymptomatic Neoplastic Pancreatic Cysts**
  (2015) The American Gastroenterological Association (AGA) published guidelines on the diagnosis and management of *asymptomatic neoplastic pancreatic cysts*, based on findings from a technical review. The technical review stated the following about molecular testing:
  - "Case series have confirmed that malignant cysts have a greater number and quality of molecular alterations, but no study has been properly designed to identify how the test performs in predicting outcome with regard to need for surgery, surveillance, or predicting interventions leading to improved survival."
  - "Molecular techniques to evaluate pancreatic cysts remain an emerging area of research, and the diagnostic utility of these tests is uncertain."

  (*Accessed June 2022*)

- **Barrett Esophagus**
  (2011) The American Gastroenterological Association (AGA) published a medical position statement on the management of *Barrett esophagus*. Based on findings from a technical review as noted below:
  - "The AGA recommended against the use of molecular biomarkers to confirm the histological diagnosis of dysplasia or as a method of risk stratification for patients with Barrett's esophagus at this time (weak recommendation, low-quality evidence)." (*Accessed June 2022*)

American College of Radiology (ACR)

(2020) The Expert Panel on Gastrointestinal Imaging of the American College of Radiology (ACR) created ACR Appropriateness Criteria® Pancreatic Cyst to determine the appropriate initial imaging study to further evaluate a pancreatic cyst that was incidentally detected on a nondedicated imaging study.

- The 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.
- The guideline does not include any information regarding the use of topographic genotyping (PancraGEN®).

The American Society of Gastrointestinal Endoscopy (ASGE)

(2016) The American Society of Gastrointestinal Endoscopy guideline states,

- Molecular analysis (which requires only 200 mL of fluid) may be most useful in small cysts with nondiagnostic cytology, equivocal cyst fluid CEA results, or when insufficient fluid is present for CEA testing. However, additional research is needed to determine the precise role molecular analysis of cyst fluid will play in evaluating pancreatic cystic lesions. (*Accessed June 2022*)

National Comprehensive Cancer Network (NCCN)

- **Esophageal and Esophagogastric Junction Cancers Version 2.2022**
    - This current NCCN guideline does not include any information regarding the use of topographic genotyping (BarreGEN®).

- **Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic Version 2.2022**
    - This current NCCN guideline does not include any information regarding the use of topographic genotyping (PancraGEN®).

- **Pancreatic Adenocarcinoma Version 1.2022**
    - This current NCCN guideline does not include any information regarding the use of topographic genotyping (PancraGEN®).

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 test (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.

PathFinderTG ® Tests		
Test	**Description**	**Specimen Types**
BarreGEN® (*previously called PathFinderTG® Barrett*)	Measures the presence and extent of genomic instability and integrates those results with histology	Esophageal tissue
PancraGEN® (*previously called PathFinderTG® Pancreas*)	Uses loss of heterozygosity markers, oncogene variants, and DNA content abnormalities to stratify individuals according to their risk of progression to cancer	Pancreatobiliary fluid/ERCP brush, pancreatic masses, or pancreatic tissue

ERCP: endoscopic retrograde cholangiopancreatography.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies:

- 02.01.23 Treatment for Gastroesophageal Reflux Disease (GERD)
- 02.01.63 Treatment of Barrett's Esophagus

Topographic genotyping using the PathfinderTG ® system (e.g., BarreGEN®, PancraGEN®) is considered **investigational** for all indications including, but not limited to the following, because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- Barrett esophagus
- Pancreatic cysts
- Solid pancreaticobiliary lesions

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81479 Unlisted molecular pathology procedure
- 81599 Unlisted multianalyte assay with algorithmic analysis
- 84999 Unlisted chemistry procedure
- 89240 Unlisted miscellaneous pathology test

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POLICY HISTORY

Date	Reason	Action
June 2022	Annual Review	Policy Revised
June 2021	Annual Review	Policy Revised
June 2020	Annual Review	Policy Revised
June 2019	Annual Review	Policy Revised
June 2018	Annual Review	Policy Revised
June 2017	Annual Review	Policy Revised
June 2016	Annual Review	Policy Revised
July 2015		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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