Medical Policy Manual Genetic Testing, Policy No. 16

PathFinderTG® Molecular Testing

Effective: June 1, 2018

Next Review: April 2019
Last Review: April 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The PathFinderTG® platform is a molecular testing system used adjunctively in cases for which a definitive pathologic diagnosis cannot be rendered on a tissue or cytology specimen, either due to inadequate specimen or equivocal histologic or cytologic findings.

MEDICAL POLICY CRITERIA

Molecular testing using the PathFinderTG® system is considered **investigational** for all indications, including, but not limited to, the evaluation of pancreatic cyst fluid, and Barrett esophagus.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

Potential uses described by the manufacturer involve multiple organ systems and clinical scenarios, such as determining reactive versus neoplastic lesions, benign versus malignant

lesions, biologically indolent versus aggressive tumors, which premalignant lesions will or will not progress into cancer, whether a synchronous or metachronous tumor represents metastatic spread or a new primary, and expected responses to treatment for various tumors.

Topographic genotyping (TG), also called molecular anatomic pathology, integrates microscopic analysis (anatomic pathology) with 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. TG may permit pathologic diagnosis when first-line analyses are inconclusive.[1]

RedPath Integrated Pathology (now Interpace® Diagnostics) has patented a proprietary platform, called PathFinderTG®, to provide variant analyses of patient specimens. The aim of PathFinderTG® testing is to integrate molecular findings into the pathology diagnosis. The patented technology permits analysis of tissue specimens of any size, and according to the manufacturer, "including minute needle biopsy specimens," and any age, "including those stored in paraffin for over 30 years."[2] Interpace® Diagnostics currently offers one test using the this platform, and has two others in the development pipeline (listed and briefly described in Table 1).[3] As stated on the company website, PancraGEN™ integrates molecular analyses with first-line results (when these are inconclusive) and pathologist interpretation.[4] The manufacturer calls this technique integrated molecular pathology. Test performance information is not provided on the website.

Table 1. PathFinderTG® Tests

Test	Description	Specimen Types
PathFinderTG® for Pancreas (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® for Barrett's Esophagus (BarreGen™)	Measures the presence and extent of genomic instability and integrates those results with histology	Esophageal tissue
PathFinderTG® for Pancreatobiliary Cancer	Uses oncogene variants and loss of heterozygosity markers to identify whether patients with biliary strictures have a malignant neoplasm or benign reactive disease	Biliary brush/supernatants

ERCP: endoscopic retrograde cholangiopancreatography.

MANAGEMENT OF 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 [MCN]), which are associated with future development of pancreatic cancers. Although mucinous neoplasms associated with cysts may cause symptoms (eg, 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.

There is no single standardized approach to evaluating and managing pancreatic cysts. Given the rare occurrence but 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 examination of cyst cytopathologic or radiographic findings and cyst fluid carcinoembryonic antigen (CEA).

In 2012, an international consensus panel published consensus statements for the management of intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) of the pancreas.[5] These statements were based on a consensus symposium held in Japan in 2010 and updated a 2006 publication by this same group.[6] The panel recommended surgical resection for all surgically fit patients with main duct IPMN or MCN. For branch duct IPMN, surgically fit patients with cytology that is 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); 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.

In 2015, the American Gastroenterological Association published a guideline on the evaluation and management of pancreatic cysts; it recommends patients undergo further evaluation with endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) only if the cyst has 2 or more worrisome features (size ≥3 cm, a solid component, a dilated main pancreatic duct).[7] The guideline recommends that patients with a solid component, dilated pancreatic duct and/or "concerning features" on EUS-FNA should undergo surgery.

MANAGEMENT OF 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 (GERD). The metaplastic columnar epithelium is a precursor to esophageal adenocarcinoma (EAC). These tumors frequently spread before symptoms are present so detection at an early stage might be beneficial. Surveillance for EAC is recommended for those diagnosed with Barrett esophagus.[8] 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]) regarding management of Barrett esophagus were published.[8,9] ACG recommendations for surveillance are stratified by presence of dysplasia. When no dysplasia is detected, ACG reports the estimated risk of progression to cancer for patients ranges from 0.2% to 0.5% per year and ACG recommends endoscopic surveillance every 3 to 5 years. For low-grade dysplasia, the estimated risk of progression is about 0.7% per year and ACG recommends endoscopic therapy or surveillance every 12 months. For high-grade dysplasia, the estimated risk of progression is about 7% per year and ACG recommends endoscopic therapy.[9] 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.[8]

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Patented diagnostic tests (eg, PancraGEN™) are available only through Interpace® Diagnostics (Pittsburgh, PA and New

Haven, CT; formerly RedPath Integrated Pathology) under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[10] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

PathFinderTG® (Interpace® Diagnostics) variant profiles are intended to inform complex diagnostic dilemmas in patients who are at risk of cancer. The manufacturer's website states specifically that the PancraGEN™ technology is "intended to be an adjunct to first line testing" and suggests that the test is useful in assessing who will benefit most from surveillance and or surgery.[11]

When this evidence review was originally created, it evaluated 3 representative applications of topographic genotyping—pancreatic cysts, gliomas, and Barrett esophagus. At present, Interpace® Diagnostics offers tests using its technology to evaluate patients with pancreatic cysts and Barrett esophagus, which are the focus of the current review.

Molecular tests using the RedPathTG platform are best evaluated within the framework of a diagnostic or prognostic test, because such frameworks provide diagnostic and prognostic information that assists in treatment decisions. Assessment of a diagnostic or prognostic tool typically focuses on 3 categories of evidence: (1) analytic validity; (2) clinical validity (ie, statistically significant association between the test result and health outcomes); and (3) clinical utility (ie, demonstration that use of the diagnostic or prognostic information clinically can improve health outcomes compared with patient management without use of the tool). Because the test is an adjunct to the usual diagnostic workup, it is important to evaluate whether the test provides incremental information above the standard workup to determine if the test has utility in clinical practice.

PANCREATIC CYSTS

Analytic Validity

No studies describing the technical performance or analytic validity of PancraGEN™ were found. The laboratory that performs the analyses for PancraGEN™ is certified under the Clinical Laboratory Improvement Amendments (CLIA).

Clinical Validity

The diagnosis of cystic pancreatic lesions is usually performed by endoscopic, ultrasound-guided fine-needle aspiration 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, procedural difficulties, etc. 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. Information provided by additional testing modalities would, therefore, be potentially useful. The clinical purpose of PancraGEN™ is to allow patients with low-risk cysts to avoid unnecessary surgery or to more accurately select patients with malignant lesions for surgery. 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.

The PathFinderTG® Pancreas test combines measures of loss of heterozygosity (LOH) markers, oncogene variants, and DNA content abnormalities to stratify patients according to their risk of progression to cancer.[4] According to a 2015 publication of results from a registry established with support from the manufacturer,[12] the current diagnostic algorithm is as follows in Table 2.

Table 2. Diagnostic Algorithm for PancraGEN™[12]

Diagnostic Category	Molecular Criteria[a]	Coexisting Concerning Clinical Features[b]
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

[a] Molecular criteria: (1) a single high-clonality variant, (2) elevated level of high-quality DNA, (3) multiple low-clonality variant; (4) a single low-clonality oncogene variant.
[b] Includes any of the following: cyst size >3 cm, growth rate >3 mm/y, duct dilation >1 cm, carcinoembryonic antigen level >1000 ng/mL, cytologic evidence of high-grade dysplasia.

Several studies have reported on the diagnostic and prognostic characteristics of individual molecular components of this test (e.g., *KRAS* variant or LOH markers) with mixed results.[13-25] Gillis (2015) in Ireland conducted a systematic review of the literature on molecular analysis including assessment for *KRAS* variants, DNA quantification, and LOH in the diagnosis of pancreatic cystic lesions compared to surgical pathology as the reference standard. They included 9 studies that reported performance characteristics for *KRAS* variants.[16,18-24,26] The sensitivities of selected studies ranged from 0.12 to 0.75, with a pooled estimate of 0.39 (95% confidence interval [CI], 0.28 to 0.51). The specificities ranged from 0.67 to 1.00 with a pooled estimate of 0.95 (95% CI, 0.83 to 0.99) Evidence for LOH and DNA quantification was insufficient to form conclusions.[27]

For the evaluation of clinical validity of the PancraGEN™ test (including the algorithm), studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the patented PathFinder Pancreas or PancraGEN™ technology for classifying patients into prognostic categories for malignancy

- Included a suitable reference standard (long-term follow-up for malignancy; histopathology from surgically resected lesions)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Several studies were excluded from the evaluation of the clinical validity of the PancraGEN™ test because they evaluated components of the test separately for the malignancy outcome,[13-25] did not include information needed to calculate performance characteristics for the malignancy outcome,[26] did not describe how the reference standard diagnoses was established,[28] did not use a suitable reference standard,[29,30] did not adequately describe the patient characteristics,[15,25,31] or patient selection criteria.[14,15,25,26,31] The following paragraphs describe the included studies which consist of 1 systematic review and 3 retrospective studies.

In 2010, a systematic review of LOH-based topographic genotyping with PathFinderTG® was prepared for the Agency for Healthcare Research and Quality technology assessment program.[1] Key questions addressed published evidence on analytic test performance, diagnostic ability, and clinical validity of the test, and what evidence there is comparing the PathFinderTG® test with conventional pathology. Conclusions were that no studies included in the systematic review directly measured whether using LOH-based topographic genotyping with PathFinderTG® improved patient-relevant clinical outcomes and that eligible studies on diagnostic and prognostic ability of the test were small in sample size, had overt methodologic limitations, and all but 1 performed retrospective assessments. The review pointed out that studies did not provide important information on patient selection, patient characteristics, treatments received, clinical end point definitions, justification of sample size, selection of test cut points, and selection among various statistical models. In addition, reviewers noted that there were strong indications that the selection of certain test cut points was determined post hoc, in that cutoffs varied widely across studies and were not validated in an external population.

Table 3 describes the included retrospective studies on clinical validity. A summary paragraph of each study follows the table.

Table 3. Retrospective Studies of Clinical Validity of PancraGEN™

Study	Population	Reference Standard	Performance Characteristics for PancraGEN™ (95% CI)	Performance Characteristics for Comparator (95% CI)
Malhotra (2014)	26 patients with pancreaticobiliary masses with cytologic diagnosis of atypical, negative, or indeterminate and minimum 3-mo FU	Surgical pathology or oncology FU report	Sensitivity: 47% (24% to 71%) Specificity: 100% (63% to 100%) PPV: 100% (60% to 100%) NPV: 50% (27% to 73%)	NA
Winner (2015)	36 patients evaluated for pancreatic cysts, had surgical resection, cyst fluid, and molecular analysis	Surgical pathology	Sensitivity: 67% (31% to 91%) Specificity: 81% (61% to 93% PPV: 55% (25% to 82%) NPV: 88% (68% to 97%)	NA
Al -Haddad (2015)	492 patients who had undergone IMP testing prescribed by their	Long-term FU,	**PancraGEN™** Sensitivity: 83% (72% to 91%)	**International consensus guidelines**

	physician and for whom clinical outcomes were available with 23-mo FU	surgical pathology	Specificity: 91% (87% to 93%) PPV: 58% (47% to 68%) NPV: 97% (95% to 99%)	Sensitivity: 91% (81% to 97%) Specificity: 46% (41% to 51%) PPV: 21% (16% to 26%) NPV: 97% (94% to 99%)

CI: confidence interval; FU: follow-up; IMP: integrated molecular pathology; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value.

Malhotra (2014) at RedPath retrospectively evaluated 30 patients who presented with pancreaticobiliary masses and had a minimum follow-up of 3 months.[32] Cytology correctly diagnosed 4 of 21 malignant cases (sensitivity, 19%), and identified 7 of 9 patients with nonaggressive disease (specificity, 78%). Only 26 patients with a cytologic diagnosis of atypical, negative, or indeterminate underwent PathFinderTG® variant profiling, precluding assessment of diagnostic performance. PathFinderTG® correctly diagnosed 8 of 17 malignant cases (sensitivity, 47%) and identified all 9 patients with nonaggressive disease (specificity, 100%). Although the combination of positive cytology and positive PathFinderTG® results improved sensitivity to 57% (12/21), 9 malignant cases were missed by both tests.

In 2015, Winner published a retrospective analysis of prospectively collected data from 40 patients that were evaluated for pancreatic cysts between 2006 and 2012 who had surgical resection and cyst fluid molecular analysis with PathFinder.[33] The authors reported that the population tended to be low or intermediate risk according to Sendai international consensus criteria for surgical resection. Surgical pathology was the reference standard. The molecular results were classified as “favor benign” or “favor aggressive” based on “clinical impression, fluid cytology, CEA and amylase results as well as the molecular cyst fluid analysis and adjunct tests.” It is not clear whether these were the diagnosis classifications provided on the PathFinder reports. Results are reported for 36 cysts (the reasons for 4 exclusions are not given). PathFinder correctly classified 6 of the 9 malignant cysts as “favor aggressive” (sensitivity, 67%, 95% CI, 31%, 91%) and correctly classified 22 of 27 benign cysts as “favor benign” (specificity, 81%, 95% CI, 61% to 93%). The positive predictive value (PPV) was 55% (95% CI, 25% to 82%) and the negative predictive value (NPV) was 88% (95% CI, 68% to 97%). Confidence intervals were calculated from the data provided.

In 2011, RedPath Integrated Pathology established the National Pancreatic Cyst Registry, and in 2015, published results of 492 (26%) of 1864 registered patients.[12] The Registry website describes the registry as a prospective study “to evaluate the performance characteristics and clinical utility of integrated molecular pathology and determine the predictive value of both traditional first-line tests and integrated molecular pathology.” Ten academic medical centers and community-based practices registered patients who had pancreatic cysts, underwent PathFinderTG® testing, and were followed for development of malignancy. Benign outcomes included benign surgical pathology results, low- or intermediate-grade dysplasia, resolution of cyst, or clinical follow-up by imaging for a minimum of 23 months without evidence of malignant outcome; malignant outcomes were determined by surgical pathology diagnosis of high-grade dysplasia, carcinoma in situ, or adenocarcinoma, newly diagnosed malignant cytology results, clinically confirmed pancreatic cancer in patient records, or death attributed to pancreatic cancer. Investigators compared the diagnostic performance of PathFinderTG® to that of an international consensus classification scheme.[5] Both classification schemes categorize patients with pancreatic cysts as high or low risk for malignancy; those considered high risk undergo surgical resection and those considered low

risk may elect observation with surveillance. At median follow-up of 35 months for patients with benign and statistically indolent diagnoses (range, 23-92 months), 66 (35%) patients were diagnosed with malignancy. Sensitivity, specificity, PPV, and NPV were 83% (95% CI, 72% to 91%), 91% (95% CI, 87% to 93%), 58% (95% CI, 47% to 68%), and 97% (95% CI, 95% to 99%) for PathFinderTG® versus 91% (95% CI, 81% to 97%, p=0.17 PathFinder vs consensus), 46% (95% CI, 41% to 51%, p<0.001), 21% (95% CI, 16% to 26%, p<0.001), and 97% (95% CI, 94% to 99%, p=0.88) for international consensus classification. Accuracy was 90% (95% CI, 87% to 92%) for PathFinderTG® versus 52% (95% CI, 48% to 57%) for the international consensus classification. The negative likelihood ratio was very similar for PancraGEN™ (0.2; 95% CI, 0.1 to 0.3) and the international consensus classification (0.2; 95% CI, 0.1 to 0.4). However, the positive likelihood ratio was much higher for PancraGEN™ (8.9; 95% CI, 6.5 to 12.2) than for the international consensus classification (1.7; 95% CI, 1.5 to 1.9). The authors noted that the PathFinderTG® diagnostic criteria have evolved over time and older cases in the registry were recategorized using the new criteria. Of the 492 registry cases included, 468 (95%) had to be recategorized using the current diagnostic categories. A strength of the study is the inclusion of both surgery and surveillance groups. Limitations include the retrospective design, resulting in the exclusion of 74% of all registry patients due primarily to insufficient follow-up; relatively short follow-up for observing malignant transformation of benign lesions; and the exclusion of patients classified as malignant by international consensus criteria who would not have undergone PathFinderTG® testing. The reclassification of the majority of the PathFinderTG® diagnoses due to evolving criteria between 2011 and 2014 also make it questionable whether the older estimates of performance characteristics are relevant. Because of these limitations, the evidence is not sufficient to draw conclusions on clinical validity.

Clinical utility

The widespread use and increasing sensitivity of computed tomography and magnetic resonance imaging scans have been associated with marked increase in the finding of incidental pancreatic cysts.[34-36] Although data have suggested that the malignant transformation of these cysts is very rare,[37] due to the potential life-threatening prognosis of pancreatic cancer, an incidental finding can start an aggressive clinical workup. International consensus recommends surgical resection for all surgically fit patients with mucinous cystic neoplasm (MCN) or main duct intraductal papillary mucinous neoplasm (IPMN).[5] This is due to the uncertainty of the natural history of MCN and main duct IPMN and the presumed malignant potential of all types.[6,38,39] Estimates of morbidity and mortality following resection vary. The 2015 American Gastroenterological Association (AGA) technical review combined estimates into a pooled mortality rate of about 2% and serious complication rate of about 30%.[40] Therefore, there is a need for more accurate prognosis to optimize detection of malignancy while minimizing unnecessary surgery and treatment. Direct demonstration of clinical utility would require evidence that PancraGEN™ can produce incremental improvement in survival (by detecting malignant and potentially malignant cysts) and decreased morbidity of surgery (by avoiding surgery for cysts that are highly likely benign) when used adjunctively with the current diagnostic and prognostic standards. Indirect demonstration of clinical utility would require demonstration that the clinical validity of PancraGEN™ is such that if results were used to change management decisions, the resulting change in management would lead to improved outcomes.

The 2010 Agency for Healthcare Research and Quality (AHRQ) systematic review concluded that there were that no studies at that time directly measuring whether using LOH-based topographic genotyping with PathFinderTG® improved patient-relevant clinical outcomes.[41]

Das published a simulation study in 2015 comparing 4 management strategies in a hypothetical cohort of 1000 asymptomatic patients with a 3-cm pancreatic cyst.[42] The first strategy (watch and wait) used cross-sectional imaging and surgical consultation for resection only if symptoms or high-risk morphologic features developed. The second strategy (resect if operable) referred all patients for surgical consultation for cyst resection, and operability was determined according to a surgical risk score. In the third strategy (standard of care), hypothetical patients had cross-sectional imaging and EUS- FNA; mucinous cysts were referred for surgical resection and nonmucinous cysts were followed with periodic imaging. The fourth strategy (standard of care plus integrated molecular pathology) was the same as strategy 3 but also included molecular testing using PathFinderTG®. The strategies were compared using a linear decision tree terminating in a Markov model. The estimates for the model variables were derived from published information or expert opinion. Specifically, the performance characteristics of the PathFinderTG® assay used in strategy 4 were estimated using data from a literature search covering the years 1977 to 2012. Strategy 4 resulted in the highest estimated quality-adjusted life years (QALYs) of the 4 strategies in the base case (10.36 in strategy 1; 9.95 in strategy 2; 11.22 in strategy 3; 12.33 in strategy 4) and for most of the sensitivity analyses.[42] Confidence intervals were not reported for the QALY estimates. The quality of the data behind many of the model assumptions was low, including the assumptions about the PathFinderTG® performance characteristics. Given the uncertainty with the model assumptions, the relevance of the estimates from this simulation is unclear.

The 2015 publication from the National Pancreatic Cyst Registry also assessed evidence of clinical utility by describing how the PancraGEN™ might provide incremental benefit over consensus guidelines.[12] In 289 patients who met consensus criteria for surgery, 229 had a benign outcome. The PancraGEN™ algorithm correctly classified 193 (84%) of the 229 as benign or statistically indolent. The consensus guidelines classified 203 patients as appropriate for surveillance and 6 of them had a malignant outcome. The PancraGEN™ correctly categorized 4 of 6 as high risk (see Table 4). The complete cross- classification of the 2 classification strategies by outcomes was not provided.

Using the same subset of 491 patients described in the previous section from the National Pancreatic Cyst Registry, Loren published results in 2016 comparing the association between PancraGEN™ diagnoses and Sendai and Fukouka consensus guideline recommendations with clinical decisions regarding intervention and surveillance.[43] Patients were categorized as (1) “low-risk” or “high-risk” using the Interspace 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. In addition, 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 actually 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™ (calculated from data in Table 3). 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 (OR) for the association between PancraGEN™ diagnoses and real-world

decision was higher (OR=16.8; 95% CI, 9.0 to 34.4) than the OR for the association between the consensus guidelines recommendations versus real-world decision (OR=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 7 of these cases, the patient actually received an intervention resulting in the discovery of an additional 4 malignancies that would have been missed using the consensus guideline classification alone and in the remaining 1 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 actually 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.[43] Table 4 shows the cross-tabulation of PancraGEN™ and international consensus classification by outcome. This study demonstrated that results from PancraGEN™ testing are associated with real-world decisions although other factors (eg, physician judgment, patient preferences) could affect these decisions. 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.

Table 4. PancraGEN™ and International Consensus Classifications by Outcome (N=491)

Malignant Outcome			**Benign Outcome**		
Consensus Classification	**PancraGEN™ Classification**		**Consensus Classification**	**PancraGEN™ Classification**	
	Low Risk	**High Risk**		**Low Risk**	**High Risk**
Surveillance	2	**4**	Surveillance	193	**4**
Surgery	**9**	50	Surgery	**193**	36

Section Summary

There are no studies describing the analytic validity of this technology. The evidence for the clinical validity of PancraGEN™ consists of several retrospective studies. Most studies evaluated performance characteristics of PancraGEN™ for classifying pancreatic cysts according to risk of malignancy without comparison to current diagnostic algorithms. The best evidence of incremental clinical validity comes from the report from the National Pancreatic Cyst Registry which compared PancraGEN™ performance characteristics to 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%) compared to the consensus guidelines. The registry study included a very select group of patients, only a small fraction of the enrolled patients, and used a retrospective design. Longer follow-up including more of the registry patients is needed. 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, and the data reporting outcomes in patients where the PancraGEN™ and consensus guideline diagnoses disagreed is limited. There are no prospective studies with a concurrent control demonstrating that PancraGEN™ can affect patient-relevant outcomes (eg, survival, time to tumor recurrence, reduction in unnecessary surgeries). The evidence reviewed does not demonstrate that PathFinderTG® has incremental clinical value for diagnosis or prognosis of pancreatic cysts and associated cancer.

BARRETT ESOPHAGUS

The American Gastroenterological Association defines Barrett esophagus as replacement of normal epithelium at the distal esophagus by intestinal metaplasia, which predisposes to malignancy.[44] Although grading of dysplasia in mucosal biopsies is the current standard for assessing risk of malignant transformation, esophageal inflammation may mimic or mask dysplasia and interobserver variability may yield inconsistent risk classifications.[45] Additional prognostic information therefore may be potentially useful.

The Interpace website describes BarreGEN™ as a molecular diagnostic test to "determine the risk of progressing to esophageal cancer in patients with Barrett's Esophagus."[19]

Analytic Validity

No studies describing the analytic validity or technical performance of BarreGEN™ were found. The laboratory that performs the analyses for BarreGEN™ is CLIA-certified.

Clinical validity

The 2010 AHRQ a systematic review of LOH-based topographic genotyping with PathFinderTG® did not find any publications of the PathFinderTG® technology evaluating test performance, diagnostic ability, clinical validity or clinical utility for Barrett esophagus.[41]

Khara (2014) examined LOH in microsatellite regions of the *TP53* and *CDKN2A* tumor suppressor genes and in 8 other tumor suppressor genes (total 10 loci) as prognostic markers in Barrett esophagus.[46] Formalin-fixed paraffin-embedded tissues from 415 patients from 3 study sites who had histologically diagnosed Barrett esophagus were microdissected to yield 877 specimens. Each was histologically classified as: normal squamous epithelium, columnar mucosa, intestinal metaplasia, indefinite for dysplasia (applied when cellular atypia is present but criteria for dysplasia are not met), low-grade dysplasia, high-grade dysplasia, or esophageal adenocarcinoma. At 1 study site, consensus diagnosis required agreement between 2 of 3 pathologists. All pathologists were blinded to molecular results, but it is unclear whether those conducting molecular analyses were blinded to pathology results. In molecular analysis, thresholds for defining significant LOH were determined using normal specimens; standard deviation greater than 2 was defined as "LOH present." High clonality was defined as LOH variant in more than 75% of DNA. Mutational load for each genomic locus was calculated by summing the proportional value of LOH and microsatellite instability (eg, 0.5 for low clonality, 1 for high clonality, 0.75 for microsatellite instability at a single locus, 0.5 for microsatellite stability at each additional locus). Mean mutational load (ML) increased with increasingly severe histology. Categories of ML (none, low [lower 95th percentile], high [upper 5th percentile]) appeared to discriminate less severe and more severe histology, but there was considerable overlap between no and low ML and between low and high ML.

Eluri (2015) published a case-control study evaluating ML as a predictor of progression to high-grade dysplasia or esophageal adenocarcinoma in Barrett esophagus.[47] Twenty-three patients had Barrett esophagus with no or low-grade dysplasia at baseline who developed high-grade dysplasia or esophageal adenocarcinoma during follow-up. Forty-six controls also had no dysplasia or low-grade dysplasia but no progression during follow-up. Controls were matched in a 2:1 ratio to cases by age, sex, index biopsy histology, and length of follow-up. The ML assessments were made using the method described above in Khara (2014). ML ranged from 0 to 10. Mean follow-up was 4 years and patients were mostly male with mean age around 63 years. Mean ML in baseline biopsies was higher in cases (2.21) than in controls (0.42; $p<0.0001$). The performance characteristics of the ML test for predicting progression

were evaluated with different ML cutoffs ranging from 0.5 to 1.5. Sensitivity of the test was 100% at an ML of 0.5 or more while specificity was 96% at an ML of 1.5 of more. Accuracy was highest (90%) for an ML of 1 or more. All 10 genetic loci included in the ML score showed a higher rate of variant in cases compared with controls.

Clinical Utility

No studies describing the clinical utility of BarreGEN™ were found.

Section Summary

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

PRACTICE GUIDELINE SUMMARY

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2015, the American Gastroenterological Association (AGA) published a guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts[7] based on findings from a technical review.[40] The technical review states 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." The AGA guideline also states "Molecular techniques to evaluate pancreatic cysts remain an emerging area of research, and the diagnostic utility of these tests is uncertain."

In 2011, American Gastroenterological Association (AGA) published a medical position statement on the management of Barrett esophagus. Based on findings from a technical review, AGA "suggest[s] 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)."[48]

SUMMARY

There is not enough research to know if molecular testing based on the PathFinderTG® platform leads to improvement in overall health outcomes. The role of these tests in clinical decision-making for any indication, including selecting treatment options, has not been defined. Therefore, molecular testing using the PathFinderTG® system is considered investigational for all indications, including but not limited to, the evaluation of pancreatic cyst fluid and Barret's esophagus.

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CODES

Codes	Number	Description
CPT	81479	Unlisted molecular pathology procedure
	84999	Unlisted chemistry procedure
	89240	Unlisted miscellaneous pathology test
HCPCS	None	

Date of Origin: *January 2011*