Anthem

Medical Policy

Subject: Topographic Genotyping
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Description/Scope

This document addresses topographic genotyping which has been proposed as a means to provide diagnostic and prognostic information based on the analysis of specimens.

Topographic genotyping (TG) utilizes microdissection and subsequent molecular analysis to directly correlate genetic alterations with histology in different areas within a specimen. TG has been proposed as a tool to facilitate the diagnosis of and optimal treatment of individuals with certain tumors, cysts, or masses when microscopic analysis and special staining methods cannot provide a definitive diagnosis from specimens.

Position Statement

Investigational and Not Medically Necessary:

Topographic genotyping is considered **investigational and not medically necessary** for all indications.

Rationale

Topographic genotyping, also referred to as integrated molecular pathology (IMP), is a type of quantitative genetic mutational analysis. Interpace Diagnostics® (Parsippany, NJ), a subsidiary of Interspace Biosciences®, Inc. (Pittsburgh, PA),t currently manufactures commercialized molecular diagnostic tests that utilize the PathFinderTG® (RedPath Integrated Pathology, Pittsburgh, PA) platform to integrate microscopic analysis with molecular tissue analysis. These tests are proposed as adjunctive tools when a definitive pathologic diagnosis or prognosis is inconclusive.

Pancreatic Cancer

Al-Haddad and colleagues (2015) reported the results of a multicenter study to determine if IMP, a combined molecular analysis with cytology, imaging, and fluid chemistry, could be used to determine the malignant potential of pancreatic cysts, and the utility of IMP testing under current guideline recommendations for managing pancreatic cysts. The authors analyzed clinical outcomes data obtained from retrospective review of medical records for individuals included in the National Pancreatic Cyst Registry. A total of 492 participants, who had undergone previous PancraGEN testing and for whom clinical outcomes were available, were included in the study. The performance of each case was categorized according to four IMP diagnostic categories: “benign,” “statistically indolent,” “statistically higher risk (SHR),” and “aggressive” in the International Consensus Guideline (ICG) criteria model (Sendai 2012) for "surveillance" vs. "surgery." A Cox proportional hazards model was used to determine hazard ratios for malignancy. Cases diagnosed as benign using the PancraGEN test had a 97% probability of benign follow-up for up to 71 months after the initial PancraGEN testing. Cases that were categorized as SHR and aggressive had relative hazard ratios for malignancy of 30.8 and 76.3, respectively (both $P<0.0001$). Although cases classified as surveillance using the ICG criteria demonstrated a 97% probability of benign follow-up for up to 71 months, cases classified as surgical showed a hazard ratio of 9.0 ($p<0.0001$). Amongst those participants classified as surgical, benign and statistically indolent IMP diagnoses had a > 93% probability of benign follow-up, with relative hazard ratios for SHR and aggressive IMP diagnoses of 16.1 and 50.2, respectively (both $p<0.0001$). The authors concluded that IMP (the PancraGEN test) may improve management by justifying more relaxed observation in individuals meeting Sendai surveillance criteria. This study did not prospectively show that use of IMP led to improved outcomes.

Loren and colleagues (2016) retrospectively investigated whether initial adjunctive IMP testing using the PancraGEN test affected future real-world pancreatic cyst management decisions for intervention or surveillance relative to the ICG recommendations, and if this resulted in improved individual outcomes. The researchers used data from the National Pancreatic Cyst Registry. Participants in this registry had received IMP testing at the discretion of their treating physician. Details of how that decision was made are not available. Researchers evaluated the relationship between real-world decisions (intervention vs. surveillance), ICG model recommendations (surgery vs. surveillance) and IMP (PancraGEN) diagnoses (high-risk vs. low-risk). Kaplan Meier and hazard ratio analyses as well as 2 × 2 tables were used to assess time to malignancy. Logistic regression was used to determine odds ratios for surgery decision. Of 491 participants, 206 received clinical intervention at follow-up (183 surgery, 4 chemotherapy, 19 presumed by malignant cytology). At 2.9 years follow-up, 13% (66/491) of participants had a malignant outcome and 87% (425/491) had a benign outcome. When ICG and IMP were concordant recommendations for surveillance or surgery, 83% and 88% of participants actually underwent surveillance or surgery, respectively. However, when ICG recommended surveillance and IMP indicated high risk, 88% of participants underwent an intervention within 1 year of IMP testing, suggesting that IMP influenced the decision for intervention. At 2.9 years follow-up, this subgroup demonstrated a malignant outcome rate of 57%. Similarly, when ICG recommended surgery but IMP indicated low risk, approximately 55% of participants opted for surveillance. At 2.9 years follow-up, this group demonstrated a benign outcome rate of 99%. This study is limited by potential inclusion bias due to the lack of information about how the decision to use IMP testing was made. The retrospective design limits generalizability to prospective decision making.

In 2019, Farrell and colleagues reported results of a cohort study of 478 participants to determine the incremental predictive value of molecular analysis of pancreatic cyst fluid to assess for malignancy risk over the long term. A total of 209 participants had surgical pathology-derived outcomes and 269 had clinical follow-up of > 2 years. Eleven percent had malignant outcomes. Forty-two participants had high risk stigmata (HRS), 272 lacked both HRS and worrisome features (WFs), and 164 lacked HRS but had WFs. DNA abnormalities did not statistically change the long-term malignancy risk in participants with HRS nor in those individuals who were lacking both HRS and WFs. Although the presence of ≥ 2 DNA abnormalities in the cohort with WFs significantly increased the malignancy risk (relative risk, 5.2; $p=0.002$) and the absence of all DNA abnormalities significantly decreased risk (relative risk, .4; $p=0.040$), this testing did not provide prospective evidence of impact on clinical outcomes. Sensitivity analysis confirmed results of survival analysis over differing baseline malignancy probabilities.

The Agency for Healthcare Research and Quality (AHRQ) conducted a technology assessment systematic review in 2010 of the published literature on loss-of-heterozygosity based topographic genotyping with the PathFinderTG (Trikalinos, 2010). Most studies

were excluded because they only described the molecular profile of different tumors, without assessing the impact of testing on diagnosis, prognosis, treatment guidance, or clinical outcomes. The researchers conclude:

> It is theoretically and biologically plausible that topographic genotyping (including loss-of-heterozygosity based topographic genotyping with PathFinderTG®) may have prognostic and diagnostic ability, if one examines a suitable genetic marker panel for each type of cancer. However, all studies are small, they have important methodological limitations, and they do not address patient-relevant outcomes.

In a technical review published by the American Gastroenterological Association (AGA) in 2015, the authors concluded the following:

> 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 the need for surgery, surveillance or predicting interventions leading to improved survival. This adjunct to fine needle aspiration (FNA) may provide value in distinct clinical circumstances, such as confirmation of a serous lesion due to a lack of KRAS or GNAS mutation in a macrocystic serous cystadenoma, but its routine use is not supported at the present time (Scheiman, 2015).

The AGA Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts did not include the use of topographic genotyping in their recommendations for the evaluation of pancreatic cysts. Likewise, the National Comprehensive Cancer Network (NCCN, V2.2023) Clinical Practice Guidelines on pancreatic adenocarcinoma did not address the use of topographic genotyping nor any specific test. Similarly, the International consensus guidelines for the management of intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) of the pancreas do not include topographic genotyping as a tool in the management of IPMN or MCN of the pancreas (Tanaka, 2012; Vege, 2015).

According to the American Association for Gastrointestinal Endoscopy (ASGE):

> 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. (ASGE, 2016).

According to the American College of Gastroenterology (ACG) clinical guideline: Diagnosis and Management of Pancreatic Cysts (Elta, 2018), the following excerpts are noted:

> Pancreatic cysts are very common with the majority incidentally identified. There are several types of pancreatic cysts; some types can contain cancer or have malignant potential, whereas others are benign. However, even the types of cysts with malignant potential rarely progress to cancer. At the present time, the only viable treatment for pancreatic cysts is surgical excision, which is associated with a high morbidity and occasional mortality. The small risk of malignant transformation, the high risks of surgical treatment, and the lack of high-quality prospective studies have led to contradictory recommendations for their immediate management and for their surveillance. This guideline will provide a practical approach to pancreatic cyst management and recommendations for cyst surveillance for the general gastroenterologist, as follows:

1. We recommend caution when attributing symptoms to a pancreatic cyst. The majority of pancreatic cysts are asymptomatic and the nonspecific nature of symptoms requires clinical discernment (Conditional recommendation, very low quality of evidence).
2. Magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) are the tests of choice because of their non-invasiveness, lack of radiation, and greater accuracy in assessing communication between the main pancreatic duct and the cyst (which is a characteristic of side-branch IPMNs). Pancreatic protocol computed tomography (CT) or endoscopic ultrasound (EUS) are excellent alternatives in patients who are unable to undergo MRI. Indeterminate cysts may benefit from a second imaging modality or cyst fluid analysis via EUS (Conditional recommendation, very low quality of evidence).
3. Use caution when using imaging to diagnose cyst type or concomitant malignancy; the accuracy of MRI or MRCP in diagnosing cyst type is 40–50% and in determining benign vs. malignant is 55–76%. The accuracy for CT and EUS without FNA is similar (Conditional recommendation, very low quality of evidence).
4. EUS-FNA and cyst fluid analysis should be considered in cysts in which the diagnosis is unclear, and where the results are likely to alter management. Analysis of cyst fluid carcinoembryonic antigen (CEA) may be considered to differentiate IPMNs and MCNs from other cyst types, but cannot be used to identify IPMNs and MCNs with high-grade dysplasia or pancreatic cancer (Conditional recommendation, very low quality of evidence).
5. Cyst fluid cytology should be sent to assess for the presence of high-grade dysplasia or pancreatic cancer when the imaging features alone are insufficient to warrant surgery (Conditional recommendation, very low quality of evidence).
6. Molecular markers may help identify IPMNs and MCNs. Their use may be considered in cases in which the diagnosis is unclear and the results are likely to change management (Conditional recommendation, very low quality of evidence).
7. Patients with IPMNs or MCNs with any of the following features should undergo EUS±FNA and/or be referred to a multidisciplinary group for further evaluation (Strong recommendation, very low quality of evidence):
    - Any of the following symptoms or signs: jaundice secondary to the cyst, acute pancreatitis secondary to the cyst, significantly elevated serum CA 19-9;
    - Any of the following imaging findings: the presence of a mural nodule or solid component either within the cyst or in the pancreatic parenchyma, dilation of the main pancreatic duct of > 5 mm, a focal dilation of the pancreatic duct concerning for main duct IPMN or an obstructing lesion, mucin-producing cysts measuring ≥ 3 cm in diameter;
    - The presence of high-grade dysplasia or pancreatic cancer on cytology (Elta, ACG, 2018).

Barrett's Esophagus

The utility of loss of heterozygosity (LOH), also described as mutational load (ML), for risk stratification in individuals with Barrett's esophagus and indefinite dysplasia (BE-IND) was evaluated in a single-center, retrospective pilot study by Trindade and colleagues (2019). A high ML was previously identified as a potential indicator of progression to more advanced disease (Lin, 2009; Eluri, 2015). The study's ML assessments were performed using the BarreGEN test on biopsy tissue that was blinded to the individual's future progression status. A total of 28 participants diagnosed with Barrett's esophagus (BE) and categorized as indefinite for dysplasia (IND), based on baseline biopsies, were included in the analysis. Of the 28 participants, 10 did not have disease progression and lacked all detectable genomic instability. There were 8 participants that progressed to either low-grade dysplasia (LGD) or high-grade dysplasia (HGD), 7 of whom had some degree of genomic instability detected in their IND biopsy as evidenced by an ML greater than or equal to 0.5. The sensitivity and specificity for identifying progression to either LGD or HGD with an ML at this threshold was 88% and 50%, respectively. Participants who progressed to HGD had comparably higher ML of greater than or equal to 1.5 with a sensitivity and specificity at this level of 100% and 85%, respectively. For an ML cut off greater than 1.5, the risk of progression to HGD was 33% compared to 0% (p=0.005). ML assessment may be a useful tool for risk stratification in BE-IND, but larger studies are

necessary.

Given that the progression of BE to esophageal adenocarcinoma (EAC) is associated with accumulated genomic instability, Khara and colleagues (2014), including the founder of RedPath Integrated Pathology, investigated the presence and extent of genomic instability in advanced and less advanced BE histology. They used ML assessment in a cross-sectional study of participants from multiple study cohorts. Khara and colleagues also assessed inter-observer variability in histologic classification of BE which had previously been reported by other studies. Their team performed mutational analysis on 877 target specimens from 415 participants. Based on the distribution of their specimen population three levels of ML were established: no ML, low mL, and high ML. Of the target specimens classified as IND 18% had no ML, 66% had low ML, and 16% had high ML. There was an increase in the percentage of ML as the severity of the histologic classification increased. Target specimens with a histologic classification of HGD had 95% high ML and 5% low ML. Those classified as EAC had 96% high ML and 4% low ML. Consistent with previous studies, there was higher disagreement of pathologist observed classification for IND and LGD target specimens with a with a 63% and 88% disagreement respectively. For specimens classified as HGD, there was 50% disagreement. Inter-rater variability in histologic diagnoses may have influenced the study's results. This study has not prospectively shown that use of ML leads to improved health outcomes. The cross-sectional design of this study prevents drawing conclusions about the ability of this testing to guide clinical management.

The AGA Medical Position Statement on the Management of Barrett's Esophagus (2011) includes the following statement regarding biomarkers:

> We suggest 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).
>
> Although biomarkers show promise, they cannot be used to confirm the diagnosis of Barrett's dysplasia and have not been shown to predict which patients with Barrett's are at risk for progression. To date, neither individual biomarkers nor panels of markers can be recommended (Spechler, 2011).

The ACG clinical guideline addressing the diagnosis and management of Barrett's Esophagus (2016), includes the following statement:

> 20. Use of additional biomarkers for risk stratification of patients with BE is currently not recommended (strong recommendation, low level of evidence).

Summary

Currently, there is insufficient evidence in the published, peer-reviewed, scientific literature to demonstrate that topographic genotyping is an effective method to aid in the diagnosis or management of individuals with pancreatic cysts, BE, or other neoplasms when other testing methods, such as endoscopic ultrasound and 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, BE, or other neoplasms results in improved clinical outcomes.

Background/Overview

Topographic genotyping has been proposed as a tool to facilitate the diagnosis and optimal treatment of individuals with certain cancers when microscopic analysis and special staining methods are unable to provide a definitive diagnosis using the specimens.

PathFinderTG is a patented topographic genotyping test platform that combines anatomic pathology with quantitative genetic mutational analysis. Interpace Diagnostics acquired RedPath Integrated Pathology and has since cultivated and developed the PancraGEN, BarreGEN, and RespriDX molecular pathology tests on the PathFinderTG platform. These tests are intended to be used to supplement decision making when a definitive pathologic diagnosis using histologic or cytologic findings is inconclusive.

These laboratory-developed tests are regulated by the Centers for Medicare and Medicaid under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 and do not require approval by the U.S. Food and Drug Administration for clinical use.

Definitions

Cytology: The study of the formation and function of cells.

DNA (deoxyribonucleic acid): A type of molecule that contains the code for genetic information.

Genotype: The genetic structure (constitution) of an organism or cell.

Histology: The study of the microscopic structure of tissue and cells.

Mutation: A permanent, structural change in the DNA.

Topographic genotyping: An integration of anatomic pathology with molecular analysis. The process involves analyzing microdissected tissue samples to identify and procure abnormal cells from existing pathology specimens. The following processes are then performed: DNA extraction and amplification (for example, polymerase chain reaction [PCR]); DNA sequencing to identify oncogenic mutations; and lastly, integration of this molecular information with the cytologic or histologic findings provided by the pathologist of record to determine a definitive diagnosis.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
	For the following unlisted codes when specified as a topographic genotyping test:
81479	Unlisted molecular pathology procedure [*for example, PancraGEN, BarreGEN, RespriDX tests*]
84999	Unlisted chemistry procedure [*for example, PancraGEN, BarreGEN, RespriDX tests*]
89240	Unlisted miscellaneous pathology test [*for example, PancraGEN, BarreGEN, RespriDX tests*]

ICD-10 Diagnosis

All diagnoses

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Peer Reviewed Publications:

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Government Agency, Medical Society, and Other Authoritative Publications:

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Rationale and References sections. Revised Coding section, added 89240 NOC.
Reviewed	02/16/2023	MPTAC review. The Rationale, Background, Definitions, Index and References sections were updated.
Reviewed	02/17/2022	MPTAC review. The Rationale and References sections were updated.
Reviewed	02/11/2021	MPTAC review. The Rationale, Background/Overview, Definitions, References, and Index sections were updated.
Reviewed	02/20/2020	MPTAC review. References were updated.
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Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. The Rationale and References sections were updated.
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Reviewed	05/20/2009	Hematology/Oncology Subcommittee review. Updated review date, References and History sections of the document.

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New	05/14/2008	Hematology/Oncology Subcommittee initial document development.
