

Medical Coverage Policy | Molecular Testing for the Management of Pancreatic Cysts and Solid Pancreaticobiliary Lesions



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OVERVIEW

Tests that integrate microscopic analysis with molecular tissue analysis are generally called topographic genotyping. These molecular tests are intended to be used adjunctively when a definitive pathologic diagnosis cannot be made, because of the inadequate specimen or equivocal histologic or cytologic findings, to inform appropriate surveillance or surgical strategies.

This policy addresses molecular testing using the PathfinderTG® platform (e.g. PancaGEN®). For BarreGEN®, refer to the Related Policies section, below.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

PathfinderTG® molecular testing (e.g. PancaGEN®) for the evaluation of pancreatic cyst fluid and solid pancreaticobiliary lesions is not covered for Medicare Advantage Plans and is considered not medically necessary for Commercial Products as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

BACKGROUND

True pancreatic cysts are fluid-filled, cell-lined structures, which are most commonly mucinous cysts (intraductal papillary mucinous neoplasm [IPMN] and mucinous cystic neoplasm), which are associated with future development of pancreatic cancers. Incidence of IPMNs is generally equal between men and women, while mucinous cystic neoplasms occur almost exclusively in women (accounting for about 95% of cases). Pancreatic cancer arising from IPMNs and mucinous cystic neoplasms account for about 4% of pancreatic malignancies. Although mucinous neoplasms associated with cysts may cause symptoms (e.g. pain, pancreatitis), an important reason that such cysts are followed is the risk of malignancy, which is estimated to range from 0.01% at the time of diagnosis to 15% in resected lesions.

Solid pancreaticobiliary lesions refer to lesions found on the pancreas, gallbladder, or biliary ducts. A solid lesion may be detected as an incidental finding on computed tomography scans performed for another reason, though this occurs rarely. The differential diagnosis of a solid pancreatic mass includes primary exocrine pancreatic cancer, pancreatic neuroendocrine tumor, lymphoma, metastatic cancer, chronic pancreatitis, or autoimmune pancreatitis.

Topographic genotyping, 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. Topographic genotyping may permit pathologic diagnosis when first-line analyses are inconclusive.

RedPath Integrated Pathology (now Interpace Diagnostics) has patented a proprietary platform called PathFinderTG®; it provides mutational analyses of patient specimens. The patented technology permits analysis of tissue specimens of any size, "including minute needle biopsy specimens," and any age, "including those stored in paraffin for over 30 years."

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. PancaGEN®) 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.

PancaGEN® - Interpace Diagnostics

In addition to the articles submitted with comments, PubMed and Google Scholar were searched for peer-reviewed, evidence-based literature that provided information regarding the analytic and clinical validity and clinical utility for the PancaGEN® test. Key words used to search in combination included: PancaGEN®, PathfinderTG®, molecular testing, topographic genotyping, pancreatic cyst(s), pancreatic cyst fluid, solid pancreatic lesions, and KRAS and/or GNAS mutations.

Thirty-five total publications addressing the analytical validity, clinical validity, and/or clinical utility of the PancreGEN® prognostic test were identified. The papers identified focused on both individuals with pancreatic cysts and with solid pancreaticobiliary lesions.

In 2006, a patent was filed for a topographic genotyping molecular analysis test, which would later become PathfinderTG® and then PancreGEN®. The test was designed to classify the risk of pancreatic cysts and solid pancreaticobiliary lesions when first line evaluation results were inconclusive. According to the patent, the test directly measured several aspects of a specimen: DNA quality, loss of heterozygosity (LOH) in tumor suppressor genes, mutations in oncogenes (only K-ras oncogene specifically named), other less well defined genetic targets (e.g., “structural alterations in DNA”), percentage of mutated DNA per identified DNA abnormality, and “specific temporal sequence of mutation accumulation” as determined from the aforementioned percentages of mutated DNA. Altogether, these measurements would be used for “diagnosing and/or determining the prognosis of a pancreatic anomaly in a patient suffering from pancreatic cysts” and used for “determining a course of treatment for a pancreatic anomaly.”

Since the original patent, significant changes have been made to the original test’s data input and the presentation of test results. In 2012, the test results were changed from 3 categorical results (benign, statistically indolent, and aggressive) to 4 results (benign, statistically indolent, statistically higher-risk, and aggressive). Since result categories are tied to specific prognostic outcomes and advise different next steps in clinical care, changing the number and type of categories changes the test output, thereby creating a new test. The most recent version of PancreGEN® added analysis of the GNAS oncogene. Since mutations in GNAS would be considered a “significant molecular alteration,” testing of GNAS would potentially reclassify any specimens that had been classified based on KRAS alone. Considering the result categories and genes analyzed were both changed, the latest version of PancreGEN® is a new, distinct test. The literature for older versions of PathfinderTG® are not comparable to the current version of PancreGEN®.

Of the 35 publications identified, 26 publications described an earlier version of the PancreGEN® test that utilized less molecular data and provided fewer categorical results than the currently offered PancreGEN® test. The Agency for Healthcare Research and Quality (AHRQ) performed a technical review of an earlier version of PancreGEN®. The 2015 AGA Guidelines for diagnosis and management of pancreatic cysts does not name PancreGEN® directly in its section about molecular testing, but instead only cites 2 papers discussing older versions of the PancreGEN®/Pathfinder test.

Five of the 35 publications identified did not analyze the PancreGEN® test’s primary output (categorical results) but instead evaluated specific components of the test (i.e., molecular test data). In fact, the study by Shen and colleagues stated that it was not meant “to evaluate the scientific methods or validity of this commercially available test.”

Of the 35 publications identified, there were only 4 papers that evaluated the current version of the PancreGEN® including the 4 categorical results. One retrospective study addressed PancreGEN®’s clinical validity and clinical utility for pancreatic cysts. Two retrospective studies utilizing data from Al-Haddad and colleagues’ study addressed the clinical utility of PancreGEN® for pancreatic cysts. One paper addressed PancreGEN®’s clinical validity and clinical utility for solid pancreaticobiliary lesions.

PancreGEN® (also known as PathfinderTG® and Integrated molecular pathology [IMP]) has received multiple updates to its input data and algorithmic categorization of risk since its initial release. Comparison of early example reports to the most recent example report (available on the PancreGEN® website) clearly demonstrate this evolution. The current version of the PancreGEN® report relies on algorithmic assessment of molecular data, cyst fluid test results, and radiologic findings to determine a patient’s risk for developing high grade dysplasia (HGD) and/or carcinoma. The algorithm is clearly described and diagrammed in the sample report. The algorithmic stratification of risk is heavily weighted towards molecular data, with the absence of “significant molecular alterations” automatically resulting in “Benign” categorization and the presence of 2 or more “significant molecular alterations” automatically resulting in “Aggressive” categorization. The “Benign” category confers a “97% probability of benign disease over the next 3 years”

and the “Aggressive” category confers a “91% probability of HGD/carcinoma”. Per the sample report, 5 “significant molecular alterations” are described:

1. “High levels of DNA”
2. “High clonality KRAS point mutation”
3. “High clonality GNAS point mutation”
4. “Single high clonality LOH tumor suppressor gene mutation”
5. “Two or more low clonality LOW tumor suppressor gene mutations”

The current body of literature does not support the clinical validity of the PancraGEN® test. Since the algorithm primarily categorizes risk via “significant molecular alterations” and the “Benign” category is defined as absence of these alterations, not testing any of the above 5 alterations would result in an underestimation of patients with potential higher risk of HGD/carcinoma. Therefore, adequate assessment of clinical validity of the current version of PancraGEN® would require assessment of all 5 alterations in study populations. None of the 4 studies assessing the current version of PancraGEN® fully assess all 5 alterations.⁹ For example, in the 3 retrospective studies derived from National Pancreatic Cyst Registry, a significant number of patients (“468/492 IMP diagnoses”) were NOT tested for GNAS because their data was collected from earlier versions of the PancraGEN® test that did not include GNAS testing. Another study, from Khosravi and colleagues, addresses the 4 categorical results (simplifying them into 2 categories for the paper: low and high risk) but does not discuss GNAS or clonality of identified mutations. As a result, PancraGEN® studies lack the statistical integrity required to establish the clinical validity of the current version of PancraGEN®.

Additionally, there are no studies supporting the clinical utility of the PancraGEN® test.

First, there are no prospective studies for PancraGEN® that directly evaluate its effect on patient management and outcome. The 4 studies evaluating the current version of PancraGEN® are all retrospective, assessing patient populations who received PancraGEN® testing as part of their clinical care; however, the assessment of PancraGEN®’s effect on patient management and outcome is extrapolated from reading patient charts after the fact.

Second, cysts with a potential to develop into pancreatic cancer, like an Intraductal Papillary Mucinous Neoplasm (IPMN), can take over a decade to become malignant. Thus, when PancraGEN® categorizes a specimen as “Benign” or “Statistically Indolent” with a “97% probability of benign disease over the next 3 years”, the results may provide patients with a false sense of security and/or delay instituting a longer-term follow-up plan, potentially resulting in patient harm. Moreover, none of the studies available for PancraGEN® follow up their entire patient populations for over 10 years. In fact, the “97% probability of benign disease over the next 3 years” is based on a 492 patient, 2015 study from Al-Haddad and colleagues where patients were followed from 23 months to 7 years and 8 months. Notably, 54% of the patients were followed less than 3 years.

Third, current society and expert guidelines do not endorse or mention the current version of PancraGEN® as necessary in the work-up of pancreatic cysts which further demonstrates the lack of evidence for PancraGEN®’s clinical utility.

In summary, the body of literature for PancraGEN® is insufficient to establish both clinical validity and clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING

Medicare Advantage Plans and Commercial Products

There is no established CPT or HCPCS code which adequately describes the procedure; therefore, it may be reported using an unlisted CPT code (84999 or 81479).

RELATED POLICIES

Adjunctive Techniques for Screening, Surveillance, and Risk Classification of Barrett Esophagus and Esophageal Dysplasia
Biomarker Testing Mandate
Genetic Testing Services
Unlisted Procedures

PUBLISHED

Provider Update, March 2026
Provider Update, May/November 2025
Provider Update, December 2024
Provider Update, November 2023
Provider Update, December 2022

REFERENCES

1. Centers for Medicare and Medicaid Services. Local Coverage Determination: Genetic Testing in Oncology: Specific Tests (L39365).
2. Centers for Medicare and Medicaid Services. Local Coverage Determination Article: Billing and Coding: Molecular Pathology and Genetic Testing (A58917).
3. Centers for Medicare and Medicaid Services. Local Coverage Determination Article: Billing and Coding: Genetic Testing in Oncology: Specific Tests (A59125).

DRAFT

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