Cigna Medical Coverage Policy

Subject **Topographic Genotyping (PathFinderTG® Test)**

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Hyperlink to Related Coverage Policies

Tumor Markers for Cancer

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Coverage Policy

Cigna does not cover topographic genotyping (PathFinderTG® test) for any indication because it is considered experimental, investigational or unproven.

General Background

Topographic genotyping refers to a method of mutational analysis that incorporates minute tumor samples selected according to histopathologic considerations, polymerase chain reaction (PCR) amplification and direct sequencing. The mutational alterations that are found are then correlated with the histology of the tumor. It has been proposed that the results of this testing will provide predictive information that will influence the management of certain cancers. PathFinderTG® (RedPath Integrated Pathology Inc., Pittsburgh, PA) is a patented test that is also referred to as topographic genotyping. PathFinderTG has been proposed as an adjunctive tool to be used when a definitive pathologic diagnosis cannot be determined on tissue or cytology specimen. The inability to obtain a definitive diagnosis using standard methods may be due to an inadequate specimen to equivocal histological or cytological findings. PathFinderTG is purported to provide quantitative genetic mutational analysis of the specimen. The RedPath website notes that the test is "molecular DNA-based cancer diagnostic test which obtains a genetic fingerprint of mutations from routine histology and cytology slides as well as fluid samples."

According to the RedPath website, the PathFinderTG can be utilized to "resolve indeterminate, atypical, suspicious, equivocal and non-diagnostic specimen diagnoses from the original pathology specimen". The RedPath website notes that PathFinderTG test combines quantitative genetic mutational analysis with pathology in order to differentiate between:

- reactive versus neoplastic lesions
- grade of dysplasia
- benign versus malignant lesions
- metastatic, synchronous and recurrent tumors
- biologically indolent versus aggressive tumors

Proposed applications include cancers of the GI tract, pancreas, head and neck, brain, breast, genito-urinary, and gynecologic tracts. Using a proprietary process, the testing begins with the microdissection of cells from targeted areas of interest from chemically fixed histology and cytology slides. The process is described as incorporating DNA amplification, as well as molecular profiling against a broad panel of mutations (15 to 20 different markers) that include tumor suppressor genes and oncogenes known to be part of the mutational profile for each tumor type.

After the test is performed, the PathFinderTG report is provided to the ordering physician. RedPath describes this as, "a comprehensive description that incorporates the morphologic review with the molecular analysis in a form that is easily understood. A written summary of the number and type of mutations found, if any, is provided and the temporal sequence of mutation acquisition is described. A diagnosis with detailed commentary, including a summary of the molecular profile of the patient's specimen, is provided in the context of available clinical history and pathology information. "

U.S. Food and Drug Administration (FDA)
No FDA approval was located for PathFinderTG testing. Generally laboratory developed tests are not regulated by the FDA. RedPath Integrated Pathology is accredited by the College of American Pathologists (CAP) Laboratory Accreditation program and has Certificate of Accreditation from Clinical Laboratory Improvement Act of 1988 (CLIA).

Literature Review
Malhotra et al (2014) reported on a study of the supporting role that mutational profiling (MP) of DNA from microdissected cytology slides and supernatant specimens have in the diagnosis of malignancy in fine-needle aspirates (FNA) and biliary brushing specimens from 30 patients with pancreaticobiliary masses. MP of DNA from microdissected cytology slides and from discarded supernatant fluid was analyzed in 26 patients with atypical, negative or indeterminate cytology. Cytology correctly diagnosed aggressive disease in four patients. Cytological diagnoses for the remaining 26 were as follows: 16 negative (nine false negative), nine atypical, one indeterminate. MP correctly determined aggressive disease in one false negative cytology case and confirmed a negative cytology diagnosis in seven of seven cases of non-aggressive disease. Of the nine atypical cytology cases, MP correctly diagnosed seven as positive and one as negative for aggressive disease. One specimen that was indeterminate by cytology was correctly diagnosed as non-aggressive by MP. This study was limited in the small sample size, and retrospective nature of the study. While the mutational profiling detected additional cases of aggressive disease, nine cases of malignancy were missed. The authors noted that the false negative results are likely due to a combination of the less than perfect sensitivity of both tests as well as to sampling limitations related to FNA and brushing techniques. Further large-scale studies are needed to demonstrate the clinical utility of this testing.

Al-Haddad et al. (2013) reported on a prospective, cohort study of 286 patients to quantify the test characteristics of molecular (DNA) analysis in suspected low-risk mucinous pancreatic cysts (MPCs). Patients with suspected MPCs underwent endoscopic ultrasound fine-needle aspiration (EUS-FNA) and cyst fluid DNA analysis with Pathfinder TG. Surgical resection was performed in 48 patients (17%), confirming a mucinous pathology in 38 (79%) in this group. The molecular analysis had a sensitivity of 50% and a specificity of 80% in identifying MPCs (accuracy of 56.3%). The combination of molecular analysis with cyst fluid carcinoembryonic antigen (CEA) and cytology was found to have a higher MPC diagnostic performance than either one of its individual components, with a sensitivity, specificity, and accuracy of 73.7%, 70%, and 72.9%, respectively. There was no significant difference in accuracy between molecular analysis and CEA/cytology in this group. The authors concluded that molecular analysis aids in the diagnosis of MPCs when cytology is nondiagnostic or cyst fluid is insufficient for CEA or its level is indeterminate. The authors note that 17% of the patients recruited underwent pancreatectomy for which surgical pathology was used as the reference standard. The study was designed to include cysts strongly suspected to be mucinous—therefore, serous cystadenomas and pseudocysts (based on review of clinical history, cyst morphology, and CEA/cytology) were excluded. It was noted that molecular analysis is

unlikely necessary and often unjustified for these types of cysts, however the authors note that some mucinous cysts may have been erroneously excluded based on this classification. The authors note that at the onset of the study, the lab required a minimum of 1 mL of cyst fluid for CEA analysis, which decreased to 0.5 mL during the last year of the study. The smaller volume requirement may have made CEA levels available for additional patients, which may have lessened the incremental diagnostic value of molecular analysis. In addition, the authors note that some labs are able to perform CEA analysis on as little as 0.2 mL of cyst fluid. At this time while the study compared molecular analysis with CEA and cytology, the study is preliminary and should be confirmed in larger randomized, controlled studies.

Panarelli et al. (2012) examined the utility of PathfinderTG in classifying fine-needle aspiration biopsies from small pancreatic cystic lesions. Twenty pancreatic cyst cytology aspirates, all of which met radiographic criteria for close observation, were cytologically classified as consistent with pseudocyst, serous cystadenoma, or mucinous neoplasm with lowgrade, intermediate-grade, or high-grade dysplasia and analyzed for carcinoembryonic antigen. Redpath Integrated Pathology Inc. rendered diagnoses of nonmucinous (reactive/indolent or serous) or mucinous (low-risk or at risk) cyst on the basis of results of the PathfinderTG panel (KRAS mutations, DNA content, and loss of heterozygosity at microsatellites linked to tumor suppressor genes). Cytologic and commercial laboratory diagnoses were found to be concordant in only seven (35%) cases. Seven cysts classified as mucinous with low-grade dysplasia by cytology were interpreted as nonmucinous on the basis of the PathfinderTG panel, two of which were resected mucinous cysts. Two pancreatitis-related pseudocysts were misdiagnosed as low-risk mucinous cysts; one mucinous cyst with low-grade dysplasia was considered at risk for neoplastic progression using the PathfinderTG panel. One cyst misclassified as pseudocyst by cytology, but low-risk mucinous cyst by molecular analysis, proved to be a mucinous cystic neoplasm with low-grade dysplasia after surgical resection. The authors concluded that the PathfinderTG panel may aid in the classification of pancreatic lesions, but it is often inaccurate and should not replace cytologic evaluation of these lesions.

A technology assessment and systematic review regarding topographic genotyping with PathFinderTG was commissioned by Centers for Medicare and Medicaid Services (CMS) and conducted by the Tufts Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ) (Trikalinos TA, et al., 2010). The review included studies evaluating the patented technology, specifically those using loss of heterozygosity (LOH) analysis. LOH is a frequent genetic alteration that is found in many cancers. It is thought that LOH alterations may have prognostic significance. Fifteen studies were included—these pertained to: lung cancer (n=4); pancreatic and biliary tree tumors (n=4); hepatocellular carcinoma (n=4); gliomas, thyroid tumors, lacrimal gland tumors and mucinous tumors of the appendix (n=1 for each). The sample size in the studies ranged from 11 to 103. The review identified no studies regarding the analytic validity of LOH based topographic genotyping with PathFinderTG. The studies were retrospective in design and utilized available archival tissue blocks. One study, molecular profiles of gliomas and reactive gliosis were determined retrospectively and they were used prospectively on 16 diagnostically challenging cases of reactive gliosis versus glial tumors. There were no studies found that evaluated whether the use of LOH based topographic genotyping with PathFinderTG affects patient outcomes. There were no studies identified that compared LOH based topographic genotyping with PathFinderTG with conventional pathology. The review found that “all studies are small, they have important methodological limitations, and they do not address patient-relevant outcomes.”

A prospective multicenter study examined a cohort of 113 patients with pancreatic cysts (Khalid, et al., 2009). Aspirated cyst fluid was examined by PathFinderTG and the results were compared to cytology and pathologic examination of surgically obtained cysts. The study found that the PathFinderTG analysis had 96% specificity in identifying malignant lesions. The cytologic examination missed ten out of 40 malignant lesions, which were correctly identified by PathFinderTG testing. Limitations of the study included limited follow-up, selection bias, lack of investigator blinding to results of DNA analysis.

Studies published regarding topographic genotyping consist mainly of small retrospective studies. Many of these studies do not involve PathFinderTG test. The studies generally focus on the association of the topographic genotyping results with tumor characteristics (Sawhney, et al., 2009; Shen, et al., 2009; Sreenarasimhaiah, et al., 2009; Finkelstein, et al., 2003; Pollack, et al., 2001; Finkelstein, et al., 1998; Riberio, et al., 1998; Kounelis, et al., 1998; Jones, et al., 1997a; Jones, et al., 1997b; Holst, et al., 1997; Pricolo, et al., 1997; Safatle-Ribeiro, et al., 1996; Ribeiro, et al., 1996; Kanbour-shakir, et al., 1996; Finkelstein, et al., 1996; Papadaki, et al., 1996; Przygodzki, et al., 1996; Pricolo, et., 1996; Jacoby, et al., 1995; Finkelstein, et al., 1995).

Studies comparing topographic genotyping with established testing methods are lacking. There do not appear to be prospective studies published in the peer-reviewed medical literature that focus on the clinical validity, the clinical utility of the test or the impact of the test on clinical outcomes.

The RedPath website includes a publication section. Review of this section indicates that generally these articles involve genetic mutational testing of various types of cancers, but do not appear to be specific to the PathFinderTG test and do not allow conclusions to be drawn regarding the clinical utility of the PathFinderTG test.

Professional Societies/Organizations
The use of topographic genotyping or PathFinderTG in the diagnosis or management of cancer does not appear to be included in guidelines from medical professional societies and organizations.

Use Outside of the US
No relevant information

Summary
There is insufficient evidence in the published, peer-reviewed, scientific literature to demonstrate that topographic genotyping or the PathFinderTG® (RedPath Integrated Pathology Inc., Pittsburgh, PA) can be used as methods to assist in the diagnosis or management of individuals with cancer when microscopic analysis and staining fail to provide a definitive diagnosis. This testing has not been adequately compared with established testing methods and impact on health outcomes is not known at this time. The clinical utility of topographic genotyping and the PathFinderTG in the diagnosis and management of cancer has not yet been established through well-designed clinical trials.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Experimental/Investigational/Unproven/Not Covered when used to report topographic genotyping (PathFinderTG® test):

CPT®* Codes	Description
81479	Unlisted molecular pathology procedure
84999	Unlisted chemistry procedure

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