MEDICAL POLICY

POLICY TITLE	PATHFINDER TG MOLECULAR TESTING
POLICY NUMBER	MP-2.266

Original Issue Date (Created):	**October 1, 2014**
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Effective Date:	**October 1, 2014**

I. POLICY

Molecular testing using the PathFinderTG® system is considered **investigational** for all indications including the evaluation of pancreatic cyst fluid and of suspected or known gliomas. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

This test has multiple potential uses including use in diagnosis, determining prognosis, and predicting response to therapies. All uses are considered investigational.

II. PRODUCT VARIATIONS

TOP

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N]	Capital Cares 4 Kids	[N]	Indemnity
[N]	PPO	[N]	SpecialCare
[N]	HMO	[N]	POS
[Y]	SeniorBlue HMO*	[Y]	FEP PPO**
[Y]	SeniorBlue PPO*		

*Refer to Novitas Solutions Local Coverage Determination (LCD) L31144: Loss of Heterozygosity Based Topographic Genotyping with Pathfinder TG with regards to coverage/consideration for Pancreatic Cyst / Pancreatic Mass only. Information regarding coding and individual consideration of Medicare claims for this test was released in a provider bulletin from Highmark Medicare Services in June 2007 (available online at: https://secure.highmark.com/ldap/medicalpolicy/wpa-highmark/printerfriendly/L-83-001.html). The CPT code suggested by Highmark Medicare Services for this test (which also

appears on a test requisition form on the company website) is code 84999 – unlisted chemistry procedure.

**Refer to FEP Medical Policy Manual MP-2.04.52 PathFinder TG® Molecular Testing. The FEP Medical Policy manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

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The patented PathFinderTG® test is a molecular test to be 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. This approach may be referred to as molecular anatomic pathology. RedPath, the test provider, suggests that the PathFinderTG® results provide useful and definitive diagnostic and prognostic information and reliably predict treatment response for multiple organ systems.

Background

The testing involves the following steps:

- manual microdissection to identify and procure abnormal cells from existing pathology specimens
- DNA extraction and amplification (e.g., polymerase chain reaction [PCR])
- DNA sequencing to identify oncogenic mutations
- Integration of this molecular information with the cytologic or histologic findings provided by the pathologist of record to provide a definitive diagnosis

For some specimens such as fluid aspirates, DNA is extracted from the fluid, since there may be little or no cellular content. The molecular testing consists of applying panels of molecular markers previously defined for each organ system or clinical question.

Potential uses described by the company include 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. RedPath proposes that PathFinderTG® is appropriate in clinical practice when the results will alter clinical decision making.

Some of the tests RedPath offers (e.g., 1p/19q loss, microsatellite instability) are offered by other laboratories as single clinical tests. The remainder of the tests RedPath offers (e.g., KRAS point mutation and loss of heterozygosity [LOH] panels) are typically performed in research settings. The aim of PathFinderTG® testing is to integrate molecular findings into the pathology diagnosis.

This patented diagnostic test is only available through RedPath Integrated Pathology (Pittsburgh, PA). The PathFinderTG® Molecular Test is not subject to review by the U.S.

Food and Drug Administration (FDA) because it is a laboratory-developed test (LDT) conducted only at RedPath Integrated Pathology's licensed laboratory. Laboratories performing LDTs must be licensed for high-complexity testing under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). RedPath is licensed under CLIA.

IV. RATIONALE

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RedPath offers the PathFinderTG® molecular test as a way to provide definitive diagnoses and prognostic information and predict responses to chemotherapy. While integrating the molecular information that a test like PathFinderTG® provides is of interest and the subject of research for neoplasms, currently the specific molecular features, associated genetic biomarkers and their relationships with clinical outcomes, are not well-defined. Accordingly, their role in clinical decision making, including selecting treatment options, has not been defined.

Because of the scope of claims by the company for widespread application of PathFinderTG® in multiple organ systems and clinical scenarios, and more than 500 papers they reference "supporting the clinical efficacy of PathFinderTG®" (Available online at: http://www.redpathip.com/publications.asp. Last accessed April 2008), we chose two representative applications to address in this policy—pancreatic cysts and gliomas. Published studies reviewed for this policy include those cited by RedPath as providing "clinical validation" for PathFinderTG®, as well as those representative of the current medical literature describing what is known of the molecular profiles of various tumor types (specifically pancreatic cystic and glial neoplasms) and their potential role in clinical decision making.

Pancreatic Cysts

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 are often performed on fluid from the cyst to aid in the diagnosis (e.g., amylase, lipase, carcinoembryonic antigen levels), but results can still be equivocal. Information provided by additional testing modalities would, therefore, be potentially useful.

The PathFinderTG® test is suggested to serve the following purposes based on panels of molecular markers, including KRAS point mutations and loss of heterozygosity (LOH), in pancreatic cyst samplings/fluid:

- definitively discriminate reactive from neoplastic conditions of the pancreas (especially in aspirated fluid specimens from pancreatic cysts)
- identify which premalignant diseases (specifically, mucinous cystic neoplasms [MCN]) will progress to cancer and those that will not

- distinguish nonmucinous from mucinous cysts

Evidence

The most recent search was performed though March 15, 2013. From a convenience sample of tissue specimens archived between 1999 and 2004, Lapkus et al. described mutations in brushing samples from pancreatic and bile duct lesions. (1) No description of patients or tumor stage was reported. Various molecular findings and mutations from 40 pancreatic duct and 21 biliary brushing specimens were described, including LOH for a panel of 15 markers (1p, 3p, 5q, 9p, etc.) in addition to point mutation in KRAS-2 for cells obtained from cytologic preparations that had been diagnosed by conventional cytology as malignant (n=10), atypical (n=20), or benign (n=10). The authors suggested "knowing that cancer evolves through a temporal process of mutation acquisition raises the question whether this sequence can be determined in clinical specimens." Tissue histologic findings were available for 4 samples in the malignant group (all carcinomas), 4 in the benign group (3 were benign), and 9 in the atypical group (4 carcinomas). These results provided little evidence to support clinical value of the mutation patterns. Results from just 17 of 40 samples were compared to tissue diagnoses; therefore, measures of accuracy are not calculable. The cross-sectional study design further prevented meaningful conclusion.

Khalid et al. reported results from a retrospectively assembled case series using LOH in the diagnosis of pancreatic malignancy. (2) In an apparent convenience sample of 26 patients with either surgical removal (n=25) or "long-term follow-up" (n=1), there were 17 cancers (6 pancreatic and 11 cholangiocarcinomas) and 9 non-cancers. No description of patients or tumor stage was reported. Using "standard" microscopic analysis of the cytology specimens, 8 were judged malignant, 10 were indeterminate, and 8 were benign. Results of various molecular tests (LOH, KRAS, etc.) were evaluated on cytology and tissue specimens. Reported sensitivity was 100% (95% confidence interval [CI]: 83–100%) and specificity 100% (95% CI: 70–100%; CIs calculated) for a diagnosis of malignancy by PathFinderTG®. Whether the molecular findings would have had clinical impact was unclear. In addition, results were not presented in a manner that allowed direct comparison between the molecular and standard testing, both for the cytology analysis and the tissue specimens.

In a case series, Khalid et al. prospectively collected fluid from 116 pancreatic cysts. (3) Molecular analyses were restricted to 31 patients who underwent surgery and "5 patients [who] reached a final diagnosis of malignancy based on cytology...." In this subgroup of 36, molecular analyses included KRAS point mutation and a broad panel of LOH markers. Whether those conducting molecular assays were blinded to confirmatory results was not reported. Cutoff points defining significant LOH at loci were established using normal specimens—a standard deviation greater than 2 was defined as abnormal. The sensitivity and specificities of KRAS mutation alone distinguishing premalignant from malignant cysts were 93% (95% CI: 62–100%) and 87% (95% CI: 62–96%) (CIs calculated). Subsequent testing for LOH did not alter sensitivity and correctly reclassified one false-positive result, increasing specificity to 93% (95% CI: 70–100%). Analysis from this small sample did not demonstrate incremental value for LOH testing added to KRAS.

These studies highlight important issues pertaining to test accuracy and whether there is evidence that PathFinderTG® results provide incremental information that informs diagnostic and prognostic decision making for patients with pancreatic cysts, including the following:

1. whether progression of genetic mutations is sufficiently defined to use for diagnosis and prognosis
2. sampling variability of fluid and tissue specimens
3. study design and conduct including patient (sample) selection and blinding of personnel performing assays to clinical outcomes
4. small sample sizes and absence of sufficient tissue samples to compare with PathFinderTG® results for a substantial proportion of patients
5. lack of adequate patient follow-up and validation/replication of findings

First, stepwise accumulation of KRAS mutations and allelic losses (LOH) accompanying cancer progression in pancreatic ductal adenocarcinomas have been found. (4, 5) However, overlap between molecular findings in inflammatory and neoplastic conditions has also been described—specifically KRAS mutations in chronic pancreatitis. (6-9) Progression of genetic mutations in mucinous pancreatic tumors has been described and, although there appear to be similarities with pancreatic ductal adenocarcinomas, the precise pattern and progression of these mutations remain to be elucidated. For example, while suggesting the pattern of KRAS mutation followed by allelic loss predicts malignancy in pancreatic cysts, Khalid et al. also noted a lack of clarity in the "pattern and rate of mutation accumulation…." (3)

Second, potential sampling discrepancies between the molecular profile of a pancreatic cyst wall aspirate or fluid and tissue specimen needs to be further addressed. This is particularly important in mucinous cystic neoplasms (MCNs) of the pancreas, which may show differing histologic features in different areas of the tumor and may have focal invasion. (10) To further complicate this issue, RedPath does not address the genetic heterogeneity seen among the subtypes of MCNs (for example, KRAS mutations have been described as occurring in 20% of mucinous cystic adenomas, 33% of adenomas with moderate dysplasia, and 89% with carcinoma in situ). (10)

Third, whether those performing the assay were blinded to surgical results was not stated in the studies reviewed. Clear description of case selection (e.g., consecutive or convenience) was absent.

Fourth, sample sizes were small, as reflected in the wide confidence intervals calculated for reported sensitivities and specificities.

Finally, both adequate follow-up and replicated results (validation) are required to demonstrate whether PathFinderTG® results inform diagnostic and prognostic decision making in a manner that will benefit patients. We are unaware of long-term studies with defined clinical outcomes using PathFinderTG® to differentiate neoplastic pancreatic cysts from those determined by the test as "definitely benign," implying that progression to cancer is improbable. RedPath suggests that some cases of MCN of the pancreas need not be resected based on "benign" molecular profiles that predict indolent behavior. However, international

guidelines state that "unless there are contraindications for operation, all MCNs should be resected." (11) This is due to the uncertainty of the natural history of MCN and the presumed malignant potential of all types. (11-13)

Khalid et al. published the results of a prospective multicenter study to validate their initial results from a single center pilot study, (3) and to evaluate the role of pancreatic cyst fluid DNA analysis in differentiating mucinous from nonmucinous cysts. (14) Patients included in the study were seen for endoscopic ultrasound (EUS)-guided evaluation of a pancreatic cyst between July 2004 and June 2006 at 1 of 7 participating centers. DNA analysis was performed only in cases that reached conclusion (defined as surgical resection of the lesion or a diagnosis of malignancy based on fine-needle aspiration cytology). DNA analysis consisted of direct sequencing of the first exon of the KRAS gene and PCR amplification of individual microsatellite markers to determine allelic imbalance (reported as allelic loss amplitude or ALA). A total of 391 patients were enrolled in the study, and after exclusions for various reasons including no cyst seen by EUS or insufficient cyst fluid, 299 patients remained, 124 of whom reached a final pathologic diagnosis based on surgical resection (n=98) or malignant cytology (n=26). An additional 11 cases were excluded for various pathologic diagnoses not included in the study methods (e.g., islet cell tumors). The remaining 113 cysts were classified as benign nonmucinous (n=25) or mucinous (n=88). Of the mucinous, 40 were malignant and 48 were premalignant. Cyst fluid KRAS mutation with allelic loss showed a specificity of 96% for the diagnosis of malignancy but low sensitivity of 37%. Optimal cutoff points for ALA were established and, at the level set, the sensitivity and specificity for distinguishing nonmucinous from mucinous cysts were 67% and 66%, respectively. A separate cutoff value for malignancy yielded a 90% sensitivity and 67% specificity. Limitations of the study were acknowledged. These included lack of investigator blinding to the results of the DNA analysis and potential selection bias, as only lesions with confirmed pathologic findings were included. Therefore, the study population consisted of a higher number of patients with malignant cysts than would have been expected.

A systematic review of LOH-based topographic genotyping with PathFinderTG® was prepared for the Agency for Healthcare Research and Quality (AHRQ) technology assessment program. (15) Key questions addressed the published evidence on the analytic test performance, diagnostic ability, and clinical validity of the test and what evidence there is comparing the PathFinder test with conventional pathology. The conclusions were that none of the studies included in the systematic review directly measured whether using LOH-based topographic genotyping with PathFinderTG® improved patient-relevant clinical outcomes and that the eligible studies on the diagnostic and prognostic ability of the test were small in sample size, had overt methodologic limitations, and all but one performed retrospective assessments. The review points out that the studies did not provide important information on patient selection, patient characteristics, treatments received, clinical endpoint definitions, justification of sample size, selection of test cutoffs, and selection among various statistical models. In addition, the review notes that there were strong indications that the selection of certain test cutoffs was determined post-hoc, in that the cutoffs varied widely across studies and were not validated in an external population.

In summary, the evidence reviewed does not demonstrate that PathFinderTG® has incremental clinical value for diagnosis or prognosis of pancreatic cysts and associated cancer.

Gliomas

Limitations of pathologic examination for diagnosing and grading gliomas have been described. (16, 17) This is partly due to the small brain biopsy size, as well as to interobserver variability between pathologists. In addition, different glial tumors may respond differently to therapy. Defining prognosis and predicting therapeutic response is therefore of considerable interest. The PathFinderTG® test is proposed to address these issues using panels of LOH markers from stereotactic brain biopsies or fine-needle aspirations to:

- provide glioma diagnosis and classification
- assess tumor aggressiveness (discriminating between low- and high-grade gliomas)
- discriminate glioma from reactive gliosis
- predict tumor response to certain chemotherapeutic regimens through analysis of the chromosomal 1p/19q deletion and identified LOH mutations

Evidence

In one study cited as clinical validation for PathFinderTG®, investigators retrospectively analyzed archived tissue from 197 gliomas, performing polymerase chain reaction (PCR) for a panel of 12 to 16 LOH markers.(18) Loss of 1p and 19q were analyzed in all cases, with a subset (n=93) undergoing an extended panel of 16 markers. The authors reported, "The qualitative and quantitative aspects of glioma allelic loss were correlated with the clinical impression of treatment response [to procarbazine, CCNU, vinblastine] as determined by imaging studies." Treatment response was classified as none, partial (25% decrease in size with stable or decreasing steroid doses), or complete ("disappearance of all contrast-enhancing tissue for gliomas and resolution of abnormalities on FLAIR sequences for low-grade gliomas"). However, tables reported "major response" (undefined) rather than "complete response." Of 96 patients with high-grade gliomas, 49 had follow-up of 6 months or longer and were assessed for therapy response: 11 had "no response," 17 "partial," and 21 "major" response; deaths occurring prior to 6 months were not reported. Predictive values (calculated from reported data) of at least partial response for 1p loss were positive predictive value (PPV) 100% (95% CI: 89–100%) and negative predictive value (NPV) 65% (95% CI: 41–83%); for 19q loss, PPV was 82% (95% CI: 64–92%) and NPV was 21% (95% CI: 8–43%). It is not clear whether the molecular data results were blinded for the classification of treatment response. The retrospective design, lack of follow-up information for 47 patients, and no report of any censoring due to mortality are significant study limitations.

In a retrospective case series, Finkelstein et al. described LOH to distinguish neoplasms from reactive gliosis. (19) The study included archival tissue from 15 patients with reactive gliosis and 54 patients with gliomas of varying histologic type and grade. Molecular analyses were conducted blinded to the clinical diagnosis, and the results showed no LOH in any of the cases of gliosis. From the group of 54 patients, 14 of 19 (74%) well-differentiated neoplasms showed allelic loss, 35 of 35 high-grade gliomas showed at least one allelic loss alteration (33

of 35 had more than one loss). Within this same study, they then analyzed LOH in an additional 16 cases with indeterminate histopathology (reactive gliosis vs. gliomas). Of the 16 indeterminate cases, 9 were subsequently determined to be neoplastic based on clinical follow-up; LOH correctly identified 8 of these 9—sensitivity 89% (95% CI: 56–99%) and specificity 88% (95% CI: 53–99%). LOH correctly reclassified 3 of 9 as neoplasms initially diagnosed with benign disease and 1 of 7 with benign disease initially diagnosed as neoplastic. While their results were consistent with the study hypothesis, it will be necessary to apply the criteria determined in this study to additional validation samples. In addition, within this study, the sample size was small and confidence intervals were wide.

The only molecular test currently being performed on a relatively frequent basis for gliomas is the 1p/19q chromosomal loss for oligodendrogliomas. Yet optimal use of this test in the clinical care of patients remains unclear. (20) Although LOH involving multiple chromosomes has been observed in gliomas, and in some studies, LOH is predictive of tumor response to particular chemotherapeutic regimens, it is not clear that the information is meaningfully incremental to that provided by the 1p/19q data alone. (21) Also, some studies have shown conflicting results in terms of chemoresponsiveness for tumors with LOH involving chromosomes other than 1p/19q…" (21) As noted by Lassman and Holland, "Current wisdom suggests that one of the main reasons for the poor responsiveness (of gliomas to therapy) is the existence of multiple genetic subsets of gliomas and the related lack of molecular stratification prior to treatment. Therefore, several strategies have been employed to divide gliomas into molecular subgroups that are either more or less responsive to existing therapies. Whether such stratification will result in effective therapies specific for each glioma subset is not yet clear…. To what extent molecular subdivision of gliomas will be clinically useful remains to be seen." (20)

The evidence reviewed does not demonstrate that PathFinderTG® testing for diagnosis or predicting response to therapy provides a benefit to patients with gliomas.

Summary

The evidence reviewed for 2 representative uses for this test has significant limitations, as discussed. Demonstrating the utility of a test for diagnostic and prognostic purposes or to predict therapeutic response requires that results accurately inform clinical decision making in a manner leading to a net health benefit defined by clinical outcomes. Results must also be clearly reproducible, as shown by applying the test (with priori-defined cutoff points) to independent samples for validation. Because the impact of this technology on health outcomes is not known and because outcomes with this technology compared with existing alternatives (i.e., incremental value) are not known, the PathFinderTG® testing is considered investigational for all indications, including evaluation of pancreatic cyst fluid and suspected/known gliomas.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

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Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational therefore not covered:

CPT Codes®								
84999	89240							

POLICY TITLE	PATHFINDER TG MOLECULAR TESTING
POLICY NUMBER	MP-2.266

HCPCS Code	Description

ICD-9-CM Diagnosis Code*	Description

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2015:

ICD-10-CM Diagnosis Code*	Description

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES

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Other:

Novitas Solutions. Local Coverage Determination (LCD) L33142 Biomarkers for Oncology. Effective 1/1/14.
Novitas Solutions Local Coverage Determination (LCD) L31144: Loss of Heterozygosity Based Topographic Genotyping with Pathfinder TG. Effective 8/1/13.

X. POLICY HISTORY

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MP-2.266	**CAC 5/20/14** Policy criteria removed from MP-2.212 Tumor Markers and Tumor Related Molecular Testing. References updated and rationale added. No changes to policy statements. Medicare variation added and revised. Policy coded.

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