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RET Proto-Oncogene Testing

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Last Review 04/25/2024
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Policy

Scope of Policy

This Clinical Policy Bulletin addresses RET proto-oncogene testing.

I. Medical Necessity

Aetna considers the following testing medically necessary:

A. Tests for germline point mutations in the RET gene medically necessary for members who meet any of the following high-risk criteria:

1. Members who have first-degree blood relatives (ie, parent, full-sibling, child) with medullary thyroid carcinoma (MTC)*; or
2. Members who have first- (i.e., parent, full-sibling, child) or second-degree (i.e., aunt, uncle, grandparent, grandchild, niece, nephew, half-sibling) blood relatives and germline RET mutations (Testing strategy: Test for specific familial mutation); or
3. Members with any of the following*:

    a. C-cell hyperplasia;
    b. Endocrine tumors, two or more;

        i. Hirschsprung disease;
        ii. MTC; paraganglioma;
        iii. Parathyroid carcinoma; or
        iv. Pheochromocytoma.

*Testing Strategy: Sequencing of the RET gene may be considered.

B. Diagnostic testing for germline point mutations in the RET gene for members with apparently sporadic medullary thyroid carcinoma.

II. Experimental, Investigational, or Unproven

Tests for germline point mutations in the RET gene are considered experimental, investigational, or unproven for all other indications (e.g., non-small cell lung cancer; not an all-inclusive list) because its effectiveness for indications other than the ones listed above has not been established.

III. Related Policies

- See CPB 0140 - Genetic Testing (../100_199/0140.html) for policy on genetic testing for non-member relatives of Aetna members

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
CPT codes covered if selection criteria are met:	
81404 - 81406	Molecular pathology procedures
88271	Molecular cytogenetics; DNA probe, each (e.g., FISH)
HCPCS codes not covered for indications listed in the CPB:	
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
ICD-10 codes covered if selection criteria are met:	
C73 - C75.9	Malignant neoplasm of the thyroid and other endocrine glands
E07.0	Hypersecretion of calcitonin
Q43.1	Hirschsprung's disease
Z80.8	Family history of malignant neoplasm of other organs or systems [thyroid cancer]
ICD-10 codes not covered for indications listed in the CPB:	
C34.00 - C34.92	Malignant neoplasm of bronchus and lung [non-small cell lung cancer]
C75.5	Malignant neoplasm of aortic body and other paraganglia
D35.6	Benign neoplasm of aortic body and other paraganglia
D44.7	Neoplasm of uncertain behavior of aortic body and other paraganglia

Background

Multiple endocrine neoplasia (MEN) is a rare heritable disorder that affects the endocrine system and consists of the development of tumors (neoplasia) in at least two endocrine glands, though tumors can also develop elsewhere. These tumors can be noncancerous (benign) or cancerous (malignant). There are three major types of MEN: type 1 (MEN1), type 2 (MEN2) and type 4 (MEN4).

MEN1 is characterized by tumors of the parathyroid glands, anterior pituitary and pancreatic islet cells and is caused by mutations in the MEN1 gene.

Medullary Thyroid Carcinoma (MTC) is a cancer of the thyroid gland that starts in cells that release calcitonin. MTC is a common characteristic among individuals with MEN2. Some individuals with MEN2 also have pheochromocytoma, a tumor of the

adrenal gland which causes high blood pressure. MEN2 is divided into three subtypes: type 2A (MEN2A), type 2B (MEN2B) and familial medullary thyroid carcinoma (FMTC). MEN2 is caused by mutations in the RET gene.

MEN4 appears to have similar signs and symptoms to MEN1; however, it is caused by mutations in the CDKN1B gene.

Genetic testing for RET germline mutation has shown 100 % sensitivity and specificity for identifying those at risk for developing inherited medullary thyroid cancer (multiple endocrine neoplasia (MEN) 2A, MEN 2B, or familial medullary thyroid carcinoma (FMTC)). Use of the genetic assay allows earlier and more definitive identification and clinical management of those with a familial risk for medullary thyroid cancer when compared to the existing standard of annual biochemical monitoring.

Medullary thyroid carcinoma is surgically curable if detected before it has spread to regional lymph nodes. However, lymph node involvement at diagnosis may be found in up to 75 % of patients for whom a thyroid nodule is the first sign of disease. Thus, there is an emphasis on early detection and intervention in families, which are affected by the familial cancer syndromes of MEN types 2A and 2B and FMTC, which account for 25 % of medullary thyroid cancer.

After genetic counseling, most family members who test positive undergo surgery to remove the thyroid gland. First-degree relatives of those with MTC that appears to be sporadic in origin also undergo the biochemical test to verify that the patient's tumor is not caused by an inheritable form of this disease.

Fialkowski et al (2008) stated that multiple endocrine neoplasia type2A (MEN 2A) is a genetic syndrome manifesting as MTC, hyper-parathyroidism, and pheochromocytoma. Multiple endocrine neoplasia 2A results from mutations in the RET proto-oncogene. Hirschsprung Disease (HD) is a congenital condition characterized by a blockage of the large intestine due to poor muscle movement in the bowel. HD is a rare manifestation of MEN 2A and has been described in known MEN 2A families. These investigators described 2 MEN 2A families that were only identified after the diagnosis of HD. Kindred 1: A boy presented in infancy with HD. Genetic screening revealed a C609Y mutation, which is consistent with MEN 2A. Evaluation of his sister, father, and grandmother revealed the same mutation. All 3 had thyroidectomies demonstrating C-cell hyperplasia. The grandmother had a microscopic focus of MTC. Kindred 2: An infant boy and his sister were diagnosed with HD as neonates. Genetic testing demonstrated a C620R gene mutation consistent with MEN 2A. Total thyroidectomies revealed metastatic MTC in the father and C-cell hyperplasia in both children. The authors concluded that HD can be the initial presentation of MEN 2A. They strongly recommend that genetic screening be performed in patients presenting with HD, looking for the known RET mutations associated with MEN 2A. If a mutation consistent with MEN 2A is detected, genetic screening of all first-degree relatives in the kindred is recommended.

In a case report, Pandey et al (2011) emphasized that all patients with a history of HD should consider screening for RET mutations (it should be noted that RET mutations are the predominant but only one of a number of possible causes of HD), as there is a well-established association between HD and MEN 2A. If present, this could facilitate early diagnosis of MEN 2A with resultant thyroidectomy prior to the onset of MTC or at least prior to the development of metastatic disease.

Vaclavikova et al (2012) noted that inactivating germline mutations in the RET proto-oncogene are the major genetic cause of HD. In some cases, HD can be associated with MTC that is commonly caused by activating RET mutations. These investigators performed retrospective and prospective genetic analyses of 157

patients with HD operated on between December 1979 and June 2011; DNA was isolated from peripheral leukocytes. Patients with HD as well as family members were tested for RET mutations by direct sequencing and single-strand conformation polymorphism methods. RET mutations were detected in 16 patients (10 %). Association with MTC was found in 2 families, other 8 families had a mutation with potentially high- risk of MTC development and 4 novel mutations were detected. Total colonic aganglionosis was noted to have a high mutation detection rate (40 %). Three patients underwent total thyroidectomy (2 had clinical manifestation of MTC, 1 C-cell hyperplasia). The authors concluded that these findings showed the benefit of systematic RET mutation screening in HD patients in order to identify the risk of MTC in the preclinical stage of the disease. All patients should be tested for RET mutations at least in exon 10, and now additionally in exon 11 and 13, as well.

An UpToDate review on "Clinical manifestations and diagnosis of multiple endocrine neoplasia type 2" (Lips, 2013) states that "Hirschsprung disease (HD) is characterized by the absence of autonomic ganglion cells within the distal colonic parasympathetic plexus resulting in chronic obstruction and megacolon. In humans, inactivating mutations of the RET proto-oncogene have been associated with HD. HD is a heterogenic disorder, occurring both in a familial and in a sporadic form. In about 50 percent of familial and 15 to 35 percent of sporadic HD patients, mutations in the RET gene are involved. Most HD cases arise from loss of function mutations, RET haploinsufficiency, RET polymorphisms or haplotypes of the RET promotor region. Hirschsprung disease (HD) was found in 50 percent of children in a family with a C620 mutation .... RET proto-oncogene testing in infants presenting with Hirschsprung disease is useful and may identify new multiple endocrine neoplasia 2A kindreds".

An UpToDate review on "Medullary thyroid cancer: Clinical manifestations, diagnosis, and staging" (Tuttle, 2014) states that "In a patient with negative RET proto-oncogene testing and no family history of MEN2 syndrome, biochemical testing for coexisting tumors is typically not required".

In summary, RET proto-oncogene tests can be used to identify familial disease-causing RET point mutations in members of families known to be affected by inherited MTC. For members of families with defined RET point mutations, results of the RET proto-oncogene tests may be used to decide upon prophylactic thyroidectomy or continued monitoring is necessary. RET proto-oncogene tests may also be used to distinguish sporadic tumors from familial cancers in patients with MTC but without a previous family history of this disease, and in their first-degree relatives if the patient is found to have a germline RET mutation. Furthermore, RET proto-oncogene tests are also of clinical value for individuals with Hirschsprung disease.

Non-Small Cell Lung Cancer

Yoshida et al (2013) noted that recent discovery of ROS1 gene fusion in a subset of lung cancers has raised clinical interest, because ROS1 fusion-positive cancers are reportedly sensitive to kinase inhibitors. To better understand these tumors, these researchers examined 799 surgically resected non-small cell lung cancers (NSCLCs) by reverse transcriptase polymerase chain reaction (PCR) and identified 15 tumors harboring ROS1 fusion transcripts (2.5 % of adenocarcinomas). The most frequent fusion partner was CD74 followed by EZR. The affected patients were often younger non-smoking female individuals, and they had overall survival (OS) rates similar to those of the ROS1 fusion-negative cancer patients. All the ROS1 fusion-positive tumors were adenocarcinomas except 1, which was an adenosquamous carcinoma. Histologic examination identified an at least focal presence of either solid growth with signet-ring cells or cribriform architecture with abundant extracellular mucus in 53 % of the cases. These 2 patterns were reportedly also characteristic of anaplastic lymphoma kinase (ALK)-rearranged lung cancers, and these data

suggested a phenotypic resemblance between the ROS1-rearranged and ALK-rearranged tumors. All tumors except 1 were immune-reactive to thyroid transcription factor-1. Fluorescence in-situ hybridization (FISH) using ROS1 break-apart probes revealed positive re-arrangement signals in 23 % to 93 % of the tumor cells in ROS1 fusion-positive cancers, which were readily distinguished using a 15 % cutoff value from 50 ROS1 fusion-negative tumors tested, which showed 0 % to 6 % re-arrangement signals. However, this perfect test performance was achieved only when isolated 3' signals were included along with classic split signals in the definition of re-arrangement positivity. Fluorescence in-situ hybridization signal patterns were unrelated to 5' fusion partner genes. All ROS1 fusion-positive tumors lacked alteration of epidermal growth factor receptor (EGFR), KRAS, HER2, ALK, and RET genes.

Lira et al (2014) stated that approximately 7 % of NSCLCs harbor oncogenic fusions involving ALK, ROS1, and RET. Although tumors harboring ALK fusions are highly sensitive to crizotinib, emerging pre-clinical and clinical data demonstrated that patients with ROS1 or RET fusions may also benefit from inhibitors targeting these kinases. Using a transcript-based method, these investigators designed a combination of 3' over-expression and fusion-specific detection strategies to detect ALK, ROS1 and RET fusion transcripts in NSCLC tumors. They validated the assay in 295 NSCLC specimens and showed that the assay is highly sensitive and specific. ALK results were 100 % concordant with FISH (n = 52) and 97.8 % concordant with IHC (n = 179) [sensitivity, 96.8 % (95 % confidence interval [CI]: 91.0 % to 98.9 %); specificity, 98.8 % (95 % CI: 93.6 % to 99.8 %)]. For ROS1 and RET, these researchers also observed 100 % concordance with FISH (n = 46 and n = 15, respectively). They identified 7 ROS1 and 14 RET fusion-positive tumors and confirmed the fusion status by RT-PCR and FISH. One RET fusion involved a novel partner, cutlike homeobox 1 gene (CUX1), yielding an in-frame CUX1-RET fusion. ROS1 and RET fusions were significantly enriched in tumors without KRAS/EGFR/ALK alterations. ALK/ROS1/RET/EGFR/KRAS alterations were mutually exclusive. The authors concluded that as a single-tube assay, this test showed promise as a more practical and cost-effective screening modality for detecting rare but targetable fusions in NSCLC.

Wijesinghe et al (2015) noted that ROS1 and RET gene fusions were recently discovered in NSCLC as potential therapeutic targets with small-molecule kinase inhibitors. The conventional screening methods of these fusions are time-consuming and require samples of high quality and quantity. These researchers described a novel and efficient method by coupling the power of multiplexing PCR and the sensitivity of mass spectrometry. The multiplex mass spectrometry platform simultaneously tests samples for the expression of 9 ROS1 and 6 RET fusion genes. The assay incorporated detection of wild-type exon junctions immediately up-stream and down-stream of the fusion junction to exclude false-negative results. To flag false-positives, the system also comprised 2 independent assays for each fusion gene junction. The characteristic mass spectrometric peaks of the gene fusions were obtained using engineered plasmid constructs. Specific assays targeting the wild-type gene exon junctions were validated using complimentary DNA from lung tissue of healthy individuals. The system was further validated using complimentary DNA derived from NSCLC cell lines that express endogenous fusion genes. The expressed ROS1-SLC34A2 and CCDC6-RET gene fusions from the NSCLC cell lines HCC78 and LC-2/ad, respectively, were accurately detected by the novel assay. The assay is extremely sensitive, capable of detecting an event in test specimens containing 0.5 % positive tumors. The authors concluded that the novel multiplexed assay is robustly capable of detecting 15 different clinically relevant RET and ROS1 fusion variants.

Rossi et al (2017) stated that immunohistochemistry (IHC) is a widely-tested, low-cost and rapid ancillary technique available in all laboratories of pathology. This method is generally used for diagnostic purposes, but several studies have

investigated the sensitivity and specificity of different immunohistochemical antibodies as a surrogate test in the determination of predictive biomarkers in NSCLC, particularly for epidermal EGFR gene mutations, ALK gene and ROS1 re-arrangements. In this review, a critical examination of the works comparing the consistency of IHC expression and conventional molecular techniques to identify genetic alterations with predictive value in NSCLC was discussed. Summarizing, data on sensitivity and specificity of antibodies against ALK and ROS1 are very consistent and time has comes to trust in IHC at least as a cost-effective screening tool to identify patients with re-arranged tumors in clinical practice. On the other hand, mutant-specific antibodies against EGFR demonstrated a good specificity but a low-to-fair sensitivity, then raising some cautions on their employment as robust predictive biomarkers. A brief comment on preliminary experiences with antibodies against BRAF, RET, HER2 and c-MET was also included.

Furthermore, National Comprehensive Cancer Network's clinical practice guideline on "Non-small cell lung cancer" (Version 4.2016) states that "Emerging biomarkers include HER@ …. ROS1 and RET gene rearrangement".

Hess and colleagues (2021) noted that contradictory and limited data are available regarding the presentation and outcomes of patients with RET-fusion positive metastatic NSCLC as compared to patients without RET fusions. In an observational study, these researchers employed a linked electronic health records (EHR) database to genomics testing results and compared characteristics, tumor response, progression-free (PFS) and OS outcomes by RET fusion status among patients with metastatic NSCLC treated with standard therapies. Adult patients with metastatic NSCLC with linked EHR and genomics data who received systemic anti-cancer therapy on or after January 1, 2011 were eligible. Adjusted, using all available baseline co-variates, and unadjusted analyses were performed to compare tumor response, PFS and OS between patients with RET-fusion positive and RET-fusion negative disease as detected by next-generation sequencing (NGS). Tumor response outcomes were analyzed using Fisher's exact test, and time-to-event analyses were conducted using Cox proportional hazards model. There were 5,807 eligible patients identified (RET+ cohort, n = 46; RET- cohort, n = 5,761). Patients with RET fusions were younger, more likely to have non-squamous disease and be non-smokers and had better performance status (all $p < 0.01$). In unadjusted analyses, there were no significant differences in tumor response ($p = 0.17$) or PFS ($p = 0.06$) but OS was significantly different by RET status (hazard ratio [HR], HR = 1.91, 95 % CI: 1.22 to 3.0, $p = 0.005$). There were no statistically significant differences by RET fusion status in adjusted analyses of either PFS or OS (PFS HR = 1.24, 95 % CI: 0.86 to 1.78, $p = 0.25$; OS HR = 1.52, 95 % CI: 0.95 to 2.43, $p = 0.08$). The authors concluded that patients with RET fusions had different baseline characteristics that contributed to favorable OS in unadjusted analysis. However, after adjusting for baseline co-variates, there were no significant differences in either OS or PFS by RET status among patients treated with standard therapy prior to the availability of selective RET inhibitors.

Pheochromocytoma / Paraganglioma

Pheochromocytoma is a rare, usually noncancerous (benign) tumor that develops in cells in the center of an adrenal gland, leading to attacks of raised blood pressure, palpitations and headache. Paraganglioma is a tumor of the tissue composing the paraganglion, a small round body containing chromaffin cells, found near the aorta and in the kidney, liver heart and gonads.

Brito and associates (2015) noted that the presence of germline mutations in sporadic pheochromocytomas and paragangliomas (SPPs) may change the clinical management of both index patients and their family members. However, the frequency of germline mutations in SPPs is unknown. In a systematic review, these researchers described the frequency of germline mutations in SPPs and determined

the value of testing index patients and their family members for these mutations. They searched databases through June 2012 for observational studies of patients with SPPs who underwent germline genetic testing. The criteria used to define sporadic tumors were

(i) the absence of a family history of PCC/PG (ii) the absence of syndromic features (iii) the absence of bilateral disease, and (iv) the absence of metastatic disease.
These investigators included 31 studies including 5,031 patients (mean age of 44 years). These patients received tests for any of these 10 mutations: SDHAF2, RET, SDHD, SDHB, SDHC, VHL, TMEM127, MAX, isocitrate dehydrogenase (IDH) mutation and NF1. The overall frequency of germline mutation in SPP was 551 of 5,031 (11 %); when studies with patients fulfilling 4 criteria for sporadic tumors were used, the frequency was 171 of 1,332 (13 %). The most common germline mutation was SDHB 167 of 3,611 (4.6 %). Little outcome data were available to assess the benefits of genetic testing in index cases and family members. The authors concluded that the frequency of germline mutations in SPPs is approximately 11 to 13 % and the most common mutations affect less than 1 in 20 patients (5 %). They stated that the value of testing for germline mutations in patients with SPPs and their family members is unknown, as the balance of potential benefits and harms remains unclear.

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The above policy is based on the following references:

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