Genetic Testing for Germline Mutations of the RET Proto-Oncogene

Policy Number: AHS – M2078	Prior Policy Name and Number, as applicable: N/A
Initial Effective Date: June 1, 2023	Current Effective Date: June 1, 2023
Line(s) of Business: HMO; PPO; QUEST Integration; Medicare; FEP	Precertification: Required

I. Policy Description

The rearranged during transfection (*RET*) proto-oncogene encodes a transmembrane receptor tyrosine kinase that regulates a complex network of signal transduction pathways during development, survival, proliferation, differentiation, and migration of the enteric nervous system progenitor cells. Disruption of RET signaling by mutation, gene rearrangement, overexpression or transcriptional up-regulation of the *RET* gene is implicated in several human cancers, most commonly thyroid cancer, but also chronic myelomonocytic leukemia, acute myeloid leukemia, and lung, breast, pancreatic, and colon cancers. Mutation of the *RET* gene in a germline cell results in an autosomal dominant hereditary cancer syndrome, multiple endocrine neoplasia type 2 (MEN2) characterized by medullary thyroid carcinoma (MTC), pheochromocytoma (PHEO), and primary parathyroid hyperplasia (PPTH).

This policy covers genetic testing for germline variants in the *RET* gene. For information on testing of tumors for *RET* variants in order to guide chemotherapy, see M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy, M2030 Testing for Targeted Therapy of Non-Small-Cell Lung Cancer, and M2108 Molecular Markers in Fine Needle Aspirates of the Thyroid.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

1) Genetic testing for *RET* proto-oncogene point mutations **MEETS COVERAGE CRITERIA** in any of the following situations:
   a) Individual is a member of a family with defined *RET* gene mutations
   b) Individual is a member of a family known to be affected by inherited medullary thyroid cancer, but not previously evaluated for *RET* mutations
   c) Individual with apparently sporadic medullary thyroid carcinoma (MTC)
   d) Individual is a first-degree relative of individuals with sporadic medullary thyroid cancer
   e) Individual with a diagnosis of MTC or clinical diagnosis of MEN2 (multiple endocrine neoplasia type 2) or primary C-cell hyperplasia

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

2) Genetic testing for germline point mutations in the *RET* gene **DOES NOT MEET COVERAGE CRITERIA** in all other situations.

III. Scientific Background

The *RET* gene encodes a receptor tyrosine kinase that transduces growth and differentiation signals from the glial cell-derived neurotrophic factor family of ligands. *RET* is expressed in the neuroendocrine parafollicular C-cells of the thyroid gland, adrenal medulla, neurons, and other tissues. Unlike loss of function mutations that inactivate tumor suppressor proteins, oncogenic *RET* mutations result in a gain of function, inducing ligand-independent autophosphorylation of the RET receptor, uncontrolled activation of MAPK and phosphoinositide 3-kinase pathways, and ultimately uncontrolled growth and cell dedifferentiation.

Oncogenic activation of the *RET* gene can result from either somatic or germline alterations. Activating germline point mutations in *RET* with autosomal dominant heritability have been identified as the primary initiating events causative of malignancy in C-cells of the thyroid gland (MTC) and other clinical presentations of MEN2. These mutations are identified in 98-100% of MEN2 cases, which are responsible for 25% of MTC cases overall. An estimated 64,000 patients are diagnosed with thyroid cancer in the United States annually, and 1-2% of these cases are due to MTC. The most common alterations in the *RET* proto-oncogene are missense gain-of-function mutations mainly located in the extracellular domain of the *RET* gene (exons 10 or 11) and in the *RET* tyrosine kinase domain (exons 13, 14, 15 and 16).

Germline *RET* mutations are associated with clear genotype-phenotype correlations. These clinical phenotypes can be divided into two subclasses of MEN2: multiple endocrine neoplasia type 2A (MEN2A) including familial medullary thyroid carcinoma (FMTC) and MEN type 2B (MEN2B). Over 100 *RET* point mutations, duplications, insertions, deletions, and fusions have been identified in patients with MEN2A, with the C634R mutation in exon 11 being the most common mutation, whereas only two *RET* mutations have been identified in patients with MEN2B (mainly M918T, and rarely A883F). New variants continue to be reported. For example, in a case study of a 7-year-old girl in Italy, a “de novo” new germline *RET* deletion in exon 11 was found to cause features of both MEN2B without PHEO (pheochromocytoma), but “with a pelvic plexiform neurofibroma and with HPTH (primary hyperparathyroidism), which is typical of MEN2A.”

MEN2A is characterized by MTC and variable rates of PHEO, PPTH or both, with *RET* mutations in codons 609, 611, 618, or 620 of exon 10 and codon 634 of exon 11. Subtypes of classical MEN2A include development of cutaneous lichen amyloidosis and Hirschsprung disease. Absence of any clinical finding other than MTC in at least four family members is classified as FMTC.

MEN2B is characterized by highly aggressive MTC, usually PHEO, but not PPTH, and may exhibit musculoskeletal abnormalities and developmental defects with *RET* mutations in codons 918 and 883 of exon 15.

Figure 1: *RET* point mutations in MEN2A, MEN2B, and FMTC.

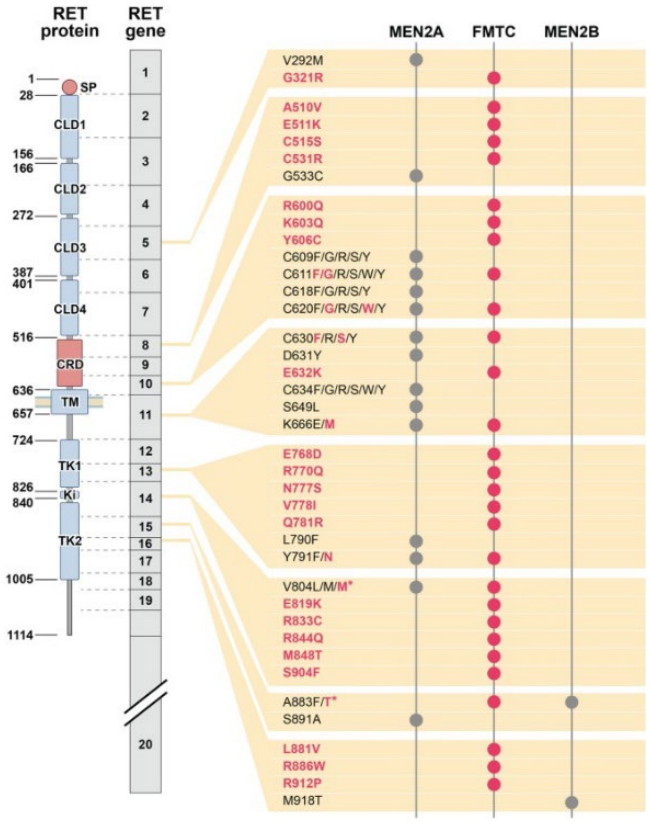

Table 1: Clinical expression of familial MTC-associated syndromes.

	FMTC (%)	MEN2A (%)	MEN2B (%)
MTC	100	100	100
Pheochromocytoma	0	10-60	50
Hyperparathyroidism	0	10-30	0
Marfanoid habitus	0	0	100
Intestinal ganglioneuromatosis	0	0	60-90
Mucosal neuromas	0	0	70-100

Clinical Validity

The development of tyrosine kinase inhibitors that specifically target *RET* has allowed for genetic analysis of *RET* germline mutations to become the standard of care in the initial workup for detecting germline mutations and familial risk and identifying targeted therapy in MTC. Further, somatic *RET* rearrangements have recently been implicated in a variety of cancers, including chronic myelomonocytic leukemia; acute myeloid leukemia; and lung, breast, pancreatic, and colon cancers; a patient previously diagnosed with lung cancer underwent genomic profiling, and the identification of a *RET* point mutation associated with MTC allowed researchers to determine that this lung cancer diagnosis was incorrect. A change in treatments proved to be very helpful for this patient. Other researchers have reported *RET* translocations in lung cancer cases, but they state that this is extremely rare.

Guan et al. (2020) identified *RET* mutations in human epithelial ovarian cancer, providing another area of benefit from genetic testing of the *RET* gene for developing targeted therapies. Results showed that R693H and A750T mutants, in the juxtamembrane region and intracellular kinase domain, respectively, could promote the MAPK and AKT signaling pathway in ovarian cancer, and that the RET inhibitor vandetanib could decrease signal transduction and inhibit cancer growth.

Researchers have also found in two *RET* L790F index patients that somatic *RET* variants were not responsible for the early onset and aggressiveness of MTC in a *RET* germline mutation carrier. Normally, variations in MTC presentation could be attributed to *RET* germline variants. However, Mathiesen et al. (2020) found an *FLT3* R387Q variant - FLT3 being a protein commonly found in hematopoietic malignancies - that could have been a genetic modifier instead.

Clinical Utility

The strong genotype-phenotype correlation of *RET* mutations makes genetic screening of significant value in diagnosis, prognosis, and management of MEN2 and resultant MTC, PHEO, and PPTH. Each specific *RET* mutation correlates with MEN2 presentation, age at onset of MTC, and MTC aggressiveness. Screening and early treatment of the manifestations of MEN2 can prevent metastasis of MTC and the morbidity and mortality caused by PHEO. Moreover, screening has been associated with improved survivorship and outcomes. Based upon these genotype-phenotype correlations, *RET* mutations have been stratified into three risk levels based on the penetrance and aggressiveness of the MTC. Consequently, mutation type should guide major management decisions, such as whether and when to perform thyroidectomy. Children in the highest risk category should undergo thyroidectomy in their first year of life, and perhaps even in their first months of life. Those with mutations in the high-risk category (codon 634 mutations) "should undergo thyroidectomy before reaching the age of 5 years". Annual biochemical screening in patients with a family history of FMTC or MEN2 can also be stopped in those patients who test negative for mutations.

Martins-Costa et al. (2018) performed *RET* genetic sequencing on exons 8, 10, 11, and 13-16 in 247 patients with MTC or who are at risk of developing MTC due to family history. Before genetic testing, 54 of these patients were diagnosed with sporadic disease and six were diagnosed with hereditary disease; after genetic testing, 31 patients were diagnosed with sporadic disease and 29 with hereditary disease. *RET* screening allowed several patients to be classified as hereditary who were initially diagnosed with sporadic MTC; 73 at-risk relatives were identified as mutation carriers, which will assist in long-term life and reproductive decisions.

A meta-analysis consisting of 438 Indian patients with MTC and 489 healthy controls of similar ages and genders was completed; all participants received molecular genetic testing including *RET* gene sequencing and SNP genotyping. This study identified *RET* SNPs as a significant risk factor for developing hereditary MTC; *CDKN2A* and *NAT2* SNPs with a significant risk of developing sporadic MTC.

RET genetic screening was also provided to a total of 2031 Italian subjects; this included 1264 patients with sporadic MTC symptoms, 117 patients with hereditary MTC symptoms, and 650 relatives. The researchers state, "A *RET* germline mutation was found in 115/117 (98.3%) hereditary and in 78/1264 (6.2%) apparently sporadic cases: in total, 42 distinct germline variants were found." This thereby underscores the significance of genetic screening in unsuspected MEN2 families. Sporadic MTC cases were present most commonly with a V804M mutation, and all M918T mutations were *de novo* "and exclusively associated with MEN2B." These researchers also identified several variants of unknown significance (VUS).

Similarly, a paper by Milićević et al. (2021) focused on examining the crude annual incidence rate of MTC and *RET* mutation frequency. The study involved Slovenian patients at the Institute of Oncology Ljubljana from 1995 to 2015 and involved their family members who participated in genetic counseling and testing there. It was found that among 143 patients with MTC, 37 (25.9%) harbored a germline *RET* mutation, and said mutations were uncovered in exons 10, 11, 13, 14, and 16. Also, the researchers noted that "*RET* germline mutations are quite commonly discovered even in the apparently sporadic form of the disease", such that 14.2% of patients with a negative family history were presented with them. It was also reported that the most frequent *RET* germline mutations were found on codons 634 and 618 (30.0%) and exon 11 was the most frequently altered, though mutations of codons 790, 804, and 918 were observed in smaller but noticeable percentages (25.0%, 10.0%, and 5.0%, respectively). However, despite the low compliance of family members resulting in a smaller pool of participants, the authors extol the use of genetic counseling in this case, as "Annual incidence increase and nation-specific frequency of discovered *RET* mutations justify the continuation of gene counseling and testing of MTC patients in Slovenia."

Another study by Fussey et al. (2021) aimed to lend their perspective on the diagnostic potential of *RET* genetic testing. Between 1997 and 2018, the Exeter Genomics Laboratory at the Royal Devon and Exeter NHS Foundation Trust collected information on 1058 index patients with MTC and other MEN2-related clinical features. They found that in total, 92 of the 766 UK patients with MTC were harboring a germline *RET* pathogenic variant, and that variants in 10, 11, and 14 comprised its bulk, with codons 634 in exon 11 and 804 in exon 14 being most often affected. As such, the researchers believe that "the use of somatic *RET* analysis to confirm the diagnosis of sporadic MTC in patients with no identified germline RET variants may be a useful adjunct both in terms of reassuring family members about the lack of a heritable pathogenic germline variant, and risk-stratifying sporadic tumours based on somatic variants."

RET genetic screening could also disclose new variants with their respective phenotypes. Yang et al. (2020) described a compound C634Y/V292M transmutation in a northern Chinese family that was associated with a more aggressive clinical presentation. Carriers of this variant had bilateral MTC with PHEO or lymph node metastasis with faster cell growth (cell growth speed identified *in vitro*). On the other hand, carriers of the V292M variant were asymptomatic, and carriers of the C634Y mutation only had elevated calcitonin. This has demonstrated the striking variability in MTC clinical presentation based on *RET* gene variants, making it critical to aid in any future potential treatment regimen.

IV. Guidelines and Recommendations

European Society for Medical Oncology (ESMO)

The ESMO has published clinical practice guidelines on diagnosis, treatment, and follow-up of thyroid cancer, stating that "All patients with MTC should be offered genetic counselling and screened for germline *RET* mutations." Filetti et al. (2020) also stated that "screening for somatic *RET* mutations is only recommended if *RET* inhibitor therapy is planned."

In 2021, ESMO Translational Research and Precision Medicine Working Group expanded upon the algorithm to identify patients eligible for anti-RET therapy across three scenarios based on the malignancies. The recommendations are captured below:

"Scenario A: Patients affected by NSCLC, non-MTC or other solid tumours, with available formalin-fixed, paraffin-embedded (FFPE) specimen need to be screened for detection of RET fusion. If NGS is not available, FISH or RT-PCR is indicated in NSCLC and non-MTC, depending on local availability, cost and/or amount of tumour cells. In case of a negative test result, it is recommended to perform an NGS panel. It should be noted, however, that the recent ESMO recommendations suggest using multigene NGS to assess NSCLC level I alterations, including *RET* fusions.

In addition to *RET* fusion testing, patients affected by other solid tumours may need to be tested also for *RET* mutation according to the results of pending clinical trials. This can be done preferably by NGS; if this is not available, Q-PCR can be used. In none of the above cases is RET IHC testing recommended.

Scenario B: For patients affected by NSCLC, non-MTC or other solid tumours whose FFPE specimens are not available or are exhausted, we suggest performing a liquid biopsy (cell-free nucleic acid NGS panel) to test for *RET* alteration.

It is important to notice that if an *RET* alteration is not detected by liquid biopsy, then tumour tissue testing is still required to definitively exclude the possibility of an RET fusion.

Scenario C: Patients affected by MTC need to be screened for detection of *RET* mutation. They should be referred to genetic counselling in order to study the presence of MEN syndrome or FMTC. Mutations in the RET gene, in fact, are canonical in hereditary MTC, but can be found also in sporadic MTC. A Q-PCR or NGS can be carried out on sputum or blood of the patient. In case of known familial *RET* mutation, a simple Sanger test can be carried out on blood leukocyte DNA. If a germline *RET* mutation is present, family counselling is indicated. In case of absence of germline *RET* mutations, if the patient with MTC becomes metastatic, a Q-PCR of NGS analysis on FFPE tissue specimens from metastatic site of disease should be carried out in order to confirm or reject the presence of this alteration.

In none of the above cases is RET IHC testing recommended.

American Thyroid Association (ATA)

The ATA published revised guidelines which state that:

- "Initial testing for patients with MEN2A phenotype is either a single or multi-tiered analysis to detect *RET* mutations in exon 10 (codons 609, 611, 618, and 620), exon 11 (codons 630 and 634), and exons 8, 13, 14, 15, and 16. Grade B Recommendation"
- Initial testing for patients with MEN2B phenotype should be tested for the *RET* codon M918T mutation (exon 16), and if negative, the *RET* codon A883F mutation (exon 15).
- "Sequencing of the entire coding region should be reserved for situations in which no *RET* mutation is identified or there is a discrepancy between the MEN2 phenotype and the expected genotype. Grade B Recommendation

- Patients with the MEN2B phenotype should be tested for the *RET* codon M918T mutation (exon 16), and if negative, the *RET* codon A883F mutation (exon 15). If there are no mutations identified in these two exons the entire RET coding region should be sequenced. Grade B Recommendation
- Patients with presumed sporadic MTC should have genetic testing to detect a germline *RET* mutation. If a *RET* mutation is found the patient should have genetic testing. Grade B Recommendation
- In very rare families who meet the clinical criteria for MEN2A or 2B, despite negative sequencing of the entire *RET* coding region, the relatives at risk should be periodically screened by conventional methods for MTC, PHEO, and HPTH. After the initial evaluation, screening should continue at 1- to 3-year intervals. Grade C Recommendation
- Genetic counseling and genetic testing for *RET* germline mutations should be offered to
  - First-degree relatives of patients with proven hereditary MTC,
  - Parents whose infants or young children have the classic phenotype of MEN2B,
  - Patients with CLA [cutaneous lichen amyloidosis], and
  - Infants or young children with HD and exon 10 *RET* germline mutations, and adults with MEN2A and exon 10 mutations who have symptoms suggestive of HD"

National Comprehensive Cancer Network

NCCN guidelines for neuroendocrine and adrenal tumors recommends that for diagnosis of or clinical suspicion of MEN2, genetic counseling and *RET* genetic testing should be offered in the following cases:

- "individuals with MTC or primary C-cell hyperplasia or a clinical diagnosis of MEN2"
- "at-risk relative of an individual with a known germline *RET* mutation at a very young age."
- "50% of cases have *de novo RET* mutations; therefore, even if a family history is not suggestive of a hereditary syndrome, genetic testing for *RET* mutations should still be performed on the affected individual."
- "All patients with MTC should be tested for germline mutation of the *RET* oncogene even if the family history is not suggestive of a hereditary syndrome, because about 50% of patients with presumed sporadic MTC have a *de novo* germline mutation."

NCCN Guidelines for Thyroid Carcinoma stated that as part of the additional workup after medullary thyroid carcinoma is identified by initial thyroid surgery, a "Screen for germline *RET* proto-oncogene mutations (exons 10, 11, 13-16)" and "Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling."

The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP)

The 2013 guidelines from CAP, IASLC and AMP for molecular testing in lung cancer patients have been updated in 2018; new recommendations state that *RET* testing is approved in lung cancer specimens "as

part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative" because "*RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial."

The British Thyroid Association

The BTA has stated, in regards to MTC, that "In all confirmed cased of MTC, *RET* mutation analysis to establish the possible genetic basis for the disease within an individual or kindred, should be performed even in the absence of a positive family history."

European Thyroid Association

The ETA Executive Committee in 2012 issued guidelines specifically devoted to *RET* genetic screening for patients affected by medullary thyroid cancers (MTC) with reference to three different phenotypes: multiple endocrine neoplasia types 2A and 2B and familial MTC (FMTC). In their attempt to improve the quality of care for patients and families with MTC, they made recommendations with varying valences, grading their own recommendations by the quality of evidence (QOE), which is indicated by plus signs at three levels, and the strength of recommendation (SOR) score, indicated by a 1 (strong recommendation for or against) or a 2 (" weak recommendation or a suggestion that may not be appropriate for every patient, depending on the context, patient values, and preferences"). The relevant parts of the guidelines are

From Recommendation 4:

"(a) Exons 5, 8, 10, 11, 13, 14, 15, and 16 should always be analyzed starting from the most likely involved in the presenting syndrome (i.e. exon 10 in MEN 2A, exon 16 in MEN 2B, etc.). DNA from MTC patients with a strong suggestion of familial disease should also be analyzed for all other uncommonly mutated exons when those listed above are negative… (QOE = +++; SOR = score 1)."

(b) Subjects belonging to the few families (2–5% of all MEN 2/FMTC families) with clinically evident MEN 2/FMTC features but lacking evidence of an associated germline *RET* mutation should be followed up annually by measurement of basal serum Ct, metanephrines, calcium, and PTH. Neck and abdomen ultrasound could also be useful although not absolutely required if biochemical tests are still negative (QOE = ++; SOR = score 1).

(c) Once a germline *RET* mutation has been identified, all first-degree relatives and other relevant family members should be screened for the specific causative mutation (QOE = +++; SOR = score 1).

(d) Once a germline *RET* mutation has been discovered, further sequencing adds little, although some cases of double or triple RET mutations have been reported. These peculiar cases would likely be missed if RET screening was stopped when the first mutation was identified. The completeness of RET gene analysis is particularly indicated when the first identified mutation is rare and with a low or null transforming ability. These rare cases should be referred to specialized tertiary centers for a complete characterization of the mutation and its relationship with the disease (QOE = ++; SOR = score 2).

(e) Family members negative for the mutation are not at risk for the development of MTC and their children are not at risk either. Such individuals should be reassured and do not require further investigation or follow-up (QOE = +++; SOR = score 1)."

From Recommendation 5:

"(a) All patients with either apparently sporadic or familial MTC should be screened for germline *RET* mutations (QOE = +++; SOR = score 1)."

From Recommendation 6:

"(a) Patients with bilateral PHEO [pheochromocytoma] should be considered for RET genetic screening when other MEN 2A endocrinopathies (MTC and/or PHPT [primary hyperparathyroidism]) or CLA are present in the same subject or if a family history of MEN 2A or 2B is present. The screening becomes mandatory if the basal serum Ct is above the normal range, independently of the presence of other MEN 2A endocrinopathies (QOE = ++; SOR = score 1).

(b) Patients with multiple adenomatosis of the parathyroid glands and PHPT should be considered for RET genetic screening if other MEN 2A endocrinopathies (MTC and/or PHEO) or CLA are present in the same subject or if a family history of MEN 2A is present. Also in this case, RET genetic screening must be performed if basal serum Ct levels are above the normal range, even if no other MEN 2A endocrinopathies are diagnosed (QOE = ++; SOR = score 1).

(c) Subjects with CLA should be investigated clinically and should undergo genetic testing for MEN 2A. In particular RET codon 634 in exon 11 should be analyzed (QOE = +++; SOR = score 1).

(d) Patients with Hirschsprung disease should have RET genetic screening for mutations involved in Hirschsprung disease, but analyses performed specifically to investigate an association with MEN 2 should be limited to exon 10 (QOE = +++; SOR = score 1)."

V. State and Federal Regulations, as applicable

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coveragedatabase/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

A search of the FDA database on 10/31/2021 using the term "genotyping" yielded 25 results. Additional tests may be considered laboratory developed tests (LDTs) if they are developed, validated, and performed by individual laboratories. LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST Integration members under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VII. Evidence-based Scientific References

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VIII. Policy History

Policy approved by Medical Directors	9/20/2022
Policy approved at UMC	12/16/2022
Policy effective	6/1/2023

Updated Lines of Business	12/18/2023