I. Description

Genetic testing involves the analysis of chromosomes, DNA (deoxyribonucleic acid), RNA (ribonucleic acid), genes or gene products to detect inherited (germline) or non-inherited (somatic) genetic variants related to disease or health. This policy addresses some of the most prevalent familial cancer syndromes.

This is accomplished several ways:
- Direct DNA or RNA mutation analysis (also known as molecular testing) that examines the direct base pair sequence of a gene for specific gene mutations.
- Indirect DNA or RNA testing is possible when a marker has been identified as being associated with a disease.
- Chromosome analysis (also known as cytogenetics) which looks for chromosome abnormalities.

Testing for gene mutations can identify those at increased risk for developing cancer although there is often little or no evidence that changes in medical management of the patient improves outcomes or increases survival.

Genetic tests are performed on those with or without disease and have a family or personal medical history or belong to an ethnic group with high probability of mutation. Genetic testing can identify cancer-related germline mutations in disease-free individuals. Disease-free individuals who have positive test results are candidates for aggressive primary preventive measures.

For the purpose of this policy, first-degree relatives are defined as parents, full siblings, and offspring. Second-degree relatives are defined as grandparents, grandchildren, aunts, uncles, nephews, nieces, half-siblings and third-degree relatives are defined as great-grandparents, great-aunts, great-uncles, first cousins.

Refer to separate HMSA policies for Genetic Testing for Hereditary Breast and/or Ovarian Cancer and for Lynch Related Syndromes and Other Inherited Colon Cancer Syndromes/APC.

II. Policy Criteria

A. Genetic testing is covered (subject to Limitations and Administrative Guidelines) when all of the following criteria are met:

1. There must be a reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists and the
individual displays clinical features or is at direct risk of inheriting the mutation in question based on family history or ethnic background

2. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.

3. The clinical utility of the test must be established and the result of the test will directly impact the treatment or prevention of the disease.

B. Genetic testing is covered (subject to Limitations and Administrative Guidelines) when the above criteria are met (A.1., 2., 3) and the patient has a cancer or a strong suspicion of cancer for the following:

1. Hereditary Diffuse Gastric Syndrome (CDH1 gene)
   a. The evaluation should include a detailed three-generation family pedigree,
   b. Histopathological confirmation of DGC diagnoses and/or
   c. Precursor lesions (in situ or pagetoid spreading of signet ring cells)

2. Medullary thyroid carcinoma (MEN2)
   a. Patient has a first-degree relatives with proven hereditary MTC; or
   b. Patient is a parent whose infant or young children have the classic phenotype of MEN2B; or
   c. Patient has CLA (cutaneous lichen amyloidosis) and
   d. Infants or young children with Hirschsprung’s Disease (HD) and exon 10 RET germline mutations, and adults with MEN2A and exon 10 mutations who have symptoms suggestive of HD

3. Retinoblastoma
   a. After history, physical examination, pedigree analysis, genetic counseling, completion of appropriate conventional diagnostic studies, a definitive diagnosis

4. Multiple Endocrine Neoplasia Type 1/MENIN
   a. Individuals have a personal history of two of the three main MEN1 related cancers (islet cell pancreatic, parathyroid (hyperplasia) and/or pituitary adenoma; or
   b. Individual with at least 1 main MEN 1 related cancer and a positive family history of 2 cases of pancreatic (islet cell) cancer, parathyroid (hyperplasia) and/or pituitary adenoma (can be the same person); or;
   c. Unaffected individuals who have family history of a documented MEN 1 gene mutation in a first or second degree relative

5. Von-Hippel-Lindau (VHL)
   a. Members who have one or more characteristic lesions with or without family history; or
   b. Unaffected individuals who have a family history of a documented VHL gene mutation in a first or second degree relative

6. Pancreatic cancer syndrome
   a. Individual has a personal history of pancreatic cancer; or
   b. Unaffected individuals with a first or second degree relative with a documented BRCA2 mutation; or
   c. Unaffected individuals with two or more first degree relatives with pancreatic cancer; or
   d. Unaffected individuals with two or more second degree relatives with pancreatic cancer, one of whom developed it at an early age (under the age 50)
7. Thyroid (RET proto-oncogene point mutations associated with inheritance of MEN2A, MEN2B and FMTC)
   a. Asymptomatic patients of well-characterized families with defined RET gene mutations; or
   b. Members of families known to be affected by inherited medullary thyroid carcinoma but not previously evaluated for RET mutations; or
   c. Members with apparently sporadic medullary thyroid carcinoma; or
   d. Patients with first-degree relatives with apparently sporadic medullary thyroid carcinoma

8. Malignant Gliomas (Methylation analysis of the O6-methylguanine DNA methyltransferase (MGMT) gene promoter from glioma tumor tissue)
   a. Member has a tumor type consistent with high-grade malignant glioma (e.g., glioblastoma multiforme, anaplastic astrocytoma); AND
   b. Member is a candidate for temozolomide therapy or radiotherapy; AND
   c. Methylation results will be used to direct the member’s therapy choices.

9. Breast cancer (see policies for Genetic Testing for Hereditary Breast and/or Ovarian Cancer)

10. Lynch Syndrome/Colorectal Cancer (see policy for Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes)

C. Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network.

D. One Pre- and one post-test genetic counseling session by a physician or a licensed or certified genetic counselor is covered for patients who meet the above criteria for genetic testing.

III. Limitations
A. Genetic testing is not covered for:
   1. Family members of subscribers, who themselves are not subscribers,
   2. Members if the results of the genetic testing are for the benefit of family members who are not covered by HMSA,
   3. In the absence of associated signs, symptoms or complaints or sufficient family history,
   4. Home genetic testing.

B. Genetic testing for cancer susceptibility using panels of genes (with or without next generation sequencing) is not covered because it is not known to be effective in improving health outcomes. However, individual components of a panel may be considered medically necessary as noted above when criteria in II. Criteria/Guidelines are met.

C. For a known deleterious mutation, HMSA will only cover a targeted single site analysis genetic test not a full analysis (i.e., testing for the mutation that has been identified in the family).

D. Genetic tests outlined in this policy are performed once per lifetime

E. Laboratories that conduct genetic testing must be CLIA certified.

F. Because of the rapidly evolving field of genetic testing, this policy does not address every genetic test available. Conditions not mentioned in this policy will be reviewed based on medical necessity and the policy criteria.

IV. Administrative Guidelines
A. Precertification is required. Complete HMSA’s Precertification Request and fax or mail the form as indicated with the following information:
1. Specify the condition for which the genetic test is being performed and if there are any known first- or second-degree relatives with the condition
2. Other types of biochemical testing apart from molecular genetic testing (enzyme activity assays, hemoglobin electrophoresis, blood chemistries, etc.), phenotypic findings and relevant clinical history and exam details
3. Specify how the results of the genetic test will impact the clinical management of the patient in terms of improving health outcomes
4. If precertification is not sought, the member will not be held responsible for payment

B. Documentation supporting the medical necessity should be legible, maintained in the patient’s medical record and must be made available to HMSA upon request. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria. The member will not be held responsible for payment of denied services unless an Agreement of Financial Responsibility is completed and signed.

<table>
<thead>
<tr>
<th>ICD-10 Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>C16.1</td>
<td>Hereditary Diffuse Gastric Syndrome (CDH1 gene)</td>
</tr>
<tr>
<td>C16.2</td>
<td>Malignant neoplasm of body of stomach</td>
</tr>
<tr>
<td>C16.9</td>
<td>Malignant neoplasm of stomach, unspecified</td>
</tr>
<tr>
<td>C25.0</td>
<td>Malignant neoplasm of head of pancreas</td>
</tr>
<tr>
<td>C25.1</td>
<td>Malignant neoplasm of body of pancreas</td>
</tr>
<tr>
<td>C25.2</td>
<td>Malignant neoplasm of tail of pancreas</td>
</tr>
<tr>
<td>C25.7</td>
<td>Malignant neoplasm of other parts of pancreas</td>
</tr>
<tr>
<td>C25.8</td>
<td>Malignant neoplasm of overlapping sites of pancreas</td>
</tr>
<tr>
<td>C64.9</td>
<td>Wilms tumor (Malignant neoplasm of unspecified kidney, except renal pelvis)</td>
</tr>
<tr>
<td>C69.21</td>
<td>Malignant neoplasm of right retina</td>
</tr>
<tr>
<td>C69.22</td>
<td>Malignant neoplasm of left retina</td>
</tr>
<tr>
<td>C71.2</td>
<td>Malignant neoplasm of temporal lobe</td>
</tr>
<tr>
<td>C71.9</td>
<td>Malignant neoplasm of brain, unspecified</td>
</tr>
<tr>
<td>C73</td>
<td>Malignant neoplasm of thyroid gland</td>
</tr>
<tr>
<td>D09.3</td>
<td>Carcinoma in situ of thyroid and other endocrine glands (Medullary thyroid carcinoma[MEN2])</td>
</tr>
<tr>
<td>E31.21</td>
<td>Multiple Endocrine Neoplasia Type 1/MENIN</td>
</tr>
<tr>
<td>Q85.8</td>
<td>Von-Hippel-Lindau (VHL)</td>
</tr>
<tr>
<td>Z15.81</td>
<td>Genetic susceptibility to multiple endocrine neoplasia [MEN]</td>
</tr>
<tr>
<td>Z85.07</td>
<td>Personal history of malignant neoplasm of pancreas</td>
</tr>
<tr>
<td>Z85.840</td>
<td>Personal history of malignant neoplasm of eye</td>
</tr>
<tr>
<td>Z85.850</td>
<td>Personal history of malignant neoplasm of thyroid</td>
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<table>
<thead>
<tr>
<th>CPT codes</th>
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</thead>
<tbody>
<tr>
<td>81287</td>
<td>MGMT (0-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme), methylation analysis</td>
</tr>
<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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</tbody>
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<thead>
<tr>
<th>CPT codes</th>
<th>Codes that do not require precertification (specific tests covered by these code may require precertification, see Policy Criteria section II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) ANG (angiogenin, ribonuclease, rNASE A family – Includes Von-Hippel-Lindau (VHL))</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or</td>
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</tbody>
</table>
characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis – Includes Von-Hippel-Lindau (VHL), Medullary thyroid carcinoma (MEN2)

81405 Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) – Includes Multiple Endocrine Neoplasia Type 1/MENIN, Medullary thyroid carcinoma (MEN2)

81406 Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) – Includes Hereditary Diffuse Gastric Cancer CDH1, Thyroid (RET proto-oncogene point mutations), Medullary thyroid carcinoma (MEN2)

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
</tr>
<tr>
<td>S3840</td>
<td>DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2</td>
</tr>
<tr>
<td>S3841</td>
<td>Genetic testing for retinoblastoma</td>
</tr>
<tr>
<td>S3842</td>
<td>Genetic testing for von Hippel-Lindau disease</td>
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The following codes do not meet payment determination and are not covered.

<table>
<thead>
<tr>
<th>CPT Codes</th>
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<tbody>
<tr>
<td>81350</td>
<td>UGT1A1 (UDP Glucuronosyltransferase 1 family, polypeptide A1) (e.g., irinotecan metabolism), gene analysis, common variants (e.g., *28, *36,*37)</td>
</tr>
<tr>
<td>86152</td>
<td>Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood)</td>
</tr>
<tr>
<td>86153</td>
<td>Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required</td>
</tr>
</tbody>
</table>

V. Scientific Background

Many genetic tests are imperfect predictors of either existing disease or disease susceptibility, particularly when used in the context of population screening, where individuals without family histories of disease, risk factors or symptoms are tested. For example, the probability exists that a disease may still occur, even when a negative test result is obtained. Conversely, a specific disease may not occur when there is a positive test result. While these concepts hold true for at-risk individuals as well, the probability of both these occurrences is greater in population screening, so test results are more difficult to interpret in a manner that will meaningfully affect health outcomes. With a few limited exceptions (e.g., PKU testing), general screening of populations for diseases that can be attributed to genetic mutations is not advocated in the published scientific literature.

The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.
Analytical validity

Analytical validity is an indicator of how well a test measures the property or characteristic it is intended to measure, and it is made up of three components: Analytical sensitivity: the test is positive when the relevant gene mutation is present. Analytical specificity: the test is negative when the gene mutation is absent and reliability: the test obtains the same result each time.

Clinical Validity

Clinical validity in genetic testing is a measurement of the accuracy with which a test identifies or predicts a clinical condition and involves the following:

- **Clinical sensitivity**: the probability that the test is positive if the individual being tested actually has the disease or a predisposition to the disease.
- **Clinical specificity**: the probability that the test is negative if the individual does not have the disease or a predisposition to the disease.
- **Positive predictive value**: the probability that an individual with positive test results will get the disease.
- **Negative predictive value**: the probability that an individual with negative test results will not get the disease.
- **Heterogeneity**: different mutations within the same gene may cause the same disease and can result in different degrees of disease severity; a failure to detect all disease-related mutations reduces a test’s clinical sensitivity.
- **Penetrance**: the probability that the disease will appear when a disease-related genotype is present. Penetrance is incomplete when other genetic or environmental factors must be present for a disease to develop.

There are both benefits and risks associated with genetic tests. Genetic tests that are not fully assessed for analytical and clinical validity prior to their use in clinical practice have the potential for causing harm to patients. For example, patients who are wrongly classified as at-risk may be subjected to increased and unnecessary surveillance or treatments, some of which may be harmful, or even irreversible. Likewise, false negative test results may lead to delays in diagnosis and treatment.

The development of genetic tests that can diagnose or predict disease occurrence has far outpaced the development of interventions to treat, ameliorate or prevent those same diseases. Clinical utility refers to the ability of genetic test results, either positive or negative, to provide information that is of value in the clinical setting. Specifically for positive test results, this could involve instituting treatments or surveillance measures, making decisions concerning future conception, or avoiding harmful treatments. Negative test results can have clinical utility in that unnecessary treatments or surveillance can be avoided. In the absence of such interventions, the benefits of testing are limited, and in fact, can cause psychological harm.

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), 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 consider the application of this Medical Policy to the case at issue.

VII. References