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Medical Coverage Policy

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Coverage Policy Number.....0518

Genetic Testing for Hereditary Cancer Susceptibility Syndromes

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Related Coverage Resources

[Colorectal Cancer Screening and Surveillance Genetics](#)
[Skin Cancer Surveillance Technologies](#)
[Transvaginal Ultrasound, Non-Obstetrical](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s).

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Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses genetic testing for germline pathogenic or likely pathogenic variants related to hereditary cancer susceptibility syndromes. Germline variants are inherited; that is, passed down in families by blood relatives. Types of testing include single-site testing, full sequence analysis, duplication/deletion analysis or multi-gene panel testing.

Genetic counseling is required prior to genetic testing for germline pathogenic or likely pathogenic variants related to all hereditary cancer susceptibility syndromes to educate and promote informed choices regarding testing options.

Coverage Policy

Coverage for genetic testing and genetic counseling services varies across plans. Please refer to the customer's benefit plan document for coverage details.

Genetic counseling is required prior to and after genetic testing for ALL hereditary cancer susceptibility syndromes as outlined in this Coverage Policy. Please refer to the following criteria for additional information regarding coverage for genetic counseling and genetic testing.

General Criteria for Germline Pathogenic or Likely Pathogenic Variant Genetic Testing: Hereditary Cancer Susceptibility/Risk Assessment

Medically Necessary

Syndrome/hereditary condition specific genetic testing for hereditary cancer susceptibility is considered medically necessary when ALL of the following criteria are met:

- gene testing results will impact medical management
- there are National Comprehensive Cancer Network® (NCCN Guidelines®) category 1, 2A or 2B guidelines and/or other published evidence-based management recommendations for an individual who tests positive for the condition/syndrome-specific gene(s) for which testing is being requested
- the individual being tested is the most appropriate person to test or the most appropriate family member is unavailable for testing
- EITHER of the following:
 - individual meets criteria for at least one of the syndromes below
 - personal and/or family history is consistent with the hereditary cancer syndrome being tested for when syndrome is not specifically addressed in this policy
- a recommendation for testing is confirmed by ONE of the following:
 - an independent Board-Certified or Board-Eligible Medical Geneticist

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- a nurse credentialed as either a Clinical Genomics Nurse (CGN) or an Advanced Clinical Genomics Nurse (ACGN) by the Nurse Portfolio Credentialing Commission (NPCC), or an Advanced Genetics Nurse-Board Certified (AGN-BC) by the American Nurses Credentialing Center (ANCC), who is not employed by a commercial genetic testing laboratory. (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- an individual who has achieved the National Consortium of Breast Centers (NCBC) Cancer Genetics Risk Assessment (CGRA) certification for breast cancer genetics risk assessment, accredited by the National Commission for Certifying Agencies (NCCA).
- a treating breast surgeon, who has determined that the results of testing will influence surgical decision making in an individual recently diagnosed with early stage breast cancer who:
 - has evaluated the individual
 - completed a three-generation pedigree
 - intends to engage in post-test follow-up counseling or, if a breast surgeon treating a patient with recently diagnosed breast cancer, intends to refer to an appropriately credentialed independent genetic counselor for post-test counseling

Germline Testing Following Identification of a Somatic Pathogenic or Likely Pathogenic Variant

Medically Necessary

Germline testing, after a somatic variant is identified through the evaluation of solid or hematologic malignancy, is considered medically necessary when ALL of the following criteria are met:

- there are NCCN Guidelines® category 1, 2A or 2B and/or other published management recommendations specific to the variant identified
- the variant identified has a high rate of germline incidence based on gene and tumor type and/or family history (e.g., BRCA1 in any tumor type, TP53 in adenoid cystic carcinoma diagnosed in a child)

Germline Pathogenic or Likely Pathogenic Variant Genetic Testing for Hereditary Cancer Susceptibility Syndromes

Medically Necessary

Genetic testing is considered medically necessary when the individual meets the general criteria for hereditary cancer genetic testing above AND current National Comprehensive Cancer Network® (NCCN®) category 1, 2A or 2B recommendations for the testing requested for ANY of the following hereditary cancer susceptibility syndromes (see NCCN Guidelines® for associated gene(s)):

- Genetic/Familial High-Risk Assessment: Colorectal (e.g., Lynch syndrome** genes, FAP/MUTYH and other polyposis syndromes)

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- Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (including prostate cancer, Cowden syndrome/PTEN hamartoma tumor syndrome and Li Fraumeni syndrome) Prostate Cancer
- Neuroendocrine and Adrenal Tumors (e.g., MEN1, MEN2, VHL, PGL/PCC)
- Gastric Cancer (e.g., Diffuse gastric cancer)
- Melanoma: Cutaneous
- Myelodysplastic Syndromes
- Acute Myeloid Leukemia
- Kidney Cancer

** Lynch syndrome related-cancers for criteria evaluation are: colorectal, endometrial, keratoacanthoma, stomach, ovarian, small bowel, ureter or renal pelvis, sebaceous adenoma or carcinoma, hepatobiliary, pancreas, brain cancer.

When appropriate tumor is available and a familial pathogenic or likely pathogenic variant is not known, Lynch syndrome tumor analysis should be performed prior to germline testing.

Lynch syndrome somatic variant analysis is discussed in Cigna Coverage Policy: Molecular and Proteomic Diagnostic Testing for Hematology and Oncology Indications.

Retinoblastoma-RB1

Medically Necessary

Genetic testing for retinoblastoma (RB1 gene) is considered medically necessary when an individual meets general criteria for hereditary cancer genetic testing as noted above for EITHER of the following indications:

- germline DNA testing (e.g., peripheral blood, saliva) for ANY of the following:
 - at-risk individual from a family with a pathogenic or likely pathogenic variant RB1 gene
 - bilateral retinoblastoma
 - unilateral retinoblastoma with ONE of the following:
 - first-, second-, and third-degree relative*** with history of retinoblastoma
 - tumor tissue is not available
 - pathogenic or likely pathogenic variant(s) identified in tumor tissue
 - multifocal retinoblastoma
- testing of retinoblastoma tumor tissue for EITHER of the following:
 - unilateral retinoblastoma and no first-, second-, and third-degree blood relative*** with a history of retinoblastoma
 - bilateral retinoblastoma with BOTH of the following:
 - no family history of retinoblastoma
 - a pathogenic or likely pathogenic variant has not been detected in the blood

***A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

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A third-degree relative is defined as a blood relative with whom an individual shares approximately 12.5% of his/her genes, including the individual's great-grandparents and first-cousins.

Genetic testing for retinoblastoma is considered medically necessary using ANY of the following genetic testing methods when DNA sequence and deletion/duplication analysis is negative and clinical suspicion of a pathogenic or likely pathogenic variant in the RB1 gene remains high:

- methylation analysis (tumor)
- sequence analysis of RNA (blood)

Not Medically Necessary

Genetic testing for hereditary cancer susceptibility syndromes is considered not medically necessary if the above criteria are not met.

Genetic testing for hereditary cancer susceptibility for screening in the general population is considered not medically necessary.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

According to the National Cancer Institute, (2024), some key cancer incidence and mortality disparities in the United States include:

- Black/African American people have higher death rates than all other racial/ethnic groups for many, although not all, cancer types.
- Despite having slightly lower incidence rates of breast cancer than those of white women, Black/African American women are more likely than white women to die of the disease.
- The incidence rates of colorectal, lung, and cervical cancers are much higher in people who live in rural Appalachia than in those who live in urban areas in the region.
- Black/African American men are more than twice as likely as white men to die of prostate cancer and continue to have the highest prostate cancer mortality rates among all US racial/ethnic groups.
- People with more education are less likely to die prematurely (before the age of 65) from colorectal cancer than those with less education, regardless of race or ethnicity.
- Hispanic/Latino, Black/African American, and American Indian/Alaska Native women have higher incidence rates of cervical cancer than women of other racial/ethnic groups, with Black/African American women having the highest rates of death from the disease.

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- American Indians/Alaska Natives have higher death rates from kidney cancer than any other racial/ethnic group.
- American Indians/Alaska Natives have the highest incidence and mortality rates of liver and intrahepatic bile duct cancer, followed by Hispanics/Latinos and Asians/Pacific Islanders.

Racial and socioeconomic disparities in access to hereditary cancer risk assessment, counseling, and genetic testing have been identified. Data from the 2020 Health Information National Trends Survey was analyzed to determine cancer genetic testing knowledge, utilization, and perceived importance of genetic information for cancer care. Data was analyzed by race and ethnicity. In a cross sectional study, 37.8% reported having heard of genetic testing for cancer risk and 3.9% stated that they underwent cancer genetic testing. Being non-Hispanic Black (odds ratio [OR]=0.47, 95% confidence interval [CI]=0.30–0.75) or Hispanic (OR=0.56, CI=0.35–0.90) was associated with lower odds of genetic testing knowledge. Although Hispanic or non-Hispanic Black respondents were more likely to perceive higher importance of genetic information versus non-Hispanic whites, they had a lower predicted probability of cancer genetic testing. The authors concluded that cancer genetic testing seemed not to be received uniformly across race and ethnicity groups, and future interventions should aim to improve access to genetic testing among potential cancer patients from racial and ethnic minority backgrounds (Hong et al., 2024).

General Background

Hereditary cancer syndromes are a heterogeneous group of disorders; the presence of one or a combination of gene variants may increase the risk for development of specific cancers. Germline variants are inherited; that is, passed down in families by blood relatives. For example, Lynch syndrome may increase the risk for colorectal, endometrial, gastric, ovarian and small bowel cancer. Other hereditary cancer syndromes include hereditary breast and ovarian cancer, retinoblastoma, von Hippel-Lindau, multiple endocrine neoplasia type 1 (MEN1), type 2A and 2B and RET, hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome, Peutz-Jeghers syndrome, hereditary diffuse gastric cancer and prostate cancer. Variations in the CHEK2 and PALB2 genes have also been implicated for an increased risk for hereditary breast cancer. Support for germline pathogenic or likely pathogenic variant testing and genetic counseling for hereditary cancer syndromes is available in the form of published evidence-based management recommendations and evidence in the published, peer-reviewed scientific literature.

Genetic Counseling

Genetic counseling is defined as the process of helping an individual understand and adapt to the medical, psychological and familial indications of genetic contributions to disease. Genetic counseling services span the life cycle from preconception counseling to infertility evaluation, prenatal genetic screening and diagnosis, and include predisposition evaluation and genetic diagnosis (National Society of Genetic Counselors [NSGC], 2024; Edwards, 2010).

A variety of genetics professionals provide these services, including board-certified or board-eligible medical geneticists; genetic counselors certified by the American Board of Medical Genetics or American Board of Genetic Counseling; nurses credentialed as either a Clinical Genomics Nurse (CGN) or an Advanced Clinical Genomics Nurse (ACGN) by the Nurse Portfolio Credentialing Commission (NPCC), or as an Advanced Genetics Nurse-Board Certified (AGN-BC) by the American Nurses Credentialing Center (ANCC); individuals who have achieved the National Consortium of Breast Centers (NCBC) Cancer Genetics Risk Assessment (CGRA) accreditation for breast cancer genetics risk assessment; and treating breast surgeons (American Society of Breast Surgeons [ASBrS], 2021).

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Pre- and post- test genetic test counseling is essential for all hereditary cancer susceptibility syndromes to interpret family and medical histories and assess the chance of disease occurrence and recurrence, educate regarding inheritance, testing, management prevention and resources, and counsel to promote informed choices and adaptation to risk or condition.

Germline Pathogenic or Likely Pathogenic Variant Testing for Hereditary Cancer Susceptibility/Risk Assessment

Germline variants are inherited; that is, passed down in families by blood relatives. The goal of germline pathogenic or likely pathogenic variant genetic testing is to identify variants that may be passed down in families by blood relatives. As described in this Coverage Policy, genetic testing may be appropriate when the individual for which testing is being considered meets the genetic testing criteria and is recommended by an appropriately credentialed genetics professional, or in an individual with early stage breast cancer, when the treating breast surgeon determines that the results of genetic testing will influence surgical management and intends to refer the individual to an appropriately credentialed independent genetic counselor for follow-up counseling.

Germline testing for hereditary cancer susceptibility syndromes is supported by a number of published evidence-based recommendations, including consensus guidelines by the National Comprehensive Cancer Network® (NCCN) (NCCN Guidelines®). The NCCN has published Category 1, 2A and 2B recommendations for this testing as an important component in the assessment and management of several hereditary cancer susceptibility syndromes. These include Lynch syndrome, familial adenomatous polyposis/attenuated familial adenomatous polyposis, MYH-associated polyposis, hereditary breast and ovarian cancer syndrome, juvenile polyposis syndrome, Peutz-Jeghers, Cowden and Li Fraumeni syndrome, multiple endocrine neoplasia types 1 and 2, and diffuse gastric cancer. Detailed information regarding these recommendations can be found on the NCCN website at <https://www.nccn.org>.

Germline variant testing for adult onset diseases in at-risk children <18 years is generally not recommended. Testing for hereditary cancer syndromes in children <18 who do not have a phenotype for the disorder (i.e., are asymptomatic) is only indicated when the related risks and management guidelines impact individuals prior to age 18. There is insufficient evidence in the published, peer-reviewed medical literature to demonstrate improved health outcomes for general population screening for hereditary cancer susceptibility.

Testing methodology, targeting DNA and/or RNA, has been clinically validated and is the most accurate method unless technical limitations (e.g. poor sample quality) necessitate the need for alternate testing strategies.

Germline Testing Following Identification of a Somatic Pathogenic or Likely Pathogenic Variant

As tumor testing, especially broad molecular profiling becomes more common, it is expected that there will be an increase in the number of somatic variants identified in genes associated with hereditary cancer syndromes. In most cases, this is associated with a risk that a germline pathogenic or likely pathogenic variant will be identified, but with certain cancer types and genes, the likelihood of an underlying germline variant remains low. In addition, many types of tumors have a high rate of variation in genes associated with hereditary cancer syndromes, but unrelated to the same tumor type. An often cited example of this is the high rate of APC variants identified in endometrial cancer, despite the fact that germline variations in APC are not associated with an increased risk of endometrial cancer.

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Several studies have shown that the prevalence of pathogenic germline variants among those in whom somatic variants have been identified is high enough to consider germline testing in most actionable genes (Schrader, et al., 2016; Catenacci, et al., 2015). It has been noted that identification of TP53, STK11, PTEN and APC in tumor tissue are less likely to be associated with germline variations (Jain, et al., 2016). For instance, TP53 variants are identified in almost 85% of ovarian tumors (COSMIC data), but fewer than 3% of patients with apparently hereditary ovarian cancer syndromes will test positive for a TP53 variant. Therefore, additional factors, such as clinical presentation, family history, or data obtained from variant databases regarding likelihood of a germline origin should be considered when determining medical necessity of germline testing for these actionable genes.

U.S. Food and Drug Administration (FDA): Most genetic tests for hereditary cancer susceptibility syndromes are laboratory-developed tests (i.e., in vitro diagnostic tests that are designed, manufactured and used within a single laboratory). These types of tests go to market without independent analysis. While the FDA retains enforcement discretion over laboratory-developed tests, it generally does not regulate them, though manufacturers may choose to submit lab-developed tests for FDA clearance or approval. Some examples of FDA-approved or cleared genetic tests related to hereditary cancer susceptibility syndromes include BRACAnalysis CDx® (Myriad Genetics, Salt Lake City, UT; 2014), and the Hereditary Prostate Cancer (HOXB13-Related) test (23andMe, Inc., South San Francisco, CA; 2022).

Germline Genetic Testing for Hereditary Cancer Susceptibility Syndromes

Genetic/Familial High-Risk Assessment: Colorectal (e.g., Lynch syndrome genes, FAP/MUTYH and other polyposis syndromes): Lynch syndrome (LS) is the most common type of hereditary colorectal cancer, accounting for 20–35% of all inherited forms. Disease-specific criteria for genetic testing for Lynch syndrome-associated cancers, familial adenomatous polyposis/attenuated familial adenomatous polyposis, juvenile polyposis and MYH-associated polyposis have been established by professional consensus guidelines, including those published by the NCCN and include timeframes and methods for surveillance and recommendations for testing when there is a personal and/or family history of these hereditary cancer syndromes.

LS-related cancers include colorectal, endometrial, keratocanthoma, stomach, ovarian, small bowel, ureter or renal pelvis cancers as well as sebaceous adenoma or carcinoma, hepatobiliary, pancreas and brain cancer. Several clinical prediction models exist to determine an individual's risk for LS. These computer programs give probabilities of variants and/or of the development of future cancers based on family and personal history. In general, genetic testing for LS is not recommended for at-risk individuals under the age of 18. However, it is recommended that cancer screening begin two to five years before the earliest age of cancer onset in the family. Therefore, in some situations, screening may need to begin before the age of 18 years (Idos and Valle, 2004).

Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (including prostate cancer, Cowden syndrome/PTEN hamartoma tumor syndrome and Li Fraumeni syndrome): While the vast majority of breast cancer cases do not demonstrate strong familial tendencies, it has been reported that 5–10% are due to inherited forms of the disease, with similar rates reported for ovarian cancer (National Cancer Institute [NCI], 2024). Several genes associated with the predisposition to breast and ovarian cancers have been identified. Specific genetic variants found in two autosomal dominant cancer predisposition genes, Breast Cancer Susceptibility 1 (BRCA1) and Breast Cancer Susceptibility 2 (BRCA2) are thought to account for the majority of inherited forms of breast and ovarian cancers through an autosomal dominant inheritance pattern for predisposition. The risk of developing cancer depends on numerous variables, including the penetrance of the variant, the biological sex and the age of the individual.

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The goal of BRCA1 and BRCA2 testing is to provide patients and their physicians with information that will allow them to make informed decisions regarding cancer prevention, screening, surveillance, and treatment options (e.g., prophylactic surgery). A significant benefit of genetic testing is the ability to quantify cancer risk estimates more precisely, thereby improving the process of determining the most appropriate management strategies in patients who test positive. For patients who test negative, unnecessary treatment (e.g., prophylactic surgery) may be avoided.

Disease-specific criteria for genetic testing for hereditary breast and ovarian cancer syndrome have been established by published evidence-based recommendations, including those distributed by the NCCN. There is sufficient evidence in the published, peer-reviewed scientific literature to demonstrate that testing methods used to identify BRCA variants are accurate in detecting specific variations. Sensitivity of BRCA testing has been reported to identify up to 98% of all variants, and sequencing should detect almost 100% of all nucleotide differences. The specificity of BRCA testing has not been well studied.

Cowden syndrome is a disorder characterized by multiple noncancerous, tumor-like growths called hamartomas and an increased risk of developing certain cancers. Cowden syndrome is inherited in an autosomal dominant pattern. Other cases may result from new mutations in the gene.

Li Fraumeni syndrome is a very rare hereditary cancer syndrome predisposing an individual to an increased risk for breast cancer, osteosarcoma and cancers of the soft tissues, particularly in children and young adults. Other cancers commonly seen in this syndrome include brain tumors, leukemias, and adrenocortical carcinoma. This disorder is related to germline variations in the TP53 gene. Li-Fraumeni syndrome is inherited in an autosomal dominant pattern. Genetic testing criteria are estimated to have a high positive predictive value and high specificity, but low sensitivity.

Prostate Cancer: Recommendations for germline genetic pathogenic or likely pathogenic variant testing are based on recommendations from the NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer. Germline genetic testing should be considered for an individual with early stage, non-metastatic cancer when there is a strong family history of hereditary cancer. Germline genetic variant testing (i.e., MLH1, MSH2, MSH6, PMS2, BRCA 1, BRCA2, ATM PALB2, CHEK2, and RAD51D) is recommended for an individual with localized stage III (i.e., NCCN high-risk and very high-risk group), regional or metastatic prostate cancer to assist with genetic counseling, decisions regarding early use of platinum chemotherapy or eligibility for clinical trials, such as those for Poly (ADP-ribose) polymerase (PARP) inhibitors.

Neuroendocrine and Adrenal Tumors (e.g., MEN1, MEN2, VHL, PGL/PCC): Multiple endocrine neoplasia (MEN) is a group of disorders that affect the endocrine system. Multiple endocrine neoplasia involves tumors (neoplasia) in at least two endocrine glands which can be benign or cancerous. If the tumors are cancerous they can be life-threatening. Type 1 frequently involves tumors of the parathyroid glands, the pituitary gland, and the pancreas. Type 2 is a form of thyroid cancer called medullary thyroid carcinoma; an adrenal gland tumor called a pheochromocytoma, develops in some individuals with resulting elevated blood pressure.

Hereditary paraganglioma-pheochromocytoma is a condition characterized by the growth of noncancerous (benign) tumors in groups of cells that are found near nerve cell bunches. A type of paraganglioma known as a pheochromocytoma develops in the adrenal glands. Several genes have been identified as causative in this syndrome, including SDHD (type 1), SDHAF2 (type 2), SDHC (type 3) and SDHB (type 4). Inheritance is in an autosomal dominant pattern. Gene variants lead to the loss or reduction of SDH enzyme activity.

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Gastric Cancer (e.g., Diffuse Gastric Cancer): Diffuse gastric cancer (DGC) is a hereditary cancer syndrome that is transmitted in an autosomal dominant pattern. It is characterized by the development of diffuse (signet ring) cancers. More than 120 inherited variations in the CDH1 gene have been identified. Individuals with the CDH1 gene variants associated with hereditary DGC have an approximately 80 percent chance of developing gastric cancer in their lifetimes. Women with these variants also have a 40 to 50 percent chance of developing lobular breast cancer.

Melanoma (Cutaneous): Cutaneous melanoma is a type of skin cancer that originates in pigment-producing cells called melanocytes. Development of melanoma can occur from already existing moles and skin growths, or new growths. In most cases, the genetic changes occur throughout a person's lifetime and can only be detected in the melanocytes. Around ten percent of cases are familial cases caused by inherited germline mutations including genes CDKN2A and MC1R.

Myelodysplastic Syndromes: Myelodysplastic syndromes (MDS) are bone marrow disorders in which the bone marrow does not make enough healthy blood cells from stem cells housed in the bone marrow. In MDS, some of the stem cells are abnormal interfering with the development into normal cells. This causes a crowding out of the normal cells in the bone marrow. The World Health Organization recognizes six main types of MDS: MDS with single lineage dysplasia (MDS-SLD); MDS with ring sideroblasts (MDS-RS); MDS with multilineage dysplasia (MDS-MLD); MDS with excess blasts; MDS, unclassifiable (MDS-U); MDS with isolated del(5q). Approximately 50% of patients have a detectable cytogenetic abnormality, most commonly a deletion of all or part of chromosome 5 or 7, or trisomy 8. MDS with isolated del(5q) is associated with an isolated del(5q) cytogenetic abnormality (NCI, 2022).

Acute Myeloid Leukemia: Acute myeloid leukemia (AML) is a type of blood cancer that starts in the blood stem cells of bone marrow. Through the maturing process to form blood cells, blood stem cells first mature into either myeloid progenitor cells or lymphoid progenitor cells. Myeloid progenitor cells further mature into myeloblasts (that further mature into granulocytes [a type of white blood cell]), red blood cells, or platelets. AML affects myeloid progenitor cells stopping myeloblasts from becoming mature blood cells. This results in a buildup of myeloblasts in the marrow and blood, and not enough red blood cells, platelets and mature granulocytes. Approximately 50% of patients with AML have detectable chromosomal abnormalities making cytogenetic analysis effective in the evaluation of suspected AML (NCI, 2024).

Kidney Cancer Syndromes: Hereditary kidney cancer accounts for 5%–8% of all kidney cancers and is usually linked to a hereditary cancer syndrome. The most common hereditary syndromes that may predispose patients to renal cell carcinoma (RCC) are: BAP1 tumor predisposition syndrome (BAP1-TPDS); Birt-Hogg-Dubé syndrome (BHDS); HLRCC (FH-deficient); hereditary papillary renal carcinoma (HPRC); hereditary paraganglioma/ pheochromocytoma (PGL/PCC); syndrome (SDH-deficient); tuberous sclerosis complex (TSC); and von Hippel-Lindau (VHL) disease (NCCN, 2024).

Of the hereditary types of RCC, von Hippel-Lindau is the most common. von Hippel-Lindau (VHL) disease or syndrome is an autosomally dominant inherited multisystem disorder characterized by abnormal growth of blood vessels. VHL is characterized by hemangioblastomas of the brain, spinal cord and retinas; clear cell renal cell carcinomas; pheochromocytomas; endolymphatic sac tumors of the middle ear, serous cystadenoma, neuroendocrine tumors of pancreas and papillary cytadenoma of the epididymis. Tumors may be cancerous or benign; however, even if noncancerous they may be life-threatening.

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Unlike most autosomal dominant conditions, in which one altered copy of a gene in each cell is sufficient to cause the disorder, two copies of the VHL gene must be altered to trigger tumor and cyst formation. The majority of individuals with one VHL variant will acquire a second altered gene during their lifetime. It is estimated that 80% of individuals with VHL syndrome have an affected parent, and approximately 20% have VHL syndrome as the result of a de novo gene mutation. Mutations of the VHL gene have a high penetrance with almost all individuals with a variant exhibiting disease-related symptoms by age 65 years (van Leeuwen, et al., 2024).

Molecular genetic testing of the VHL gene detects variation in nearly 100% of affected individuals with suspected or known VHL. For individuals with manifestations of VHL syndrome who do not meet strict diagnostic criteria and who do not have a detectable VHL germline variant, somatic mosaicism for a de novo VHL disease-causing variant should be considered (Sgambati, et al., 2000). Because early detection of at-risk individuals affects medical management, testing of individuals during childhood who have no symptoms is beneficial. Since ophthalmological screening for those at risk for VHL begins before age five, molecular genetic testing may be considered in young children if the results would alter the medical management.

Retinoblastoma (RB1): Retinoblastoma occurs in heritable (25%–30%) and nonheritable or sporadic (70–75%) forms and primarily occurs before the age of five years (NCI, 2024). Germline retinoblastoma is associated with a gene variant that occurs in all of the body’s cells. With the germline form of the disease there is an increased risk of developing other cancers such as pinealoma, osteosarcoma and melanoma. Germline disease includes those patients with a positive family history (e.g., hereditary disease) and those patients who have sustained a new germline variant at the time of conception. The gene variant is transferred in an autosomal dominant pattern. Genetic testing may assist in identifying individuals with a germline variant.

Single Nucleotide Polymorphisms (SNPs)

Unlike high-penetrance cancer susceptibility gene variants (e.g. BRCA1/2), cancer single nucleotide polymorphisms (SNPs) convey smaller risks for a much larger number of people. SNPs may be characterized as low to moderate penetrant gene variants and involve prediction of an individual’s risk for disease based on genetic polymorphisms common in the population. Until their individual and collective influences on cancer risk are evaluated prospectively, they are not considered clinically relevant (NCI, 2024). Clinical validity and clinical utility of cancer risk predictive SNP testing is unknown. Whether SNP testing can lead to biologically useful information is under debate. Controlled clinical trial data regarding SNP testing demonstrating improved health outcomes are lacking in the published peer-reviewed scientific literature. Unlike guidelines and criteria that have been established for BRCA testing, criteria have yet to be defined for requirements for when genetic testing of candidate genes or SNPs should be implemented in routine diagnostics (Ripperger, et al., 2009). At this time the role of SNP testing has not been established for the diagnosis or management of hereditary cancer syndromes.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Next Generation Sequencing (NGS) (90.2)	1/27/2020
LCD	CGS Administrators, LLC	MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer (L39017)	4/18/2024
LCD	National Government Services, Inc.	Molecular Pathology Procedures (L35000)	8/6/2023

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	Contractor	Determination Name/Number	Revision Effective Date
LCD	Multiple LCDs	BRCA1 and BRCA2 Genetic Testing	Varies
LCD	First Coast Service Options, Inc.	Genetic Testing for Lynch Syndrome (L34912)	10/1/2019
LCD	First Coast Service Options, Inc.	Molecular Pathology Procedures (L34519)	12/12/2021
LCD	Multiple LCDs	MoIDX: Melanoma Risk Stratification Molecular Testing	Varies
LCD	Multiple LCDs	MoIDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer	Varies
LCD	Novitas	Biomarkers for Oncology (L35396)	12/13/2020
LCD	Novitas	Biomarkers Overview (L35062)	12/12/2021

Note: Please review the current Medicare Policy for the most up-to-date information.

(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Appendix

Professional Societies/Organizations

Hereditary Cancer Susceptibility/Risk Assessment

American College of Obstetricians and Gynecologists (ACOG): ACOG (2015, updated 2019) published a Committee Opinion regarding hereditary cancer syndromes and risk assessment. The Opinion notes:

- "A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Assessments should be performed by obstetrician-gynecologists or other obstetric-gynecologic care providers and should be updated regularly."
- "If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both."
- "Genetic testing may be performed using a panel of multiple genes through next-generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance, and it also allows for testing for pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes)."

American Society of Clinical Oncology (ASCO): ASCO published a policy statement regarding genetic testing for cancer susceptibility. The ASCO statement includes recommendations that genetic counseling and testing be offered when:

- The individual has personal or family history and the features suggestive of a genetic cancer susceptibility condition.
- The genetic test can be adequately interpreted.
- The test results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

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In addition, ASCO recommends that genetic testing only be done in the setting of pre- and post-test counseling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities. It is also noted by the ASCO that none of the cancer susceptibility tests currently available is as yet appropriate for screening of asymptomatic individuals in the general population. However, in the setting of clinically-defined cancer susceptibility syndromes or suggestive individual cancer histories with or without family history information, the identification of a variant in an affected member of the family may influence medical management and can be used as a critical baseline in the testing of other family members.

In 2015, ASCO affirmed that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility (Robson, et al., 2015).

National Comprehensive Cancer Network® (NCCN Guidelines®) Clinical Practice Guidelines in Oncology: The NCCN has published guidelines for the management of the following hereditary cancer susceptibility syndromes:

- genetic/familial high-risk assessment: colorectal
- genetic/familial high-risk assessment: breast, ovarian, and pancreatic
- prostate cancer
- neuroendocrine and adrenal tumors
- gastric cancer
- melanoma: cutaneous
- myelodysplastic syndromes
- acute myeloid leukemia
- kidney cancer

Genetic/Familial High-Risk Assessment: Colorectal (e.g., Lynch Syndrome genes, FAP/MUTYH and other polyposis syndromes)

American College of Gastroenterology (ACG): Shaukat et al. (2021) published the ACG Clinical Guidelines: Colorectal Cancer Screening 2021 with the following recommendations:

- “We recommend colorectal cancer (CRC) screening in average-risk individuals between ages 50 and 75 year to reduce incidence of advanced adenoma, CRC, and mortality from CRC” (Strong recommendation strength; Moderate quality of evidence)
- “We suggest CRC screening in average-risk individuals between ages 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC” (Conditional recommendation strength; Very low quality of evidence)
- “We suggest consideration of the following screening tests for individuals unable or unwilling to undergo a colonoscopy or fecal immunochemical testing (FIT): flexible sigmoidoscopy, multitarget stool DNA test, CT colography, or colon capsule” (Conditional recommendation strength; Very low quality of evidence)
- “We suggest against Septin 9 for CRC screening” (Conditional recommendation strength; Very low quality of evidence)
- “We suggest that the following intervals should be followed for screening modalities: multitarget stool DNA test every 3 years” (Conditional recommendation strength; Very low quality of evidence)
- “We suggest consideration of genetic evaluation with higher familiar CRC burden (higher number and/or younger age of affected relatives)” (Conditional recommendation strength; Very low quality of evidence)

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- “We suggest initiating CRC screening at age 40 or 10 years before the youngest affected relative and then resuming average-risk screening recommendations for individuals with CRC or advances polyp in one FDR at age ≥ 60 years” (Conditional recommendation strength; Very low quality of evidence)
- “In individuals with one second-degree relative with CRC or advanced polyp, we suggest following average-risk CRC screening recommendations” (Conditional recommendation strength; Low quality of evidence)

On behalf of the ACG, Giardiello et al. (2014) published a US multi-society task force consensus guideline for the genetic evaluation and management of colorectal cancer. The guideline notes testing for MMR deficiency of newly diagnosed colorectal cancers (CRC) should be performed in all CRC or CRC in an individual ≤ 70 years or in an individual > 70 with a family history concerning for lynch syndrome (LS). Individuals who have a personal history of a tumor showing evidence of MMR deficiency (without evidence of MLH1 promoter methylation); uterine cancer diagnosed at younger than age 50 years; a known family MMR gene variant; fulfill Amsterdam criteria or revised Bethesda guidelines; and / or have a personal risk of $\geq 5\%$ chance of LS based on prediction models should undergo genetic evaluation for LS.

American College of Obstetricians and Gynecologists (ACOG): ACOG (2014, reaffirmed 2019) published the following recommendations regarding genetic risk assessment for LS (based on limited or inconsistent scientific evidence [Level B]):

- Unaffected women who have a first degree relative affected with endometrial or colorectal cancer who was either diagnosed before age 60 or who is identified to be at risk of Lynch syndrome by one of the systematic clinical screens that incorporates personal and family medical history.
- Whenever possible, molecular evaluation for Lynch syndrome should begin with tumor testing.

American Gastroenterological Association (AGA): In 2022, the AGA, the American Society for Gastrointestinal Endoscopy, and the ACG formed the US Multi-Society Task Force on Colorectal Cancer and compiled a clinical practice guideline for diagnosis and management of cancer risk in the gastrointestinal hamartomatous polyposis syndromes (Boland, et al., 2022). The 14 published recommendations on genetic evaluation, surveillance and treatment best practices are as follows:

- “The task force recommends patients with any of the following undergo a genetic evaluation: 2 or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first or second-degree relatives. Genetic testing (if indicated) should be performed using a multigene panel test.
- The task force recommends genetic evaluation for any individual with the following: 1) 2 or more histologically confirmed Peutz-Jeghers polyps, 2) any number of Peutz-Jeghers polyps in an individual who has a family history of Peutz-Jeghers syndrome in a first-degree relative, 3) characteristic mucocutaneous pigmentation in a person with a family history of Peutz-Jeghers syndrome, 4) any number of Peutz-Jeghers polyps in a person with the characteristic mucocutaneous pigmentation of Peutz-Jeghers syndrome.
- Patients with Peutz-Jeghers syndrome are at increased risk for cancer in multiple organs including cancer of the breast, small bowel, colon, stomach, pancreas, ovaries, testes, and lungs. Given this risk, we recommend a multidisciplinary approach to cancer surveillance in these organs.
- The task force recommends genetic evaluation for any individual with 1) 5 or more juvenile polyps of the colon or rectum; or 2) 2 or more juvenile polyps in other parts of the

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gastrointestinal tract; or (3) any number of juvenile polyps and 1 or more first-degree relatives with juvenile polyposis syndrome.

- Juvenile polyposis syndrome patients are at increased risk for cancer in multiple organs including cancer of the colon and stomach. Given this risk, the task force recommends patients with juvenile polyposis syndrome undergo surveillance of the colon and stomach.
- The task force suggests patients with SMAD4 pathogenic variants be clinically evaluated for HHT at the time of the diagnosis, including screening for and appropriate management of cerebral and pulmonary AVMs.
- The task force recommends individuals with multiple gastrointestinal hamartomas or ganglioneuromas undergo genetic evaluation for Cowden's syndrome and related conditions.
- In PTEN hamartoma tumor syndrome, patients are at increased risk for cancer in multiple organs, including cancer of the breast, thyroid, kidney, uterus, colon, and skin. Given this risk, the task force recommends a multi-disciplinary approach to cancer surveillance in these organs."

On behalf of the AGA, Rubenstein et al. (2015) published a medical position statement regarding the diagnosis and management of Lynch syndrome. The statement included the following recommendations regarding testing strategy for Lynch syndrome:

- In patients without a personal history of colorectal or another cancer but with a family history suggestive of Lynch syndrome, the American Gastroenterological Association (AGA) suggests that risk prediction models be offered rather than doing nothing. (Conditional recommendation, Very low quality of evidence)
- In patients without a personal history of colorectal or another cancer but with a family history suggestive of Lynch syndrome, the AGA suggests that risk prediction models be offered rather than proceeding directly with germline genetic testing. (Conditional recommendation, Very low quality of evidence)
- The AGA recommends testing the tumors of all patients with colorectal cancer with either immunohistochemistry (IHC) or for micro satellite instability (MSI) to identify potential cases of Lynch syndrome versus doing no testing for Lynch syndrome. (Strong recommendation, Moderate quality of evidence)
- The AGA suggests that in patients with colorectal cancer with IHC absent for MLH1, second-stage tumor testing for a BRAF mutation or for hypermethylation of the MLH1 promoter should be performed rather than proceeding directly to germline genetic testing. (Conditional recommendation, Very low quality of evidence)

American Society of Clinical Oncology (ASCO): Regarding CRC, ASCO published a guideline for Hereditary Colorectal Cancer Syndromes which endorsed the European Society of Medical Oncology recommendations regarding germline testing for this same indication (Stoffel, et al., 2015):

- If loss of MSH2, MSH6, PMS2 is observed in tumor analysis, germline genetic testing should be carried out for the genes corresponding to the absent proteins (e.g., MSH2, MSH6, EPCAM, PMS2, or MLH1).
- Full germline genetic testing for Lynch syndrome should include DNA sequencing and large rearrangement analysis.
- Patients with multiple colorectal adenomas should be considered for germline genetic testing of APC and/or MUTYH.
- Full germline genetic testing of APC should include DNA sequencing and large rearrangement analysis.
- Germline testing of MUTYH can be initiated by screening for the most common mutations (G396D, Y179C) in the white population followed by analysis of the entire gene in

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heterozygotes. Founder mutations among ethnic groups should be taken into account. For nonwhite individuals, full sequencing of MUTYH should be considered.

American Society of Colon and Rectal Surgeons: Herzig et al. (2017) published clinical practice guidelines for the management of inherited polyposis syndromes. Recommendations note:

- Polyposis syndromes should typically be considered in patients with greater than 20 lifetime adenomas, patients with a personal history of desmoid tumor or other extracolonic manifestations of FAP, or family members of individuals with known FAP, AFAP, or MAP. (Grade of Recommendation: Strong recommendation based on low-quality evidence)
- At-risk family members of a patient with an identified mutation are screened for the mutation. For children and those who decline genetic testing, endoscopic surveillance is recommended until either genetic testing is performed or a diagnosis is clear based on phenotype. At-risk family members who do not carry the mutation should have the same screening as the average-risk population. (Grade of Recommendation: Strong recommendation based on moderate-quality evidence)

Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (Including Prostate Cancer, Cowden Syndrome/PTEN Hamartoma Tumor Syndrome And Li Fraumeni Syndrome)

American College of Obstetricians and Gynecologists: ACOG (2017) published clinical management guidelines regarding hereditary breast and ovarian cancer syndrome which include the following guidelines related to genetic counseling and genetic testing:

- Genetic counseling is recommended for all women with epithelial ovarian cancer (includes fallopian tube or primary peritoneal cancer) and for individuals who have a personal or family history of breast or ovarian cancer (Level B recommendation-based on good and consistent scientific evidence).
- Genetic testing is recommended when the results of a detailed risk assessment that is performed as a part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management (Level C recommendation-based primarily on consensus and expert opinion).
- The two main genetic testing options for hereditary breast and ovarian cancer are BRCA mutation testing and multigene panel testing that includes both BRCA and other genetic mutations (Level C recommendation-based primarily on consensus and expert opinion).

American Society of Breast Surgeons (ASBrS): ASBrS (2019) published a consensus document regarding genetic testing for hereditary breast cancer. Recommendations include:

- Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing.
- Genetic testing should be made available to all patients with a personal history of breast cancer.
- Patients who had genetic testing previously may benefit from updated testing
- Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines
- Variants of uncertain significance are DNA sequences that are NOT clinically actionable.

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American Society of Clinical Oncology: In 2018, a provision committee opinion was published by ASCO related to evaluating susceptibility to pancreatic cancer:

- All patients diagnosed with pancreatic adenocarcinoma should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk for pancreatic adenocarcinoma.
- Assessment of risk should include a comprehensive review of family history of cancer.
- Individuals with a family history of pancreatic cancer affecting two first-degree relatives meet criteria for familial pancreatic cancer (FPC).
- Individuals (cancer affected or unaffected) with a family history of pancreatic cancer meeting criteria for FPC, those with three or more diagnoses of pancreatic cancer in same side of the family, and
- Individuals meeting criteria for other genetic syndromes associated with increased risk for pancreatic cancer have an increased risk for pancreatic cancer and are candidates for genetic testing.
- Germline genetic testing for cancer susceptibility may be discussed with individuals diagnosed with pancreatic cancer, even if family history is unremarkable.
- Benefits and limitations of pancreatic cancer screening should be discussed with individuals whose family history meets criteria for FPC and/or genetic susceptibility to pancreatic cancer.

U.S. Preventive Services Task Force (USPSTF): The USPSTF published updated evidence-based recommendations regarding the risk assessment, genetic counseling and genetic testing for BRCA-related cancer in women (USPSTF, 2019). The recommendations include:

- The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing. (Grade B recommendation)
- The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful BRCA1/2 gene mutations. (Grade D recommendation)

National Institute for Health and Care Excellence (NICE): The NICE guidelines for familial breast cancer include the following recommendations for genetic testing (NICE, 2023):

- Genetic testing:
 - All eligible people should have access to information on genetic tests aimed at mutation finding.
 - Pre-test counselling (preferably two sessions) should be undertaken.
 - Discussion of genetic testing (predictive and mutation finding) should be undertaken by a healthcare professional with appropriate training.
 - Eligible people and their affected relatives should be informed about the likely informativeness of the test (the meaning of a positive and a negative test) and the likely timescale of being given the results.
- Mutation tests:
 - Tests aimed at mutation finding should first be carried out on an affected family member where possible.
 - If possible, the development of a genetic test for a family should usually start with the testing of an affected individual (mutation searching/screening) to try to identify a mutation in the appropriate gene (such as BRCA1, BRCA2 or TP53)

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- A search/screen for a mutation in a gene (such as BRCA1, BRCA2 or TP53) should aim for as close to 100% sensitivity as possible for detecting coding alterations and the whole gene(s) should be searched.
- Carrier probability at which genetic testing should be offered:
 - Discuss the potential risk and benefits of genetic testing. Include in the discussion the probability of finding a mutation, the implications for the individual and the family, and the implications of either a variant of uncertain significance or a null result (no mutation found).
 - Inform families with no clear genetic diagnosis that they can request review in the specialist genetic clinic at a future date.
 - Clinical genetics laboratories should record gene variants of uncertain significance and known pathogenic mutations in a searchable electronic database.
- Genetic testing for a person with no personal history of breast cancer but with an available affected relative:
 - Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a combined BRCA1 and BRCA2 mutation carrier probability of 10% or more.
- Genetic testing for a person with no personal history of breast cancer and no available affected relative to test:
 - Offer genetic testing in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined BRCA1 and BRCA2 mutation carrier probability is 10% or more and an affected relative is unavailable for testing.
- Genetic testing for a person with breast or ovarian cancer:
 - Offer genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if their combined BRCA1 and BRCA2 mutation carrier probability is 10% or more.
- Genetic testing for BRCA1, BRCA2 and TP53 mutations within 4 weeks of diagnosis of breast cancer:
 - Offer people eligible for referral to a specialist genetic clinic a choice of accessing genetic testing during initial management or at any time thereafter.

Neuroendocrine and Adrenal Tumors (e.g., MEN1, MEN2, VHL, PGL/PCC)

American Thyroid Association (ATA): On behalf of the ATA, Wells et al. (2015) published revised management guidelines for medullary thyroid cancer. The guidelines include the following recommendations regarding genetic testing:

- The recommended method of initial testing for MEN2A 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)
- 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)
- 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

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- patients with CLA
- 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. (Grade B Recommendation)

Recommendation B: The recommendation is based on fair evidence that the service or intervention can improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.

National Cancer Institute (NCI): The NCI (2024) notes genetic testing for MEN1 pathogenic variants is recommended for individuals meeting clinical diagnostic criteria and may be considered in a subset of the less common tumors. MEN2 is a well-defined hereditary cancer syndrome for which genetic testing is considered an important part of the management for at-risk family members. It meets the criteria related to indications for genetic testing for cancer susceptibility outlined by the American Society of Clinical Oncology in its most recent genetic testing policy statement. At-risk individuals are defined as first-degree relatives (parents, siblings, and children) of a person known to have MEN2. Testing allows the identification of people with asymptomatic MEN2 who can be offered risk-reducing thyroidectomy and biochemical screening as preventive measures.

Regarding pheochromocytoma (PCC) and paraganglioma (PGL), NCI (2022) notes a significant proportion of individuals presenting with apparently sporadic PCC or PGL are carriers of germline pathogenic variants. Up to 33% of patients with apparently sporadic PCC, and up to 40% of patients with apparently sporadic PGLs, actually have a recognizable germline pathogenic variant in one of the classical PGL/PCC susceptibility genes. PGLs and PCCs can be seen as part of several well-described tumor susceptibility syndromes including von Hippel-Lindau disease (VHL), MEN2, neurofibromatosis type 1, Carney-Stratakis syndrome, and familial paraganglioma (FPGL) syndrome.

Endocrine Society: Lenders et al. (2014) published clinical practice guidelines for pheochromocytoma and paraganglioma (PPGL). Regarding genetic testing, the guidelines include these recommendations:

- All patients with PPGLs should be engaged in shared decision making for genetic testing.
- The use of a clinical feature-driven diagnostic algorithm to establish the priorities for specific genetic testing in PPGL patients with suspected germline mutations.
- Suggest that patients with paraganglioma undergo testing of succinate dehydrogenase (SDH) mutations and that patients with metastatic disease undergo testing for SDHB mutations
- That genetic testing for PPGL is delivered within the framework of health care. Specifically, pretest and post-test counseling should be available. All tests for PPGL genetic testing should be performed by accredited laboratories.

Retinoblastoma

Canadian Retinoblastoma Society (2009): Guidelines for genetic testing for retinoblastoma (Rb) include the following recommendations for genetic testing:

- RB1 gene mutation identification testing for the first affected person (proband) in each Rb family (Level 2*)

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- any tumor removed from a Rb patient be stored in a form appropriate for DNA studies (Level 2*)
- For bilaterally affected and familial unilateral probands, recommend that blood be studied, aided by tumor tissue as required (Level 2*)
- For unilateral, nonfamilial probands, it is recommended that tumor be studied first. If no tumor is available, recommend that blood be studied (Level 2*)
- When chromosome 13q14 deletion is discovered, recommend any genetic test report suggesting deletion or rearrangement of chromosome 13q14 in a child or adult trigger an urgent referral to ophthalmology within 48–72 hours (Level 2*)
- When the family RB1 mutation is known:
 - recommend genetic testing for all at-risk relatives (Level 2*)
 - recommend frequent clinical surveillance to detect Rb in children who carry the RB1 mutant allele of their family (Level 2*)
 - recommend awareness counseling about cancer in adult relatives who carry the RB1 mutant allele of their family (Level 2*)
 - recommend that surveillance for relatives not at risk be discontinued (Level 2*)
 - recommend early prenatal counseling, including a discussion of the advantages and disadvantages of invasive prenatal testing to support informed family planning decisions, and perinatal management of affected babies to facilitate the earliest possible treatment of tumors (Level 2*)
- when the family RB1 mutation is not known:
- With a positive family history but no knowledge of the RB1 mutation, recommend that each at-risk family member be screened until age seven years, according to the empiric risk of developing Rb (Level 2*)

*Level 2: RCTs (or meta-analyses) with important limitations, Observational studies (non-RCTs or cohort studies) with overwhelming evidence

Level 3: Other observational studies (prospective cohort studies, case-control studies, case series)

Multi-Gene Germline Mutation Panel Testing

Society of Gynecologic Oncology (SGO, 2014): The SGO notes advantages include decreased cost and improved efficiency of cancer genetic testing by decreasing the time involved, number of patient visits, and number of tests sent. Disadvantages include the increased complexity of results. For many genes, clear risk reduction strategies for mutation carriers are not established. A major concern is the increased likelihood of identifying results of uncertain clinical significance.

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

General Criteria for Germline Pathogenic or Likely Pathogenic Variant Genetic Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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CPT®* Codes	Description
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants

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CPT®* Codes	Description
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

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CPT®* Codes	Description
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
81437	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
81438	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
81479 [†]	Unlisted molecular pathology procedure
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family
0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (<u>15</u> genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
0102U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (<u>17</u> genes [sequencing and deletion/duplication])
0129U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
0157U	APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)

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CPT®* Codes	Description
0158U	MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0159U	MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0160U	MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)

†Note: Considered Medically Necessary when used to report:

- **CHEK2 gene mutation testing**
- **CHEK2 genetic testing with full sequence analysis**
- **CHEK2 genetic testing with deletion/duplication analysis**
- **PALB2 deletion/duplication analysis.**
- **RAD15D gene mutation testing**
- **SDHAF2 gene testing, SDHB or SDHD deletion/duplication analysis**

HCPCS Codes	Description
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
S3842	Genetic testing for Von Hippel-Lindau disease

Considered Not Medically Necessary:

CPT®* Codes	Description
0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)
0131U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)
0132U	Hereditary ovarian cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)
0133U	Hereditary prostate cancer-related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)
0134U	Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure)
0135U	Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA

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CPT®* Codes	Description
	sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)
0136U	ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure)
0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)
0474U	Hereditary pan-cancer (eg, hereditary sarcomas, hereditary endocrine tumors, hereditary neuroendocrine tumors, hereditary cutaneous melanoma), genomic sequence analysis panel of 88 genes with 20 duplications/deletions using next generation sequencing (NGS), Sanger sequencing, blood or saliva, reported as positive or negative for germline variants, each gene
0475U	Hereditary prostate cancer related disorders, genomic sequence analysis panel using next-generation sequencing (NGS), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and array comparative genomic hybridization (CGH), evaluation of 23 genes and duplications/deletions when indicated, pathologic mutations reported with a genetic risk score for prostate cancer

Retinoblastoma – RB1

Considered Medically Necessary when used to report RB1 genetic testing with full sequence analysis or deletion/duplication analysis:

CPT®* Codes	Description
81479	Unlisted molecular pathology procedure

HCPCS Codes	Description
S3841	Genetic testing for retinoblastoma

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	<ul style="list-style-type: none">Add kidney cancer to policy statement for germline genetic testing for hereditary cancer susceptibility syndromes.	8/15/2024
Focused review	<ul style="list-style-type: none">Revised policy statement to add additional entity to recommend hereditary genetic testing.	5/15/2024

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