Genetic Testing for Hereditary Cancer Susceptibility Syndromes

**Table of Contents**

Overview ............................................................... 2  
Coverage Policy ....................................................... 2  
  General Criteria for Germline Pathogenic or Likely Pathogenic Variant Genetic Testing: Hereditary Cancer Susceptibility/Risk Assessment .................................................. 2  
  Germline Testing Following Identification of a Somatic Pathogenic or Likely Pathogenic Variant ................................................. 3  
  Germline Pathogenic or Likely Pathogenic Variant Genetic Testing for Hereditary Cancer Susceptibility Syndromes .......................... 3  
General Background .................................................. 8  
  Genetic Counseling ............................................... 8  
  General Criteria for Germline Pathogenic or Likely Pathogenic Variant Testing for Hereditary Cancer Susceptibility/Risk Assessment .................................................. 9  
  Germline Testing Following Identification of a Somatic Pathogenic or Likely Pathogenic Variant .................................................. 9  
  Germline Genetic Testing for Hereditary Cancer Susceptibility Syndromes .................................................. 10  
Appendix A ............................................................. 14  
Coding/Billing Information .......................................... 19  
References ................................................................ 25

**Related Coverage Resources**

Genetics  
Genetic Testing Collateral File  
Prophylactic Mastectomy  
Prophylactic Oophorectomy or Salpingo-oophorectomy With or Without Hysterectomy  
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. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage
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

Many benefit plans limit coverage of genetic testing and genetic counseling services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

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.

For additional information regarding coverage for specific genetic tests please refer to the Genetic Testing Collateral File.

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
  - an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a
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:

- the variant is pathogenic or likely pathogenic
- 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 (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 as above AND current National Comprehensive Cancer Network™ (NCCN Guidelines™) category 1, 2A or 2B guidelines for the testing requested for ANY of the following hereditary cancer susceptibility syndromes:

- Lynch syndrome**: MLH1, MSH2, MSH6, PMS2, EPCAM
- familial adenomatous polyposis (FAP)/Attenuated familial adenomatous polyposis (AFAP): APC
- MYH-associated polyposis: MYH
• hereditary breast and ovarian cancer syndrome: BRCA 1 and BRCA 2
• juvenile polyposis syndrome: BMPR1A, SMAD4
• Peutz-Jeghers syndrome: STK11
• Cowden syndrome/PTEN Hamartoma tumor syndrome PTEN
• Li Fraumeni syndrome: TP53
• multiple endocrine neoplasia type 1: MEN1
• multiple endocrine neoplasia type 2: MEN type 2A and type 2B, RET
• diffuse gastric cancer: CDH1

** Lynch syndrome related-cancers for criteria evaluation are: colorectal, endometrial, keratocanthoma, 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 tumor analysis is discussed in Cigna Coverage Policy: Tumor Profiling, Gene Expression Assays and Molecular Diagnostic Testing for Hematology/Oncology Indications.

---

**CHEK2**

**Medically Necessary**

Genetic testing for CHEK2 is considered medically necessary when the individual meets general criteria for hereditary cancer as above and ANY of the following criteria are met:

• personal history of female breast cancer diagnosed ≤ age 45 years
• personal history of female breast cancer diagnosed ≤ age 50 years with ANY of the following:
  ➢ additional primary breast cancer at any age
  ➢ first- or second-degree relative*** (male or female) with breast cancer at any age
  ➢ an unknown or limited family history (i.e., fewer than two first or second degree female blood relatives*** in either lineage surviving beyond age 60 years)
• personal history of female breast cancer diagnosed at any age with ANY of the following:
  ➢ first- or second-degree blood relative*** with breast cancer (in a male or female) at ≤ age 50 years or male breast cancer at any age
  ➢ two first- or second-degree blood relatives*** on the same side of the family with breast cancer (in a male or female) at any age
• personal history of male breast cancer at any age with a first-or second degree blood relative*** with breast cancer (in a male or female) at any age
• personal history of localized stage III (i.e., NCCN high-risk and very high-risk group), regional or metastatic prostate cancer
• family history includes EITHER of the following:
  ➢ individual has a first-or second-degree blood relative*** who meets any of the above CHEK2 criteria
  ➢ at-risk individual from a family with a pathogenic or known pathogenic variant in the CHEK2 gene

***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.

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.

Hereditary Paraganglioma-Pheochromocytoma Syndrome (PGL/PCC)

Medically Necessary

Genetic testing with full sequence and deletion/duplication analysis or multi-gene panel testing is considered medically necessary for hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome when the individual meets general criteria for hereditary cancer genetic testing as above and ALL of the following criteria are met:

- individual with pheochromocytoma or paraganglioma
- other syndromes and causes of PGL/PCC have been ruled out (e.g., multiple endocrine neoplasia [MEN] types I and II)

Single-site genetic testing is considered medically necessary for an at-risk individual with a blood relative who has a pathogenic or likely pathogenic variant.

PALB2

Medically Necessary

Genetic testing for PALB2 is considered medically necessary when the individual meets general criteria for hereditary cancer genetic testing as above and ANY of the following criteria are met:

- personal history of female breast cancer diagnosed ≤ age 45 years
- personal history of female breast cancer diagnosed ≤ age 50 years with ANY of the following:
  - additional primary breast cancer at any age
  - first- or second-degree blood relative*** with ANY of the following
    - pancreatic cancer
    - female breast cancer ≤ age 50 years
    - male breast cancer
    - two primary breast cancers (in a male or female) at any age
  - an unknown or limited family history (i.e., fewer than two first or second degree female blood relatives in either lineage surviving beyond 60 years)
  - two first- or second-degree blood relatives*** on the same side of the family with breast cancer (in a male or female) at any age
- personal history of female breast cancer diagnosed with two primary breast cancers with EITHER of the following:
  - first- or second-degree blood relative*** with ANY of the following:
    - pancreatic cancer
• male breast cancer
• breast cancer (in a male or female) ≤ age 50 years
• two primary breast cancers (in a male or female) at any age
  ➢ two first- or second-degree blood relatives*** on the same side of the family with breast cancer
    (in a male or female) at any age
• personal history of female breast cancer diagnosed at any age with EITHER of the following:
  ➢ two first- or second-degree blood relatives*** on the same side of the family with ANY of the
    following:
    o breast cancer at any age
    o two primary breast cancers (in a male or female)
    o pancreatic cancer
  ➢ three first- or second-degree blood relatives*** with pancreatic cancer or breast cancer (in a
    male or female) at any age
• personal history of male breast cancer at any age with EITHER of the following:
  ➢ first- or second-degree blood relative*** with ANY of the following:
    o pancreatic cancer
    o male breast cancer
    o breast cancer (in male or female) ≤ age 50 years
    o two primary breast cancers (in a male or female) at any age
  ➢ two first- or second-degree blood relatives*** on the same side of the family with breast cancer (in
    a male or female) at any age
• personal history of pancreatic cancer with ANY of the following:
  ➢ first- or second-degree blood relative*** with ANY of the following:
    o male breast cancer
    o breast cancer (in a male or female) ≤ age 50 years
    o two primary breast cancers (in a male or female)
  ➢ two first- or second-degree blood relatives*** on the same side of the family with
    breast cancer (in a male or female) or pancreatic cancer at any age
  ➢ two first or second-degree blood relatives*** on the same side of the family with pancreatic
    cancer at any age
• personal history of localized stage III (i.e., NCCN high-risk or very high-risk group), regional or metastatic
  prostate cancer
• family history includes EITHER of the following:
  ➢ individual has a first or second degree blood relative who meets any of the above PALB2 criteria
  ➢ at risk-individual from a family with a pathogenic or likely pathogenic variant PALB2 gene

***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.

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.

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

- 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.

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)

-----------------------------------------------------------------------------------------------------------------------------

von Hippel-Lindau Syndrome-VHL

Medically Necessary

Genetic testing is considered medically necessary for von Hippel-Lindau (VHL) syndrome when individual meets general criteria for hereditary cancer genetic testing as noted above and ANY of the following indications:

- At risk individual from a family with a pathogenic or likely pathogenic variant VHL gene
- Retinal angioma/hemangioblastoma
- Spinal or cerebellar hemangioblastoma
- Adrenal or extra-adrenal pheochromocytoma
- Renal cell carcinoma, if the patient is < age 47 years or has a personal or family history of any other tumor typical of VHL
- Multiple renal and pancreatic cysts
- Neuroendocrine tumors of the pancreas
- Endolymphatic sac tumors
- Multiple papillary cystadenomas of the epididymis or broad ligament

Prostate Cancer

Medically Necessary

Germline genetic testing is considered medically necessary for early stage, non-metastatic prostate cancer when the individual meets the general criteria for hereditary cancer genetic testing as described above.

Germline testing for pathogenic or likely pathogenic variants in MLH1, MSH2, MS6, PMS2, BRCA1, BRCA2, ATM, PALB2, CHEK2 and RAD51D genes is considered medically necessary for localized stage III (i.e., NCCN® high-risk and very high-risk group), regional or metastatic prostate cancer.

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.

Experimental, Investigational or Unproven

Cancer risk prediction testing (e.g., single nucleotide polymorphism testing) is considered experimental, investigational or unproven.

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, 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]; Edwards, 2010).

A variety of genetics professionals provide these services: Board-Certified or Board-Eligible Medical Geneticists, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor, and genetic nurses credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC). Individuals should not be employed by a commercial genetic testing laboratory, although counseling services by these individuals 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.

Pre- and post-test genetic test counseling is required 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.

**General Criteria for 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.

**Professional Society/Organization**
For a summary of professional society recommendations/guidelines regarding germline pathogenic or likely pathogenic variant genetic testing for hereditary cancer susceptibility syndromes please click [here](#).

**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.

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 (Catenacci et al. 2015; Schrader et al. 2016). One of the largest studies to date, using a broad molecular profiling platform, predicted that variations in high-risk cancer genes were likely pathogenic or pathogenic in 3.1 to 7% of tumor samples tested; however, the study design did not compare the tumor DNA to normal. Additionally, this study noted the rate of germline variants varies widely by tissue type and gene (Hall 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.

**Germline Genetic Testing for Hereditary Cancer Susceptibility Syndromes**

**Lynch Syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM), Familial Adenomatous Polyposis/Attenuated Familial Polyposis (APC), Juvenile Polyposis Syndrome (BMPR1A) and MYH-Associated Polyposis (MYH):** 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 ten 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 (Kohlmann and Gruber, 2014).

**Professional Society/Organization**
For a summary of professional society recommendations/guidelines regarding Lynch syndrome-related cancer testing please click here.

**Hereditary Breast and Ovarian Cancer Syndromes (BRCA1 and BRCA2):** 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], 2017). 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.

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.

Professional Society/Organization
For a summary of professional society recommendations/guidelines regarding genetic testing for susceptibility to breast and ovarian Cancer (e.g., BRCA1 & BRCA2 testing) please click here.

Peutz-Jeghers Syndrome-STK11: Peutz-Jeghers syndrome is an early-onset autosomal dominant disorder characterized by melanocytic macules on the lips, the perioral region, and buccal region; and multiple gastrointestinal polyps, both hamartomatous and adenomatous. PJS is caused by variations in the STK11 gene.

Professional Society/Organization
For a summary of professional society recommendations/guidelines regarding genetic testing for Peutz-Jeghers syndrome please click here.

Cowden Syndrome/PTEN Hamartoma Tumor Syndrome-PTEN: 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 (Genetics Home Reference [GHR], 2016).

Professional Society/Organization
For a summary of professional society recommendations/guidelines regarding genetic testing for Cowden Syndrome/PTEN Hamartoma tumor syndrome please click here.

Li Fraumeni Syndrome-TP53: 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 (GHR, 2016). 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.

Professional Society/Organization
For a summary of professional society recommendations/guidelines regarding genetic testing for Li Fraumeni syndrome please click here.

Multiple Endocrine Neoplasia Type 1 (MEN1), Type 2A and 2B and RET: 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.
Professional Society/Organization
For a summary of professional society recommendations/guidelines regarding genetic testing for multiple endocrine neoplasia type 1 and type 2 please click here.

Hereditary Diffuse Gastric Cancer-CDH1: 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 (GHR, 2016).

Professional Society/Organization
For a summary of professional society recommendations/guidelines regarding genetic testing for diffuse gastric cancer please click here.

CHEK2: CHEK2 has been identified as a breast cancer susceptibility gene. This gene provides instruction for a protein: checkpoint kinase 2, which functions as a tumor suppressor and regulates cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way (Genetics Home Reference, 2016). According to the NCCN (2019), deleterious CHEK2 variants have been reported to occur with a higher frequency in Northern and Eastern European countries compared with North America. The cumulative lifetime risk for breast cancer in a woman with a CHEK2 variant and familial breast cancer ranges between 28%-37%.

Genetic testing for an individual with a CHEK2 variant is supported by published evidence-based recommendations in the peer-reviewed scientific literature.

Hereditary Paraganglioma-Pheochromocytoma Syndrome: 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 (type2), 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 (GHR, 2016).

Genetic testing is supported by published, professional consensus statements and evidence in the published, peer reviewed scientific literature.

PALB2: Variations in the partner and localizer of BRCA2 (PALB2) gene are associated with an increased risk for breast cancer (NCCN, 2019). In an individual with breast cancer the risk is estimated to be 1-3% in women and 1%-2%in men with breast cancer who tested negative for a BRCA2 variant. Breast cancer risk increases with age in women with a lifetime risk of 14% by age 50 and a 35% risk by age 70. As the number of relatives affected with breast cancer increases so does the risk of a PALB2 variant (NCCN, 2019).

Genetic testing for an individual with a PALB2 variant is supported by published, evidence-based recommendations and evidence in the peer-reviewed scientific literature.

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, 2017). 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.

Professional Society/Organization
For a summary of professional society recommendations/guidelines regarding genetic testing for retinoblastoma please click here.
**von Hippel-Lindau Syndrome (VHL):** von Hippel-Lindau (VHL) disease or syndrome is an autosomal dominant inherited multisystem disorder characterized by abnormal growth of blood vessels. VHL is characterized by hemangioblastomas of the brain, spinal cord and retinas; renal cysts and clear cell renal cell carcinomas; pheochromocytomas; and endolymphatic sac tumors. Tumors may be cancerous or benign; however, even if noncancerous they may be life-threatening.

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 (GHR, 2016). 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 (Frantzen, et al., 2012).

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 (American Society of Clinical Oncology [ASCO], 2003). 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.

**Professional Society/Organization**
For a summary of professional society recommendations/guidelines regarding genetic testing for von Hippel-Lindau please click here.

**Prostate Cancer:** Recommendations for germline genetic pathogenic or likely pathogenic variant testing are based on recommendations from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®) for Prostate Cancer (2019). 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.

**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, 2017). 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., 2008). At this time the role of SNP testing has not been established for the diagnosis or management of hereditary cancer syndromes.

**Centers for Medicare & Medicaid Services (CMS)**
- National Coverage Determinations (NCDs): No NCD found.
- Local Coverage Determinations (LCDs): Multiple LCDs found. Refer to the LCD table of contents link in the reference section.

**Use Outside of the US**
For a summary of professional society recommendations/guidelines regarding genetic testing please click here.
HEREDITARY CANCER SUSCEPTIBILITY/RISK ASSESSMENT

American College of Obstetricians and Gynecologists (ACOG, 2015, update 2017): ACOG 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.
• 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.


• 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.

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 (ASCO, 2003; Robson, et al., 2010).

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

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:

• Lynch syndrome: MLH1, MSH2, MSH6
• Familial adenomatous polyposis (FAP)/Attenuated familial adenomatous polyposis (AFAP): APC
• MYH-associated polyposis: MYH
• hereditary breast and ovarian cancer syndrome: BRCA 1 and BRCA 2
• juvenile polyposis syndrome: BMPR1A, SMAD4
• Peutz-Jeghers syndrome: STK11
• Cowden syndrome/PTEN Hamartoma tumor syndrome PTEN
• Li Fraumeni syndrome: TP53
• multiple endocrine neoplasia type 1: MEN1
• multiple endocrine neoplasia type 2: MEN type 2A and type 2B, RET
• diffuse gastric cancer: CDH1
• prostate cancer
LYNCH SYNDROME (LS) GERMLINE TESTING
American College of Gastroenterology ([ACG], 2014): On behalf of the ACG, Giardiello et al. 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 CRC should be performed in all colorectal cancers (CRC) or CRC in an individual ≤70 years or in an individual >70 with a family history concerning for 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 ≥ 5 % chance of LS based on prediction models should undergo genetic evaluation for LS.

American College of Obstetricians and Gynecologists ([ACOG], 2014, reaffirmed 2019): ACOG 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], 2015): On behalf of the AGA, Rubenstein et al. 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 Oncologists ([ASCO], 2015):
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 (2014):

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

- 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.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROMES (E.G., BRCA1, BRCA2)

American College of Obstetricians and Gynecologists ([ACOG], 2017): ACOG 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 (2019): The Society 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.

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 (Moyer, et al., 2014). The recommendations include:

- The USPTF recommends primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1 or BRCA2). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (B recommendation)

- The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1 or BRCA2 genes. (D recommendation)
National Institute for Health and Care Excellence ([NICE], 2013, updated 2017): NICE guidelines for familial breast cancer include the following recommendations for genetic testing:

- 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).
  - 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.

MULTIPLE ENDOCRINE NEOPLASIA

American Thyroid Association ([ATA], 2015): On behalf of the ATA, Wells et al. 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
  ➢ 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, 2018): The NCI 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. Testing allows the identification of people with asymptomatic MEN2 who can be offered risk-reducing thyroidectomy and biochemical screening as preventive measures.

HEREDITARY PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME (PPGL)
The Endocrine Society (2014): Lenders et al. 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*)
• 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)

VON HIPPEL LINDAU:
National Cancer Institute (NCI, 2018): The NCI notes VHL pathogenic variants are highly penetrant, with manifestations found in more than 90% by age 65 years. Almost all carriers develop one or more types of syndrome-related neoplasms. A family member with a clinical diagnosis of VHL or who is showing signs and symptoms of VHL is initially offered genetic testing. Germline pathogenic variants in VHL are detected in more than 99% of families affected by VHL.

PANCREATIC CANCER:
American Society of Clinical Oncology (ASCO, 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.

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/Billing Information**

**Note:** 1) This list of codes may not be all-inclusive.
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:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81162</td>
<td>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)</td>
</tr>
<tr>
<td>81163</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81164</td>
<td>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)</td>
</tr>
<tr>
<td>81165</td>
<td>BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81166</td>
<td>BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)</td>
</tr>
<tr>
<td>81167</td>
<td>BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)</td>
</tr>
<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81211</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) (Code deleted 12/31/2018)</td>
</tr>
<tr>
<td>81212</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants</td>
</tr>
<tr>
<td>81213</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants (Code deleted 12/31/2018)</td>
</tr>
<tr>
<td>81214</td>
<td>BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) (Code deleted 12/31/2018)</td>
</tr>
<tr>
<td>81215</td>
<td>BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81216</td>
<td>BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81217</td>
<td>BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
</tr>
<tr>
<td>81292</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81293</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81294</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>81296</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81297</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81298</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81299</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81300</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81301</td>
<td>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</td>
</tr>
<tr>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81321</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81322</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81323</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant</td>
</tr>
<tr>
<td>81401</td>
<td>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)</td>
</tr>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, 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)</td>
</tr>
<tr>
<td>81404</td>
<td>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)</td>
</tr>
<tr>
<td>81405</td>
<td>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)</td>
</tr>
<tr>
<td>81406</td>
<td>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, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td>81408</td>
<td>Molecular pathology procedure, Level 9 (eg, analysis of &gt;50 exons in a single gene by DNA sequence analysis)</td>
</tr>
<tr>
<td>81432</td>
<td>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</td>
</tr>
<tr>
<td>81433</td>
<td>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</td>
</tr>
<tr>
<td>81435</td>
<td>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</td>
</tr>
<tr>
<td>81436</td>
<td>Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel,</td>
</tr>
</tbody>
</table>
must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81479†</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
</tr>
</tbody>
</table>

CHEK2

Considered Medically Necessary when used to report CHEK2 genetic testing with full sequence analysis or deletion/duplication analysis:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81479†</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

Hereditary Paraganglioma-Pheochromocytoma Syndrome (PGL/PCC)

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

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81404</td>
<td>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)</td>
</tr>
<tr>
<td>81405</td>
<td>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)</td>
</tr>
<tr>
<td>81437</td>
<td>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</td>
</tr>
<tr>
<td>81438</td>
<td>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</td>
</tr>
<tr>
<td>81479†</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

†Note: Considered Medically Necessary when used to report SDHAF2 gene testing, SDHB or SDHD deletion/duplication analysis

PALB2

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

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
<tr>
<td>81479†</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>
†Note: Considered Medically Necessary when used to report PALB2 deletion/duplication analysis

Retinoblastoma – RB1

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

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3841</td>
<td>Genetic testing for retinoblastoma</td>
</tr>
</tbody>
</table>

von Hippel-Lindau Syndrome – VHL

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

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, 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)</td>
</tr>
<tr>
<td>81404</td>
<td>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)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3842</td>
<td>Genetic testing for Von Hippel-Lindau disease</td>
</tr>
</tbody>
</table>

Prostate Cancer

Considered Medically Necessary when criteria in the applicable policy statements listed above are met for localized stage III (i.e., NCCN® high-risk and very high-risk group), regional or metastatic prostate cancer:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81162</td>
<td>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)</td>
</tr>
<tr>
<td>81163</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81164</td>
<td>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)</td>
</tr>
<tr>
<td>81165</td>
<td>BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81166</td>
<td>BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)</td>
</tr>
<tr>
<td>81167</td>
<td>BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)</td>
</tr>
<tr>
<td>81211</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) (Code deleted 12/31/2018)</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>81212</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants</td>
</tr>
<tr>
<td>81213</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants (Code deleted 12/31/2018)</td>
</tr>
<tr>
<td>81214</td>
<td>BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) (Code deleted 12/31/2018)</td>
</tr>
<tr>
<td>81215</td>
<td>BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81216</td>
<td>BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81217</td>
<td>BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
</tr>
<tr>
<td>81292</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81293</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81294</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81296</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81297</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81298</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81299</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81300</td>
<td>MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81406</td>
<td>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, regionally targeted cytogenomic array analysis)</td>
</tr>
</tbody>
</table>
| 81479† | Unlisted molecular pathology procedure                                                                                      

**Note:** Considered Medically Necessary when used to report CHEK2 or RAD51D gene mutation testing

**Experimental/Investigational/Unproven**

Considered Experimental/Investigational/Unproven when used to report cancer risk prediction testing:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
</tbody>
</table>
References


40. Committee on Bioethics; Committee on Genetics, and American College of Medical Genetics and Genomics Social; Ethical; Legal Committee. Ethical and policy issues in genetic testing and screening of children. Pediatrics. 2013 Mar;131(3):620-2.


67. Gupta, Garima MD and Karel Pacak, MD, PhD, DSc, FACE on behalf of the AACE Adrenal Scientific Committee. Precision Medicine: An UPdate of Genotype-Biochemical Phenotype Relationships in Pheochromocytoma/Paraganglioma Patient. Endocrine Practice. DOI:10.4158/EP161718.RA. [Epub ahead of print]


134. Slattery ML1, John EM, Stern MC, Herrick J, Lundgreen A, Giuliano AR, Hines L, Baumgartner KB, Torres-Mejia G, Wolff RK. Associations with growth factor genes (FGF1, FGF2, PDGFB, FGFR2, NRG2, EGF,


