Genetic Testing for Hereditary Breast, Ovarian, Pancreatic and Prostate Cancer

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Medical Coverage Policy

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Description

Genetic testing is a laboratory method that is performed to analyze an individual's deoxyribonucleic acid (DNA) to detect gene variants (mutations) associated with inherited conditions including hereditary cancer such as breast, ovarian (including fallopian tube and peritoneal) and pancreatic cancer. Testing may be appropriate for an affected individual as well as asymptomatic relatives at increased risk for cancer. This type of testing may also be referred to as germline genetic testing. Additional inherited cancers include Li-Fraumeni syndrome (LFS) and PTEN hamartoma tumor syndrome/Cowden syndrome. Both are rare, inherited conditions that are associated with increased risk of many types of cancer.

A **multigene panel** is defined as a test that analyzes more than one gene simultaneously while single gene testing searches for variants in one specific gene. Multigene panels evaluate the DNA of an individual with a personal and/or family history of a hereditary condition. Multisyndrome genetic testing panels analyze genes associated with more than one hereditary cancer syndrome such as breast, colon, ovarian and uterine. Panels can be targeted or expanded. A targeted panel offers a limited number of genes associated with a specific condition while expanded panels are broad, providing analysis of a large number of genes and often include genes with unclear medical management.

Concurrent (paired) deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) genetic testing (also referred to as expanded RNA analysis) is a laboratory method that analyzes DNA in combination with RNA to purportedly aid with the detection, diagnosis and management of cancer as well as classification of variants of unknown significance (VUS). Paired testing may be offered to an individual who is at increased risk for hereditary cancer and is performed concurrent to DNA testing to identify additional variants (mutations). **+RNAinsight** is an example of paired genetic testing and is conducted as an add-on test for multigene hereditary breast and ovarian panels such as **GYNPlus, OvaNext and ProstateNext**. +RNAinsight has also been proposed for use with single gene testing (eg, *ATM, BRCA1, BRCA2* and *PALB2*).

Coverage Determination

Any state mandates for genetic testing for breast, ovarian or pancreatic cancer susceptibility take precedence over this medical coverage policy.

Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.

Hereditary Breast Cancer

Humana members may be eligible under the Plan for **single gene or multigene germline panel sequencing and deletion/duplication analysis for hereditary breast cancer** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- No known pathogenic or likely pathogenic variant in the family (if a pathogenic or likely pathogenic variant has been detected in an affected family member, genetic testing should be limited to the known familial variant; see Known Familial Pathogenic or Likely Pathogenic Variant Testing criteria below); **AND**
    - Single gene testing and/or deletion duplication analysis (performed concurrently or sequentially) of *BRCA1* (81165/81166), *BRCA2* (81216/81167), *CDH1, PALB2* (81307), *PTEN* (81321/81323) *or TP53* (81351/81352) genes; **OR**
    - Multigene germline panel sequencing and/or deletion/duplication analysis (81432/81433) (performed concurrently or sequentially); **AND**

- Personal history of breast cancer (includes invasive ductal carcinoma in situ [DCIS]); **AND**
  - Diagnosed at 50 years of age or younger; **OR**
  - Diagnosed at any age; **AND**
    - Individual is of Ashkenazi Jewish, Bahamian, Central and South American, French Canadian, Hungarian, Icelandic, Mexican, Polish, Spanish ancestry/ethnicity; **OR**
    - Lobular breast cancer with a personal history of or has a first-, second- or third-degree relative diagnosed with diffuse gastric cancer; **OR**
    - Male breast cancer; **OR**
    - Multiple primary breast cancers (synchronous [occurring simultaneously] or metachronous [occurring at different time periods]); **OR**
    - Triple-negative breast cancer; **OR**
    - At least 1 first-, second- or third-degree relative diagnosed with any of the following:
      - ❖ Breast cancer at 50 years of age or younger; **OR**
      - ❖ Male breast cancer; **OR**
      - ❖ Ovarian cancer; **OR**
      - ❖ Pancreatic cancer; **OR**
      - ❖ Prostate cancer with any of the following features:
        - Metastatic (includes distant metastasis and regional bed or nodes) established by biopsy and/or radiography; **OR**
        - Intermediate-risk with intraductal or cribriform histology; **OR**
        - High-risk or very-high-risk; **OR**
    - 3 or more total diagnoses of breast cancer and/or prostate cancer in the family (including the individual diagnosed with breast cancer and first-, second- or third-degree relatives on the same side of the family); **OR**
    - Individual with a breast cancer diagnosis but does not meet the above testing criteria for hereditary breast cancer; **AND**
      - ❖ Has a first- or second-degree relative who meets above testing criteria for hereditary breast cancer; **OR**

- ❖ Risk stratification tool (Tyrer-Cuzick, BRCAPRO, CanRisk) indicates greater than 2.5% probability for a *BRCA1/2* pathogenic variant; **OR**

- Individual without a breast cancer diagnosis; **AND**
  - Has a first- or second-degree relative who meets above testing criteria for hereditary breast cancer; **OR**
  - Risk stratification tool (Tyrer-Cuzick, BRCAPRO, CanRisk) indicates greater than 2.5% probability for a *BRCA1/2* pathogenic variant; **OR**
- Meets above testing criteria for hereditary breast cancer and tested negative on previous limited testing (single gene testing and/or absent deletion/duplication analysis) (applies to multigene germline panel sequencing only); **OR**
- Pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline

Hereditary Ovarian, Fallopian Tube or Peritoneal Cancer

Humana members may be eligible under the Plan for **single gene or multigene germline panel sequencing and deletion/duplication analysis for hereditary ovarian cancer, fallopian tube or peritoneal cancer** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- No known pathogenic or likely pathogenic variant in the family (if a pathogenic or likely pathogenic variant has been detected in an affected family member, genetic testing should be limited to the known familial variant; see Known Familial Pathogenic or Likely Pathogenic Variant Testing criteria below); **AND**
  - Single gene testing and/or deletion duplication analysis (performed concurrently or sequentially) of *ATM, BRCA1* (81165/81166), *BRCA2* (81216/81167), *BRIP1*, *EPCAM, MLH1* [81292/81294], *MSH2* [81295/81297], *MSH6* [81298/81300], *PALB2* [81307], *PMS2* [81317/81319], *RAD51C* or *RAD51D* genes; **OR**
  - Multigene germline panel sequencing and/or deletion/duplication analysis (performed concurrently or sequentially); **AND**
- Personal history of epithelial ovarian, fallopian tube or peritoneal cancer at any age; **OR**
- Individual without an ovarian cancer diagnosis; **AND**
  - Has a first-, second- or third-degree relative diagnosed with epithelial ovarian, fallopian tube or peritoneal cancer at any age; **OR**

  - Does not otherwise meet the above testing criteria hereditary ovarian, fallopian tube or peritoneal cancer and a risk stratification tool (Tyrer-Cuzick, BRCAPRO, CanRisk) indicates greater than 5% probability for a *BRCA1/2* pathogenic variant; **OR**

- Pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline

Hereditary Pancreatic Cancer

Humana members may be eligible under the Plan for **single gene or multigene germline panel sequencing and deletion/duplication analysis for hereditary pancreatic cancer** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

- No known pathogenic or likely pathogenic variant in the family (if a pathogenic or likely pathogenic variant has been detected in an affected family member, genetic testing should be limited to the known familial variant; see Known Familial Pathogenic or Likely Pathogenic Variant Testing criteria below); **AND**

  - Single gene testing and/or deletion duplication analysis (performed concurrently or sequentially) of *ATM*, *BRCA1* (81165/81166), *BRCA2* (81216/81167)*, CDKN2A, EPCAM, MLH1* [81292/81294]*, MSH2* [81295/81297]*, MSH6* [81298/81300]*, PALB2* [81307]*, PMS2* [81317/81319]*, STK11* or *TP53* [81351] genes; **OR**

  - Multigene germline panel sequencing and/or deletion/duplication analysis (performed concurrently or sequentially); **AND**

- Personal history of exocrine pancreatic cancer at any age; **OR**

- Personal history of neuroendocrine pancreatic tumors (nonfunctioning pancreatic tumors, gastrinoma, insulinoma, glucagonoma, VIPoma) at any age; **OR**

- Has a first- or second-degree relative diagnosed with exocrine pancreatic cancer at any age; **OR**

- Pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline

Hereditary Prostate Cancer

Humana members may be eligible under the Plan for **single gene or multigene germline panel sequencing and deletion/duplication analysis for hereditary prostate cancer** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

- No known pathogenic or likely pathogenic variant in the family (if a pathogenic or likely pathogenic variant has been detected in an affected family member, genetic testing should be limited to the known familial variant; see Known Familial Pathogenic or Likely Pathogenic Variant Testing criteria below); **AND**
    - Single gene testing and/or deletion duplication analysis (performed concurrently or sequentially) of *ATM*, *BRCA1* (81165/81166), *BRCA2* (81216/81167)*, CHEK2* or *HOXB13* genes; **OR**
    - Multigene germline panel sequencing and/or deletion/duplication analysis (performed concurrently or sequentially); **AND**
- Personal history of prostate cancer; **AND**
    - Any of the following features:
        - Metastatic (includes distant metastasis and regional bed or nodes) established by biopsy and/or radiography; **OR**
        - Intermediate-risk with intraductal or cribriform histology; **OR**
        - High-risk or very-high-risk; **OR**
    - At least one first-, second- or third-degree relative with any of the following:
        - Breast cancer diagnosed at or before 50 years of age; **OR**
        - Male breast cancer diagnosed at any age; **OR**
        - Triple-negative breast cancer diagnosed at any age; **OR**
        - Ovarian cancer diagnosed at any age; **OR**
        - Pancreatic cancer diagnosed at any age; **OR**
        - Prostate cancer with any of the following features diagnosed at any age:
            - Metastatic (includes distant metastasis and regional bed or nodes) established by biopsy and/or radiography; **OR**
            - High-risk or very-high-risk; **OR**
    - 3 or more total diagnoses of prostate cancer and/or breast cancer in the family (including the individual diagnosed with prostate cancer and first-, second- or third-degree relatives on the same side of the family); **OR**
    - Ashkenazi Jewish ancestry; **OR**
- Individual with a prostate cancer diagnosis but does not meet the above testing criteria for hereditary prostate cancer and has a first-, second- or third-degree relative who meets above testing criteria for hereditary prostate cancer; **OR**

- Individual without a prostate cancer diagnosis and has a first-, second- or third-degree relative who meets above testing criteria for hereditary prostate cancer; **OR**

- Pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline

Li-Fraumeni Syndrome

Humana members may be eligible under the Plan for ***TP53*** **sequencing and/or deletion/duplication analysis (performed concurrently or sequentially) for LFS** (81351) when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

- Individual to be tested meets classic LFS criteria, as demonstrated by the presence of **ALL** of the following:

  - Diagnosed with a sarcoma before 45 years of age; **AND**

  - First-degree relative diagnosed with cancer before 45 years of age; **AND**

  - An additional first- or second-degree relative, on the same side of the family, diagnosed with cancer before 45 years of age or diagnosed with a sarcoma at any age; **OR**

- Individual to be tested meets Chompret criteria as demonstrated by the presence of at least 1 of the following:

  - Diagnosed with a tumor from LFS tumor spectrum (eg, adrenocortical carcinoma, breast cancer, central nervous system [CNS] tumor, osteosarcoma, soft tissue sarcoma) before 46 years of age, **AND** at least one first- or second-degree relative with any of the previously mentioned cancers (other than breast cancer if the proband has breast cancer) before 56 years of age or with multiple primaries at any age; **OR**

  - Diagnosed with multiple tumors (except multiple breast tumors), 2 of which belong to LFS tumor spectrum (eg, adrenocortical carcinoma, breast cancer, CNS tumor, osteosarcoma, soft tissue sarcoma) with the initial cancer occurring before 46 years of age; **OR**

  - Diagnosed with adrenocortical carcinoma or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype at any age of onset, regardless of the family history; **OR**

  - Diagnosed with breast cancer before 31 years of age

- Personal or family history of pediatric hypodiploid acute lymphoblastic leukemia; **OR**

- Individual diagnosed with a cancer with a pathogenic or likely pathogenic *TP53* variant on tumor-only genomic testing when any of the following are present:
    - Individual meets at least 1 of the above testing criteria for LFS; **OR**
    - Diagnosed before 30 years of age with any cancer; **OR**
    - Individual with a clinical scenario not meeting these criteria but warranting germline evaluation per clinician discretion

PTEN Hamartoma Tumor Syndrome/Cowden Syndrome

Humana members may be eligible under the Plan for ***PTEN* sequencing and/or deletion/duplication analysis (performed concurrently or sequentially) for PHTS/CS** (81321/81323) (eg, Genomic Unity PTEN Analysis [0235U]) when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested does **NOT** meet PHTS Clinical Diagnostic Criteria and has a personal history of any of the following:
    - Adult Lhermitte-Duclos disease (cerebellar tumors); **OR**
    - Autism spectrum disorder and macrocephaly; **OR**
    - 1 major and 3 or more minor PHTS/CS Testing Criteria (If an individual has 2 or more major criteria, such as breast cancer and nonmedullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as 1 of the 3 minor criteria to meet testing criteria); **OR**
    - 2 or more biopsy-proven trichilemmomas; **OR**
    - 2 or more major PHTS/CS Testing Criteria (one must be macrocephaly); **OR**
    - 3 or more major PHTS/CS Testing Criteria without macrocephaly; **OR**
    - 4 or more minor PHTS/CS Testing Criteria; **OR**
- Personal history of Bannayan-Ryile-Ruvalcaba syndrome (BRRS); **OR**
- Individual to be tested meets PHTS Clinical Diagnostic Criteria as demonstrated by:
    - 2 major and 3 minor criteria of the PHTS Clinical Diagnostic Criteria; **OR**
    - 3 major criteria of the PHTS Clinical Diagnostic Criteria (one must include macrocephaly, Lhermitte-Duclos disease or gastrointestinal [GI] hamartomas); **OR**

- Has a first-, second- or third-degree relative with a clinical diagnosis of PHTS, CS or BRRS; **AND**
    - Individual to be tested has the presence of one major criterion of PHTS/CS Testing Criteria; **OR**
    - Individual to be tested has the presence of two minor criteria of PHTS/CS Testing Criteria; **OR**
- PTEN pathogenic or likely pathogenic variant detected by tumor genomic testing on any tumor type

Known Familial Pathogenic or Likely Pathogenic Variant Testing
Humana members may be eligible under the Plan for **known familial pathogenic or likely pathogenic variant testing* for hereditary breast, ovarian, pancreatic or prostate cancer** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested has an affected first-, second- or third-degree relative with a pathogenic or likely pathogenic variant in any of the following:
    - Hereditary breast cancer gene (*BRCA1* [81215]*, BRCA2 [81217], CDH1, PALB2* [81308]*, PTEN* [81322]*, STK11, TP53* [81353]); **OR**
    - Hereditary ovarian cancer gene (*ATM*, *BRCA1* [81215]*, BRCA2 [81217], BRIP1, EPCAM, MLH1* [81293]*, MSH2* [81296]*, MSH6* [81299], *PALB2* [81308]*, PMS2* [81318], *RAD51C, RAD51D*; **OR**
    - Hereditary pancreatic cancer gene (*ATM*, *BRCA1* [81215]*, BRCA2 [81217], CDKN2A, MLH1* [81293]*, MSH2* [81296]*, MSH6* [81299], *PALB2* [81308]*, PMS2* [81318]*, STK11, TP53)*; **OR**
    - Hereditary prostate cancer gene (*ATM*, *BRCA1* [81215]*, BRCA2 [81217], CHEK2, HOXB13*); **OR**
    - LFS gene (*TP53*) (81353); **OR**
    - PTEN hamartoma tumor syndrome/cowden syndrome gene (*PTEN*) (81322)

*****Genetic testing should be limited to the known familial variant (KFV). If the individual to be tested is of Ashkenazi Jewish ancestry, testing may be expanded to the three Ashkenazi Jewish founder specific mutations (*BRCA1 185delAG, BRCA1 5382insC and BRCA2 6174delT*).

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **genetic testing for hereditary breast, ovarian, pancreatic and prostate cancer** for the following:

- Deletion/duplication analysis is obtained as part of the sequencing procedure but submitted as an independent analysis
- Individual to be tested has an affected first-, second- or third-degree relative with a negative genetic testing result for the associated condition
- Individual to be tested is unaffected and an affected first-, second- or third-degree relative who is available for genetic testing
- KFV detection analysis if the individual to be tested previously received KFV testing, single gene analysis or multigene panel testing that would have detected the KFV

These are considered **not medically necessary** as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

Humana members may **NOT** be eligible under the Plan for **genetic testing for breast, ovarian or pancreatic cancer susceptibility** for any indications other than those listed above. This is considered experimental/investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **genetic testing for hereditary breast, ovarian, pancreatic or prostate cancer** for any indications or tests other than those listed above including, but may not be limited to:

- Concurrent (paired) DNA and RNA genetic testing including, but may not be limited to:
    - +RNAinsight for ATM (0136U)
    - +RNAinsight for BRCA1/2 (0138U)
    - +RNAinsight for BreastNext (0131U)
    - +RNAinsight for GynPlus (0135U)
    - +RNAinsight for OvaNext (0132U)
    - +RNAinsight for PALB2 (0137U)
    - +RNAinsight for ProstateNext (0133U)

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
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)	
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	
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	
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	
81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants	
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	
81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence	
81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)	
81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant	
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)	
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, cytogenomic array analysis for neoplasia)	
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	
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis	
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**

96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family	
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)	**Not Covered**
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)	**Not Covered**
0133U	Hereditary prostate cancer-related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)	**Not Covered**
0135U	Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)	**Not Covered**
0136U	ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure)	**Not Covered**
0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)	**Not Covered**
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)	**Not Covered**
0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
S0265	Genetic counseling, under physician supervision, each 15 minutes	

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Appendix

Appendix A
Pre- and Post-Test Genetic Counseling Criteria

Pre- and post-test genetic counseling performed by any of the following qualified medical professionals
Genetic counselor who is board-certified or board-eligible by the American Board of Medical Genetics and Genomics (ABMGG) or American Board of Genetic Counseling, Inc (ABGC) and is not employed by a commercial genetic testing laboratory; **OR**
Genetic clinical nurse (GCN) or advanced practice nurse in genetics (APNG) who is credentialed by the Genetic Nursing Credentialing Commission (GNCC) or the American of Nurses Credentialing Center (ANCC) and is not employed by a commercial genetic testing laboratory; **OR**
Medical geneticist who is board-certified or board-eligible by ABMGG; **OR**
Treating physician who has evaluated the individual to be tested and has completed a family history of three generations

Appendix B
Family Relationships[108]

Degree of Relationship	Relative of the Individual to be Tested
First-degree	Child, full-sibling, parent
Second-degree	Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling
Third-degree	First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle

Appendix C
Initial Risk Stratification and Staging Workup for Clinically Localized Disease[112]

Risk Group	Clinical/Pathologic Features
Very-low	All of the following: • cT1c; **AND** • Grade Group 1; **AND** • PSA less than 10 ng/mL; **AND** • Fewer than three prostate biopsy fragments/cores positive, 50% or less cancer in each fragment/core; **AND** • PSA density less than 0.15 ng/mL/g
Low	All of the following (but does not qualify for very-low-risk): • cT1-cT2a; **AND** • Grade Group 1; **AND** • PSA less than 10 ng/mL

Intermediate	All of the following:
	• No high-risk group features; **AND**
	• No very-high-risk group features; **AND**
	• Has one or more of the following intermediate risk factors:
	  ○ cT2b-cT2c
	  ○ Grade Group 2 or 3
	  ○ PSA 10-20 ng/mL

High	No very-high-risk features and exactly one of the following high-risk features: • cT3a; **OR** • Grade Group 4 or Grade Group 5; **OR** • PSA more than greater than 20 ng/mL
Very-high	At least one of the following: • cT3b-cT4 • Primary Gleason pattern 5 • Two or three high-risk features • More than four cores with Grade Group 4 or 5

Appendix D
American Joint Committee on Cancer (AJCC) TNM Staging System for Prostate Cancer[112]

Primary tumor (T)	
Clinical T (cT)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in 1 or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of 1 side or less
T2b	Tumor involves more than one-half of 1 side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
Pathological T (pT)	
T category	**T criteria**
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Note: There is no pathological T1 classification. Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis

M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.	

Appendix E

AJCC Prognostic Groups[112] (When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available)

Group	T	N	M	PSA (ng/mL)	Grade Group
Stage I	cT1a-c	N0	M0	Less than 10	1
	cT2a	N0	M0	Less than 10	1
	pT2	N0	M0	Less than 10	1
Stage IIA	cT1a-c	N0	M0	At least 10 but less than 20	1
	cT2a	N0	M0	At least 10 but less than 20	1
	pT2	N0	M0	At least 10 but less than 20	1
	cT2b	N0	M0	Less than 20	1
	cT2c	N0	M0	Less than 20	1
Stage IIB	T1-2	N0	M0	Less than 20	2
Stage IIC	T1-2	N0	M0	Less than 20	3
	T1-2	N0	M0	Less than 20	4
Stage IIIA	T1-2	N0	M0	At least 20	1-4
Stage IIIB	T3-4	N0	M0	Any	1-4
Stage IIIC	Any	N0	M0	Any	5
Stage IVA	Any	N1	M0	Any	Any
Stage IVB	Any	Any	M1	Any	Any

Appendix F

Definition of Histologic Grade Group[112] (The Gleason system has recently been compressed into Grade Groups)

Grade Group	Gleason Score	Gleason Pattern
1	Less than or equal to 6	Less than or equal to 3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Appendix G

PHTS Clinical Diagnostic Criteria – Clinical diagnosis of PHTS when 3 major criteria (one must include macrocephaly, Lhermitte-Duclos disease or GI hamartomas) or 2 major plus 3 minor criteria are present[108]:

Major Criteria	Minor Criteria

• Breast cancer
• Endometrial cancer (epithelial)
• Follicular thyroid cancer
• GI hamartomas (including ganglioneuromas but excluding hyperplastic polyps; at least 3)
• Lhermitte-Duclos disease (adult)
• Macrocephaly (at least 97th percentile: 58 cm for females, 60cm for males)
• Macular pigmentation of glans penis
• Multiple mucocutaneous lesions (any of the following):
  ○ Acral keratoses (at least three palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  ○ Mucocutaenous neuromas (at least three)
  ○ Multiple oral papillomas (particularly on tongue and gingiva) (at least 3 OR biopsy proven OR dermatologist diagnosed)
• Multiple trichilemmomas (at least three and at least one biopsy proven)
	• Autism spectrum disorder
	• Colon cancer
	• Esophageal glycogenic acanthoses (at least three)
	• Intellectual disability (IQ less than or equal to 75)
	• Lipomas (at least 3)
	• Renal cell carcinoma
	• Testicular lipomatosis
	• Thyroid cancer (papillary or follicular variant of papillary)
	• Thyroid structural lesions (eg, adenoma, multinodular goiter)
	• Vascular anomalies (including multiple intracranial developmental venous anomalies)

Appendix H
PHTS/CS Testing Criteria[108]

Major Criteria	Minor Criteria
• Breast cancer • Endometrial cancer • Follicular thyroid cancer	• Autism spectrum disorder • Colon cancer • Esophageal glycogenic acanthosis (at least 3)

• Macrocephaly (megalocephaly) (at least 97th percentile: 58cm in adult women, 60cm in adult men)
• Macular pigmentation of glans penis
• Mucocutaneous lesions
  ○ One biopsy proven trichilemmoma
  ○ Multifocal or extensive oral mucosal papillomatosis
  ○ Multiple cutaneous facial papules (often verrucous)
  ○ Multiple palmoplantar keratosis
• Multiple GI hamartomas or ganglioneuromas
	• Intellectual disability (IQ less than or equal to 75)
	• Lipomas
	• Papillary or follicular variant of papillary thyroid cancer
	• Renal cell carcinoma
	• Single GI hamartoma or ganglioneuroma
	• Testicular lipomatosis
	• Thyroid structural lesions (eg, adenoma, nodule[s], goiter)
	• Vascular anomalies (including multiple intracranial developmental venous anomalies)

Change Summary

04/25/2024 Annual Review, Coverage Change. Provider Claims Codes Update