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| Department of Origin: Integrated Healthcare Services | Effective Date: 06/05/24 |
| Approved by: Medical Policy Quality Management Subcommittee | Date Approved: 06/04/24 |
| Clinical Policy Document Genetic Testing, Hereditary Cancer Syndromes | Replaces Effective Clinical Policy Dated: 01/30/24 |
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PURPOSE:

The intent of this clinical policy is to ensure services are medically necessary.

Please refer to the member's benefit document for specific information. To the extent there is any inconsistency between this policy and the terms of the member's benefit plan or certificate of coverage, the terms of the member's benefit plan document will govern.

POLICY:

Benefits must be available for health care services. Health care services must be ordered by a provider. Licensed Genetic Counselors may also order genetic tests if it is within the scope of practice of their state licensure. Health care services must be medically necessary, applicable conservative treatments must have been tried, and the most cost-effective alternative must be requested for coverage consideration.

GUIDELINES:

Medical Necessity Criteria - Must satisfy the following: I and II, and either III or IV

- I. Requests for genetic testing - must satisfy the following: A, and either B or C
 - A. A genetic counselor, medical geneticist, or other *health care professional trained in genetics*, independent of the laboratory performing the testing, has reviewed and documented family history, advised the member of the potential harms/benefits of the testing and implications of the test results, and obtained written informed consent; and
 - B. Member is at direct risk of inheriting the mutation in question (presymptomatic), eg, based on family history; or
 - C. Member displays clinical features of a specific inheritable cancer/cancer syndrome (symptomatic).
- II. Characteristics of covered tests
 - A. Each test has been approved for its intended use by the appropriate *regulatory/oversight* body (implies *analytic validity*).
 - B. Each test has sufficient sensitivity or specificity (*clinical validity*) for targeting the member's specific clinical condition.
 - C. The results of each test will directly impact clinical decision-making and clinical care (*clinical utility*) for the individual – must satisfy any of the following: 1 - 3
 - 1. Guiding surveillance for complications (eg, increase in frequency of colonoscopies for members with hereditary non-polyposis colorectal cancer [HNPCC] gene mutation.)
 - 2. Employing direct risk reduction strategies (eg, prophylactic or bilateral mastectomy and/or oophorectomy for breast cancer [BRCA] gene mutation).
 - 3. Determining avenues of medical therapy (eg, choosing anti-neoplastic therapy).
- III. Single gene testing is medically necessary for any of the following: A - C

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- A. Members with a personal or family history of cancer (See Attachment A); or
 - B. Members displays features of a cancer/cancer syndrome (See Attachment A); or
 - C. Members with a known familial mutation (See Attachment A).
- IV. Hereditary cancer panels (eg, 81432, 81433, 81435, 81436, 0129U, 0238U) – must satisfy any of the following: A – C
(See Attachment A)
- A. Requests for a *Multi-Gene Hereditary Cancer panel* or BRCA1/BRCA2 testing in members with a personal history of a primary solid tumor cancer (excluding basal or squamous cell carcinoma) – must satisfy all of the following: 1 and 2
 - 1. The suspected hereditary cancer syndrome(s) can be diagnosed by testing two or more genes included in the specific hereditary cancer panel; and
 - 2. The member has a personal history of one of the following:
 - a. Breast cancer diagnosed at age 50 or younger; or
 - b. Metastatic breast cancer; or
 - c. Multiple primary breast cancers (prior diagnosis or bilateral cancer); or
 - d. Triple-negative breast cancer diagnosed at any age; or
 - e. Lobular breast cancer with personal or family history of diffuse gastric cancer
 - f. Breast cancer and Ashkenazi Jewish ancestry; or
 - g. Assigned male at birth with a personal history of breast cancer; or
 - h. Breast cancer and an unknown or limited family history; or
 - i. Breast cancer and at least one first- or second-degree relative with a *BRCA-Related Cancer*; or
 - j. Ovarian cancer, fallopian tube cancer, and/or primary peritoneal cancer; or
 - k. Pancreatic cancer; or
 - l. Metastatic prostate cancer;
 - m. Cancer associated with *Lynch Syndrome*; or
 - n. Paraganglioma or pheochromocytoma; or
 - o. At least two different primary solid tumor cancers (excluding basal or squamous cell carcinoma); or
 - p. At least one primary solid tumor cancer (excluding basal or squamous cell carcinoma) and a family history of one of the following: 1) – 3)
 - 1) At least one *close blood relative* with a cancer associated with *Lynch Syndrome*; or
 - 2) At least one *close blood relative* diagnosed with a primary solid tumor (excluding basal or squamous cell carcinoma) at age 40 or younger; or
 - 3) At least two *close blood relatives* (in addition to affected individual) on the same side of the family diagnosed with any primary solid tumor cancer (excluding basal or squamous cell carcinoma); or
 - q. At least one primary solid tumor cancer (excluding basal or squamous cell carcinoma) and one of the following: 1) – 4)
 - 1) A BRCA 1/2 pathogenic mutation detected in tumor tissue; or
 - 2) Tumor testing results demonstrate that the cancer was MSI-high or had immunohistochemical staining showing the absence of one or more mismatch repair proteins (MLH1, MSH2, MSH6 or PMS2); or
 - 3) Tyrer-Cuzick, BRCAPro or Penn11 Score of 2.5% or greater for a BRCA1/2 pathogenic variant; or

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- 4) The member has a PREMM5, MMRpro or MMRpredict Score of 2.5% or greater for having a *Lynch Syndrome* gene mutation.
- B. Requests for a *Multi-Gene Hereditary Cancer panel* or BRCA1/BRCA2 testing in members without a personal history of a primary solid tumor cancer (excluding basal or squamous cell carcinoma) – must satisfy: 1, and any of 2 or 3
1. The suspected hereditary cancer syndrome(s) can be diagnosed by testing two or more genes included in the specific hereditary cancer panel; and
 2. The member has a personal history of any of the following: a – c
 - a. Colorectal polyposis with at least ten adenomas; or
 - b. A Tyrer-Cuzick, BRCAPro or Penn11 Score of 5% or greater for a BRCA1/2 pathogenic variant; or
 - c. A PREMM5, MMRpro or MMRpredict Score of 5% or greater for having a *Lynch Syndrome* gene mutation.
 3. The member has a family history of any of the following: a – l
 - a. At least one *first-degree relative* diagnosed with at least two different primary solid tumor cancers (excluding basal or squamous cell carcinoma); or
 - b. At least one *first-degree relative* with a cancer associated with *Lynch Syndrome*; or
 - c. At least one *first-degree relative* with paraganglioma or pheochromocytoma; or
 - d. At least one *first- or second-degree relative* with breast cancer diagnosed at age 50 or younger; or
 - e. At least one *first- or second-degree relative* with metastatic prostate cancer; or
 - f. At least one *first- or second-degree relative* with ovarian cancer, fallopian tube cancer, and/or primary peritoneal cancer; or
 - g. At least one *first- or second-degree relative* with pancreatic cancer; or
 - h. At least one *second-degree relative* with at least two cancers associated with *Lynch Syndrome*; or
 - i. At least one *second-degree relative* with a cancer associated with *Lynch Syndrome* diagnosed at age 50 or younger; or
 - j. At least two or more *second-degree relatives* on the same side of the family with a cancer associated with *Lynch Syndrome*; or
 - k. At least three *close blood relatives*, on the same side of the family, diagnosed with any primary solid tumor cancer (excluding basal or squamous cell carcinoma); or
 - l. Ashkenazi Jewish ancestry and at least one *close blood relative* with a BRCA-related cancer.
- C. Requests for a *Multi-Gene Hereditary Cancer panel* is medically necessary in members diagnosed with cancer at age 18 or younger.

EXCLUSIONS (not limited to):

Refer to member’s Certificate of Coverage or Summary Plan Description.

The following is Investigative (see Investigative List)

- Genetic testing (DNA, mRNA [analytics], RNA) by any method (eg, NGS [next-generation sequencing], Sanger sequencing, MLPA [multiplex ligation-dependent probe amplification], array CGH [comparative genomic hybridization]) for detection of variants of unknown significance in

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hereditary cancer. Such as, but not limited to, +RNA Insight™ and CustomNext + RNA

DEFINITIONS:

BRCA-Related Cancer:

Breast cancer, ovarian cancer, pancreatic cancer or metastatic or high-risk (Gleason score greater than or equal to 7) prostate cancer

Close blood relative/close relative:

First-, second-, or third-degree blood relative from the same side of the family.

First-degree relative:

A blood relative who shares approximately 50% of the individual's genes (parents, full siblings, and children).

Health care professionals trained in genetics:

A genetics professional has experience and an educational background in genetics, counseling, and hereditary syndromes to provide accurate risk assessment and empathetic genetic counseling to patients and their families. Genetics professionals include people certified in any of the following ways:

- American Board of Genetic Counseling (ABGC) or American Board of Medical Genetics and Genomics (ABMGG) board certified/board eligible³² or a licensed genetic counselor
- Advanced Genetics Nursing Certification (AGN-BC)³²
- Advanced Clinical Genomics Nurse (ACGN) credential³²
- Clinical Genomics Nurse (CGN) certification³²
- Cancer Genetic Risk Assessment (CGRA) certification³²
- Advanced practice oncology nurse or physician assistant with specialized education in cancer genetics and hereditary cancer predisposition syndromes. The Advanced Oncology Certified Nurse Practitioner (AOCNP) credentials, or equivalent certification from the Oncology Nursing Certification Corporation (ONCC) is preferred.³²
- Board-certified/board-eligible physician with experience in cancer genetics (defined as education resulting in a certification and undergoing ongoing continuing medical education in cancer genetics and hereditary cancer predisposition syndromes)³²
- A registered nurse with specialized education in cancer genetics and hereditary cancer predisposition syndromes (defined as education resulting in a certification and undergoing ongoing continuing medical education in cancer genetics and hereditary cancer predisposition syndromes)³²
- Board-certified specialty care physician with experience in the diagnosis and treatment of the hereditary condition, eg, cardiologist ordering genetic testing for hypertrophic cardiomyopathy

High-penetrance Breast Cancer Susceptibility Genes:

Genes in which certain mutations are related to significantly increased likelihood of breast cancer. NCCN includes BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, and TP53.

High-penetrance Lynch Syndrome Susceptibility Genes:

Genes in which certain mutations are related to significantly increased likelihood of Lynch Syndrome. NCCN includes EPCAM, MLH1, MSH2, MH6/MSH6, and PMS2.

Li-Fraumeni Syndrome:

A rare cancer predisposition hereditary disorder characterized as autosomal dominant. It is also known as the sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome. The syndrome is linked to germline

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mutations of the P53 suppressor gene which encodes a transcription factor (p53) that normally regulates the cell cycle and prevents genomic mutations. The mutations can be inherited, or can arise from de novo mutations early in embryogenesis, or in one of the parent's germ cells.

Lynch Syndrome-related cancers:

Colorectal, endometrial, gastric, ovarian, pancreatic, urothelial (ureter and renal pelvis), brain [usually glioblastoma], biliary tract, small intestinal cancers, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome. The increased risk for these cancers is due to inherited mutations that impair DNA mismatch repair. Also known as hereditary nonpolyposis colorectal cancer (HNPCC).

Multi-Gene Panel:

Genetic tests that use next-generation sequencing to test multiple genes simultaneously. Also called multigene test, Multiple-Gene Panel test and multiple-gene test.

Multi-Gene Panel Types:

| TERM | DEFINITION |
|-----------------------------------|---|
| Multi-gene panel | Laboratory test that includes testing for mutations of more than one gene |
| Syndrome-specific test* | Panel that only tests for one syndrome (eg, Lynch syndrome, polyposis) |
| Cancer-specific panel* | Panel that tests for more than one gene associated with a specific type of cancer |
| "Comprehensive" cancer panel | Panel that tests for more than one gene associated with multiple cancers or multiple cancer syndromes |
| Actionable pathogenic variant | Mutation that results in a recommendation for a change in clinical management |
| Variant of uncertain significance | Genetic test result indicating a sequence variant in a gene that is of uncertain significance. Variants are generally not clinically actionable, and most (but not all) are ultimately reclassified as benign |

Retrieved from National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. GENE-2. Version 2.2022 12/07/22. Accessed 05-04-23. *See Attachment A

Regulatory/oversight body:

Such as, but not limited to, Clinical Laboratory Improvement Amendments (CLIA), Food and Drug Administration (FDA) or The Joint Commission

Second-degree relative:

A blood relative who shares approximately 25% of the individual's genes (grandparents, grandchildren, aunts, uncles, nephews, nieces, and half siblings).

Third-degree relative:

A blood relative who shares approximately 12.5% of the individual's genes (great-grandparents, great-aunts, great-uncles, great-grandchildren, and first-cousins).

Prior Authorization: Yes, per network provider agreement.

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CODING:

CPT® or HCPCS

81162 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)

81163 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81164 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

81165 BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81166 BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

81167 BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

81201 APC (adenomatous polyposis coli) (eg, familial adenomatous polyposis [FAP], attenuated FAP) gene analysis; full gene sequence

81202 APC (adenomatous polyposis coli) (eg, familial adenomatous polyposis [FAP], attenuated FAP) gene analysis; known familial variants

81203 APC (adenomatous polyposis coli) (eg, familial adenomatous polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants

81212 BRCA 1, BRCA 2 gene analysis; 185delAG, 5385insC, 6174delT variants

81215 BRCA 1 gene analysis; known familial variant

81216 BRCA 2 gene analysis; full sequence analysis

81217 BRCA 2 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

81300 MSH6 (mutS homolog 6 [E.coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion 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

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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

81401 Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using non-sequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)

81403 Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis

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 > exons in a single gene by DNA sequence analysis (when used for ATM [ataxia telangiectasia mutated] [eg, ataxia telangiectasia], full gene sequence)

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 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, 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 analysis for BRCA1, BRCA2, MLH1, MSH2, and STK11

81435 Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11

81436 Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, MSH6, EPCAM, SMAD4, and STK11

81437 Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL

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81438 Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL

0129U Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53) - BRCAplus (Ambry Genetics)

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

0238U Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions

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REFERENCES:

1. Medical Management Process Manual: UR015 Use of Medical Policy and Criteria
2. Clinical Policy: Coverage Determination Guidelines MP/C009
3. Clinical Policy Genetic Testing, Inheritable and Somatic Conditions MP/G001
4. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Hereditary Cancer Testing Criteria. Testing Criteria for High-Penetrance Breast and Ovarian Cancer Susceptibility Genes. CRIT-1, CRIT-2, CRIT-3, CRIT4. Version 3.2024, 02/12/24. Accessed 05-01-24.
5. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Hereditary Cancer Testing Criteria. Testing Criteria for Pancreatic Cancer Susceptibility Genes. CRIT-5. Version 3.2024, 02/12/24. Accessed 05-01-24.
6. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Cancer Risk Management Based on Genetic Test Results. GENE-A. Version 3.2024, 02/12/24. Accessed 05-01-24.
7. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Hereditary Cancer Testing Criteria. Testing Criteria for Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS). CRIT-8. Version 3.2024, 02/12/24. Accessed 05-01-24.
8. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Hereditary Cancer Testing Criteria. Testing Criteria for Li-Fraumeni Syndrome. CRIT-7. Version 3.2024, 02/12/24. Accessed 05-01-24.
9. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Criteria for the Evaluation of Lynch Syndrome. LS-1. Version 2.2023, 10/30/23. Accessed 05-01-24.
11. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Adenomatous Polyposis Testing Criteria. POLYP-1. Version 2.2023, 10/30/23. Accessed 05-01-24.
12. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Familial Adenomatous polyposis/AFAP. FAP/AFAP-1. Version 2.2023, 10/30/23. Accessed 05-01-24.
13. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Serrated Polyposis Syndrome. SPS-1. Version 2.2023, 10/30/23. Accessed 05-01-24.

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14. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Peutz-Jeghers Syndrome. PJS-1. Version 2.2023, 10/30/23. Accessed 05-01-24.
15. 14. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Juvenile Polyposis Syndrome. JPS-1. Version 2.2023, 10/30/23. Accessed 05-01-24.
16. National Comprehensive Cancer Network (NCCN) Guidelines. Gastric Cancer. Principles of Genetic Risk Assessment for Gastric Cancer. GAST-D 1 – 8. Version 1.2024, 03/07/24. Accessed 05-13-24.
16. National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. GENE 1- GENE 19. Version 2.2023, 10/30/23. Accessed 05-01-24.
17. Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. *JAMA* 2018;320:1266-1274.
18. Slavin T, Van Tongeren L, Behrendt C, et al. Prospective study of cancer genetic variants: Variation in rate of reclassification by ancestry. *J Natl Cancer Inst.* 2018;110(10):1059-1066.
19. American College of Obstetricians and Gynecologists (ACOG). Committee Opinion No. 793. Hereditary cancer syndromes and risk assessment. *Obstet Gynecol.* 2019 Dec;134(6): e143-e149. Reaffirmed 2020.
20. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No 182. Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol.* 2017 Sep;130(3): e110-e126. Reaffirmed 2021.
21. American College of Obstetricians and Gynecologists (ACOG). Committee Opinion No. 716: The role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer in women at average risk. *Obstet Gynecol.* 2017 Sep;130(3):e146-e149. Reaffirmed 2021.
22. American Society of Breast Surgeons (ASBrS). Consensus guideline on genetic testing for hereditary breast cancer. Published February 10, 2019. Available at: <https://www.breastsurgeons.org/resources/statements>
23. American Society of Clinical Oncology (ASCO) website. Genetics toolkit. Last reviewed: January 2021. Available at: <https://old-prod.asco.org/news-initiatives/current-initiatives/cancer-care-initiatives/genetics-toolkit>.
24. Hassett MJ, Somerfield MR, Baker ER, et al. Management of male breast cancer: ASCO guideline. *J Clin Oncol.* 2020 Jun 1;38(16):1849-1863.
25. Karam R, Conner B, LaDuca H, et al. Assessment of diagnostic outcomes of RNA genetic testing for hereditary cancer. *JAMA Netw Open.* 2019 Oct 2;2(10): e1913900.
26. LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet Med.* 2020 Feb;22(2):407- 415.
27. Landrith T, Li B, Cass AA, et al. Splicing profile by capture RNA-seq identifies pathogenic germline variants in tumor suppressor genes. *NPJ Precis Oncol.* 2020 Feb 24; 4:4.
28. Lee K, Seifert BA, Shimelis H, et al. Clinical validity assessment of genes frequently tested on hereditary breast and ovarian cancer susceptibility sequencing panels. *Genet Med.* 2019 Jul;21(7):1497-1506.
29. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Neuroendocrine and Adrenal Tumors. Version 1.2023, 08/02/23. Accessed 05-13-24.
30. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. Version 2.2024, 04/30/24. Accessed 05-13-24.
31. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 3.2024, 03/08/24. Accessed 05-13-24.
32. American College of Surgeons. Commission on Cancer. Optimal Resources for Cancer Care. 2020 Standards. Updated February 2024. Personnel and Services Resources. Chapter 4.4: Genetic Counseling and Risk Assessment. Retrieved from <https://www.facs.org/quality-programs/cancer-programs/commission-on-cancer/standards-and-resources/2020/>. Accessed 05-01-24.

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| Clinical Policy Document Genetic Testing, Hereditary Cancer Syndromes | Replaces Effective Clinical Policy Dated: 01/30/24 |
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Attachment A

| Genes with Strong or Very Strong Evidence for Increased Risk (well-established) of Inherited Cancer/Cancer Syndrome | Breast and Epithelial Ovarian Cancer Syndrome Genes ⁶ | | Colorectal Cancer/Cancer Syndromes Genes ¹⁶ | Gastric Cancer Gene ¹⁵ | Melanoma Cancer Gene ⁶ | Pancreatic Cancer Genes ⁶ |
|---|--|--------------------|--|-----------------------------------|-----------------------------------|--------------------------------------|
| | Breast | Epithelial Ovarian | Cowden Syndrome Adenomatous Polyposis Juvenile Polyposis Lynch Syndrome MUTYH-Associated Polyposis PTEN Hamartoma Syndrome Peutz-Jeghers Syndrome Serrated Polyposis Syndrome | Gastric | Melanoma | Pancreatic |
| APC | | | • | | | |
| ATM | • | • | | | | • |
| BARD1 | • | | | | | |
| BMPR1A | | | • | • | | |
| BRCA1 | • | • | | | | • |
| BRCA2 | • | • | | | | • |
| BRIP1 | | • | | | | |
| CDH1 | • | | | • | | |
| CDKN2A | | | | | • | • |
| CHEK2 | • | | | | | |
| EPCAM | | • | • | | | • |
| MLH1 | | • | • | | | • |
| MSH2 | | • | • | | | • |
| MH6/MSH6 | | • | • | | | • |
| MUTYH | | | • | | | |
| NF1 | • | | | | | |
| PALB2 | • | • | | | | |
| PMS2 | | | • | | | |
| PTEN | • | | • | | | |
| RAD51C | • | • | | | | |
| RAD51D | • | • | | | | |
| SMAD4 | | | • | | | |
| STK11 | • | Non-Epithelial | • | | | • |
| TP53 | • | | • | | | |

Sources:

*National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. GENE-1-19. Version 2.2023, 10/30/23. Accessed 05-01-24.

*National Comprehensive Cancer Network (NCCN) Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. GENE-A 1-11. Version 3.2024, 02/12/24. Accessed 05-01-24.

*National Comprehensive Cancer Network (NCCN) Guidelines. Gastric Cancer. GAST-D 1-8, GENE-5. Version 1.2024, 03/07/24. Accessed 05-13-24.

Nondiscrimination & Language Access Policy

Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, sex, sexual orientation, or gender identity. *We* do not exclude people or treat them differently because of race, color, national origin, age, disability, sex, sexual orientation, or gender identity.

We will:

Provide free aids and services to people with disabilities to communicate effectively with us, such as:

- Qualified sign language interpreters
- Written information in other formats (large print, audio, accessible electronic formats, other formats)

Provide free language services to people whose primary language is not English, such as:

- Qualified interpreters
- Information written in other languages

If *you* need these services, contact *us* at the phone number shown on the inside cover of this *contract*, *your* id card, or aspirushealthplan.com.

If *you* believe that *we* have failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, sex, sexual orientation, or gender identity, *you* can file a grievance with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1062
Minneapolis, MN 55440
Phone: 1.866.631.5404 (TTY: 711)
Fax: 763.847.4010
Email: customerservice@aspirushealthplan.com

You can file a grievance in person or by mail, fax, or email. If *you* need help filing a grievance, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë. Telefononi në 1.866.631.5404 (TTY: 711).

Arabic: تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف 1.866.631.5404 (رقم هاتف الصم والبك : 711)

French: ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelezle 1.866.631.5404 (ATS : 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 1.866.631.5404 (TTY: 711).

Hindi: _यान द_ : य_द आप िहंदी बोलते ह_ तो आपके िलए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_। 1.866.631.5404 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1.866.631.5404 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 1.866.631.5404 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 1.866.631.5404 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 1.866.631.5404 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1.866.631.5404 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1.866.631.5404 (TTY: 711)

Traditional Chinese: 注意: 如果您使用繁體中文, 您可以免費獲得語言援助服務。請致電 1.866.631.5404 (TTY:711)。

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1.866.631.5404 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzsch, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1.866.631.5404 (TTY: 711).

Lao: ໄປ່ດຊາຍ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັຽຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທ 1.866.631.5404 (TTY:711).