

MEDICAL POLICY

POLICY TITLE	USE OF COMMON GENETIC VARIANTS (SINGLE NUCLEOTIDE POLYMORPHISMS) TO PREDICT RISK OF NON-FAMILIAL BREAST CANCER
POLICY NUMBER	MP 2.249

CLINICAL BENEFIT	☒ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

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I. POLICY

Testing for one or more single nucleotide variants to predict an individual's risk of breast cancer is considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The GeneType[®] breast cancer risk test is considered **investigational** for all indications, including but not limited to use as a method of estimating individual patient risk for developing breast cancer as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing nomenclature for medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
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Mutation	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in DNA sequence
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association of Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-Reference:

MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

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III. DESCRIPTION/BACKGROUND

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GENE VARIANTS AND BREAST CANCER RISK

Rare, single-gene variants conferring a high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are variants in *BRCA1* and *BRCA2*. These, and a few others, account for less than 25% of inherited breast cancer. Moderate risk alleles, such as variants in the *CHEK2* gene, are also relatively rare and apparently explain very little of the genetic risk.

In contrast, several common single nucleotide variants (SNVs) associated with breast cancer have been identified primarily through genome-wide association studies of very large case-control populations. These alleles occur with high frequency in the general population, and the increased breast cancer risk associated with each is very small relative to the general population risk. Some have suggested that these common-risk SNVs could be combined for individualized risk prediction either alone or in combination with traditional predictors; personalized breast cancer screening programs could then vary by starting age and intensity according to risk. Along these lines, the American Cancer Society recommend that women at high risk (>20% lifetime risk) should undergo breast magnetic resonance imaging and a mammogram every year, and those at moderately increased risk (15%-20% lifetime risk) should talk with their doctors about the benefits and limitations of adding magnetic resonance imaging screening to their yearly mammogram.

Gene Type for Breast Cancer

GeneType for Breast Cancer (and the previous versions of the test, BREVAGenplus® and BREVAGen®) evaluates breast cancer-associated single nucleotide variants (SNVs) identified in genome-wide association studies. The first-generation test, BREVAGen, included 7 SNVs. Currently, GeneType includes over 70 SNVs. Risk is calculated by combining individual SNV risks with other risk factors. GeneType has been evaluated for use in African American, Caucasian, and Hispanic patient samples, age 35 years and older, who do not have a history of in situ or invasive breast cancer and are not carriers of a known pathogenic variant or rearrangement in a breast cancer susceptibility gene.

Health Disparities in Breast Cancer

Based on data from 2014 through 2018, age-adjusted breast cancer mortality is approximately 40% higher among Black women compared to non-Hispanic White women in the United States (27.7 vs 20.0 deaths per 100,000 women), despite a lower overall incidence of breast cancer among Black women (125.8 vs 139.2 cases per 100,000 women). Experts postulate that this divergence in mortality may be related to access issues - Black women are more likely than White women to lack health insurance, limiting access to screening and appropriate therapies. Socioeconomic status is also a driver in health and health outcome disparities related to breast cancer. Women with low incomes have significantly lower rates of breast cancer screening, a higher probability of late-stage diagnosis, and are less likely to receive high-quality care, resulting in higher mortality from breast cancer.

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REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). GeneType for Breast Cancer (Genetic Technologies) is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Summary of Evidence

For individuals who are asymptomatic and at average risk of breast cancer by clinical criteria who receive testing for common SNVs associated with a small increase in the risk of breast cancer, the evidence includes observational studies. Relevant outcomes are test validity, morbid events, and quality of life. Clinical genetic tests may improve the predictive accuracy of current clinical risk predictors. However, the magnitude of improvement is small, and clinical significance is uncertain. Whether the potential harms of these tests due to false-negative and false-positive results are outweighed by the potential benefit associated with improved risk assessment is unknown. Evaluation of this technology is further complicated by the rapidly increasing numbers of SNVs associated with a small risk of breast cancer. Long-term prospective studies with large sample sizes are needed to determine the clinical validity and utility of SNV-based models for predicting breast cancer risk. The discriminatory ability offered by the genetic factors currently known is insufficient to inform clinical practice. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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N/A

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered for Non-BRCA Breast Cancer Risk Assessment GeneType® as outlined in the policy statement.

Procedure Codes									
81599									

VIII. REFERENCES

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1. Jatoi I, Sung H, Jemal A. The Emergence of the Racial Disparity in U.S. Breast-Cancer Mortality. *N Engl J Med.* Jun 23, 2022; 386(25): 2349-2352. PMID 35713541
2. Yedjou CG, Sims JN, Miele L, et al. Health and Racial Disparity in Breast Cancer. *Adv Exp Med Biol.* 2019; 1152: 31-49. PMID 31456178
3. Elicity. Breast Cancer Risk Assessment Test Kit. 2022;
4. Genetic Technologies. GeneType for Breast Cancer. 2022;
5. American Cancer Society. Breast cancer: early detection, diagnosis, and staging topics - Can breast cancer be found early? 2022
6. Stacey SN, Manolescu A, Sulem P, et al. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet.* Jul 2007; 39(7): 865-9. PMID 17529974
7. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature.* Jun 28, 2007; 447(7148): 1087-93. PMID 17529967
8. Hunter DJ, Kraft P, Jacobs KB, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet.* Jul 2007; 39(7): 870-4. PMID 17529973
9. Thomas G, Jacobs KB, Kraft P, et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). *Nat Genet.* May 2009; 41(5): 579-84. PMID 19330030
10. Stacey SN, Manolescu A, Sulem P, et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet.* Jun 2008; 40(6): 703-6. PMID 18438407
11. Gold B, Kirchhoff T, Stefanov S, et al. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33. *Proc Natl Acad Sci U S A.* Mar 18, 2008; 105(11): 4340-5. PMID 18326623
12. Ahmed S, Thomas G, Ghousaini M, et al. Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. *Nat Genet.* May 2009; 41(5): 585-90. PMID 19330027

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13. Zheng W, Long J, Gao YT, et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. *Nat Genet.* Mar 2009; 41(3): 324-8. PMID 19219042
14. Garcia-Closas M, Hall P, Nevanlinna H, et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. *PLoS Genet.* Apr 25, 2008; 4(4): e1000054. PMID 18437204
15. Beeghly-Fadiel A, Shu XO, Lu W, et al. Genetic variation in VEGF family genes and breast cancer risk: a report from the Shanghai Breast Cancer Genetics Study. *Cancer Epidemiol Biomarkers Prev.* Jan 2011; 20(1): 33-41. PMID 21119072
16. Cai Q, Wen W, Qu S, et al. Replication and functional genomic analyses of the breast cancer susceptibility locus at 6q25.1 generalize its importance in women of chinese, Japanese, and European ancestry. *Cancer Res.* Feb 15, 2011; 71(4): 1344-55. PMID 21303983
17. Han W, Woo JH, Yu JH, et al. Common genetic variants associated with breast cancer in Korean women and differential susceptibility according to intrinsic subtype. *Cancer Epidemiol Biomarkers Prev.* May 2011; 20(5): 793-8. PMID 21415360
18. Jiang Y, Han J, Liu J, et al. Risk of genome-wide association study newly identified genetic variants for breast cancer in Chinese women of Heilongjiang Province. *Breast Cancer Res Treat.* Jul 2011; 128(1): 251-7. PMID 21197568
19. Mong FY, Kuo YL, Liu CW, et al. Association of gene polymorphisms in prolactin and its receptor with breast cancer risk in Taiwanese women. *Mol Biol Rep.* Oct 2011; 38(7): 4629-36. PMID 21125332
20. Mukherjee N, Bhattacharya N, Sinha S, et al. Association of APC and MCC polymorphisms with increased breast cancer risk in an Indian population. *Int J Biol Markers.* Jan-Mar 2011; 26(1): 43-9. PMID 21279955
21. Ota I, Sakurai A, Toyoda Y, et al. Association between breast cancer risk and the wild-type allele of human ABC transporter ABCC11. *Anticancer Res.* Dec 2010; 30(12): 5189-94. PMID 21187511
22. Ren J, Wu X, He W, et al. Lysyl oxidase 473 G A polymorphism and breast cancer susceptibility in Chinese Han population. *DNA Cell Biol.* Feb 2011; 30(2): 111-6. PMID 20929399
23. Yu JC, Hsiung CN, Hsu HM, et al. Genetic variation in the genome-wide predicted estrogen response element-related sequences is associated with breast cancer development. *Breast Cancer Res.* Jan 31, 2011; 13(1): R13. PMID 21281495
24. Ma H, Li H, Jin G, et al. Genetic variants at 14q24.1 and breast cancer susceptibility: a fine-mapping study in Chinese women. *DNA Cell Biol.* Jun 2012; 31(6): 1114-20. PMID 22313133
25. Dai J, Hu Z, Jiang Y, et al. Breast cancer risk assessment with five independent genetic variants and two risk factors in Chinese women. *Breast Cancer Res.* Jan 23, 2012; 14(1): R17. PMID 22269215
26. Long J, Cai Q, Sung H, et al. Genome-wide association study in east Asians identifies novel susceptibility loci for breast cancer. *PLoS Genet.* 2012; 8(2): e1002532. PMID 22383897

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27. Huo D, Zheng Y, Ogundiran TO, et al. Evaluation of 19 susceptibility loci of breast cancer in women of African ancestry. *Carcinogenesis*. Apr 2012; 33(4): 835-40. PMID 22357627
28. McCarthy AM, Armstrong K, Handorf E, et al. Incremental impact of breast cancer SNP panel on risk classification in a screening population of white and African American women. *Breast Cancer Res Treat*. Apr 2013; 138(3): 889-98. PMID 23474973
29. Shu X, Long J, Cai Q, et al. Identification of novel breast cancer susceptibility loci in meta-analyses conducted among Asian and European descendants. *Nat Commun*. Mar 05, 2020; 11(1): 1217. PMID 32139696
30. Schoeps A, Rudolph A, Seibold P, et al. Identification of new genetic susceptibility loci for breast cancer through consideration of gene-environment interactions. *Genet Epidemiol*. Jan 2014; 38(1): 84-93. PMID 24248812
31. Nickels S, Truong T, Hein R, et al. Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. *PLoS Genet*. 2013; 9(3): e1003284. PMID 23544014
32. Pei J, Li F, Wang B. Single nucleotide polymorphism 6q25.1 rs2046210 and increased risk of breast cancer. *Tumour Biol*. Dec 2013; 34(6): 4073-9. PMID 23888322
33. Wu X, Xu QQ, Guo L, et al. Quantitative assessment of the association between rs2046210 at 6q25.1 and breast cancer risk. *PLoS One*. 2013; 8(6): e65206. PMID 23785413
34. Liu JJ, Liu JL, Zhang X, et al. A meta-analysis of the association of glutathione S-transferase P1 gene polymorphism with the susceptibility of breast cancer. *Mol Biol Rep*. Apr 2013; 40(4): 3203-12. PMID 23334471
35. Zheng W, Zhang B, Cai Q, et al. Common genetic determinants of breast-cancer risk in East Asian women: a collaborative study of 23 637 breast cancer cases and 25 579 controls. *Hum Mol Genet*. Jun 15, 2013; 22(12): 2539-50. PMID 23535825
36. Yao S, Graham K, Shen J, et al. Genetic variants in microRNAs and breast cancer risk in African American and European American women. *Breast Cancer Res Treat*. Oct 2013; 141(3): 447-59. PMID 24062209
37. Zhou ZC, Wang J, Cai ZH, et al. Association between vitamin D receptor gene Cdx2 polymorphism and breast cancer susceptibility. *Tumour Biol*. Dec 2013; 34(6): 3437-41. PMID 23821301
38. Chen QH, Wang QB, Zhang B. Ethnicity modifies the association between functional microRNA polymorphisms and breast cancer risk: a HuGE meta-analysis. *Tumour Biol*. Jan 2014; 35(1): 529-43. PMID 23982873
39. Xu Q, He CY, Liu JW, et al. Pre-miR-27a rs895819A/G polymorphisms in cancer: a meta-analysis. *PLoS One*. 2013; 8(6): e65208. PMID 23762318
40. Zhong S, Chen Z, Xu J, et al. Pre-mir-27a rs895819 polymorphism and cancer risk: a meta-analysis. *Mol Biol Rep*. Apr 2013; 40(4): 3181-6. PMID 23266669
41. Fan C, Chen C, Wu D. The association between common genetic variant of microRNA-499 and cancer susceptibility: a meta-analysis. *Mol Biol Rep*. Apr 2013; 40(4): 3389-94. PMID 23271127
42. Ho WK, Tai MC, Dennis J, et al. Polygenic risk scores for prediction of breast cancer risk in Asian populations. *Genet Med*. Mar 2022; 24(3): 586-600. PMID 34906514

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43. Michailidou K, Hall P, Gonzalez-Neira A, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet.* Apr 2013; 45(4): 353-61, 361e1-2. PMID 23535729
44. Siddiq A, Couch FJ, Chen GK, et al. A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. *Hum Mol Genet.* Dec 15, 2012; 21(24): 5373-84. PMID 22976474
45. Garcia-Closas M, Couch FJ, Lindstrom S, et al. Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat Genet.* Apr 2013; 45(4): 392-8, 398e1-2. PMID 23535733
46. Milne RL, Herranz J, Michailidou K, et al. A large-scale assessment of two-way SNP interactions in breast cancer susceptibility using 46,450 cases and 42,461 controls from the breast cancer association consortium. *Hum Mol Genet.* Apr 01, 2014; 23(7): 1934-46. PMID 24242184
47. Joshi AD, Lindstrom S, Husing A, et al. Additive interactions between susceptibility single-nucleotide polymorphisms identified in genome-wide association studies and breast cancer risk factors in the Breast and Prostate Cancer Cohort Consortium. *Am J Epidemiol.* Nov 15, 2014; 180(10): 1018-27. PMID 25255808
48. Gu C, Zhou L, Yu J. Quantitative assessment of 2q35-rs13387042 polymorphism and hormone receptor status with breast cancer risk. *PLoS One.* 2013; 8(7): e66979. PMID 23894282
49. Gong WF, Zhong JH, Xiang BD, et al. Single nucleotide polymorphism 8q24 rs13281615 and risk of breast cancer: meta-analysis of more than 100,000 cases. *PLoS One.* 2013; 8(4): e60108. PMID 23565189
50. Wang X, He X, Guo H, et al. Variants in the 8q24 region associated with risk of breast cancer: Systematic research synopsis and meta-analysis. *Medicine (Baltimore).* Feb 2020; 99(8): e19217. PMID 32080114
51. Liu H, Wei Z, Shi K, et al. Association between ABCB1 G2677T/A Polymorphism and Breast Cancer Risk: A Meta-Analysis. *Crit Rev Eukaryot Gene Expr.* 2019; 29(3): 243-249. PMID 31679234
52. Milne RL, Burwinkel B, Michailidou K, et al. Common non-synonymous SNPs associated with breast cancer susceptibility: findings from the Breast Cancer Association Consortium. *Hum Mol Genet.* Nov 15, 2014; 23(22): 6096-111. PMID 24943594
53. Lin WY, Brock IW, Connley D, et al. Associations of ATR and CHEK1 single nucleotide polymorphisms with breast cancer. *PLoS One.* 2013; 8(7): e68578. PMID 23844225
54. Bodelon C, Malone KE, Johnson LG, et al. Common sequence variants in chemokine-related genes and risk of breast cancer in post-menopausal women. *Int J Mol Epidemiol Genet.* 2013; 4(4): 218-27. PMID 24319537
55. He XF, Wei W, Li SX, et al. Association between the COMT Val158Met polymorphism and breast cancer risk: a meta-analysis of 30,199 cases and 38,922 controls. *Mol Biol Rep.* Jun 2012; 39(6): 6811-23. PMID 22297695
56. Dai ZJ, Shao YP, Ma XB, et al. Association of the three common SNPs of cyclooxygenase-2 gene (rs20417, rs689466, and rs5275) with the susceptibility of breast cancer: an updated meta-analysis involving 34,590 subjects. *Dis Markers.* 2014; 2014: 484729. PMID 25214704

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57. Tang L, Xu J, Wei F, et al. Association of STXBP4/COX11 rs6504950 (G A) polymorphism with breast cancer risk: evidence from 17,960 cases and 22,713 controls. *Arch Med Res.* Jul 2012; 43(5): 383-8. PMID 22863968
58. He XF, Wei W, Liu ZZ, et al. Association between the CYP1A1 T3801C polymorphism and risk of cancer: evidence from 268 case-control studies. *Gene.* Oct 24, 2014;534(2):324-344. PMID 24513335
59. Tian Z, Li YL, Zhao L, et al. Role of CYP1A2 1F polymorphism in cancer risk: evidence from a meta-analysis of 46 case-control studies. *Gene.* Jul 25, 2013; 524(2): 168-74. PMID 23628800
60. Pineda B, Garcia-Perez MA, Cano A, et al. Associations between aromatase CYP19 rs10046 polymorphism and breast cancer risk: from a case-control to a meta-analysis of 20,098 subjects. *PLoS One.* 2013; 8(1): e53902. PMID 23342035
61. Agarwal D, Pineda S, Michailidou K, et al. FGF receptor genes and breast cancer susceptibility: results from the Breast Cancer Association Consortium. *Br J Cancer.* Feb 18, 2014; 110(4): 1088-100. PMID 24548884
62. Jafrin S, Aziz MA, Islam MS. Role of IL-1 rs1143634 (+3954C T) polymorphism in cancer risk: an updated meta-analysis and trial sequential analysis. *J Int Med Res.* Dec 2021; 49(12): 3000605211060144. PMID 34861128
63. Yu Z, Liu Q, Huang C, et al. The interleukin 10 -819C/T polymorphism and cancer risk: a HuGE review and meta-analysis of 73 studies including 15,942 cases and 22,336 controls. *OMICS.* Apr 2013; 17(4): 200-14. PMID 23574339
64. Zhang H, Wang A, Ma H, et al. Association between insulin receptor substrate 1 Gly972Arg polymorphism and cancer risk. *Tumour Biol.* Oct 2013; 34(5): 2929-36. PMID 23708959
65. Zheng Q, Ye J, Wu H, et al. Association between mitogen-activated protein kinase kinase kinase 1 polymorphisms and breast cancer susceptibility: a meta-analysis of 20 case-control studies. *PLoS One.* 2014; 9(3): e90771. PMID 24595411
66. Gao J, Kang AJ, Lin S, et al. Association between MDM2 rs 2279744 polymorphism and breast cancer susceptibility: a meta-analysis based on 9,788 cases and 11,195 controls. *Ther Clin Risk Manag.* 2014; 10: 269-77. PMID 24790452
67. Wang Z, Wang T, Bian J. Association between MDR1 C3435T polymorphism and risk of breast cancer. *Gene.* Dec 10, 2013; 532(1): 94-9. PMID 24070710
68. Zhong S, Xu J, Li W, et al. Methionine synthase A2756G polymorphism and breast cancer risk: an up-to-date meta-analysis. *Gene.* Sep 25, 2013; 527(2): 510-5. PMID 23845785
69. Saadat M. Paraoxonase 1 genetic polymorphisms and susceptibility to breast cancer: a meta-analysis. *Cancer Epidemiol.* Apr 2012; 36(2): e101-3. PMID 22133529
70. Pan X, Huang L, Li M, et al. The Association between PON1 (Q192R and L55M) Gene Polymorphisms and Risk of Cancer: A Meta-Analysis Based on 43 Studies. *Biomed Res Int.* 2019; 2019: 5897505. PMID 31467900
71. Xu Y, Lu Z, Shen N, et al. Association of RAGE rs1800625 Polymorphism and Cancer Risk: A Meta-Analysis of 18 Case-Control Studies. *Med Sci Monit.* Sep 19, 2019; 25: 7026-7034. PMID 31534114

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72. Qin K, Wu C, Wu X. Two nonsynonymous polymorphisms (F31I and V57I) of the STK15 gene and breast cancer risk: a meta-analysis based on 5966 cases and 7609 controls. *J Int Med Res.* Aug 2013; 41(4): 956-63. PMID 23803310
73. Chen J, Yuan T, Liu M, et al. Association between TCF7L2 gene polymorphism and cancer risk: a meta-analysis. *PLoS One.* 2013; 8(8): e71730. PMID 23951231
74. He G, Song T, Zhang Y, et al. TERT rs10069690 polymorphism and cancers risk: A meta-analysis. *Mol Genet Genomic Med.* Oct 2019; 7(10): e00903. PMID 31454181
75. Perna L, Butterbach K, Haug U, et al. Vitamin D receptor genotype rs731236 (Taq1) and breast cancer prognosis. *Cancer Epidemiol Biomarkers Prev.* Mar 2013; 22(3): 437-42. PMID 23300018
76. Zhang K, Song L. Association between vitamin D receptor gene polymorphisms and breast cancer risk: a meta-analysis of 39 studies. *PLoS One.* 2014; 9(4): e96125. PMID 24769568
77. Li J, Ju Y. Association between the Functional Polymorphism of Vascular Endothelial Growth Factor Gene, and Breast Cancer: A Meta-Analysis. *Iran J Med Sci.* Jan 2015; 40(1): 2-12. PMID 25649829
78. He Y, Zhang Y, Jin C, et al. Impact of XRCC2 Arg188His polymorphism on cancer susceptibility: a meta-analysis. *PLoS One.* 2014; 9(3): e91202. PMID 24621646
79. He XF, Wei W, Su J, et al. Association between the XRCC3 polymorphisms and breast cancer risk: meta-analysis based on case-control studies. *Mol Biol Rep.* May 2012; 39(5): 5125-34. PMID 22161248
80. Niu H, Yang J, Chen X. Associations of rs1799794 and rs1799796 polymorphisms with risk of breast cancer: A meta-analysis. *J Cancer Res Ther.* Nov 2021; 17(5): 1225-1233. PMID 34850771
81. Sakoda LC, Jorgenson E, Witte JS. Turning of COGS moves forward findings for hormonally mediated cancers. *Nat Genet.* Apr 2013; 45(4): 345-8. PMID 23535722
82. Hunter DJ, Altshuler D, Rader DJ. From Darwin's finches to canaries in the coal mine--mining the genome for new biology. *N Engl J Med.* Jun 26, 2008; 358(26): 2760-3. PMID 18579810
83. Reeves GK, Travis RC, Green J, et al. Incidence of breast cancer and its subtypes in relation to individual and multiple low-penetrance genetic susceptibility loci. *JAMA.* Jul 28, 2010; 304(4): 426-34. PMID 20664043
84. Pharoah PD, Antoniou AC, Easton DF, et al. Polygenes, risk prediction, and targeted prevention of breast cancer. *N Engl J Med.* Jun 26, 2008; 358(26): 2796-803. PMID 18579814
85. Allman R, Dite GS, Hopper JL, et al. SNPs and breast cancer risk prediction for African American and Hispanic women. *Breast Cancer Res Treat.* Dec 2015; 154(3): 583-9. PMID 26589314
86. Dite GS, Mahmoodi M, Bickerstaffe A, et al. Using SNP genotypes to improve the discrimination of a simple breast cancer risk prediction model. *Breast Cancer Res Treat.* Jun 2013; 139(3): 887-96. PMID 23774992
87. Mealliffe ME, Stokowski RP, Rhees BK, et al. Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. *J Natl Cancer Inst.* Nov 03, 2010; 102(21): 1618-27. PMID 20956782

MEDICAL POLICY

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88. Curtit E, Pivot X, Henriques J, et al. Assessment of the prognostic role of a 94-single nucleotide polymorphisms risk score in early breast cancer in the SIGNAL/PHARE prospective cohort: no correlation with clinico-pathological characteristics and outcomes. *Breast Cancer Res.* Aug 22, 2017; 19(1): 98. PMID 28830573
89. Mavaddat N, Pharoah PD, Michailidou K, et al. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst.* May 2015; 107(5). PMID 25855707
90. Armstrong K, Handorf EA, Chen J, et al. Breast cancer risk prediction and mammography biopsy decisions: a model-based study. *Am J Prev Med.* Jan 2013; 44(1): 15-22. PMID 23253645
91. Darabi H, Czene K, Zhao W, et al. Breast cancer risk prediction and individualised screening based on common genetic variation and breast density measurement. *Breast Cancer Res.* Feb 07, 2012; 14(1): R25. PMID 22314178
92. Campa D, Kaaks R, Le Marchand L, et al. Interactions between genetic variants and breast cancer risk factors in the breast and prostate cancer cohort consortium. *J Natl Cancer Inst.* Aug 17, 2011; 103(16): 1252-63. PMID 21791674
93. Zheng W, Wen W, Gao YT, et al. Genetic and clinical predictors for breast cancer risk assessment and stratification among Chinese women. *J Natl Cancer Inst.* Jul 07, 2010; 102(13): 972-81. PMID 20484103
94. Wacholder S, Hartge P, Prentice R, et al. Performance of common genetic variants in breast-cancer risk models. *N Engl J Med.* Mar 18, 2010; 362(11): 986-93. PMID 20237344
95. Cuzick J, Brentnall AR, Segal C, et al. Impact of a Panel of 88 Single Nucleotide Polymorphisms on the Risk of Breast Cancer in High-Risk Women: Results From Two Randomized Tamoxifen Prevention Trials. *J Clin Oncol.* Mar 2017; 35(7): 743-750. PMID 28029312
96. McCarthy AM, Keller B, Kontos D, et al. The use of the Gail model, body mass index and SNPs to predict breast cancer among women with abnormal (BI-RADS 4) mammograms. *Breast Cancer Res.* Jan 08, 2015; 17: 1. PMID 25567532
97. Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. *N Engl J Med.* Feb 10, 2011; 364(6): 524-34. PMID 21226570
98. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast, ovarian, pancreatic, and prostate. Version 3.2025. Updated March 6, 2025,
99. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol.* Nov 01, 2015; 33(31): 3660-7. PMID 26324357
100. Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.63, Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer. November 2024.

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POLICY TITLE	USE OF COMMON GENETIC VARIANTS (SINGLE NUCLEOTIDE POLYMORPHISMS) TO PREDICT RISK OF NON-FAMILIAL BREAST CANCER
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IX. POLICY HISTORY

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MP 2.249	04/27/2020 Consensus Review. No changes to policy statements. References updated.
	11/23/2021 Consensus Review. Changed name from BREVAGenplus to GeneType but no change to intent or criteria. Update to policy guidelines, background, and references.
	11/14/2022 Consensus Review. No change in policy statement. References updated.
	01/05/2024 Consensus Review. No change to policy statement. Cross references and references updated.
	12/26/2024 Consensus Review. No change to policy statement. Removed NCCN language. Updated background, references. Coding reviewed, no changes.
	04/02/2025 Consensus Review. No change to policy statement. No coding changes. References reviewed and updated.
	03/09/2026 Retirement Review. Services managed by EviCore.

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