PHP_2.04.63	Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer		
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Section:	2.0 Medicine	**Page:**	Page 1 of 19

State Guidelines

As of the publication of this policy, there are no applicable Medi-Cal guidelines (Provider Manual or All Plan Letter). Please refer to the Policy Statement section below.

Policy Statement

In the absence of any State Guidelines, please refer to the criteria below.

I. Testing for 1 or more single nucleotide variants to predict an individual's risk of breast cancer is considered **investigational**.

II. The GeneType® breast cancer risk test is considered **investigational** for all indications, including but not limited to use as a method of estimating individual risk for developing breast cancer.

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 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
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the 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

Variant Classification	Definition
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 for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals 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.

Coding

See the Codes table for details.

Description

Several single nucleotide variants (SNVs), which are single base-pair variations in the DNA sequence of the genome, have been found to be associated with breast cancer, and are common in the population, but confer only small increases in risk. Commercially available assays test for several SNVs to predict an individual's risk of breast cancer relative to the general population. Some of these tests incorporate clinical information into risk prediction algorithms. The intent of this type of test is to identify subjects at increased risk who may benefit from more intensive surveillance.

Summary of Evidence

For individuals who are asymptomatic and at average risk of breast cancer by clinical criteria who receive testing for common single nucleotide variants (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.

Additional Information

Not applicable.

Related Policies

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

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

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.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

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).[1] 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 of health and health outcome disparities related to breast cancer.[2] 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.

Clinical Genetic Tests

GeneType for Breast Cancer

GeneType for Breast Cancer (and the previous versions of the test, BREVAGen*plus*® 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.[3] 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.[4]

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Single Nucleotide Variants and Average Breast Cancer Risk

Clinical Context and Test Purpose

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 other genes, 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 recommends that women at high risk (>20% lifetime risk) should undergo breast magnetic resonance imaging (MRI) and a mammogram every year, and those at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram.[5]

The purpose of genetic testing in asymptomatic individuals is to predict the risk of disease occurrence. The criteria under which prognostic testing may be considered clinically useful are as follows:

- An association of the marker with the disease has been established; and
- The clinical utility of identifying the variants has been established (e.g., by demonstrating that testing will lead to changes in surveillance).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who have not been identified as being at high risk of breast cancer. This population would include individuals who do not have a family member who has had breast cancer.

Interventions
The intervention of interest is testing for common SNVs associated with a small increase in the risk of breast cancer.

Comparator
The following practice is currently being used to predict the risk of breast cancer: standard clinical risk prediction without testing for common SNVs associated with risk of breast cancer.

Outcomes
The outcomes of interest are a reclassification of individuals from normal risk and evidence of a change in management (e.g., preventive or screening strategies) that results in improved health outcomes.

Study Selection Criteria
For the evaluation of clinical validity of the SNV test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Genome-wide association studies (GWAS) examine the entire genome of thousands of subjects for SNVs at semi-regular intervals and attempt to associate SNV alleles with particular diseases. Several case-control GWAS, primarily in White women, have investigated common-risk markers of breast cancer. A number of SNVs associated with breast cancer have been reported at a high level of statistical significance and have been validated in 2 or more large, independent studies.[6,7,8,9,10,11,12,13,14] Single nucleotide variants associated with breast cancer risk in Asian and African women have been the subject of a number of articles.[15,16,17,18,19,20,21,22,23,24,25,26,27,28,29]

Systematic Reviews
A number of meta-analyses have investigated the association between breast cancer and individual SNVs. Meta-analyses of case-control studies have indicated that specific SNVs are associated with increased or decreased breast cancer risk (Table 1). Other meta-analyses have revealed the interaction between the environment (e.g., obesity, age at menarche)[30,31] or ethnicity[32,33,34,35,36] and breast cancer risk conferred by certain SNVs. Zhou et al (2013) found that a specific variant in the vitamin D receptor gene increased breast cancer risk in African-American but not White women.[37] Breast cancer risk associated with SNVs in microRNAs is commonly modified by ethnicity.[38,39,40,41,42] Meta-analyses of GWAS have identified SNVs at new breast cancer susceptibility loci.[43,44,45] All of these markers are considered to be in an investigational phase of development.

Milne et al (2014), on behalf of the Breast Cancer Association Consortium, conducted a meta-analysis of 46,450 case patients and 42,461 controls from 38 international meta-analytic studies.[46] Reviewers

assessed 2-way interactions among 3277 breast cancer-associated SNVs. Of 2.5 billion possible 2-SNV combinations, none were statistically significantly associated with breast cancer risk. The meta-analysis suggested that risk models may be simplified by eliminating interaction terms. Reviewers cautioned that despite the large sample size, the study might have been underpowered to detect very small interaction effects, which tend to be smaller than the main effects.

Joshi et al (2014), also on behalf of the Breast and Prostate Cancer Cohort Consortium, conducted a meta-analysis of 8 prospective cohort studies conducted in the United States, Europe, and Australia to examine 2-way interactions between genetic and established clinical risk factors.[47] Based on published GWAS, 23 SNVs were selected for analysis in 10,146 cases of invasive breast cancer and 12,760 controls. Patients were of European ancestry and matched on age and other factors specific to each study. After correction for multiple comparisons, a statistically significant excess in relative risk was attributed to the interaction between rs10483813 variants in the *RAD51L1* gene and body mass index (BMI).

Table 1. Examples of Meta-Analyses of SNVs and Associations With Breast Cancer

SNVs	Association			Study
	Positive	None	Protective	
2q35 [rs13387042]	●			Gu et al (2013)[48]
8q24 [G-allele of rs13281615]	●			Gong et al (2013)[49]
8q24 [homozygous A-alleles of rs13281615]			●	Gong et al (2013)[49] Wang et al (2020)[50]
ABCB1 [G2677T/A]		●		Liu et al (2019)[51]
AKAP9 [M463I]	●			Milne et al (2014)[52]
ATR-CHEK1 checkpoint pathway genes[a]		●		Lin et al (2013)[53]
ATXN7 [K264R]	●			Milne et al (2014)[52]
Chemotactic cytokines[b]		●		Bodelon et al (2013)[54]
COMT [V158M]			●	He et al (2012)[55]
COX2 [rs20417]	●			Dai et al (2014)[56]
COX2 [rs689466]			●	Dai et al (2014)[56]
COX2 [rs5275]		●		Dai et al (2014)[56]
COX11 [rs6504950]			●	Tang et al (2012)[57]
CYP1A1 [T3801C]	●			He et al (2014)[58]
CYP1A2 1F [A-allele of rs762551]	●			Tian et al (2013)[59]
CYP19 [rs10046]		●		Pineda et al (2013)[60]
Fibroblast growth factor receptor genes[c]		●		kConFab Investigators (2014)[61]
IL-1β [rs1143634]	●			Jafrin et al (2021)[62]
IL-10 [rs1800871]		●		Yu et al (2013)[63]
IRS1 [rs1801278]	●			Zhang et al (2013)[64]
MAP3K1 [C-allele of rs889312 and G-allele of rs16886165]	●			Zheng et al (2014)[65]
MDM2 [rs2279744]	●			Gao et al (2014)[66]
MDR1 [C3435T]	●			Wang et al (2013)[67]
MTR [A(2756G]	●	●		Zhong et al (2013)[68]
PON1 [L55M]	●			Saadat et al (2012)[69] Pan et al (2019)[70]
PON1 [Q192R]			●	Pan et al (2019)[70]
RAGE [rs1800625]	●			Xu et al (2019)[71]
SLC4A7 [rs4973768]	●			Zhou et al (2023)[72]
STK15 [F31I]	●			Qin et al (2013)[73]
STK15 [V57II]		●		Qin et al (2013)[73]
TCF7L2 [rs7903146]	●			Chen et al (2013)[74]
TERT [rs10069690]	●			He et al (2019)[75]; updated analysis by Zhou et al (2024)[76]
VDR [rs731236]	●			Perna et al (2013)[77]
VDR [rs2228570]	●			Zhang et al (2014)[78]

SNVs	Association	Study
VEGF [C936T]	●	Li et al (2015)[79]
XRCC2 [R188H]	●	He et al (2014)[80]
XRCC3 [A17893G]	●	He et al (2012)[81]
XRCC3 [T241M]	●	He et al (2012)[81]
XRCC3 [rs1799794]	●	Niu et al (2021)[82]
XRCC3 [rs1799796]	●	Niu et al (2021)[82]

SNV: single nucleotide variant.

[a] 40 *ATR* and 50 *CHEK1* SNVs genotyped.

[b] 34 SNVs and groups of SNVs genotyped in 8 chemokine candidate genes: *CCL3*, *CCL4*, *CCL5*, *CCL20*, *CCR5*, *CCR6*, *CXCL12*, and *CXCR4*.

[c] 384 SNVs genotyped in *FGFR1*, *FGFR3*, *FGFR4*, and *FGFRL1*.

Primary Studies

Many more genetic risk markers remain to be discovered because substantial unexplained heritability remains.[83] Michailidou et al (2013), researchers from the Collaborative Oncological Gene-Environment Study group, a mega-consortium established to follow up previous GWAS and candidate gene association studies, identified 41 additional SNVs associated with breast cancer and estimated that "more than 1000 additional loci are involved in breast cancer susceptibility."[43] One reason more genetic associations have not been found is that even large GWAS are underpowered to detect uncommon genetic variants.[84] As the cost of whole-genome sequencing continues to decrease, some predict that this will become the preferred avenue for researching risk variants.

Reeves et al (2010) evaluated the performance of a panel of 7 SNVs associated with breast cancer in 10,306 women with breast cancer and 10,383 without cancer in the U.K.[85] The risk panel also contained 5 SNVs included in the deCODE BreastCancer test and used a similar multiplicative approach. Sensitivity studies were performed using 4 SNVs and using 10 SNVs, both demonstrating no significant change in performance. Although the risk score showed marked differences in risk between the upper quintile of patients (8.8% cumulative risk to age 70 years) and the lower quintile of patients (4.4%), these changes were not viewed as clinically useful when compared with patients with an estimated overall background risk of 6.3%. Simple information on patient histories was noted; e.g., the presence of 1 or 2 first-degree relatives with breast cancer provided equivalent or superior risk discrimination (9.1% and 15.4%, respectively).

Pharoah et al (2008) considered a combination of 7 well-validated SNVs associated with breast cancer, 5 of which are included in the deCODE BreastCancer test.[86] A model that simply multiplies the individual risks of the 7 common SNVs was assumed; such a model would explain approximately 5% of the total genetic risk of nonfamilial breast cancer. Applying the model to the population of women in the U.K., the risk profile provided by the 7 SNVs did not provide sufficient discrimination between those who would and would not experience future breast cancer to enable individualized preventive treatment, such as tamoxifen. However, the authors suggested that a population screening program could be personalized with results of SNV panel testing. The authors concluded that no women would be included in the high-risk category (defined as 20% risk within the next 10 years at age 40 to 49 years, according to the National Institute for Health and Care Excellence), and therefore none would warrant the addition of MRI screening or consideration of more aggressive intervention.

BREVAGen and BREVAGenplus (previous versions of GeneType)

A study by Allman et al (2015) included 7539 African American and 3363 Hispanic women from the Women's Health Initiative.[87] Adding a risk score based on over 70 susceptibility loci improved risk prediction by about 10% to 19% over the Gail model and 18% to 26% over the International Breast Cancer Intervention Study risk prediction for African Americans and Hispanics, respectively.

Dite et al (2013) published a similar case-control study of the same 7 SNVs, assuming the same multiplicative model (based on the independent risks of each SNV).[88] The predictive ability of the Gail

model with and without the 7 SNV panel was compared in 962 case patients and 463 controls, all 35 years of age or older (mean age, 45 years). The area under the curve (AUC) of the Gail model was 0.58 (95% confidence interval [CI], 0.54 to 0.61); in combination with the 7-SNV panel, AUC increased to 0.61 (95% CI, 0.58 to 0.64; p<.001). In reclassification analysis, 12% of cases and controls were correctly reclassified, and 9% of cases and controls were incorrectly reclassified when the 7-SNV panel was added to the Gail model. Risk classes were defined by 5-year risk of developing breast cancer (<1.5%, ≥1.5% to <2.0%, and ≥2.0%). Although the addition of the 7-SNV panel to the Gail model improved predictive accuracy, the magnitude of improvement was small, overall accuracy moderate, and impact on health outcomes uncertain.

Mealiffe et al (2010) published a clinical validation study of the BREVAGen test.[89] The authors evaluated a 7-SNV panel in a nested case-control cohort of 1664 case patients and 1636 controls. A model that multiplied the individual risks of the 7 SNVs was assumed, and the resulting genetic risk score was assessed as a potential replacement for or add-on test to the Gail clinical risk model. The net reclassification improvement was used to evaluate performance. Combining 7 validated SNVs with the Gail model resulted in a modest improvement in classification of breast cancer risks, but the AUC only increased from 0.557 to 0.594 (0.50 represents no discrimination, 1.0 perfect discrimination). The impact of reclassification on the net health outcome was not evaluated. The authors suggested that the best use of the test might be in patients who would benefit from enhanced or improved risk assessment (e.g., those classified as intermediate risk by the Gail model).

Other Clinical Genetic Tests

Curtit et al (2017) analyzed 8703 patients with early breast cancer who were in prospective case cohorts (SIGNAL and PHARE).[90] The primary aim was to identify associations between a 94-SNV risk score, drawn from previous literature, and invasive disease-free survival. Patients in different quartiles of the 94-SNV risk score were assessed for invasive disease-free survival and overall survival but showed no significant difference between groups (invasive disease-free survival hazard ratio, 0.993; 95% CI, 0.981 to 1.005; p=.26). Prognostic factors such as age at diagnosis, size of tumor, and metastasis status did not correlate with the risk score, which further did not distinguish between the 3 breast cancer subtypes represented in this analysis (triple-negative, human epidermal growth factor receptor [HER] 2-positive, and hormone receptor-positive HER 2-negative).

Mavaddat et al (2015) reported a multicenter study that assessed risk stratification using 77 breast cancer-associated SNVs in 33,673 breast cancer cases and 33,381 control women of European descent.[91] Polygenic risk scores were developed based on an additive model plus pairwise interactions between SNVs. Women in the highest 1% of the polygenic risk score had a 3-fold increased risk of developing breast cancer compared with women in the middle quintile (odds ratio [OR], 3.36; 95% CI, 2.95 to 3.83). The lifetime risk of breast cancer was 16.6% for women in the highest quintile of the risk score and 5.2% for women in the lowest quintile. The discriminative accuracy was 0.622 (95% CI, 0.619 to 0.627).

Other large studies have evaluated 8 to 18 common, candidate SNVs in breast cancer cases and normal controls to determine whether breast cancer assessments based on clinical factors *plus* various SNV combinations were more accurate than risk assessments based on clinical factors alone.

- Armstrong et al (2013) examined the impact of pretest breast cancer risk prediction on the classification of women with an abnormal mammogram above or below the risk threshold for biopsy.[92] Currently, 1-year probability of breast cancer among women with Breast Imaging-Reporting and Data System (BIRADS) category 3 mammograms is 2%; these women undergo 6-month follow-up rather than biopsy. In contrast, women with BIRADS category 4 mammograms have a 6% (BIRADS category 4A) or greater (BIRADS categories 4B and 4C) probability of developing breast cancer in 1 year; these women are referred for biopsy. Using the Gail model plus 12 SNVs for risk prediction and a 2% biopsy risk threshold, 8% of women with BIRADS category 3 mammograms were reclassified above the threshold for biopsy, and

7% of women with BIRADS category 4A mammograms were reclassified below the threshold. The greatest impact on reclassification was attributed to standard breast cancer risk factors. The net health outcome was not compared between women who were reclassified and those who were not.

- Darabi et al (2012) investigated the performance of 18 breast cancer risk SNVs, together with mammographic percentage density, BMI, and clinical risk factors in predicting absolute risk of breast cancer, empirically, in a well-characterized case-control study of postmenopausal Swedish women.[93] Performance of a risk prediction model based on an initial set of 7 breast cancer risk SNVs was improved by including 11 more recently established breast cancer risk SNVs (p<.001). Adding mammographic percentage density, BMI and all 18 SNVs to a modified Gail model improved the discriminatory accuracy (the AUC statistic) from 55% to 62%. The net reclassification improvement was used to assess improvement in classification of women into 5-year low-, intermediate-, and high-risk categories (p<.001). It was estimated that using an individualized screening strategy based on risk models incorporating clinical risk factors, mammographic density, and SNVs, would capture 10% more cases. Impacts on the net health outcome from such a change are unknown.
- Campa et al (2011) found no evidence that the 17 SNV breast cancer susceptibility loci modified the associations between established risk factors and breast cancer.[94]
- Zheng et al (2010) found that 8 SNVs, combined with other clinical predictors, were significantly associated with breast cancer risk; the full model gave an AUC of 0.63.[95]
- Wacholder et al (2010) evaluated the performance of a panel of 10 SNVs associated with breast cancer that had, at the time of the study, been validated in at least 3 published GWAS.[96] Cases (n=5590) and controls (n=5998) from the National Cancer Institute's Cancer Genetic Markers of Susceptibility GWAS of breast cancer were included in the study (women of primarily European ancestry). The SNV panel was examined as a risk predictor alone and in addition to readily available components of the Gail model (e.g., diagnosis of atypical hyperplasia was not included). The authors found that adding the SNV panel to the Gail model resulted in slightly better stratification of a woman's risk than either the SNV panel or the Gail model alone but that this stratification was inadequate to inform clinical practice. For example, only 34% of the women who had breast cancer were assigned to the top 20% risk group. The area under the curve for the combined SNV and Gail model was 62% (50% is random, 100% is perfect).

Although results of these studies support the concept of clinical genetic tests, they do not represent direct evidence of their clinical validity or utility.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs evaluating the clinical utility of SNV panel testing to predict the risk of breast cancer were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

One potential use of SNV testing is to evaluate the risk of breast cancer for chemoprevention. Cuzick et al (2017) assessed whether a panel of 88 SNVs could improve risk prediction over traditional risk stratification using data from 2 randomized tamoxifen prevention trials.[97] The study included 359 cases and 636 controls, with the 88 SNVs assessed on an Illumina OncoArray that evaluated approximately half a million SNVs. The primary outcome was breast cancer or ductal carcinoma in situ. The 88 SNV score improved discriminability above the Tyrer-Cuzick risk evaluator; however, there was a modest improvement in the percentage of women who were classified as high risk. The percentage of women with a 10-year risk of recurrence of 8% or more was estimated to be 18% for Tyrer-Cuzick and 21% when the 88 SNV score was added. The SNV score did not predict which women would benefit from tamoxifen.

McCarthy et al (2015) examined the impact of BMI, Gail model risk, and a 12-SNV version of the deCODE BreastCancer test on breast cancer risk prediction and biopsy decisions among women with BI-RADS category 4 mammograms who had been referred for biopsy (N=464).[98] The original deCODE BreastCancer panel included 7 SNVs; neither panel is currently commercially available. The mean patient age was 49 years, 60% were white, and 31% were Black. In multivariate regression models that included age, BMI, Gail risk factors, and SNV panel risk as a continuous variable, a statistically significant association between SNV panel risk and breast cancer diagnosis was observed (OR, 2.30; 95% CI, 1.06 to 4.99; p=.035). However, categorized SNV panel risks (e.g., relative increase or decrease in risk compared with the general population), resembling how the test would be used in clinical practice, were not statistically associated with breast cancer diagnosis. In subgroups defined by Black or White race, SNV panel risk also was not statistically associated with breast cancer diagnosis. Risk estimated by a model that included age, Gail risk factors, BMI, and the SNV panel, reclassified 9 (3.4%) women below a 2% risk threshold for biopsy, none of whom were diagnosed with cancer.

Bloss et al (2011) reported on the psychological, behavioral, and clinical effects of risk scanning in 3639 patients followed for a short time (mean, 5.6 months).[99] These investigators evaluated anxiety, intake of dietary fat, and exercise based on information from genomic testing. There were no significant changes before and after testing and no increase in the number of screening tests obtained in enrolled patients. Although more than half of patients participating in the study indicated an intent to undergo screening in the future, during the study itself, no actual increase was observed.

Section Summary: Single Nucleotide Variants and Average Breast Cancer Risk

Common SNVs have been shown in meta-analyses and primary studies to be significantly associated with breast cancer risk; some SNVs convey slightly elevated risk compared with the general population risk. Estimates of breast cancer risk, based on SNVs derived from large GWAS and/or from SNVs in other genes known to be associated with breast cancer, are available as a laboratory-developed test service. The literature on these associations is growing, although information about the risk models is proprietary. Available data would suggest that GeneType may add predictive accuracy to clinical risk prediction. However, the degree of improved risk prediction may be modest, and clinical implications are unclear. Other panel tests have fewer data to support conclusions about their clinical validity. Independent determination of clinical validity in an intended-use population has not been performed. Use of such risk panels for individual patient care or population screening programs is premature because (1) performance of these panels in the intended-use populations is uncertain, and (2) most genetic breast cancer risk has yet to be explained by undiscovered gene variants and SNVs. The number of common low-penetrance SNVs associated with breast cancer is rapidly increasing. No studies were identified that provide direct evidence that use of SNV-based risk assessment has any impact on healthcare outcomes in this population. Indirect evidence from an improvement in risk prediction with an 88 SNV panel has been reported, although the improvement in risk prediction is modest. For the specific loci evaluated by the most recent GeneType test, there is

insufficient evidence to determine whether using breast cancer risk estimates in asymptomatic individuals changes management decisions and improves patient outcomes.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In the 2015 guidelines on genetic and genomic testing for cancer susceptibility, the American Society of Clinical Oncology (ASCO) acknowledges the role of multi-panel gene testing for high-penetrance genes of established clinical utility; however, "panel testing may identify mutations in genes associated with moderate or low cancer risks" and "testing will also identify variants of uncertain significance in a substantial proportion of patient cases." [100]

National Comprehensive Cancer Network

In its guidelines on genetic or familial high-risk assessment of breast, ovarian, and pancreatic cancers (v.1.2026), the National Comprehensive Cancer Network (NCCN) notes the potential for multigene testing to identify intermediate penetrance (moderate risk) genes, but adds that "For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests will change risk management compared to that based on other risk factors such as family history." The guideline also includes that there are "significant limitations" in the interpretation of polygenic risk scores, and that polygenic risk scores should not be used for clinical management at this time.[101]

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for single nucleotide variant testing either in conjunction with or without consideration of clinical factors to predict breast cancer risk have been identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02620852	Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer (WISDOM)	100,000	Oct 2025
NCT04474834	GENetic Risk Estimation of Breast Cancer Prior to Decisions on Preventive Therapy Uptake, Risk Reducing Surgery or Intensive Imaging Surveillance: A Study to Determine if a Polygenic Risk Score	900	Dec 2029

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Influences the Decision Making Options Amongst High Risk Women (GENRE 2)		
NCT05755269	Genetic Risk Estimation in Breast Cancer and Assessing Health Disparities	50	Jan 2033

NCT: national clinical trial.
[a] Denotes an industry sponsored or cosponsored trial

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Reason for testing, when applicable
  - Past and present diagnostic testing and results
  - Treatment plan
- Consultation report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, PET)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	81599	Unlisted multianalyte assay with algorithmic analysis

Type	Code	Description
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/01/2026	New policy.
06/01/2026	Administrative update. Definitions of Decision Determinations section updated.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status

Below is an excerpt of the language taken from California Children's Services Numbered Letter 05-1020.*

*Department of Healthcare Services Numbered Letter 05-1020. Accessed April 21, 2026, from https://www.dhcs.ca.gov/services/ccs/Documents/CCS-NL-05-1020-Experimental-and-Investigational-Services.pdf

Policy

A. The California Children's Services (CCS) Program and the Genetically Handicapped Persons Program (GHPP) will not provide coverage for experimental services unless specifically authorized by law.
B. The CCS Program and GHPP may provide coverage for an investigational service if:
    1. It is approved by the FDA under any Investigational New Drug (IND) Application; or
    2. It is authorized for use under the State of California's Right to Try Act; and
    3. Its use is consistent with its FDA-approved IND Application or the State of California's Right to Try Act;
C. Additional criteria that will be considered in the adjudication process include:
    1. Conventional therapy will not adequately treat the intended patient's condition;
    2. Conventional therapy will not prevent progressive disability or premature death;

3. The provider of the proposed service has a record of safety and success with it or equivalent to that of other providers of the investigational services;
4. Other criteria (e.g., cost and availability) may be considered in the adjudication of a given request in cases in which more than one investigational service is available;
5. There is reasonable expectation that the investigational service will significantly prolong the patient's life or will maintain or restore a range of physical and social function suited to activities of daily living; and
6. The service is not being performed as part of a research study protocol. For a beneficiary with cancer who participates in a clinical trial for cancer, California Health and Safety Code (HSC) § 1370.6 requires that all routine patient care costs related to the clinical trial be covered if the beneficiary's CCS-paneled treating physician recommends participation in the clinical trial after determining that participation in the clinical trial has a meaningful potential to benefit the enrollee. The coverage does not include investigational services that have not been approved by the FDA and that are associated with the clinical trial.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.