Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) is addressed separately in medical policy 00047.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers testing for 1 or more single nucleotide variants (SNVs) to predict an individual's risk of breast cancer to be **investigational.***

Based on review of available data, the Company considers the GeneType (and previous versions BREVAGen and BREVAGen*plus*®‡) breast cancer risk test for all indications, including but not limited to use as a method of estimating individual risk for developing breast cancer to be **investigational.***

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
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.

Background/Overview

Clinical Genetic Tests

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.

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. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

Supplemental Information

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 US professional society, an international society with US 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.

National Comprehensive Cancer Network

In its guidelines on genetic or familial high-risk assessment of breast, ovarian, and pancreatic cancers (v.3.2023), 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.

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."

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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 unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02620852[a]	Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer (WISDOM)	100,000	Mar 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 Influences the Decision Making Options Amongst High Risk Women (GENRE 2)	900	Dec 2024
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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Policy History

Original Effective Date: 09/15/2010
Current Effective Date: 01/08/2024

09/09/2010	Medical Policy Committee review
09/15/2010	Medical Policy Implementation Committee approval. New policy.
09/01/2011	Medical Policy Committee review
09/14/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2012	Medical Policy Committee review
09/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013	Coding updated
09/05/2013	Medical Policy Committee review
09/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Title changed to "Use of Common Genetic Variants (SNPs) to Predict Risk of Nonfamilial Breast Cancer." Investigational policy statement for OncoVue and BREVAGen modified to

	indicate investigational for all indications. Combined with Non-BRCA-Breast Cancer Risk Assessment (e.g., OncoVue).
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. BREVAGenplus replaces BREVAGen test in the policy.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. "Polymorphisms" changed to "variants" throughout policy. OncoVue removed from policy; it is no longer commercially available.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. No change to coverage.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. No change to coverage.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. No change to coverage.
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Senate Bill update. GeneType (and previous versions BREVAGen and BREVAGenplus) breast cancer risk test added as investigational.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Senate bill review. No change to coverage. Body of policy updated including NCCN guidelines and references.

Next Scheduled Review Date: 12/2024

Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 01/08/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81599
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.