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

Policy # 00268
Original Effective Date: 09/15/2010
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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: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers 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 BREVAGen*plus*®‡ breast cancer risk test for all indications, including but not limited to use as a method of estimating individual patient 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 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
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

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the

impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Clinical Genetic Tests

BREVAGenplus

BREVAGen*plus* evaluates breast cancer-associated single nucleotide variants (SNVs) identified in genome-wide association studies. The first-generation test, BREVAGen, included 7 SNVs. Allman et al (2015) reported the test included over 70 susceptibility SNVs. Risk is calculated by combining individual SNV risks with the Gail model risk. BREVAGen*plus* has been evaluated for use in African-American, white, and Hispanic patient samples age 35 years and older. BREVAGen*plus* does not detect known high-risk variants (eg, in *BRCA*). According to the BREVAGenplus website, the test is "not applicable to women who are already at high risk of breast cancer including those that have a personal or extensive family history of breast and/or ovarian cancer, LCIS [lobular carcinoma in situ], DCIS [ductal carcinoma in situ], AH [atypical hyperplasia] or have thoracic RT [radiotherapy] under 30y. Any women with these risk factors are already at increased risk of breast cancer and should be screened and followed as such."

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. BREVAGen*plus* (Phenogen Sciences, a subsidiary of Genetic Technologies) is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

SNVs, which are single base-pair variations in the DNA sequence of the genome, have been found to be associated with breast cancer, 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.

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 the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

In its guidelines on genetic or familial high-risk assessment of breast and ovarian cancers (v.3.2019), the National Comprehensive Cancer Network 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 are no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests are necessarily clinically actionable." In the absence of evidence, guiding follow-up to testing,

including risk management strategies, National Comprehensive Cancer Network recommends "that multi-gene testing is ideally offered in the context of professional genetic expertise, for pre- and post-test counseling."

American Society of Clinical Oncology
For breast cancer risk assessment, the American Society of Clinical Oncology (2013) recommended the Gail model or risk models for women with elevated risk based on family history (eg, Claus et al [1994] or Tyrer et al [2004]).

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	Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer (WISDOM)	100,000	Dec 2020

NCT: national clinical trial.

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Policy History

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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.

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

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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.

Next Scheduled Review Date: 11/2021

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

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Original Effective Date: 09/15/2010
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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 2019 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	C50.011-C50.029, C50.111-C50.129, C50.211-C50.229, C50.311-C50.329, C50.411-C50.429, C50.511-C50.529, C50.611-C50.629, C50.811-C50.829, C50.911-C50.929, D05.00-D05.02, D05.10-D05.12, D05.80-D05.82, D05.90-D05.92, Z80.3

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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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.