BlueCross BlueShield Minnesota

Blue Cross Blue Shield of Minnesota Medical Policy

Medical Policy:	VI-32-019
Topic:	Single-Nucleotide Polymorphism (SNP) Breast Cancer Risk Assessment
Section:	Laboratory
Effective Date:	March 3, 2025
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Annual Review:	February 2025

Single nucleotide polymorphisms (SNPs), also known as single nucleotide variants (SNVs), are single base-pair variations in the DNA sequence of the genome. Some of these have been found to be associated with breast cancer. However, these SNPs are common in the population and confer only small increases in breast cancer risk.

Proprietary laboratory-developed tests to evaluate the status of multiple SNPs have been developed. Results are incorporated with personal history measures to determine breast cancer risk. The tests do not detect known high-risk genetic factors such as pathogenic variants of the BRCA gene. Commercially available laboratory-developed tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Several Single Nuclotide Polymorphism (SNP) Breast Cancer Risk Assessment tests are commercially available, including but not limited to:

- BREVAGen®
- BREVAGenplus®
- geneType®
- OncoVue®

This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Policy Position *Coverage is subject to the specific terms of the member's benefit plan.*

NOTE: Coverage may be subject to legislative mandates, including but not limited to the following, which applies prior to the policy statements:

- Minnesota Statute 62Q.473 Biomarker Testing.

Testing for one or more single nucleotide polymorphisms, as a method for estimating individual patient risk for developing breast cancer, is considered **EXPERIMENTAL/ INVESTIGATIVE** due to the lack of clinical evidence demonstrating an impact on improved health outcomes.

Procedure Codes

81479 81599

Denial Statements

No additional statements.

Links

Summary of Evidence

Several single nucleotide polymorphisms (SNPs), 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. Estimates of breast cancer risk based on SNPs derived from large genome-wide association studies (GWASs) and/or from discovery of SNPs in other genes known to be associated with breast cancer are available as laboratory-developed test services from a number of companies. No peer-reviewed reports have been published in which these commercially available breast cancer risk estimators have been compared to each other to determine if they report similar results on the same individuals specifically for breast cancer. Until their individual and collective effect on cancer risk are evaluated, they are not considered clinically useful. (5) Clinical validity and clinical utility of cancer risk SNP testing is unknown. Whether SNP testing can lead to clinically useful information is under debate. Controlled clinical trial data regarding SNP testing demonstrating improved health outcomes are lacking in the published peer-reviewed scientific literature. Therefore, SNP analysis testing for breast cancer risk assessment is considered investigative.

Rationale

Validation of genotyping to improve treatment outcomes is a multistep process. In general, important steps in the validation process address the following:

- **Clinical validity:** measures the strength of the associations between the selected genetic markers and clinical status.
- **Clinical utility:** determines whether the use of genotyping for specific genetic markers to guide treatment decisions improves patient outcomes such as survival or adverse event rate compared to standard treatment without genotyping.
- **Analytic validity:** measures technical performance, i.e., whether the test accurately and reproducibly detects the gene markers of interest.

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. When evaluating the appropriate use of new genetic tests, clinicians and health care policymakers must consider the accuracy with which a test identifies a patient's clinical status (clinical validity) and the risks and benefits resulting from test use (clinical utility). Genetic tests in current use vary in accuracy and potential to improve health outcomes, and these test properties may be influenced by testing technology and the clinical setting in which the test is used. Analytic validity refers to the accuracy with which a particular genetic characteristic, such as a DNA sequence variant, chromosomal deletion, or biochemical indicator, is identified in a given laboratory test.

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). 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 (FDA) has chosen not to require any regulatory review of commercial single nucleotide polymorphism (SNP) breast cancer risk assessment tests. The Centers for Disease Control and Prevention (CDC), in partnership with CMS and FDA, supports the CLIA program and clinical laboratory quality.

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. 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. 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 interventional 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.

No recent ECRI or Hayes HTA reports regarding the use of SNP testing for breast cancer risk assessment were identified. Hayes published a PMR brief in April 2014 which concluded that there is insufficient published evidence to perform a Genetic Test Evaluation (GTE) health technology assessment of SNP testing for breast cancer risk assessment. The main evidence deficiencies for SNP testing for breast cancer risk assessment are insufficient data on analytical validity, clinical validity, and clinical utility.

Current guidelines from the National Comprehensive Cancer Network (NCCN) note that commercial entities providing ancestry (and sometimes health) information typically do so through microarray-based single nucleotide polymorphism (SNP) testing that has not been validated for clinical use. Third-party software applications can be used by consumers to obtain an interpretation of the raw data provided by these companies. Raw data and third-party software are not able to provide information that is appropriate for medical management, as these services are not subject to quality-control processes and recent research suggests that the error rate (40%) is substantial. In addition, the current tests only provide limited founder pathogenic variants (PVs) results without the benefit of family history. More comprehensive genetic counseling and testing for PVs in other inherited cancer risk genes may be appropriate at the time of confirmation testing.

The National Society of Genetic Counselors (NSGC) endorses the use of multi-gene panel tests when clinically warranted and appropriately applied. Before ordering a multi-gene panel test, providers should thoroughly evaluate the analytic and clinical validity of the test, as well as its clinical utility. Additional factors to consider include, but are not limited to: clinical and family history information, gene content of the panel, limitations of the sequencing and informatics technologies, and variant interpretation and reporting practices. Panels magnify the complexities of genetic testing and underscore the value of experts, such as genetic counselors, who can educate stakeholders about appropriate utilization of the technology to mitigate risks of patient harm and unnecessary costs to the healthcare system.

Reference List

1. Blue Cross Blue Shield Association. Medical Reference Policy: 2.04.63 - Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer. November 2023.
2. Burke W. Genetic tests: clinical validity and clinical utility. Curr Protoc Hum Genet. 2014;81:9.15.1- 9.15.8. Published 2014 Apr 24. doi:10.1002/0471142905.hg0915s81]
3. Centers for Disease Control and Prevention (CDC) Clinical Laboratory Improvement Amendments (CLIA). Available at: https://www.cdc.gov/clia/index.html.
4. Minnesota Statutes 2025, section 62Q.473 Ciomarker Testing; MINN. STAT 62Q.473 (2025)
5. Hayes Inc., Precision Medicine Research Brief: Single Nucleotide Polymorphism (SNP) Testing for Breast Cancer Risk Assessment, April 14, 2014.
6. National Cancer Institute (NCI) Genetics of Breast and Gynecologic Cancers (PDQ®)–Health Professional Version 2021
7. National Society of Genetic Counselors (NSGC) - Use of Multi-Gene Panel Tests, 6/15/2023 (Adopted 2017; Reaffirmed 2020 and 2023).
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 2.2024 Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. September 27, 2023.

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ATENCIÓN: Si usted habla español, servicios de asistencia lingüística, de forma gratuita, están disponibles para usted. Llame al número en la parte posterior de su tarjeta de identificación (TTY: 711).

请注意：如果您说中文，可向您提供免费语言协助服务。

请拨打您的身份证背面的号码（TTY：711）。

CHÚ Ý: Nếu quý vị nói tiếng Việt, chúng tôi cung cấp dịch vụ hỗ trợ ngôn ngữ miễn phí cho quý vị. Xin gọi số điện thoại ở mặt sau thẻ ID của quý vị (TTY: 711).

알림: 한국어를 사용하시는 분들을 위해 무료 통역이 제공됩니다. ID 카드 뒷면에 있는 번호로 전화하십시오 (TTY: 711).

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ATTENZIONE: se parla italiano, per lei sono disponibili servizi di assistenza linguistica a titolo gratuito. Contatti il numero riportato sul retro della sua carta d'identità (TTY: 711).

ACHTUNG: Wenn Sie Deutsch sprechen, steht Ihnen unsere fremdsprachliche Unterstützung kostenlos zur Verfügung. Rufen Sie dazu die auf der Rückseite Ihres Versicherungsausweises (TTY: 711) aufgeführte Nummer an.

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توجه : اگر شما به زبان **فارسی** صحبت می کنید، خدمات کمک زبان، به صورت رایگان، در دسترس شماست. با شماره واقع در پشت کارت شناسایی خود (TTY: 711) تماس بگیرید.