

Corporate Medical Policy

Use of Common Genetic Variants to Predict Risk of Non-Familial Breast Cancer AHS-M2126

File Name: use_of_common_genetic_variants_to_predict_risk_of_non-familial_breast_cancer
Origination: 1/1/2019
Last CAP Review: 3/2021
Next CAP Review: 3/2022
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Description of Procedure or Service

Single nucleotide polymorphisms (SNPs) refer to single-base pair changes that achieve a population frequency of at least 1 percent. They represent the most abundant form of genetic variation and are responsible for much of the heritable phenotypic variation observed in human populations (Raby, 2017).

Related Policies:

General Genetic Testing, Germline Disorders AHS-M2145

General Genetic Testing, Somatic Disorders AHS-M2146

Gene Expression Testing for Breast Cancer Prognosis AHS-M2020

****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.*

Policy

Use of common genetic variants to predict risk of non-familial breast cancer is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Use of Common Genetic Variants to Predict Risk is covered

Not applicable.

When Use of Common Genetic Variants to Predict Risk is not covered

Testing for one or more single nucleotide polymorphisms (SNPs) is **investigational** for all indications, including but not limited to use as a method of estimating individual patient risk for developing breast cancer. These include, but are not limited, to the OncoArray, TruSight®, and BREVAGenplus,TM breast cancer tests offered directly to consumers.

Policy Guidelines

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Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women. In the United States, breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer death in women. Approximately 1 in 8 women will develop breast cancer in their lifetime (Taghian, El-Ghamry, & Merajver, 2017).

Breast cancer risk is strongly associated with both genetic and environmental factors. Familial aggregation and twin studies have shown the substantial contribution of inherited susceptibility to breast cancer (Lichtenstein et al., 2000; Peto & Mack, 2000). Many genetic loci are known to contribute to this risk, including genes with high-penetrance mutations (notably *BRCA1* and *BRCA2*), moderate-risk alleles in genes such as *ATM*, *CHEK2* and *PALB2*, and common lower penetrance alleles (Michailidou et al., 2013), of which almost 80 have been identified so far, principally through genome-wide association studies (Ahmed et al., 2009; Antoniou et al., 2010; Bojesen et al., 2013; Cox et al., 2007; Easton et al., 2007; Fletcher et al., 2011; French et al., 2013; Garcia-Closas et al., 2013; Ghousaini et al., 2012; Haiman et al., 2011; Michailidou et al., 2013; Stacey et al., 2007; Stacey et al., 2008; Thomas et al., 2009; Turnbull et al., 2010; Vachon et al., 2017; Zheng et al., 2009). GWAS continues to uncover additional loci with 65 loci identified by Michailidou et al (2017). Coupled with established risk factors, these loci are likely to increase the utility and accuracy of clinical risk prediction.

For sporadic (nonfamilial) breast cancer, the Gail model (Gail et al., 1989) has been commonly used to produce individual risk estimates in women. The model incorporates individual risk factors including age, family history (breast cancer among first-degree relatives), personal reproductive history (age at menarche and at first live birth), and personal medical history (number of previous breast biopsies and presence of biopsy-confirmed atypical hyperplasia) to identify women who have an increased 5-year risk and lifetime risk of invasive breast cancer and may benefit from risk reduction with selective estrogen receptor (ER) modulators (Kinsinger, Harris, Woolf, Sox, & Lohr, 2002; Visvanathan et al., 2009). Therefore, this model has implications for primary prevention of invasive breast cancer. However, both the discriminatory accuracy of the Gail model and its calibration in certain populations have been challenged (Mealiffe et al., 2010).

Previous studies have analyzed the potential impact of adding genetic information from a panel of SNPs associated with breast cancer risk to the Gail model (Gail, 2008, 2009). A study that compared classification of risk using the Gail model or the Gail model plus 10 common genetic susceptibility variants, other than those associated with *BRCA1* or *BRCA2*, found that inclusion of the genetic factors only modestly improved performance of the risk model for breast cancer (Wacholder et al., 2010). Another study evaluated the inclusion of a SNP risk score, based on seven SNPs associated with risk for breast cancer, in a risk model combined with the Gail model (Mealiffe et al., 2010). The combined risk model modestly improved risk prediction performance, compared to the Gail model alone, with the greatest impact for women at intermediate risk (Elmore, 2017). These showed that real gains, albeit modest, could be achieved in reclassification of risk. Other studies have found modest potential clinical gains from combining SNP information with clinical risk factors (Gail, 2008, 2009; Pharoah, Antoniou, Easton, & Ponder, 2008; Wacholder et al., 2010). However, these studies have either been theoretical in nature (Gail, 2008, 2009; Pharoah et al., 2008) or they combined model building with evaluation (Wacholder et al., 2010), which may complicate evaluating the results in clinical context. Improvement in risk assessment from incorporating genetic information might be larger in subsets of women at intermediate risk based on clinical risk factors (Mealiffe et al., 2010).

More recently, a 76-locus polygenic risk score (PRS) was incorporated into the Breast Cancer Surveillance Consortium (BCSC) risk-prediction model (Tice et al., 2008) while accounting for its attributable risk and compared five-year absolute risk predictions between models within three studies (1643 case patients, 2397 control patients). PRS was found to be an independent risk factors across all three studies and improved discriminatory accuracy from area under the curve (AUC) AUC = 0.66 to AUC = 0.69. The study concluded that the set of 76 SNPs improves the identification of women at the highest risk. Along with the increase seen in AUC, the net-reclassification of 11% of case patients (95% CI = 7% to 15%) to a risk level where women are more likely to benefit from chemoprevention suggests that SNPs could be useful clinically. However, independent cohort data are needed to test calibration in the general population (Vachon et al., 2017).

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Peskin and Isaacs (2017) in their review state that: “Some women with suspected hereditary risks for breast cancer do not have a mutation in a moderate to high-risk gene. In such cases, a combination of low-risk mutations may explain their personal and/or family history of cancer. As an example, over 75 single-nucleotide polymorphisms (SNPs), conferring an odds ratio for breast cancer of 0.72 to 1.97, have been identified and contribute to approximately 14 percent of breast cancer cases. It is estimated that another 14 percent of breast cancer cases are attributed to unidentified SNPs. However, the clinical utility of identifying these SNPs has not been established and testing for SNPs is not widely available.”

Cuzick et al (2017) examined the extent to which the Onco Array SNP risk score could refine risk in women who receive preventative therapy. They found that “SNP88 was predictive of breast cancer risk overall (interquartile range odds ratio [IQ-OR], 1.37; 95% CI, 1.14 to 1.66; mC, 0.55), but mainly for estrogen receptor-positive disease (IQ-OR, 1.44; 95% CI, 1.16 to 1.79; P for heterogeneity = .10) versus estrogen receptor-negative disease. However, the observed risk of SNP88 was only 46% (95% CI, 19% to 74%) of expected. No significant interaction was observed with treatment arm (placebo IQ-OR, 1.46; 95% CI, 1.13 to 1.87; tamoxifen IQ-OR, 1.25; 95% CI, 0.96 to 1.64; P for heterogeneity = .5). The predictive power was similar to the TC model (IQ-OR, 1.45; 95% CI, 1.21 to 1.73; mC, 0.55), but SNP88 was independent of TC (Spearman rank-order correlation, 0.012; P = .7), and when combined multiplicatively, a substantial improvement was seen (IQ-OR, 1.64; 95% CI, 1.36 to 1.97; mC, 0.60).”

Mavaddat et al (2015) “evaluated the degree of breast cancer risk stratification that can be attained in women of European ancestry using data for 77 common genetic variants, summarized as a PRS.” They found that: “The 77-SNP PRS was associated with a larger effect than previously reported for a 10-SNP PRS. For example, our odds ratio for breast cancer for women in the highest compared with the middle quintile was 1.82 (95% CI = 1.73 to 1.90) vs 1.44 (95% CI = 1.35 to 1.53) for the 10-SNP PRS.” They concluded that: “Our results show that the PRS stratifies breast cancer risk in women without family history and refines genetic risk in women with a family history of breast cancer.”

Rudolph et al (2018) investigated the integration of PRS into risk prediction models which combine PRS and environmental risk factors to improve risk prediction by evaluation of their joint association with reproductive history, alcohol consumption, menopausal hormone therapy (MHT), height and body mass index (BMI) in retrospective review of 20 studies. They found that “The strongest evidence for a non-multiplicative joint association with the 77-SNP PRS was for alcohol consumption (P-interaction = 0.009), adult height (P-interaction = 0.025) and current use of combined MHT (P-interaction = 0.038) in ER-positive disease. Risk associations for these factors by percentiles of PRS did not follow a clear dose-response. In addition, global and tail-based goodness of fit tests showed little evidence for departures from a multiplicative risk model, with alcohol consumption showing the strongest evidence for ER-positive disease (P = 0.013 for global and 0.18 for tail-based tests).” They concluded that “The combined effects of the 77-SNP PRS and environmental risk factors for breast cancer are generally well described by a multiplicative model. Larger studies are required to confirm possible departures from the multiplicative model for individual risk factors and assess models specific for ER-negative disease.”

State and Federal Regulations, as applicable

No SNP-based test to predict breast cancer risk has been approved or cleared by FDA.

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements

American Society of Clinical Oncology

Robson et al (2015) updated the American Society of Clinical recommendation for genetic and genomic testing for cancer susceptibility stating: “ASCO recognizes that concurrent multigene testing (i.e panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of

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established clinical utility as possible explanations for a patient's personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history. Multigene panel testing will also identify variants of uncertain significance (VUSs) in a substantial proportion of patient cases, simply as a result of the multiplicity of genes tested. ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history.

National Comprehensive Cancer Network

The NCCN Guideline (NCCN, 2018a) for Genetic/Familial High-Risk Assessment: Breast and Ovarian version 1.2019 states: "Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when mutations are found for moderate-penetrance genes and when a VUS is found. For this reason, the NCCN Panel recommends that multi-gene testing be offered in the content of professional genetic expertise, with pre- and post-test counseling being offered. Panel recommendations are in agreement with recommendations by ASCO, who issue an updated statement regarding genetic testing in 2015. Carriers of a genetic mutation should be encouraged to participate in clinical trials or genetic registries." The NCCN also states in version 2.2019, "As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. In addition, certain pathogenic/likely pathogenic variants in a gene may pose higher or lower risk than other pathogenic/likely pathogenic variants in that same gene. Therefore it may be difficult to use a known pathogenic/likely pathogenic variant alone to assign risk for relatives. In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone... There is an increased likelihood of finding variants of unknown significance when testing for pathogenic/likely pathogenic variants in multiple genes (NCCN, 2018b)."

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81307, 81308, 81599

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 11/2019

Specialty Matched Consultant Advisory Panel 3/2020

Medical Director review 3/2020

Medical Director review 10/2020

Specialty Matched Consultant Advisory Panel 3/2021

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Policy Implementation/Update Information

- 1/1/2019 New policy developed. Testing for one or more single nucleotide polymorphisms (SNPs) is **investigational** for all indications, including but not limited to use as a method of estimating individual patient risk for developing breast cancer. These include, but are not limited, to the OncoVue®, OncoArray, TruSight®, deCODE BreastCancer™ and BREVA Genplus,™ breast cancer tests and tests offered directly to consumers. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
- 10/29/19 No change to policy statements. (hb)
- 12/31/19 Reviewed by Avalon 3rd Quarter 2019 CAB. Under “When Covered” section: removed OncoVue and deCODE BreastCancer tests since they are no longer commercially available. Added CPT codes 81307, 81308 to the Billing/Coding section for effective date 1/1/2020. Medical Director review 11/2019. (lpr)
- 3/31/20 Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (lpr)
- 11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Literature review only. Updated references and added Related Policies section. Medical Director review 10/2020. (lpr)
- 4/6/21 Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr)

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and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.