

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
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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, 2018).

Related Policies:

Molecular Expression Testing for Breast Cancer Prognosis AHS-M2020
General Genetic Testing, Germline Disorders AHS-M2145
General Genetic Testing, Somatic Disorders AHS-M2146

****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 and tests offered directly to consumers.

Policy Guidelines

Following skin cancer, breast cancer is tied with lung cancer as the most frequently diagnosed cancer across the globe and is the overall leading cause of cancer death in women (Bray et al., 2018). In the United States, following skin cancer, breast cancer is the second most commonly diagnosed cancer and

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following lung cancer, is the second most common cause of cancer death in women. Approximately one in eight women will develop breast cancer in their lifetime (ACS, 2022).

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; Ghoussaini 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., 2015; 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 Breast Cancer Risk Assessment Tool (BCRAT), most often referred to as the Gail model (Gail et al., 1989) is 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 et al., 2002; Visvanathan et al., 2009). While this model has implications for primary prevention of invasive breast cancer, both the discriminatory accuracy of the Gail model and its calibration in certain populations have been challenged (Mealiffe et al., 2010). In 2018, Wang et al. (2018) systematically reviewed and analyzed the performance of different versions of the Gail model. They did find that the original Gail model 1 and the Caucasian-American Gail model was well calibrated in American and European women. However, in contrast, the Caucasian-American and Asian-American Gail models likely overestimate the risk in Asian females, providing a risk roughly double that of their actual risk (Wang et al., 2018).

Previous studies have analyzed the potential impact of adding genetic information from a panel of single nucleotide polymorphisms (SNPs) associated with breast cancer risk to the Gail model (Gail, 2008, 2009). SNPs are specific locations in the genome where a nucleotide differs between individuals. 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 et al., 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).

Proprietary Testing

Proprietary tests exist for the assessment of SNPs in breast cancer risk. TruSight evaluates 94 genes and 284 SNPs related to common and rare cancers, including breast cancer (TruSight, 2016); BREVAGenplus, now GeneType for Breast Cancer, measures 66 genes and 77 loci for Caucasian

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women, 74 for African American women, and 71 for Hispanic women (GeneType, 2019; GTR, 2019); Infinium OncoArray-500k covers over 500,000 SNPs associated with many types of cancer, as well as other features such as ancestry and pharmacogenetics (Illumina, 2019). Additionally, companies, such as 23andMe, can offer direct-to-consumer SNP testing for risk of breast cancer (23andme, 2019; Begley, 2018; FDA, 2018). The amount of possible assessments and combinations of SNPs are virtually infinite.

Clinical Utility and Validity

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 factor 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; Vachon et al., 2015).

Michailidou et al. (2017) performed a GWAS on breast cancer, encompassing “122,977 cases and 105,974 controls of European ancestry and 14,068 cases and 13,104 controls of East Asian ancestry.” Overall, they identified 65 new loci associated at a genome-wide level with overall breast cancer risk (defined as $P < 5 \times 10^{-8}$). The authors concluded that “these results provide further insight into genetic susceptibility to breast cancer and will improve the use of genetic risk scores for individualized screening and prevention” (Michailidou et al., 2017).

Cuzick et al (2017) developed a SNP risk score (SNP88) using the Illumina OncoArray, which includes most known breast-cancer risk SNPs (previously validated and directly available or with close surrogates on the OncoArray) in women receiving preventative treatment. They found that “SNP88 was predictive of breast cancer risk overall (interquartile range odds ratio [IQ-OR], 1.37), but mainly for estrogen receptor-positive disease (IQ-OR, 1.44) versus estrogen receptor-negative disease. However, the observed risk of SNP88 was only 46% of expected. No significant interaction was observed with treatment arm. SNP88 was independent of TC (Spearman rank-order correlation, 0.012) and when combined multiplicatively, a “substantial” improvement was seen (IQ-OR, 1.64)” (Cuzick et al., 2017).

Mavaddat et al (2015) evaluated the value of using 77 breast cancer related SNPs for risk stratification. A total of 33,673 breast cancer cases and 33,381 controls were analyzed. All possible pair-wise multiplicative interactions were examined and a 77-SNP polygenic risk score (PRS) was created for estrogen receptor (ER) status, as well as breast cancer overall. The authors found that women in the highest 1% of the PRS had a “three-fold increased risk” compared to women in the middle quintile (odds ratio = 3.36). Lifetime risk of breast cancer for women without a family history that had a PRS in the lowest and highest quintiles were 5.2% and 16.6%, respectively (Mavaddat et al., 2015).

Rudolph et al (2018) investigated the integration of PRS into risk prediction models, combining PRS and environmental risk factors. The authors performed a retrospective review of 20 studies and evaluated joint associations of the 77-SNP PRS with several environmental factors such as body mass index (BMI) and alcohol use. They found that “the strongest evidence for a non-multiplicative joint association with the 77-SNP PRS was for alcohol consumption, adult height, and current use of combined menopausal hormone therapy 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)” (Rudolph et al., 2018). 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” (Rudolph et al., 2018).

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Schuetz et al. (2019) researched genetic variants and the relationship between inflammation, apoptosis, and autophagy in breast cancer risk. In total, 206 SNPs were tested in 54 genes related to inflammation, apoptosis, and autophagy in a population-based breast cancer study; this study included women of both European descent (658 with breast cancer and 795 controls) and East Asian descent (262 with breast cancer and 127 controls). The researchers report that “although no SNP was associated with breast cancer risk among women of European descent, we found evidence for an association among East Asians for rs1800925 (IL-13) and breast cancer risk (OR = 2.08; 95% CI: 1.32-3.28; $p = 0.000779$), which remained statistically significant after multiple testing correction” (Schuetz et al., 2019). The researchers also report that “This association was replicated in a meta-analysis of 4305 cases and 4194 controls in the Shanghai Breast Cancer Genetics Study” (Schuetz et al., 2019).

Kapoor et al. (2020) assessed potential interactions between 205 breast cancer susceptibility loci and 13 established breast cancer risk factors. A total of 28,176 cases and 32,209 controls were analyzed with the iCOGS array (a custom SNP genotyping array), and 44,109 cases and 48,145 controls were genotyped using the OncoArray. An interaction with less than or equal to 1% prior probability was found with three different SNP risk factor pairs. “SNP rs4442975 was associated with a greater reduction of risk of ER-positive breast cancer... in current users of estrogen-progesterone therapy compared with non-users. This finding was supported by replication using OncoArray data of the previously reported interaction between rs13387042 ($r^2 = 0.93$ with rs4442975) and current estrogen-progesterone therapy for overall disease (Pint = 0.004). The two other interactions suggested stronger associations between SNP rs6596100 and ER-negative breast cancer with increasing parity and younger age at first birth” (Kapoor et al., 2020).

Shu et al. (2020) performed a meta-analysis of data from GWAS conducted in Asians (24,206 cases, 24,775 controls) and European descendants (122,977 cases, 105,974). The focus of their study was identifying additional genetic susceptibility loci for breast cancer, as currently known risk variants only explain a small portion of breast cancer heritability, particularly in Asian women. In this study, they identified 31 potential novel risk loci, with the lead variant showing an association with breast cancer risk at $p < 5 \times 10^{-8}$. Of note, “the associations for 10 of these loci were replicated in an independent sample of 16,787 cases and 16,680 controls of Asian women ($P < 0.05$). In addition, we replicated the associations for 78 of the 166 known risk variants at $P < 0.05$ in Asians. These findings improve our understanding of breast cancer genetics and etiology and extend previous findings from studies of European descendants to Asian women” (Shu et al., 2020).

Zhang et al. (2020) note that “breast cancer susceptibility variants frequently show heterogeneity in associations by tumor subtype... defined by combinations of ER, [progesterone receptor] PR, [human epidermal growth factor 2] HER2 and grade: (1) luminal A-like, (2) luminal B/HER2-negative-like, (3) luminal B-like, (4) HER2-enriched-like and (5) triple-negative or basal-like” To identify novel breast cancer loci, they performed a GWAS (133,384 breast cancer cases, 113,789 controls, plus 18,908 *BRCA1* mutation carriers, 9,414 of them with breast cancer) on patients with European ancestry. They identified 32 novel susceptibility loci ($p < 5 \times 10^{-8}$), 15 of which showed associations with at least one tumor feature. Five loci showed opposite associations ($p < 0.05$) between luminal- and non-luminal subtypes. They also found that “the genetic correlations between five intrinsic-like subtypes ranged from 0.35 to 0.80. The proportion of genome-wide chip heritability explained by all known susceptibility loci was 37.6% for triple-negative and 54.2% for luminal A-like disease. The odds ratios of polygenic risk scores (PRSs), which included 330 variants, for the highest 1% quantiles compared to middle quantiles were 5.63 and 3.02 for luminal A-like and triple-negative disease, respectively. These findings provide an improved understanding of genetic predisposition to breast cancer subtypes and will inform the development of subtype-specific polygenic risk scores” (Zhang et al., 2020).

Adedokun et al. (2021) used a cross-ancestry GWAS approach to describe breast cancer risk loci. They identified breast cancer variants in individuals from African ancestry GWAS (9,421 cases, 10,193 controls) and meta-analyzed them with European ancestry GWAS data (122,977 cases, 105,974 controls). The identified “four loci for overall breast cancer risk [1p13.3, 5q31.1, 15q24 (two independent signals), and 15q26.3] and two loci for estrogen receptor-negative disease (1q41 and 7q11.23) at genome-

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wide significance.” This study suggests that replication across multiple ancestry populations will “help improve the understanding of breast cancer genetics and identify causal variants” (Adedokun et al., 2021).

Chen et al. (2022) conducted a “genome-wide association study, as well as a transcriptome-wide association study (TWAS), of age- and BMI- adjusted DA, NDA, and PMD in up to 27,900 European-ancestry women from the MODE/BCAC consortia.” In their results they identified 28 genome-wide significant loci for MD phenotypes and found that 45% of all known breast cancer SNPs were associated with at least one MD phenotype. Also, “TWAS identified two novel genes (*SHOX2* and *CRISPLD2*) whose genetically predicted expression was significantly associated with MD phenotypes”. In conclusion, their findings provided insight into the genetic background of MD phenotypes, and further demonstrated their shared genetic basis with breast cancer. (Chen et al., 2022).

State and Federal Regulations, as applicable

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

American Society of Clinical Oncology (ASCO)

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

National Comprehensive Cancer Network (NCCN)

Prior to 2020, the NCCN guidelines focused largely on testing *BRCA1/2*. However, in 2022, the NCCN updated their guidelines as “there is now strong evidence that genes beyond *BRCA1/2* confer markedly increased risk of breast and/or ovarian cancers” (NCCN 2022). The NCCN Guideline for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic version 2.2022 states: “multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome. In these cases, phenotype-directed testing based on personal and family history through a multi-gene panel test may be more efficient and/or cost-effective. Multi-gene testing may also be considered for those who tested negative for one particulate syndrome, but whom personal and family history is suggestive of an inherited susceptibility.” They also state “multi-gene tests also increase the likelihood of detecting a VUS. However, as multi-gene testing is increasingly used, the frequency of a variant being interpreted as a VUS is expected to decrease.” They recommend that “for individuals potentially meeting established criteria for one or more of the hereditary cancer syndromes, genetic testing should be considered along with appropriate pre- and post-test counseling” (category 2A).

The NCCN Panel recommends “multi-gene testing may be considered for individuals who meet these criteria [Testing Criteria for High-Penetrance Breast and Ovarian Susceptibility Genes] and who

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previously underwent single-gene and/or absent deletion duplication analysis but tested negative. Both first- and second-degree relatives of individuals who meet these testing criteria are also eligible for testing, except for second-degree relatives of individuals with pancreatic cancer or prostate cancer, for whom prior probability of a high-penetrance cancer susceptibility gene is low in the absence of additional family history of cancer; only first-degree relatives of these affected individuals should be offered testing, unless indicated for other relatives based on additional family history.” The guidelines also note that “carriers of a pathogenic or likely pathogenic variant should be encouraged to participate in clinical trials or genetic registries. Carriers should be encouraged to recontact their genetics providers every few years for updates, as laboratories may issue amended reports as the knowledge base surrounding hereditary cancer risk expands” (category 2A) (NCCN, 2022).

The NCCN also states “a major dilemma regarding multi-gene testing is that there are limited data and a lack of clear guidelines regarding degree of cancer risk associated with some of the genes assessed, and how to communicate and manage risk for carriers of these genes. This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies. Multi-gene tests often include low to moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management. Also, certain variants in a gene may be associated with a different degree of risk than other variants in that gene. For example, the presence of certain *ATM* genetic variants is associated with an increased risk for early-onset breast cancer and frequent bilateral occurrence, but the association between other *ATM* variants and breast cancer susceptibility is less clear” (NCCN, 2022).

The NCCN states, “Recently, there has been an increase in genetic test results through direct-to-consumer (DTC) services or through tumor profiling. The testing typically used by companies providing ancestry information directly to consumers is microarray-based single nucleotide polymorphism (SNP) testing that has not been validated for clinical use. These companies do not provide comprehensive genetic analysis that includes gross deletion or duplication analysis. Third-party services are available to assist patients with interpreting their raw data, but these services are not government-regulated. In addition to the errors inherent in working with raw uncrated data from DTC labs, other limitations of these services include inadequate informed consent process, uncertain clinical validity and utility, and lack of medical oversight.²⁶ Currently available tests also only provide limited founder P/LP variant results without the benefit of family history.” (NCCN, 2022)

“Given the limitations of the information obtained from DTC services, confirmatory germline testing by a certified laboratory is recommended, and changes to a patient’s medical management based solely on DTC testing results are not recommended.” (NCCN, 2022)

Finally, the NCCN also notes 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 is substantial” (NCCN, 2022).

The United States Preventive Services Task Force (USPSTF)

The USPSTF published recommendations related to genetic testing for breast cancer. In particular, “The USPSTF found adequate evidence that the benefits of risk assessment, genetic counseling, and genetic testing are moderate in women whose family history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes,” whereas for women without such family history, it stated that the benefits are small to none (Dörk et al., 2020). They concluded with moderate certainty that the net benefit of these procedures outweighs the harms in women both with and without a familial risk of potentially harmful mutations.

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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: 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

23andme. (2019). DO YOU SPEAK BRCA? 23andMe, Inc.
<https://www.23andme.com/brca/>

ACS. (2022). Key Statistics for Breast Cancer.
<https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html>

Adedokun, B., Du, Z., Gao, G., Ahearn, T. U., Lunetta, K. L., Zirpoli, G., Figueroa, J., John, E. M., Bernstein, L., Zheng, W., Hu, J. J., Ziegler, R. G., Nyante, S., Bandera, E. V., Ingles, S. A., Press, M. F., Deming-Halverson, S. L., Rodriguez-Gil, J. L., Yao, S., Huo, D. (2021). Cross-ancestry GWAS meta-analysis identifies six breast cancer loci in African and European ancestry women. *Nat Commun*, 12(1), 4198. <https://doi.org/10.1038/s41467-021-24327-x>

Ahmed, S., Thomas, G., Ghousaini, M., Healey, C. S., Humphreys, M. K., Platte, R., Morrison, J., Maranian, M., Pooley, K. A., Luben, R., Eccles, D., Evans, D. G., Fletcher, O., Johnson, N., dos Santos Silva, I., Peto, J., Stratton, M. R., Rahman, N., Jacobs, K., Easton, D. F. (2009). Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. *Nat Genet*, 41(5), 585-590.
<https://doi.org/10.1038/ng.354>

Antoniou, A. C., Wang, X., Fredericksen, Z. S., McGuffog, L., Tarrell, R., Sinilnikova, O. M., Healey, S., Morrison, J., Kartsonaki, C., Lesnick, T., Ghousaini, M., Barrowdale, D., Peock, S., Cook, M., Oliver, C., Frost, D., Eccles, D., Evans, D. G., Eeles, R., Couch, F. J. (2010). A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. *Nat Genet*, 42(10), 885-892.
<https://doi.org/10.1038/ng.669>

Begley, S. (2018). FDA approves first direct-to-consumer test for breast cancer risk. STAT.
<https://www.statnews.com/2018/03/06/fda-approves-test-breast-cancer/>

Bojesen, S. E., Pooley, K. A., Johnatty, S. E., Beesley, J., Michailidou, K., Tyrer, J. P., Edwards, S. L., Pickett, H. A., Shen, H. C., Smart, C. E., Hillman, K. M., Mai, P. L., Lawrenson, K., Stutz, M. D., Lu, Y., Karevan, R., Woods, N., Johnston, R. L., French, J. D. Dunning, A. M. (2013). Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. *Nat Genet*, 45(4), 371-384, 384e371-372. <https://doi.org/10.1038/ng.2566>

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 68(6), 394-424. <https://doi.org/10.3322/caac.21492>

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Cox, A., Dunning, A. M., Garcia-Closas, M., Balasubramanian, S., Reed, M. W., Pooley, K. A., Scollen, S., Baynes, C., Ponder, B. A., Chanock, S., Lissowska, J., Brinton, L., Peplonska, B., Southey, M. C., Hopper, J. L., McCredie, M. R., Giles, G. G., Fletcher, O., Johnson, N., Easton, D. F. (2007). A common coding variant in CASP8 is associated with breast cancer risk. *Nat Genet*, 39(3), 352-358. <https://doi.org/10.1038/ng1981>

Cuzick, J., Brentnall, A. R., Segal, C., Byers, H., Reuter, C., Detre, S., Lopez-Knowles, E., Sestak, I., Howell, A., Powles, T. J., Newman, W. G., & Dowsett, M. (2017). Impact of a Panel of 88 Single Nucleotide Polymorphisms on the Risk of Breast Cancer in High-Risk Women: Results From Two Randomized Tamoxifen Prevention Trials. *J Clin Oncol*, 35(7), 743-750. <https://doi.org/10.1200/jco.2016.69.8944>

Dörk, T., Park-Simon, T. W., & Hillemanns, P. (2020). Recommendations Related to Genetic Testing for Breast Cancer. *Jama*, 323(2), 188. <https://doi.org/10.1001/jama.2019.18214>

Easton, D. F., Pooley, K. A., Dunning, A. M., Pharoah, P. D. P., Thompson, D., Ballinger, D. G., Struwing, J. P., Morrison, J., Field, H., Luben, R., Wareham, N., Ahmed, S., Healey, C. S., Bowman, R., Luccarini, C., Conroy, D., Shah, M., Munday, H., Jordan, C., Ponder, B. A. J. (2007). Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature*, 447(7148), 1087-1093. <https://doi.org/10.1038/nature05887>

Elmore, J. (2017). Risk prediction models for breast cancer screening - *UpToDate*. In S. Vora (Ed.), *UpToDate*. <https://www.uptodate.com/contents/risk-prediction-models-for-breast-cancer-screening>

FDA. (2018, 07/29/2019). DEN170046. Retrieved from <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN170>

Fletcher, O., Johnson, N., Orr, N., Hosking, F. J., Gibson, L. J., Walker, K., Zelenika, D., Gut, I., Heath, S., Palles, C., Coupland, B., Broderick, P., Schoemaker, M., Jones, M., Williamson, J., Chilcott-Burns, S., Tomczyk, K., Simpson, G., Jacobs, K. B., Peto, J. (2011). Novel breast cancer susceptibility locus at 9q31.2: results of a genome-wide association study. *J Natl Cancer Inst*, 103(5), 425-435. <https://doi.org/10.1093/jnci/djq563>

French, J. D., Ghousaini, M., Edwards, S. L., Meyer, K. B., Michailidou, K., Ahmed, S., Khan, S., Maranian, M. J., O'Reilly, M., Hillman, K. M., Betts, J. A., Carroll, T., Bailey, P. J., Dicks, E., Beesley, J., Tyrer, J., Maia, A. T., Beck, A., Knoblauch, N.W., Dunning, A. M. (2013). Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. *Am J Hum Genet*, 92(4), 489-503. <https://doi.org/10.1016/j.ajhg.2013.01.002>

Gail, M. H. (2008). Discriminatory accuracy from single-nucleotide polymorphisms in models to predict breast cancer risk. *J Natl Cancer Inst*, 100(14), 1037-1041. <https://doi.org/10.1093/jnci/djn180>

Gail, M. H. (2009). Value of adding single-nucleotide polymorphism genotypes to a breast cancer risk model. *J Natl Cancer Inst*, 101(13), 959-963. <https://doi.org/10.1093/jnci/djp130>

Gail, M. H., Brinton, L. A., Byar, D. P., Corle, D. K., Green, S. B., Schairer, C., & Mulvihill, J. J. (1989). Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*, 81(24), 1879-1886. <http://dx.doi.org/>

Garcia-Closas, M., Couch, F. J., Lindstrom, S., Michailidou, K., Schmidt, M. K., Brook, M. N., Orr, N., Rhie, S. K., Riboli, E., Feigelson, H. S., Le Marchand, L., Buring, J. E., Eccles, D., Miron, P., Fasching, P. A., Brauch, H., Chang-Claude, J., Carpenter, J., Godwin, A. K., Kraft, P. (2013). Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat Genet*, 45(4), 392-398. <https://doi.org/10.1038/ng.2561>

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

GeneType. (2019, May 2019). *Product Specification: GeneType for Breast Cancer*. Retrieved Jul 28, 2021 from https://e13609b8-ed51-46c1-8570-6819a0110aba.filesusr.com/ugd/70aa06_079e41335b874beebc288a6fe4582276.pdf

Ghoussaini, M., Fletcher, O., Michailidou, K., Turnbull, C., Schmidt, M. K., Dicks, E., Dennis, J., Wang, Q., Humphreys, M. K., Luccarini, C., Baynes, C., Conroy, D., Maranian, M., Ahmed, S., Driver, K., Johnson, N., Orr, N., dos Santos Silva, I., Waisfisz, Q., Easton, D. F. (2012). Genome-wide association analysis identifies three new breast cancer susceptibility loci. *Nat Genet*, 44(3), 312-318. <https://doi.org/10.1038/ng.1049>

GTR. (2019). BREVA Genplus. Retrieved from <https://www.ncbi.nlm.nih.gov/gtr/tests/500060/overview/>

Haiman, C. A., Chen, G. K., Vachon, C. M., Canzian, F., Dunning, A., Millikan, R. C., Wang, X., Ademuyiwa, F., Ahmed, S., Ambrosone, C. B., Baglietto, L., Balleine, R., Bandera, E. V., Beckmann, M. W., Berg, C. D., Bernstein, L., Blomqvist, C., Blot, W. J., Brauch, H., Couch, F. J. (2011). A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer. *Nat Genet*, 43(12), 1210-1214. <https://doi.org/10.1038/ng.985>

Illumina. (2019). Infinium OncoArray-500K BeadChip. <https://www.illumina.com/products/by-type/microarray-kits/infinium-oncoarray-500k.html>

Kapoor, P. M., Lindström, S., Behrens, S., Wang, X., Michailidou, K., Bolla, M. K., Wang, Q., Dennis, J., Dunning, A. M., Pharoah, P. D. P., Schmidt, M. K., Kraft, P., García-Closas, M., Easton, D. F., Milne, R. L., & Chang-Claude, J. (2020). Assessment of interactions between 205 breast cancer susceptibility loci and 13 established risk factors in relation to breast cancer risk, in the Breast Cancer Association Consortium. *Int J Epidemiol*, 49(1), 216-232. <https://doi.org/10.1093/ije/dyz193>

Kinsinger, L. S., Harris, R., Woolf, S. H., Sox, H. C., & Lohr, K. N. (2002). Chemoprevention of breast cancer: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*, 137(1), 59-69. <http://dx.doi.org/>

Lichtenstein, P., Holm, N. V., Verkasalo, P. K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A., & Hemminki, K. (2000). Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*, 343(2), 78-85. <https://doi.org/10.1056/nejm200007133430201>

Mavaddat, N., Pharoah, P. D. P., Michailidou, K., Tyrer, J., Brook, M. N., Bolla, M. K., Wang, Q., Dennis, J., Dunning, A. M., Shah, M., Luben, R., Brown, J., Bojesen, S. E., Nordestgaard, B. G., Nielsen, S. F., Flyger, H., Czene, K., Darabi, H., Eriksson, M., Garcia-Closas, M. (2015). Prediction of Breast Cancer Risk Based on Profiling With Common Genetic Variants. *J Natl Cancer Inst*, 107(5). <https://doi.org/10.1093/jnci/djv036>

Mealiffe, M. E., Stokowski, R. P., Rhees, B. K., Prentice, R. L., Pettinger, M., & Hinds, D. A. (2010). Assessment of Clinical Validity of a Breast Cancer Risk Model Combining Genetic and Clinical Information. *J Natl Cancer Inst*, 102(21), 1618-1627. <https://doi.org/10.1093/jnci/djq388>

Michailidou, K., Hall, P., Gonzalez-Neira, A., Ghoussaini, M., Dennis, J., Milne, R. L., Chang-Claude, J., Bojesen, S. E., Bolla, M. K., Wang, Q., Dicks, E., Lee, A., Turnbull, C., Rahman, N., Fletcher, O., Peto, J., Gibson, L., Silva Idos, S., Easton, D. F. (2013). Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet*, 45(4), 353-361e352. <https://doi.org/10.1038/ng.2563>

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

Michailidou, K., Lindstrom, S., Dennis, J., Beesley, J., Hui, S., Kar, S., Lemacon, A., Soucy, P., Glubb, D., Rostamianfar, A., Bolla, M. K., Wang, Q., Tyrer, J., Dicks, E., Lee, A., Wang, Z., Allen, J., Keeman, R., Eilber, U., . . Easton, D. F. (2017). Association analysis identifies 65 new breast cancer risk loci. *Nature*, 551(7678), 92-94. <https://doi.org/10.1038/nature24284>

NCCN. (2022). *NCCN Clinical Practice Guidelines in Oncology; Genetic/Familial High-Risk Assessment: Breast and Ovarian V2.2022*. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

Peto, J., & Mack, T. M. (2000). High constant incidence in twins and other relatives of women with breast cancer. *Nat Genet*, 26(4), 411-414. <https://doi.org/10.1038/82533>

Pharoah, P. D., Antoniou, A. C., Easton, D. F., & Ponder, B. A. (2008). Polygenes, risk prediction, and targeted prevention of breast cancer. *N Engl J Med*, 358(26), 2796-2803. <https://doi.org/10.1056/NEJMsa0708739>

Raby, B. (2018). *Overview of genetic variation - UpToDate*. <https://www.uptodate.com/contents/overview-of-genetic-variation>

Robson, M. E., Bradbury, A. R., Arun, B., Domchek, S. M., Ford, J. M., Hampel, H. L., Lipkin, S. M., Syngal, S., Wollins, D. S., & Lindor, N. M. (2015). American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol*, 33(31), 3660-3667. <https://doi.org/10.1200/jco.2015.63.0996>

Rudolph, A., Song, M., Brook, M. N., Milne, R. L., Mavaddat, N., Michailidou, K., Bolla, M. K., Wang, Q., Dennis, J., Wilcox, A. N., Hopper, J. L., Southey, M. C., Keeman, R., Fasching, P. A., Beckmann, M. W., Gago-Dominguez, M., Castelao, J. E., Guenel, P., Truong, T., Garcia-Closas, M. (2018). Joint associations of a polygenic risk score and environmental risk factors for breast cancer in the Breast Cancer Association Consortium. *Int J Epidemiol*, 47(2), 526-536. <https://doi.org/10.1093/ije/dyx242>

Schuetz, J. M., Grundy, A., Lee, D. G., Lai, A. S., Kobayashi, L. C., Richardson, H., . Long, J., Zheng, W., Aronson, K. J., Spinelli, J. J., & . . Brooks-Wilson, A. R. (2019). Genetic variants in genes related to inflammation, apoptosis and autophagy in breast cancer risk. *PLoS One*, 14(1), e0209010. <https://doi.org/10.1371/journal.pone.0209010>

Shu, X., Long, J., Cai, Q., Kweon, S. S., Choi, J. Y., Kubo, M., Park, S. K., Bolla, M. K., Dennis, J., Wang, Q., Yang, Y., Shi, J., Guo, X., Li, B., Tao, R., Aronson, K. J., Chan, K. Y. K., Chan, T. L., Gao, Y. T., . . Zheng, W. (2020). Identification of novel breast cancer susceptibility loci in meta-analyses conducted among Asian and European descendants. *Nat Commun*, 11(1), 1217. <https://doi.org/10.1038/s41467-020-15046>

Stacey, S. N., Manolescu, A., Sulem, P., Rafnar, T., Gudmundsson, J., Gudjonsson, S. A., Masson, G., Jakobsdottir, M., Thorlacius, S., Helgason, A., Aben, K. K., Strobbe, L. J., Albers-Akkers, M. T., Swinkels, D. W., Henderson, B. E., Kolonel, L. N., Le Marchand, L., Millastre, E., Andres, R., . . Stefansson, K. (2007). Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet*, 39(7), 865-869. <https://doi.org/10.1038/ng2064>

Stacey, S. N., Manolescu, A., Sulem, P., Thorlacius, S., Gudjonsson, S. A., Jonsson, G. F., Jakobsdottir, M., Bergthorsson, J. T., Gudmundsson, J., Aben, K. K., Strobbe, L. J., Swinkels, D. W., van Engelenburg, K. C., Henderson, B. E., Kolonel, L. N., Le Marchand, L., Millastre, E., Andres, R., Saez, B., .Stefansson, K. (2008). Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet*, 40(6), 703-706. <https://doi.org/10.1038/ng.131>

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

Thomas, G., Jacobs, K. B., Kraft, P., Yeager, M., Wacholder, S., Cox, D. G., Hankinson, S. E., Hutchinson, A., Wang, Z., Yu, K., Chatterjee, N., Garcia-Closas, M., Gonzalez-Bosquet, J., Prokunina-Olsson, L., Orr, N., Willett, W. C., Colditz, G. A., Ziegler, R. G., Berg, C. D., Hunter, D. J. (2009). A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). *Nat Genet*, 41(5), 579-584. <https://doi.org/10.1038/ng.353>

TruSight. (2016). TruSight® Cancer Sequencing Panel. https://www.illumina.com/Documents/products/datasheets/datasheet_trusight_cancer.pdf

Turnbull, C., Ahmed, S., Morrison, J., Pernet, D., Renwick, A., Maranian, Seal, S., Ghoussaini, M., Hines, S., Healey, C. S., Hughes, D., Warren-Perry, M., Tapper, W., Eccles, D., Evans, D. G., Hoening, M., Schutte, M., van den Ouweland, A., Houlston, R., Easton, D. F. (2010). Genome-wide association study identifies five new breast cancer susceptibility loci. *Nat Genet*, 42(6), 504-507. <https://doi.org/10.1038/ng.586>

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Vachon, C. M., Pankratz, V. S., Scott, C. G., Haeberle, L., Ziv, E., Jensen, M. R., Brandt, K. R., Whaley, D. H., Olson, J. E., Heusinger, K., Hack, C. C., Jud, S. M., Beckmann, M. W., Schulz-Wendtland, R., Tice, J. A., Norman, A. D., Cunningham, J. M., Purrington, K. S., Easton, D. F., Couch, F. J. (2015). The contributions of breast density and common genetic variation to breast cancer risk. *J Natl Cancer Inst*, 107(5). <https://doi.org/10.1093/jnci/dju397>

Visvanathan, K., Chlebowski, R. T., Hurley, P., Col, N. F., Ropka, M., Collyar, D., Morrow, M., Runowicz, C., Pritchard, K. I., Hagerty, K., Arun, B., Garber, J., Vogel, V. G., Wade, J. L., Brown, P., Cuzick, J., Kramer, B. S., & Lippman, S. M. (2009). American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. *J Clin Oncol*, 27(19), 3235-3258. <http://doi.org/10.1200/jco.2008.20.5179>

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

Wacholder, S., Hartge, P., Prentice, R., Garcia-Closas, M., Feigelson, H. S., Diver, W. R., Thun, M. J., Cox, D. G., Hankinson, S. E., Kraft, P., Rosner, B., Berg, C. D., Brinton, L. A., Lissowska, J., Sherman, M. E., Chlebowski, R., Kooperberg, C., Jackson, R. D., Buckman, D. W., Hunter, D. J. (2010). Performance of common genetic variants in breast-cancer risk models. *N Engl J Med*, 362(11), 986-993. <https://doi.org/10.1056/NEJMoa0907727>

Wang, X., Huang, Y., Li, L., Dai, H., Song, F., & Chen, K. (2018). Assessment of performance of the Gail model for predicting breast cancer risk: a systematic review and meta-analysis with trial sequential analysis. *Breast Cancer Res*, 20(1), 18. <https://doi.org/10.1186/s13058-018-0947-5>

Zhang, H., Ahearn, T. U., Lecarpentier, J., Barnes, D., Beesley, J., Qi, G., Jiang, X., O'Mara, T. A., Zhao, N., Bolla, M. K., Dunning, A. M., Dennis, J., Wang, Q., Ful, Z. A., Aittomaki, K., Andrulis, I. L., Anton-Culver, H., Arndt, V., Aronson, K. J., Garcia-Closas, M. (2020). Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. *Nat Genet*, 52(6), 572-581. <https://doi.org/10.1038/s41588-020-0609-2>

Zheng, W., Long, J., Gao, Y. T., Li, C., Zheng, Y., Xiang, Y. B, Wen, W., Levy, S., Deming, S. L., Haines, J. L., Gu, K., Fair, A. M., Cai, Q., Lu, W., & Shu, X. O. (2009). Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. *Nat Genet*, 41(3), 324-328. <https://doi.org/10.1038/ng.318>

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

Medical Director review 3/2021

Medical Director review 11/2022

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 BREVAGenplus,™ 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)

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- 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)
- 11/16/21 Reviewed by Avalon 3rd Quarter 2021 CAB. Updated policy guidelines and references. Medical Director review 10/2021. (lpr)
- 12/13/22 Reviewed by Avalon 3rd Quarter 2022 CAB. Medical Director review 11/2022. Updated policy guidelines and references. Deleted CPT codes 81307, 81308 from Billing/Coding section. No change to policy statement. (lpr)

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