Sentara Health Plans

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Non-Familial Breast Cancer

Policy Number: AHS – M2126 – Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Non-Familial Breast Cancer	Prior Policy Name and Number, as applicable:
Policy Revision Date: 12/01/2024 Initial Policy Effective Date: 12/01/2024	

I. Policy Description

Single nucleotide polymorphisms (SNPs) are single-base pair changes that achieve a population frequency of at least one percent. They represent the most common form of genetic variation and are responsible for much of the heritable phenotypic variation observed in human populations, but are not clearly deleterious (Attia, 2024; MedlinePlus, 2024).

II. Related Policies

Policy Number	Policy Title
AHS-M2020	Molecular Diagnostics for Breast Cancer Prognosis

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

1) For all situations, testing for one or more single nucleotide polymorphisms (SNPs) to estimate an individual's risk for developing breast cancer (e.g., OncoArray, TruSight®, and BREVAGenplus™ breast cancer tests; tests offered directly to consumers) **DOES NOT MEET COVERAGE CRITERIA**.

IV. Table of Terminology

Term	Definition
ASCO	American Society of Clinical Oncology
ATM	*ATM serine/threonine kinase*
AUC	Area under the curve
BCRAT	Breast cancer risk assessment tool
BCSC	Breast cancer surveillance consortium
BMI	Body mass index
BRCA1	*BRCA1 DNA repair associated*
BRCA2	*BRCA2 DNA repair associated*
CHEK2	*Checkpoint kinase 2*
CLIA '88	Clinical Laboratory Improvement Amendments Of 1988
CMS	Centers For Medicare and Medicaid Services
CRISPLD2	*Cysteine rich secretory protein LCCL domain containing 2*
DA	Dense tissue
ER	Estrogen receptor
FDA	Food and Drug Administration
GWAS	Genome-wide association studies
HER2	Human epidermal growth factor 2
IL-13	*Interleukin 13*
IQ-QR	Interquartile range odds ratio
LDT	Laboratory developed test
MD	Mammographic density
NCCN	National Comprehensive Cancer Network
NDA	Non-dense tissue
PALB2	*Partner and localizer of BRCA2*
PMD	Percent density
PR	Progesterone receptor
PRS	Polygenic risk score
SNP88	Single nucleotide polymorphism risk score
SNP	Single nucleotide polymorphism
SHOX2	*Short stature homeobox 2*
TWAS	Transcriptome-wide association study
USPSTF	United States Preventive Services Task Force
VUS	Variant of uncertain significance

V. Scientific Background

In the United States, breast cancer is the second most diagnosed cancer, following skin cancer, and, the second most common cause of cancer death in women, following lung cancer. Approximately one in eight women will develop breast cancer in their lifetime (ACS, 2024).

Breast cancer risk is strongly associated with both genetic and environmental factors. Familial aggregation and twin studies have shown that inherited susceptibility plays a substantial role in

risk of developing breast cancer (Lichtenstein et al., 2000; Peto & Mack, 2000). Many genetic loci are known to contribute to this risk. These loci fall into three categories: 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, principally through genome-wide association studies (GWAS) (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 identify additional risk 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 who 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).

It has been noted that the "effect of single SNPs in complex disease to date has been small (i.e., odds ratios in the 1.1-1.6 range)" (Attia, 2024). However, 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, excluding those associated with *BRCA1* or *BRCA2*, found that inclusion of these genetic factors only modestly improved performance of the BCRAT (Wacholder et al., 2010). Another study evaluated the inclusion of a SNP risk score combined with the Gail model, basing the SNP risk score on seven SNPs associated with risk for breast cancer (Mealiffe et al., 2010). 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 a clinical context. Incorporating genetic information has the greatest

improvement in risk assessment in subsets of women that are at an intermediate risk based on their clinical risk factors (Mealiffe et al., 2010). Moreover, it should be cautioned that though "Success in creating risk scores with a handful of SNPs has led some to try creating risk scores with tens or hundreds of thousands of SNPs, hoping to increase predictive power", the predictive power of these attempts tend to level off very rapidly. In one instance, increasing the number of SNPs examined from tens to millions only explained two to four percent of the variance in disease risk (Attia, 2024; Khera et al., 2018).

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 (Illumina, 2024b); BREVAGen*plus*, now GeneType for Breast Cancer, measures 66 genes and 77 loci for Caucasian women, 74 for African American women, and 71 for Hispanic women (GeneType, 2019, 2024); 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, 2024a). Additionally, companies, such as 23andMe, can offer direct-to-consumer SNP testing for risk of breast cancer (23andme, 2024; Begley, 2018; FDA, 2024). The number 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 to assess its attributable risk, comparing five-year absolute risk predictions between models within three studies (1643 case patients, 2397 control patients). The PRS was found to be an independent risk factor across all three studies and improved discriminatory accuracy for area under the curve (AUC) from 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, there was a 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. This suggests that SNPs could be clinically useful. 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).

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 (r2 = 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 associate with breast cancer risk at $p<5x10^{-8}$. 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 ($p<5x10^{-8}$), 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-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).

Jia et al. (2023) studied the association between SNPs and overall breast cancer risk in the Chinese female population, stating that "frequencies vary across ethnic group." Thirty-four SNPs were included in the study, all of which had been previously identified by GWAS. The authors conducted an association analysis, including 1848 patients with breast cancer and 709 healthy controls. The authors identified a a significant association between SNP rs12493607 and breast cancer risk, as well as invasive carcinoma, estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, HER2-negative, and young (aged younger than 45) breast cancer. The authors also identified "less conservatively" significant association with rs4784227 and rs2046210 and breast cancer risk. Overall, the authors concluded that the results "shed light on the relationship between SNPs and breast cancer susceptibility within a vast Chinese cohort, supporting the development of polygenetic risk scores for the Chinese population" (Jia et al., 2023).

VI. Guidelines and Recommendations

American Society of Clinical Oncology (ASCO)

An update from the ASCO included recommendations 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 based on the presented 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" (Robson et al., 2015).

National Comprehensive Cancer Network (NCCN)

Prior to 2020, the NCCN guidelines focused largely on testing *BRCA1/2.* However, the NCCN has since updated their guidelines based on "strong evidence that genes beyond *BRCA1/2*, *TP53*, and *PTEN* confer markedly increased risk of breast and/or ovarian cancers" (NCCN, 2024). These NCCN guidelines acknowledge that "Multi-gene testing can detect P/LP variants not found in single-gene testing", but "Since more than one gene can explain an inherited cancer syndrome, phenotype-directed testing based on personal and family history through a multi-gene panel test is often more efficient and/or cost-effective" (NCCN, 2024). Furthermore, "Multi-gene testing may also be considered for those who tested negative for one particular syndrome, but whose personal and family history is suggestive of an inherited susceptibility." The NCCN also stated that "Multi-gene tests also increase the likelihood of detecting a VUS." The NCCN recommends 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" (NCCN, 2024).

The NCCN Panel recommends that "Multi-gene testing may be considered for individuals who meet testing criteria and who 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 based on additional family history" (NCCN, 2024). It should be noted that "Carriers of a P/LP 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" (NCCN, 2024).

However, "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 exacerbated by the "low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies," and the fact that "Multi-gene tests include moderate-penetrance genes, and they often also include low-penetrance genes for which there are little available data regarding degree of cancer risk and guidelines for risk management"(NCCN, 2024).

The NCCN states, "Reports regarding germline findings that may impact medical management should come from laboratories that are certified by the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA), with some U.S. states (eg, New York) having additional reporting requirements.. 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 data from DTC labs, other limitations of these services include inadequate informed consent process, uncertain clinical validity and utility, and lack of medical oversight" (NCCN, 2024). As such, "Given the limitations of the information obtained from DTC services, confirmatory germline testing by a certified laboratory is clinically indicated, and changes to medical management based solely on DTC testing results are not recommended" (NCCN, 2024).

Finally, "Confirmatory germline testing through an appropriately certified laboratory is clinically indicated when a potential P/LP variant is identified through various data sources" as listed below:

- "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 results without the benefit of family history. More comprehensive genetic counseling and testing for pathogenic variants in other inherited cancer risk genes may be appropriate at the time of confirmation testing."

- "Commercial laboratories utilizing consumer-initiated or direct-to-consumer (DTC) marketing of DNA sequence-based cancer predisposition tests vary substantially in providing information necessary to make informed decisions regarding results and may vary in accuracy in their variant interpretation"
- "Research: Patients may have participated in research studies that included germline genomic analysis. In such cases, it is clinically indicated to review the patient's findings with a genetics professional and/or the reporting laboratory to establish whether the original report was generated by an appropriately certified laboratory, or whether confirmatory testing is clinically indicated" (NCCN, 2024).

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 (USPSTF, 2019). 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. The USPSTF does not address the use of SNPs as a screening method for cancer (USPSTF, 2019).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81599	Unlisted multianalyte assay with algorithmic analysis

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
12/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
12/01/2024	Initial Policy Implementation