Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Non-familial Breast Cancer

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DESCRIPTION

Note: *This policy is not intended to address testing for a known familial variant for breast cancer or testing of patient at high risk based on family history.*

Several single nucleotide variants (SNVs), which are single base-pair variations in the DNA sequence of the genome, have been found to be associated with breast cancer and are common in the population but confer only small increases in risk (1%). There are commercially available assays that test for a number SNVs to predict an individual's risk of breast cancer relative to the general population which may incorporate clinical

information into risk prediction algorithms. The intent of this type of test is to identify those individuals at increased risk who may benefit from more intensive surveillance.

Several common single nucleotide variants (SNVs) associated with breast cancer have been identified primarily through genome-wide association studies (GWAS) of very large case-control populations. These alleles occur with high frequency in the general population, and the increased breast cancer risk associated with each is very small relative to the general population risk. Some have suggested that these common-risk SNVs could be combined for individualized risk prediction either alone or in combination with traditional predictors; personalized breast cancer screening programs could then vary by starting age and intensity according to risk. Along these lines, the American Cancer Society has recommended that women at high risk (>20% lifetime risk) should undergo breast magnetic resonance imaging and a mammogram every year, and those at moderately increased risk (15%-20% lifetime risk) should talk with their doctors about the benefits and limitations of adding magnetic resonance imaging screening to their yearly mammogram.

Breast cancer is the most common malignancy in genotypical XX individuals in the United States and is second only to lung cancer as a cause of cancer death. The American Cancer Society has estimated that 290,560 individuals will be diagnosed with breast cancer and 43,780 will die of the disease in the United States in 2022.

Breast cancer risk is strongly associated with both genetic and environmental factors. For non-familial breast cancer, the Gail Model has been commonly used to produce individual risk estimates. 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 individuals who have an increased 5-year risk and lifetime risk of invasive breast cancer and may benefit from breast cancer risk reduction interventions such as risk-reduction agents (i.e., tamoxifen, raloxifene, anastrozole, exemestane) or risk-reduction surgery (risk-reducing mastectomy [RRM]).

Clinical Context and Test Purpose

Rare, single-gene variants conferring a moderate to high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are variants in ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, and TP53. These genes account for less than 25% of inherited breast cancer.

In contrast, several common single nucleotide variants (SNVs) associated with breast cancer have been identified primarily through genome-wide association studies of very large case-control populations. These alleles occur with high frequency in the general population, and the increased breast cancer risk associated with each is very small relative to the general population risk. Some have suggested that these common-risk SNVs could be combined for individualized risk prediction either alone or in combination with traditional predictors; personalized breast cancer screening programs could then

vary by starting age and intensity according to risk. Along these lines, the American Cancer Society recommends that women at high risk (>20% lifetime risk) should undergo breast magnetic resonance imaging (MRI) and a mammogram every year, and those at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram.

The purpose of genetic testing in asymptomatic individuals is to predict the risk of disease occurrence. The criteria under which prognostic testing may be considered clinically useful are as follows:

- An association of the marker with the disease has been established; **and**
- The clinical utility of identifying the variants has been established (e.g., by demonstrating that testing will lead to changes in surveillance).

Populations
The relevant population of interest is individuals who have not been identified as being at high risk of breast cancer. This population would include individuals who do not have a family member who had breast cancer (non-familial).

Interventions
The intervention of interest is testing for common single nucleotide variants (SNVs) associated with a small increase in the risk of breast cancer. Patients who are asymptomatic and at average risk of breast cancer by clinical criteria are actively managed in an outpatient clinical setting.

Example of Meta-Analyses of SNVs and Associations with Breast Cancer

SNVs	Association		
	Positive	None	Protective
2q35 [rs13387042]	x		
8q24 [G-allele of rs13281615]	x		
8q24 [homozygous A-alleles of rs13281615]			x
ABCB1 [G2677T/A]		x	
AKAP9 [M463I]	x		
ATR-CHEK1 checkpoint pathway genes[a]		x	
ATXN7 [K264R]	x		
Chemotactic cytokines[b]			
COMT [V158M]			x
COX2 [rs20417]	x		
COX2 [rs689466]			x
COX2 [rs5275]	x		

COX11 [rs6504950]			x
CYP1A1 [T3801C]	x		
CYP1A2 1F [A-allele of rs762551]	x		
CYP19 [rs10046]		x	
Fibroblast growth factor receptor genes[c]		x	
IL-10 [rs1800871]		x	
IRS1 [rs1801278]	x		
MAP3K1 [C-allele of rs889312 and G-allele of rs16886165]	x		
MDM2 [rs2279744]	x		
MDR1 [C3435T]	x		
MTR [A(2756G]	x		
PON1 [L55M]	x		
PON1 [Q192R]			x
RAGE [rs1800625]	x		
STK15 [F31I]	x		
STK15 [V571I]			
TCF7L2 [rs7903146]		x	
TERT [rs10069690]	x		
VDR [rs731236]	x		
VDR [rs2228570]	x		
VEGF [C936T]		x	
XRCC2 [R188H]		x	
XRCC3 [A17893G]			x
XRCC3 [T241M]	x		

Commercially Available Assays
Commercially available assays purportedly test for several SNVs and predict an individual's risk of breast cancer relative to the general population. Some of these assays incorporate clinical information into risk prediction algorithms.

Examples of genetic testing assays for non-familial breast cancer risk assessment include but are not limited to the following:

OncoVue
The OncoVue Breast Cancer Risk Test (InterGenetics, Inc., Oklahoma City, OK) is a proprietary test that evaluates multiple, low risk single nucleotide variants (SNVs) associated with breast cancer. The results are combined with personal history measures to determine breast cancer risk at different times during adulthood. The test does not detect known high-risk genetic factors such as BRCA mutations associated with hereditary

breast and ovarian cancer. OncoVue synthesizes various genetic and medical history risk measures into a personalized single risk estimate for premenopause, perimenopause and postmenopause for each patient, with comparison to the average population risk at each of these life stages. The test is stated to be "an aid in the qualitative assessment of breast cancer risk and not intended as a stand-alone test for the determination of breast cancer risk in women."

For women without a strong family history of breast cancer and at average risk prior to testing, OncoVue purports to estimate a woman's individual risk and place her in standard, moderate or high-risk groups. The results are intended to help a woman and her physician decide if more frequent exams and/or more sophisticated surveillance techniques are indicated. For women already known to be at high risk based on a family history consistent with hereditary breast cancer, the test is represented as having added value by indicating greater or lesser risk at different life stages.

The OncoVue test is available only through the Breast Cancer Risk Testing Network (BCRTN), described as a network of Breast Care Centers engaged in frontline genetic identification of breast cancer risk levels in their patients. BCRTN member centers will provide genetic breast cancer risk testing for their patients using OncoVue as part of a comprehensive education program to help OncoVue "at-risk" women understand their risk level and intervention strategies. BCRTN members will be selected for the network based on a number of criteria, including quality standards of care, level of breast cancer surveillance technology, and the capability of providing patient education on genetic testing and future risk management protocols. Participating centers located throughout the United States are listed on the OncoVue website. OncoVue is not listed in the Genetic Testing Registry of the National Center for Biotechnology Information.

GeneType for Breast Cancer
GeneType for Breast Cancer (and the previous versions of the test, BREVAGen*plus*® and BREVAGen®) evaluates breast cancer-associated single nucleotide variants (SNVs) identified in genome-wide association studies. The first-generation test, BREVAGen, included 7 SNVs. Currently, GeneType includes over 70 SNVs. Risk is calculated by combining individual SNV risks with other risk factors. GeneType has been evaluated for use in African American, Caucasian, and Hispanic patient samples, age 35 years and older, who do not have a history of *in situ* or invasive breast cancer and are not carriers of a known pathogenic variant or rearrangement in a breast cancer susceptibility gen

TruSight Cancer Sequencing Panel
The TruSight Cancer Sequencing Panel (Illumina), targets 94 genes suspected to play a role in predisposing to cancer, including genes associated with both common (e.g., breast, colorectal) and rare cancers. In addition, the panel includes 284 SNVs suspected to be associated with cancer through genome-wide association studies (GWAS).

OncoArray-500K BeadChip
The Infinium OncoArray-500K BeadChip is a 24-sample format Illumina array with content drawing on many features of the Collaborative Oncological Gen-environmental Study (iCOGS) array1. The OncoArray offers the most comprehensive, highest-density BeadChip available for researching cancer predisposition and risk. The OncoArray contains 500,000 SNVs with genome wide backbone of 275,000 tag SNVs. Additional SNVs include genetic variants associated with breast, colorectal, lung, ovarian and prostate cancers.

Comparator
The following practice is currently being used to predict the risk of breast cancer: standard clinical risk prediction without testing for common SNVs associated with risk of breast cancer.

Outcomes
The outcomes of interest are a reclassification of individuals from normal risk and evidence of a change in management (e.g., preventive or screening strategies) that results in improved health outcomes. Follow-up over 5 to 10 years is needed to monitor the occurrence of breast cancer.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Studies have analyzed the potential impact of adding genetic information from a panel of SNVs associated with breast cancer risk to the Gail Model. These studies showed modest (limited) clinical gains in reclassification of risk. These studies have either been theoretical in nature or they combined model building with evaluation which may complicate evaluating the result in clinical context.

One potential use of SNV testing is to evaluate the risk of breast cancer for chemoprevention.

In 2019, Kapoor et. al., performed a comprehensive assessment of potential effect modification of 205 common susceptibility variants by 13 established breast cancer risk factors, including replication of previously reported interactions. Analyses was performed using 28,176 cases and 32,209 controls genotyped with iCOGS array and 44,109 cases and 48,145 controls genotyped using OncoArray from the Breast Cancer Association Consortium (BCAC). Gene-environment interactions were assessed using unconditional logistic regression and likelihood ratio tests for breast cancer risk overall and by estrogen-receptor (ER) status. Bayesian false discovery probability was used to assess the note worthiness of the meta-analyzed array-specific interactions. Noteworthy evidence of interaction at ≤1% prior probability was observed for three single nucleotide polymorphism (SNP)-risk factor pairs. SNP rs4442975 was associated with a greater reduction of risk of ER-positive breast cancer [odds ratio (OR) = 0.85 (0.78-0.93), $P = 2.8 \times 10^{-4}$] and overall breast cancer [OR = 0.85 (0.78-0.92), $P = 7.4 \times 10^{-5}$) 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 ($P = 0.004$). The two other interactions suggested stronger associations between SNP rs6596100 and ER-negative breast cancer with increasing parity and younger age at first birth. The authors concluded that our study provides the most comprehensive evaluation to date of potential effect modification of all known common genetic susceptibility variants by environmental risk factors for breast cancer. Our findings are based on the largest available dataset on breast cancer. Despite its large sample size, the study may remain statistically underpowered, considering the rather modest effect sizes of most of the common variants associated with breast cancer risk and further limitation of our study is that the findings may not be generalizable to other racial/ethnic groups since the analyses were restricted to women of European ancestry. Overall, the results from our analyses do not suggest strong effect modification of the association between breast cancer susceptibility loci and risk of breast cancer by established epidemiological risk factors.

In 2019, Pan et. al. conducted a meta-analysis of all eligible case-control studies to assess the association between PON1 (Q192R and L55M) gene polymorphisms and risk of cancer. With the STATA 14.0 software, evaluation of the strength of the association by using the odds ratios (ORs) and 95% confidence intervals (CIs) was completed. A total of 43 case-control publications 19887 cases and 23842 controls were employed in this study. In all genetic models, a significant association between PON1-L55M polymorphisms and overall cancer risk was observed. Moreover, in the stratified analyses by cancer type, polymorphism of PON1-L55M played a risk factor in the occurrence of breast cancer, hematologic cancer, and prostate cancer. Similarly, an increased risk was observed in the Caucasian and Asian population as well as hospital-based group and population-based group. For PON1-Q192R polymorphisms, in the stratified analyses by cancer type, PON1-Q192R allele was associated with reduced cancer risks in breast cancer. Furthermore, for racial stratification, there was a reduced risk of cancer in recession model in Caucasian population. Similarly, in the stratification analysis of control source, the overall risk of cancer was reduced in the heterozygote comparison and

dominant model in the population-based group. In conclusion, PON1-Q192R allele decreased the cancer risk especially breast cancer; there was an association between PON1-L55M allele and increased overall cancer risk. However, the authors concluded we need a larger sample size, well-designed in future and at protein levels to confirm these findings.

In 2019 He et. al. performed a meta-analysis on the association of telomerase reverse transcriptase (TERT) gene polymorphism rs10069690 (C>T) is associated with cancer risk. The authors conducted a search in PubMed, Google Scholar and Web of Science to select studies on the association between rs10069690 and cancer risk. Stratification by ethnicity, cancer type, cancers' classification, source of control, sample size, and genotype method was used to explore the source of heterogeneity. The pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were evaluated using random effects models. Sensitivity, publication bias, false-positive report probability (FPRP) and statistical power were also assessed. The results demonstrated that rs10069690 was significantly associated with an increased risk of cancer overall (OR = 1.09, 95% CI: 1.06-1.12, $p < .001$) under the allele model. Stratification analysis revealed an increased cancer risk in subgroups of breast cancer, ovarian cancer, lung cancer, thyroid cancer, and renal cell carcinoma (RCC). However, a significantly decreased association was observed in pancreatic cancer in the European population (OR = 0.93,95% CI: 0.87-0.99, $p = .031$). In the subgroup analysis based on cancer type, no significant association was found in prostate cancer, leukemia, colorectal cancer and glioma. The authors concluded This meta-analysis suggested that the TERT rs10069690 polymorphism may be a risk factor for cancer, especially breast cancer, ovarian cancer, lung cancer, thyroid cancer, and RCC. Further functional studies are warranted to reveal the role of the polymorphism in carcinogenesis.

In 2018, Rudolph et.al., evaluated joint associations of a 77-single nucleotide polymorphism (SNP) polygenic risk scores (PRS) with reproductive history, alcohol consumption, menopausal hormone therapy (MHT), height and body mass index (BMI). They tested the null hypothesis of multiplicative joint associations for PRS and each of the environmental factors and performed global and tail-based goodness-of-fit tests in logistic regression models. The outcomes were breast cancer overall and by estrogen receptor (ER) status. The study sample comprised 28,239 cases and 30,445 controls of European ancestry from 20 studies: two case-control studies nested in prospective cohorts, eight population-based case-control and 10 non-population-based case-control studies, all participating in the Breast Cancer Association Consortium (BCAC). Eligible studies had at least 200 cases and 200 controls, with genotype data and information on at least one of the environmental risk factors of interest. Studies that oversampled cases with family history of breast cancer were excluded. 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). 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.

In 2017, Cuzick et. al. assessed whether a panel of 88 SNPs could improve risk prediction over traditional risk stratification using data from 2 randomized tamoxifen prevention trials. The study included 359 cases and 636 controls, with the 88 SNPs assessed on an Illumina OncoArray that evaluated approximately half a million SNPs. The primary outcome was breast cancer or ductal carcinoma in situ. The 88 SNP score improved discriminability above the Tyrer-Cuzick risk evaluator; however, there was modest improvement in the percentage of women who were classified as high risk. The percentage of women with a 10-year risk of recurrence of 8% or more was estimated to be 18% for Tyrer-Cuzick and 21% when the 88 SNP score was added. The SNP score did not predict which women would benefit from tamoxifen.

Section Summary
Common single nucleotide variants (SNVs) have been shown in meta-analyses and primary studies to be significantly associated with breast cancer risk; some SNVs convey slightly elevated risk compared with the general population risk. Estimates of breast cancer risk, based on SNVs derived from large genome-wide association studies (GWAS) and/or from SNVs in other genes known to be associated with breast cancer, are available as a laboratory-developed test service. The literature on these associations is growing, although information about the risk models is proprietary. Available data would suggest that GeneType (previous versions of the test, BREVAGenplus® and BREVAGen®) may add predictive accuracy to clinical risk prediction. However, the degree of improved risk prediction may be modest, and clinical implications are unclear. Other panel tests (OncVue, TruSight Cancer Sequencing Panel, OncoArray-500K Bead Chip) have fewer data to support conclusions about their clinical validity. Independent determination of clinical validity in an intended-use population has not been performed. Use of such risk panels for individual patient care or population screening programs is premature because (1) performance of these panels in the intended-use populations is uncertain, and (2) most genetic breast cancer risk has yet to be explained by undiscovered gene variants and SNVs. The number of common low-penetrance SNVs associated with breast cancer is rapidly increasing. No studies were identified that provide direct evidence that use of SNV-based risk assessment has any impact on health care outcomes in this population. Indirect evidence from an improvement in risk prediction with an 88 SNV panel has been reported, although the improvement in risk prediction is modest. For the specific loci evaluated by the most recent GeneType test (previous versions of the test, BREVAGenplus® and BREVAGen®), there is insufficient evidence to determine whether using breast cancer risk estimates in asymptomatic individual's changes management decisions and improves patient outcomes.

Summary of Evidence
For individuals who are asymptomatic and at average risk of breast cancer by clinical criteria who receive testing for common single nucleotide variants (SNVs) associated with a small increase in the risk of breast cancer, the evidence includes observational studies. Clinical genetic tests may improve the predictive accuracy of current clinical risk predictors. However, the magnitude of improvement is small, and clinical significance is uncertain. Whether the potential harms of these tests due to false-negative and false-positive results are outweighed by the potential benefit associated with improved risk assessment is unknown. Evaluation of this technology is further complicated by the rapidly increasing numbers of SNVs associated with a small risk of breast cancer. Long-term prospective studies with large sample sizes are needed to determine the clinical validity and utility of SNV-based models for predicting breast cancer risk. The discriminatory ability offered by the genetic factors currently known is insufficient to inform clinical practice. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists
In 2017, the American College of Obstetricians and Gynecologists issued a practice bulletin (number 179, replaces practice bulletin number 122 August 2011), regarding breast cancer risk assessment and screening in average risk women which states the following:

Clinical Considerations and Recommendations:

- How should individual breast cancer risk be assessed?
  - Health care providers periodically should assess breast cancer risk by reviewing the patient's history. Breast cancer risk assessment is based on combination of the various factors that can affect risk. Initial assessment should elicit information about reproductive risk factors, results of prior biopsies, ionizing radiation exposure and family history of cancer. Health care providers should identify cases of breast, ovarian, colon, prostate, pancreatic, and other types of germline mutation associated cancer in first-degree, second-degree and possibly third-degree relatives as well as the age of diagnosis. Women with potentially increased risk of breast cancer based on initial history should have further risk assessment. Assessments can be conducted with one of the validated assessment tools available online, such as the GAIL, BRCAPRO, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, International Breast Cancer Intervention Studies (IBIS, also known as Tyrer-Cuzick), or the Claus model.
  - Risk assessment is important to determine if a woman is at average or increased risk of breast cancer to guide counseling regarding breast cancer surveillance, risk reduction and genetic testing. Risk assessment should not be used to consider a woman ineligible for screening appropriate for her age. Rather risk assessment should be used to identify women who may benefit from genetic

counseling, enhanced screening such as magnetic resonance imaging screening, more frequent clinical breast examinations, or risk-reduction strategies.

National Comprehensive Caner Network (NCCN)

Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic – Version 2.2022

This current NCCN guideline on genetic or familial high-risk assessment of breast, ovarian, and pancreatic cancers (version 2.2022), notes the potential for multigene testing to identify intermediate penetrance (moderate risk) genes, but adds that "For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests are necessarily clinically actionable." The guideline also includes that there are "significant limitations" in the interpretation of polygenic risk scores, and that polygenic risk scores should not be used for clinical management at this time.

High – Penetrance Breast Cancer Susceptibility Genes: ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, and TP53

Other Elements of Risk
For women not considered to be at risk for familial/hereditary breast cancer, an evaluation of other elements of risk that contribute to increased breast cancer risk is recommended. These include demographic factors such as gender, age, and ethnicity/race.

Breast Cancer Risk Reduction Version 1.2022
Individual does not meet any of the familial risk criteria or tests negative for a genetic predisposition: Assess elements that increase risk

Elements that Increase Risk

- Family history
- Increasing age
- Ethnicity/race
- Lifestyle factors
    - Increased body mass index (BMI)
    - Alcohol consumption
    - Current or prior estrogen and progesterone hormone agent
- Reproductive history
    - Younger age at menarche
    - Nulliparity/Lower parity
    - Older at first live birth
    - Older age at menopause
- Other

- History of lobular carcinoma in situ (LCIS); Atypical hyperplasia (ductal and/or lobular)
- Number of prior breast biopsies
    - Procedure done with the intent to diagnose cancer; multiple biopsies (needle/excision) of the same lesion are scored as one biopsy
- Mammographic breast density (heterogeneously and/or extremely dense breasts)
- Prior thoracic radiation therapy (RT) < 30 years of age

Elements that Decrease Risk

- Menopause before age 45 years
- Prior risk-reducing agent
- Exercise
- Breastfeeding

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this testing.

PRIOR APPROVAL

Not applicable.

POLICY

Note: *This policy is not intended to address testing for a known familial variant for breast cancer or testing of patient at high risk based on family history.*

Non-familial genetic testing including but not limited to the following panels tests for common low-penetrance single nucleotide variants (SNVs) utilized as a method of estimating an individual's risk of developing breast cancer is considered **investigational**, because the evidence is insufficient to determine the effects of the technology on health outcomes:

- GeneType for Breast Cancer (previous versions of the test, BREVAGenplus® and BREVAGen®)
- OncoArray-500K BeadChip
- OncoVue Breast Cancer Risk Test
- TruSight Cancer Sequencing Panel

Testing for one or more of the following single nucleotide variants (SNVs) to predict an individual's risk of breast cancer is considered **investigational,** because the evidence is insufficient to determine the effects of the technology on health outcomes:

2q35 [rs13387042]
8q24 [G-allele of rs13281615]
8q24 [homozygous A-alleles of rs13281615]
ABCB1 [G2677T/A]
AKAP9 [M463I]
ATR-CHEK1 checkpoint pathway genes
ATXN7 [K264R]
Chemotactic cytokines
COMT [V158M]
COX2 [rs20417]
COX2 [rs689466]
COX2 [rs5275]
COX11 [rs6504950]
CYP1A1 [T3801C]
CYP1A2 1F [A-allele of rs762551]
CYP19 [rs10046]
Fibroblast growth factor receptor genes
IL-10 [rs1800871]
IRS1 [rs1801278]
MAP3K1 [C-allele of rs889312 and G-allele of rs16886165]
MDM2 [rs2279744]
MDR1 [C3435T]
MTR [A(2756G]
PON1 [L55M]
PON1 [Q192R]
RAGE [rs1800625]
STK15 [F31I]
STK15 [V571I]
TCF7L2 [rs7903146]
TERT [rs10069690]
VDR [rs731236]

VDR [rs2228570]
VEGF [C936T]
XRCC2 [R188H]
XRCC3 [A17893G]
XRCC3 [T241M]

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81479 Unlisted molecular pathology procedure
- 81599 Unlisted multi-analyte assay with algorithmic analysis

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POLICY HISTORY		
Date	**Reason**	**Action**
April 2022	Annual Review	Policy Revised
April 2021	Annual Review	Policy Revised
April 2020	Annual Review	Policy Revised
April 2019	Annual Review	Policy Revised
April 2018	Annual Review	Policy Revised
April 2017	Annual Review	Policy Revised
April 2016	Annual Review	Policy Revised
May 2015	Annual Review	Policy Revised
June 2014	Annual Review	Policy Revised
August 2013		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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