Protocol

Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer

(20463)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 09/20
Preauthorization	No	**Review Dates**: 09/10, 09/11, 09/12, 09/13, 09/14, 09/15, 09/16, 09/17, 09/18, 09/19	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic and at average risk of breast cancer by clinical criteria	Interventions of interest are: • Testing for common single nucleotide variants associated with a small increase in the risk of breast cancer	Comparators of interest are: • Standard clinical risk predictors	Relevant outcomes include: • Test validity • Morbid events • Quality of Life

DESCRIPTION

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, are common in the population, but confer only small increases in risk. Commercially available assays test for several SNVs to predict an individual's risk of breast cancer relative to the general population. Some of these tests incorporate clinical information into risk prediction algorithms. The intent of this type of test is to identify subjects at increased risk who may benefit from more intensive surveillance.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic and at average risk of breast cancer by clinical criteria who receive testing for common SNVs associated with a small increase in the risk of breast cancer, the evidence includes observational studies. Relevant outcomes are test validity, morbid events, and quality of life. 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 the effects of the technology on health outcomes.

POLICY

Testing for one or more single nucleotide variants to predict an individual's risk of breast cancer is considered **investigational**.

The BREVAGen*plus*® breast cancer risk test is considered **investigational** for all indications, including but not limited to use as a method of estimating individual patient risk for developing breast cancer.

POLICY GUIDELINES

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

CLINICAL GENETIC TESTS

BREVAGen*plus*® is not offered over the Internet or directly to consumers. A physician must order this test. *BRCA*

genetic testing should be used in those from high-risk families (see the Genetic Testing for Hereditary Breast, Ovarian Cancer Syndrome and Other High-Risk Cancers Protocol for details).

MEDICARE ADVANTAGE

For Medicare Advantage testing for one or more single nucleotide polymorphisms (SNPs) for chromosomal abnormalities is considered **not medically necessary**.

BACKGROUND

GENE VARIANTS AND BREAST CANCER RISK

Rare, single-gene variants conferring a high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are variants in BRCA1 and BRCA2. These, and a few other genes, account for less than 25% of inherited breast cancer. Moderate risk alleles, such as variants in the CHEK2 gene, are also relatively rare and apparently explain very little of the genetic risk.

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 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.[1]

Clinical Genetic Tests

BREVAGenplus

BREVAGenplus evaluates breast cancer-associated SNVs identified in genome-wide association studies. The first-generation test, BREVAGen, included seven SNVs. Allman et al (2015) reported the test included over 70 susceptibility SNVs.[2] Risk is calculated by combining individual SNV risks with the Gail model risk. BREVAGenplus has been evaluated for use in African-American, white, and Hispanic patient samples age 35 years and older. BREVAGenplus does not detect known high-risk variants (e.g., in BRCA). According to the BREVAGenplus website, the test is "not applicable to women who are already at high risk of breast cancer including those that have a personal or extensive family history of breast and/or ovarian cancer, LCIS [lobular carcinoma in situ], DCIS [ductal carcinoma in situ], AH [atypical hyperplasia] or have thoracic RT [radiotherapy] under 30y. Any women with these risk factors are already at increased risk of breast cancer and should be screened and followed as such."[3]

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. BREVAGenplus® (Phenogen Sciences, a subsidiary of Genetic Technologies) is available under the auspices 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 test.

RELATED PROTOCOL

Genetic Testing for Hereditary Breast, Ovarian Cancer Syndrome and Other High-Risk Cancers

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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