PALB2 Genetic Testing for Cancer Risk

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Introduction

PALB2 genetic testing is addressed by this guideline.

Procedure addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure(s) addressed by this guideline	Procedure code(s)
PALB2 deletion/duplication analysis	81479
PALB2 known familial mutation analysis	81308
PALB2 sequencing	81307

Criteria

Introduction

Requests for PALB2 testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous testing that would detect the familial mutation, and
  - Known family mutation in PALB2 identified in 1st, 2nd, or 3rd degree relative(s), AND
- Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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Full Sequence Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - Member has had BRCA1/2 analysis and no mutations were found, and
  - Member has not had previous PALB2 sequencing, AND
- Diagnostic Testing in Symptomatic Individuals and Presymptomatic Testing in Asymptomatic individuals:
  - Member has met criteria for BRCA1/2 analysis,** AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**For information on BRCA1/2 testing, please refer to the guideline *BRCA Analysis,* as this testing is not addressed here.

Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - Member meets above criteria for PALB2 full sequence analysis, and
  - Member has had PALB2 full sequence analysis and no mutations were found, and
  - Member had not had previous PALB2 deletion/duplication analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

PALB2 testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

What is PALB2 genetic testing?

Breast cancer is the most frequently diagnosed malignancy and one of the leading causes of cancer mortality in women around the world. Hereditary breast cancer accounts for 5% to 10% of all breast cancer cases.[1] Two cancer susceptibility genes, BRCA1 and BRCA2, are implicated in 40-45% of all hereditary breast cancer cases.[1] Other genes have also been identified in the literature as being associated with inherited breast cancer risk, including ATM, BARD1, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, and TP53.[1-4] PALB2 is a gene that encodes a protein that

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may be involved in tumor suppression, and is considered a partner and localizer of BRCA2.[2] Mutations in PALB2 increase the chance a person will develop certain cancers and, in particular, female breast cancer.[1-5]

Prevalence

In one study, pathogenic mutations in 12 genes associated with hereditary breast cancer were found in 5.06% of 32,347 women with breast cancer. Of those with a mutation, 0.46% had a mutation in PALB2.[1] Over 160 truncating mutations in PALB2 have been detected among families with breast cancer worldwide.[6]

Symptoms

One study of over 500 families with PALB2 pathogenic variants estimated a relative risk (RR) of 7.8 (95% CI, 5.82-8.85) for female breast cancer, 2.91 (95% CI, 1.40-6.04) for ovarian cancer, 2.37 (95% CI, 1.24-4.50) for pancreatic cancer and 7.34 (95% CI, 1.28-42.18) for male breast cancer.[6] A meta-analysis of three studies estimated a RR of 5.3 (90% CI, 3.0-9.4) for female breast cancer.[7] Another study documented a lifetime risk of breast cancer of 32% in women with a PALB2 mutation.[1] Per the National Comprehensive Cancer Network, the absolute risk for breast, ovarian, and pancreatic cancer are quoted as 41-60%, 3-5% and 2-5%, respectively.[8]

Cause

Pathogenic mutations in the PALB2 gene cause the aforementioned associated cancer risks.[1-8]

Diagnosis

The diagnosis is established with identification of a pathogenic mutation in the PALB2 gene.

Inheritance

PALB2 mutations are inherited in an autosomal dominant manner.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

PALB2 mutations inherited in an autosomal recessive manner cause Fanconi Anemia.[8] Testing for Fanconi Anemia is not addressed in this guideline.

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Management

Screening and prevention options are available to specifically address the increased risk of cancer in an individual with a PALB2 pathogenic mutation.[8]

Test information

Introduction

PALB2 testing may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

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Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2021) published a clinical practice resource for management of individuals with PALB2 pathogenic mutations. They stated the following:[9]

- "ACMG recommends:
  - the use of personalized risk estimates (e.g., CanRisk) in guiding clinical management.
  - that PALB2 should be included in breast, ovarian, and pancreas germline cancer gene panels.
  - that PALB2 VUS [variants of uncertain significance] are not used to guide clinical management.
  - prospective collection of clinical data from PALB2 heterozygotes to establish clear metrics on treatment outcome and survival.
  - surveillance for breast cancer should be equivalent to that for BRCA1/2 heterozygotes.
  - risk-reducing mastectomy can be considered as an option. The decision should be guided by personalized risk assessment.
  - ovarian cancer surveillance should not be offered, and risk-reducing salpingo-oophorectomy should include shared decision making and should rarely be considered before the age of 50.
  - pancreatic cancer surveillance should be considered, but ideally as part of a clinical trial.
  - PALB2 heterozygotes should be considered for the same therapeutic regimens and trials as those for BRCA1/2."
- "ACMG does not recommend testing partners of PALB2 heterozygotes in the reproductive setting, unless they are from a country with founder variants or it can be justified by the partner's family history of cancer."

American Society of Breast Surgeons

The American Society of Breast Surgeons (ASBrS, 2019) published a consensus guideline on genetic testing for hereditary breast cancer. They stated the following:[10]

- "Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing. When the patient’s history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels

available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes."

- "Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies."
- “Patients who had genetic testing previously may benefit from updated testing. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing. Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2."
- “Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of “uninformative negative” results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above."

American Society of Clinical Oncology and Society of Surgical Oncology

A 2024 American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) joint guideline for germline testing in individuals with breast cancer stated the following:[11]

- "Testing for high penetrance genes beyond BRCA1/2, including PALB2, TP53, PTEN, STK11, and CDH1, could inform medical therapy, influence surgical decision making, refine estimates of risks of second primary cancer, and inform family risk assessment, and thus should be offered to appropriate patients."

European School of Oncology and European Society of Medical Oncology

The European School of Oncology (ESO, 2022) and the European Society of Medical Oncology (ESMO, 2022) held the fifth International Consensus Conference for Breast Cancer in Young Women leading to the publication of consensus recommendations. The following was stated regarding PALB2 genetic testing:[12]

- "Although BRCA1/2 are the most frequently mutated genes, other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counselor or if they will impact therapeutic interventions."
- "When a hereditary cancer syndrome is suspected and a mutation in BRCA1/2 has not been identified, multi-gene panel testing may be considered. Practice should be guided by high quality national/international guidelines."
- "As commercially available multi-gene panels include different panels of genes, the choice of the specific panel and quality-controlled laboratory is crucial."
- "For BRCA1/2 mutation carriers and others at high risk based on family history or predisposing mutations in other genes (e.g. p53, PALB2, CHEK2, ATM) and for those at increased risk because of a personal history of therapeutic radiation, annual surveillance with MRI and mammography with or without ultrasound is recommended."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) evidence and consensus-based guidelines addressed test indications for breast, ovarian, and pancreatic cancer susceptibility genes, including PALB2.[8] These guidelines included recommendations related to unaffected individuals with a family history of cancer, those with a known mutation in the family, those with a personal history of breast cancer, exocrine pancreatic cancer, ovarian cancer, and men with breast cancer. They take into consideration age of diagnosis, tumor pathology, degree of relationship, treatment implications, and Ashkenazi Jewish ancestry.

These recommendations are Category 2A, defined as "lower-level evidence" with "uniform NCCN consensus that the intervention is appropriate" and are frequently updated.[8]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for PALB2 testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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