PALB2 Genetic Testing for Breast Cancer Risk

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.

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What is PALB2 genetic testing

Definition

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer mortality in women around the world. Hereditary breast cancer accounts for 5% to 10% of all breast cancer cases.

- Screening with breast magnetic resonance imaging (MRI) is recommended for women with a greater than 20% lifetime risk for disease based on estimates of risk models that are largely dependent on family history. A large body of evidence indicates that an increased lifetime risk of >20% can also be established through genetic testing. In particular, two cancer susceptibility genes, BRCA1 and BRCA2, are implicated in about 20% of all hereditary breast cancer cases. Other genes have also been identified in the literature as being associated with inherited breast cancer risk, including ATM, CDH1, CHEK2, NBM, NF1, PALB2, PTEN, STK11, and TP53.¹²

- In particular, PALB2 is a gene that encodes a protein that may be involved in tumor suppression, and is considered a partner and localizer of BRCA2. Specifically, ~50 truncating mutations in PALB2 have been detected among breast cancer families worldwide. Kluska et al. (2017) estimates that a relative risk (RR) of 2.3 (95% CI, 1.4 to 3.9) is conferred by PALB2 mutations, indicating an approximate two-fold increased risk of developing hereditary breast cancer.³ A meta-analysis of three studies estimated a relative risk of 5.3 (90% CI, 3.0-9.4).⁴
• The availability of multiple gene panel testing of variant genes implicated in hereditary breast cancer has led to increased interest in hereditary risk assessment in clinical practice. Clinical decisions based on risk assessment measures include screening with breast magnetic resonance imaging (MRI) and risk-reduction surgery, which have been shown to reduce the morbidity and mortality associated with breast cancer. However, results of peer-reviewed published clinical studies evaluating the clinical validity and clinical utility of multiple gene panels, particularly of unknown clinical significance, or of low-to-moderate penetrance, are still unclear. Broad application of such testing has yet to be fully adopted.5

  o Genetic testing allows patients with an increased risk of cancer to receive appropriate medical management that may reduce risk for themselves and their family members. Early identification of at-risk women allows for increased clinical surveillance and may prompt more aggressive prevention strategies, such as prophylactic surgery or chemoprevention. The National Comprehensive Cancer Network (NCCN) guidelines have been expanded to incorporate genes known to be associated with an increased risk of breast cancer into medical management recommendations.6,7

Test information

• **Full sequence analysis** of the PALB2 gene looks at all of the coding regions of the PALB2 gene.

• **Deletion/duplication analysis** looks for large rearrangements, duplications, and deletions in the PALB2 gene.

• **Known familial mutation testing** looks for a specific mutation in the PALB2 gene previously identified in a family member.

Guidelines and evidence

• The National Comprehensive Cancer Network (NCCN, 2019) includes breast cancer risk and management recommendations for individuals with PALB2 in a table located in their Genetic/Familial High-Risk Assessment: Breast and Ovarian guideline. However, it is noted that, “The inclusion of a gene on this table below does not imply endorsement either for or against multi-gene testing for moderate-penetrance genes.” Recommendations are as follows:7

  o “Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast at 30y.” This may be modified based on family history. Typically begin screening 5-10 years earlier than the youngest diagnosis in the family but not later than 30y.

  o “RRM: Evidence insufficient, manage based on family history.”

• The American Society of Breast Surgeons (2019) published a consensus guideline on genetic testing for hereditary breast cancer. They state the following:8
"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."

"Genetic testing should be made available to all patients with a personal history of breast cancer. 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."

The European Society for Medical Oncology (ESMO, 2016) states the following prevention and screening strategies for individuals with a PALB2 mutation:

- Clinical breast examination every 6-12 months starting from age 20-25
- Annual breast MRI from age 20-29
- Annual breast MRI and/or mammogram at age 30-75."
- Consider risk-reducing mastectomy.

ESMO (2016) also states the following regarding PALB2 testing, "The following genes might have moderate- to high-penetration germline mutations for breast or ovarian cancer: p53, PTEN, CDH1, PALB2, CHEK2, ATM, RAD51C, STK11, RAD51D, BRIP1, MLH1, MSH, MSH6, and PMS2. Prevention and screening strategies for these mutations are summarized in Table 1 – due to limited research in individuals harboring these mutations, the level of evidence for these
recommendations is mostly expert opinion, and a full discussion is beyond the scope of these guidelines.”

- The Third International Consensus Conference for Breast Cancer in Young Women (BCY3, 2017) led to publication of consensus recommendations. The following is stated regarding PALB2 genetic testing:

  “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. 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 genes, the choice of the specific panel and quality-controlled laboratory is crucial, and should at least include high penetrance genes (BRCA1/2, p53, PTEN) and moderate-high penetrance genes (e.g., CDH1, CHEK2, PALB2, RAD51C, BRIP1, ATM).”

- A review of the available PALB2 literature revealed the following:

  Direct evidence from a number of case control studies reporting relative risk and odds ratio values suggest that PALB2 testing accurately identifies PALB2 mutations, which are associated with an increased risk of developing breast cancer. Indirect evidence suggests that the clinical utility of PALB2 testing may alter clinical decision making enough to lead to improved patient health outcomes.

  Direct and indirect evidence regarding clinical validity and clinical utility suggest that expanded panel testing may be used to identify more women who can benefit from appropriate breast cancer risk reduction strategies. However, gaps in knowledge persist regarding the precise cancer risk estimates for PALB2 (e.g., wide confidence intervals) and the predictive value in individuals and relatives who test negative for pathogenic variants yet have a strong family history of disease.

  Before clinical utility of PALB2 testing can be adequately established, well-designed studies are crucial to directly evaluate the clinical utility of PALB2 to alter treatment and overall disease management strategies and improve morbidity and mortality outcomes in women who develop hereditary breast cancer.

**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 full sequence testing or deletion/duplication analysis, 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.

**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 had 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.

**Please see the guideline *BRCA Analysis* for criteria

**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.
References


