Overview

Useful For
Establishing a diagnosis of hereditary breast and ovarian cancer (HBOC)

Identification of familial BRCA1 or BRCA2 mutation to allow for predictive testing in family members

Genetics Test Information
This test includes next-generation sequencing and multiplex ligation-dependent probe amplification to evaluate for mutations and large deletions/duplications in the BRCA1 and BRCA2 genes. Sanger sequencing may also be performed to confirm detected variants. Testing includes evaluation for the 3 Ashkenazi Jewish founder mutations commonly known as c.185delAG and c.5385insC in BRCA1, and c.6174delT in BRCA2, as well as the BRCA1 gene founder deletions prevalent in the Dutch population.(1)

Prior Authorization is available for this assay; see Special Instructions.

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- BRCA1/BRCA2 Genes, Full Gene Analysis (BRCAZ) Prior Authorization Ordering Instructions
- Informed Consent for Genetic Testing (Spanish)

Method Name
Custom Sequence Capture and Targeted Next Generation Sequencing Followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available
Yes

Specimen

Specimen Type
Varies

Shipping Instructions
Specimen should arrive within 96 hours of collection.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send specimen in original tube.

Additional Information:

1. To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.
2. Prior Authorization is available for this assay; see Special Instructions. Submit the required form with the specimen.

Forms

1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)
2. BRCA1/BRCA2 Genes, Full Gene Analysis (BRCAZ) Prior Authorization Ordering Instructions in Special Instructions
3. Molecular Genetics: Inherited Cancer Syndromes Patient Information (T519) in Special Instructions

Specimen Minimum Volume

1 mL

Reject Due To

No specimen should be rejected.

Specimen Stability Information

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varies</td>
<td>Refrigerated (preferred)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ambient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frozen</td>
<td></td>
</tr>
</tbody>
</table>

Clinical and Interpretive

Clinical Information

Hereditary breast and ovarian cancer (HBOC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the BRCA1 or BRCA2 genes. Mutations within these 2 genes account for the majority of hereditary breast and ovarian cancer families. HBOC is predominantly characterized by young-onset breast cancer
and ovarian cancer. However, HBOC is also associated with increased risks for prostate cancer, pancreatic cancer, fallopian tube cancer, and male breast cancer. HBOC is highly penetrant; the risk for developing an invasive breast cancer is about 60% to 65% and the risk for developing ovarian cancer is about 40% by age 70. Some individuals develop multiple primary or bilateral cancers. The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with HBOC.

There are founder mutations in BRCA1 and BRCA2 described in several populations including the Dutch, Icelandic, and Ashkenazi Jewish populations. The 3 common founder mutations in the Ashkenazi Jewish population are c.185delAG and c.5385insC in BRCA1, and c.6174delT in BRCA2.

Reference Values
An interpretive report will be provided.

Interpretation
All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions
Clinical Correlations:

Some individuals who have a diagnosis of hereditary breast and ovarian cancer (HBOC) may have a mutation that is not identified by this method (eg, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of a diagnosis of HBOC. For predictive testing, it is important to first document the presence of a BRCA1 or BRCA2 gene mutation in an affected family member.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete. We strongly recommend that patients undergoing predictive testing receive genetic counseling both prior to testing and after results are available.

Technical Limitations:

In some cases, DNA variants of undetermined significance may be identified. Due to the limitations of next-generation sequencing, we can detect greater than 93% of insertions and deletions up to 20 bases and 43 bases, respectively. If a diagnosis is still suspected, consider full gene sequencing using traditional Sanger methods. Single or multi-exon deletions as well as whole gene deletions will be detected by multiplex ligation-dependent probe amplification (MLPA). Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In addition to disease-related probes, the MLPA technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently not validated.
Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically re-review likely deleterious alterations or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Clinical Reference


Performance

Method Description


Gene dosage analysis by multiplex ligation-dependent probe amplification (MLPA) is used to test for the presence of large deletions and duplications in the BRCA1 and BRCA2 genes. (Unpublished Mayo method)

Reported variants detected by next-generation sequencing will be confirmed by Sanger sequencing.

PDF Report

No
Day(s) and Time(s) Test Performed
Performed weekly; Varies

Analytic Time
3 weeks

Maximum Laboratory Time
4 weeks

Specimen Retention Time
Whole Blood: 2 weeks (if available) Extracted DNA: Indefinitely

Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
81162

LOINC® Information

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Test Order Name</th>
<th>Order LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCAZ</td>
<td>BRCA1/BRCA2 Full Gene Analysis</td>
<td>In Process</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result ID</th>
<th>Test Result Name</th>
<th>Result LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>37802</td>
<td>Result Summary</td>
<td>50397-9</td>
</tr>
<tr>
<td>37803</td>
<td>Result</td>
<td>82939-0</td>
</tr>
<tr>
<td>37804</td>
<td>Interpretation</td>
<td>69047-9</td>
</tr>
<tr>
<td>37805</td>
<td>Additional Information</td>
<td>48767-8</td>
</tr>
<tr>
<td>37806</td>
<td>Specimen</td>
<td>31208-2</td>
</tr>
<tr>
<td>37807</td>
<td>Source</td>
<td>31208-2</td>
</tr>
<tr>
<td>37808</td>
<td>Released By</td>
<td>18771-6</td>
</tr>
</tbody>
</table>
Prior Authorization

Insurance preauthorization is available for this testing; forms are available in Special Instructions.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.