Assess HBOC risk with a proven 4-step protocol

1. **SCREEN**
   - Screen every patient for personal and family history of cancers and age of diagnosis
   - Update information annually

2. **IDENTIFY**
   - Assess for red flags
   - Discuss BRACAnalysis® testing with appropriate patient

3. **ORDER**
   - Order BRACAnalysis® test using Myriad’s collection kit
   - Interpret result and assign risk

4. **MANAGE**
   - Establish appropriate medical management plan according to clinical guidelines and recommendations

Technical information

**BRACAnalysis®**: A multistep diagnostic test for hereditary breast/ovarian cancer (HBOC) syndrome and cancers related to mutations in BRCA1 and BRCA2 genes. Genetic testing is performed by both full sequencing and large rearrangement methodologies.

- **Sequencing**: The majority of mutations in the BRCA1 and BRCA2 genes are detected through sequencing technology, which is considered to be the gold standard for molecular diagnostics. Myriad Genetics currently offers large sequencing technology:
  - The BRCA1 gene is located on chromosome 17q21 and consists of 14,480 base pairs in 22 coding exons. Full sequencing is performed in the forward and reverse direction of all coding regions and 1000 base pairs in non-coding regions to permit the detection of large rearrangements.
  - The BRCA2 gene is located on chromosome 13q12 and consists of 14,480 base pairs in 22 coding exons. Full sequencing is performed in the forward and reverse direction of all coding regions and 1000 base pairs in non-coding regions.

- **Large rearrangements**: Approximately 10% of all mutations in high-risk patients (18% risk for a deleterious mutation) and 1% of low-risk patients cause rearrangements in the BRCA1 or BRCA2 gene (reference 7). Large structural rearrangements (deletions, duplications, etc.) are usually not detectable through sequencing technology. Myriad Genetics utilizes Multiplex Ligation-Dependent Probe Amplification (MLPA), a very robust and reliable technology for detecting large rearrangements. Myriad limits the use of MLPA to those mutations detected by BRACAnalysis®. A detailed report of the test result (or name of the gene mutation) from family members who have tested positive will be required prior to testing.

**BRACAnalysis®**: Sequencing and large rearrangement analysis of the BRCA1 and BRCA2 genes. The test is for people who do not have any known gene mutations in the family.

- **Single-site BRACAnalysis®**: This test is for individuals who already know a BRCA1 or BRCA2 gene mutation is in the family. A copy of the test result from one of the gene family members whose identified position will be required prior to testing.

- **Multisite BRACAnalysis®**: This test examines the three most common (BRCA1 and BRCA2 gene mutations in individuals of Ashkenazi Jewish (Central/Eastern European) ancestry. These three mutations (BRCA1: 187delAG, 538insC and BRCA2: 617delT) are present in up to 2.5% of individuals of Ashkenazi Jewish decent. If an individual of Ashkenazi Jewish (Central/Eastern European) ancestry. These three mutations

**TEST OFFERINGS**

- **BRACAnalysis®**: Sequencing and large rearrangement analysis of the BRCA1 and BRCA2 genes. The test is for people who do not have any known gene mutations in the family.

- **Single-site BRACAnalysis®**: This test is for individuals who already know a BRCA1 or BRCA2 gene mutation is in the family. A copy of the test result from one of the gene family members whose identified position will be required prior to testing.

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**References**


BRACAnalysis® testing benefits

FOR PATIENTS:
- Empower patients with knowledge to make informed surveillance, preventive, surgical, and treatment decisions.
- Provide families with useful information on inherited risks.

FOR PRACTICE:
- Comply with international societal guideline recommendations.1-3
- Provide individualized medical management plans for your patients.
- Provide families with useful information on inherited risks.

INCREASED RISK FOR PRIMARY AND SECONDARY CANCERS*:
Mutations dramatically increase the risk of developing cancer

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Risk Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>50%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>11%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>4%</td>
</tr>
</tbody>
</table>

* Risks are based on the occurrence of cancer in the family and are specific to the BRCA mutation.

VALUABLE INFORMATION TO SHARE WITH YOUR PATIENTS:
- HBOC-associated cancers include breast, ovarian, and pancreatic cancer.
- Assessment criteria based on medical society guidelines. For these individual society guidelines, go to www.myriadpro.com/guidelines.
- Two red flags:
  - Breast self-exam before age 25
  - History of breast cancer diagnosed ≤25 years

CHECK PERSONAL OR FAMILY HISTORY FOR THESE RED FLAGS:

- Breast cancer
- Breast cancer diagnosed ≤25 years
- Two primary breast cancers in the same individual
- Two individuals with breast cancer on the same side of the family
- Male breast cancer
- Triple-negative breast cancer
- Personal cancer with additional HBOC-associated cancer**
- Ashkenazi Jewish ancestry with an HBOC-associated cancer**
- A previously identified BRCA mutation in the family

THE UNMET MEDICAL NEED:
Only ~10% of BRCA mutation carriers have been identified.*

Our mission is to provide an updated report to healthcare professionals.

DEFINING VUS:
A genetic variant of uncertain significance is a variation in the DNA sequence that may or may not contribute to breast or ovarian cancer risk.

MANAGING THE PATIENT:
- Management is to be based on personal and/or family history of cancer.
- Reclassifying a variant:
  - When data allows a previously reclassified variant to be reclassified as harmless or deleterious, Myriad Genetics provides an updated report to healthcare professionals.

Myriad has the lowest VUS rate globally with a < 3% VUS rate for BRCA1 / BRCA2 mutations.

THE VALUE OF TEST RESULTS
MAKING SENSE OF THE POSSIBLE OUTCOMES OF THE BRACAnalysis® TEST, AND HOW TO PROCEED WITH PATIENT CARE

POWER OF A POSITIVE RESULT
DIAGNOSES OF HBOC SYNDROME INCREASE CANCER RISK
Follow medical management guidelines for mutation carriers

The National Comprehensive Cancer Network and European Society for Medical Oncology (ESMO) are some of the many organizations with published medical management recommendations for BRCA mutation carriers, which include:
- Prophylactic mastectomy
- Prophylactic oophorectomy

THE UNMET MEDICAL NEED:
Our patients and healthcare professionals are caring for individuals with a known or suspected genetic predisposition to breast cancer.

POWER OF A NEGATIVE RESULT
NO DELETIOUS MUTATION DETECTED

The National Comprehensive Cancer Network and European Society for Medical Oncology (ESMO) are some of the many organizations with published medical management recommendations for mutation carriers.

POWER OF EXPERIENCE
MANAGE BASED ON PERSONAL/FAMILY HISTORY OF CANCER

The testing and the surgeries were by far the best decision I ever made. I feel as though I had a chance to look through a crystal ball to see my possible future, and I was able to make choices while I was healthy.

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MEDICAL INTERVENTION GREATLY REDUCES RISK:
Reduce risk of hereditary cancer with proven medical management

USE CLINICAL GUIDELINES TO ADDRESS UNIQUE SURVEILLANCE AND SURGICAL NEEDS OF BRCA-POSITIVE PATIENTS
- According to NCCN guidelines for breast-conserving therapy, requiring radiation therapy to women with a known or suspected genetic predisposition to breast cancer.
- May have higher risk of ipsilateral recurrence or contralateral breast cancer with breast-conserving therapy.
- Prophylactic bilateral mastectomy for breast reduction should be considered prior to radiation.
- NCCN guidelines, the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) make specific screening suggestions for BRCA patients.1,2,4

For this patient who was 17 at the time of diagnosis, Table 1 shows the 5-, 10-, and 15-year risks of breast cancer.

Table 1

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age to begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self-exam</td>
<td>18 years</td>
<td>monthly</td>
</tr>
<tr>
<td>Clinical breast exam</td>
<td>25 years</td>
<td>yearly</td>
</tr>
<tr>
<td>Mamography</td>
<td>25 years</td>
<td>yearly</td>
</tr>
<tr>
<td>Ovarian cancer screening</td>
<td>30 years</td>
<td>yearly</td>
</tr>
<tr>
<td>MRI breast, age 40+</td>
<td>25 years</td>
<td>yearly</td>
</tr>
<tr>
<td>TVUS and CA-125</td>
<td>30 years</td>
<td>yearly</td>
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** HBOC-associated cancers include breast, ovarian, and pancreatic cancer.

† For reference and supporting data on risk factors and medical management visit www.myriadpro.com/references

‡ For reference and supporting data on risk factors and medical management visit www.myriadpro.com/references

§ For reference and supporting data on risk factors and medical management visit www.myriadpro.com/references

Took me 7 years to be tested for the BRCA mutation. It took me fewer than 4 months to have all the prophylactic surgeries to try and prevent becoming a victim of cancer.

---
** HBOC-associated cancers include breast, ovarian, and pancreatic cancer.

** CHECK PERSONAL OR FAMILY HISTORY FOR THESE RED FLAGS

† For reference and supporting data on risk factors and medical management visit www.myriadpro.com/references

** Mutations dramatically increase the risk of developing cancer

INCREASED RISK FOR PRIMARY AND SECONDARY CANCER†

** A previous identified BRCA mutation in the family

FOR YOUR PATIENTS

- Empower patients with knowledge to make informed surveillance, preventive, surgical, and treatment decisions.
- Provide families with useful information on inherited risks.

FOR YOUR PRACTICE

- Comply with international societal guideline recommendations 1-3
- Provide individualized medical management plans for your patients.

AMONG BREAST CANCER PATIENTS

70% of women diagnosed undergo BRCA mutation testing, and 79% of these women used genetic test results to aid in their surgical decision making .6

76% of women chose to undergo BRCA mutation testing, and 79% of these women used genetic test results

AMONG BREAST CANCER PATIENTS:

** Risk of cancer (%)

- Breast self-exam
- Clinical breast exam
- Breast MRI
- Pelvic exam
- Oral contraceptive tamoxifen
- Mastectomy oophorectomy
- Breast cancer
- Ovarian Cancer

** FrequencyAge to beginProcedure

- Clinical breast exam
16 years
- Breast self-exam
- Breast MRI
- Pelvic exam
- Oral contraceptive tamoxifen
- Mastectomy oophorectomy

** NCCN guidelines suggest patients who do not elect RRBSO consider concurrent transvaginal ultrasound (TVUS) and cancer antigen-125 (CA-125) blood testing every 6 months starting at age 30, or 5 to 10 years before the earliest age of first diagnosis of ovarian cancer in the family. NCCN guidelines suggest risk-reducing salpingo-oophorectomy (RRBSO), ideally between 35 and 40 years of age, and upon completion of child bearing or individualized based on earliest age of onset of ovarian cancer in the family.

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** BRCA1 / BRCA2 mutations.

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The value of test results

Making sense of the possible outcomes of the BRACAnalysis® test, and how to proceed with patient care

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</tr>
<tr>
<td>Mammography</td>
<td>25 years</td>
<td>yearly</td>
</tr>
<tr>
<td>Ovarian cancer surveillance*</td>
<td>30 years in patients for whom a BRCA mutation has been identified or not electing RRBSO</td>
<td>twice a year</td>
</tr>
<tr>
<td>CA-125</td>
<td>25 years</td>
<td>yearly</td>
</tr>
</tbody>
</table>

*See your genetic counselor for additional guidelines on surveillance. **See your genetic counselor for additional guidelines on surveillance. The American Society of Clinical Oncology and the College of American Pathologists (CAP) and other professional organizations agree that surveillance in the 20s, including breast MRI, should be considered in women with a personal or family history of cancer. The National Comprehensive Cancer Network and European Society for Medical Oncology (ESMO) make specific screening suggestions for HBOC patients. 1,2,4

Myriad has the lowest VUS rate globally with a < 3% VUS rate for BRCA1 / BRCA2 mutations.

Use clinical guidelines to address unique surveillance and surgical needs of BRCA-positive patients

- According to NCCN, and to reduce breast-consenting and surveillance recommendations.
- May have higher risk of bilateral recurrence or contralateral breast cancer with breast-consenting therapy.
- Prophylactic bilateral mastectomy and/or reduction should be considered prior to radiation therapy.
- NCCN guidelines, the American Society of Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO) make specific screening suggestions for HBOC patients. **

The testing and the surgeries were by far the best decision I ever made. I feel as though I had a chance to look through a crystal ball to see my possible future, and I was able to make choices while I was healthy.**

Stefanie B.
Assess HBOC risk with a proven 4-step protocol

1 SCREEN
- Screen every patient for personal and family history of cancer/age of diagnosis
- Update information annually

2 ELIGIATE
- Assess for red flags
- Discuss BRACAnalysis® testing with appropriate patient

3 CONSIDER
- Order BRACAnalysis® test using Myriad’s collection kit
- Interpret result and assign risk

4 MANAGE
- Establish appropriate medical management plan according to clinical guidelines and recommendations

Myriad Genetics support makes it easy

Our dedicated team of representatives and other staff can provide in-person and online assistance to help you

1. Screen every patient for personal and family history of cancer/age of diagnosis.
2. Update information annually.
3. Assess for red flags.
4. Discuss BRACAnalysis® testing with appropriate patient.
5. Order BRACAnalysis® test using Myriad’s collection kit.
6. Interpret result and assign risk.
7. Establish appropriate medical management plan according to clinical guidelines and recommendations.

Technical information

BRACAnalysis® is a molecular diagnostic test for hereditary breast/ovarian cancer (HBOC) syndrome and cancers related to mutations in BRCA1 and BRCA2 genes. Genetic testing is performed by both full sequencing and large rearrangement methodologies.

Sequencing: For majority of mutations in the BRCA1 and BRCA2 genes are detected through sequencing technology, which is considered to be the gold standard for molecular diagnostics. Myriad Genetics currently uses large sequencing technology:
- BRCA1 is located on chromosome 17p13.1 and is composed of 1448 base pairs in 22 coding exons. It is sequenced in a forward and reverse direction to detect all coding exons and 700 base pairs in non-coding regions.
- BRCA2 is located on chromosome 13q12.2 and is composed of 9142 base pairs in 73 coding exons. It is sequenced in the forward and reverse direction of all coding exons and 750 base pairs in non-coding regions.

Large rearrangements: Approximately 15% of all mutations in high-risk patients (30% risk for a deleterious mutation) and 1% of all patients require large rearrangement testing in the BRCA1 or BRCA2 gene (reference 6-8). Large structural rearrangements (deletions, duplications, etc.) are usually not detectable through sequencing technologies. Myriad Genetics utilizes Multiplex Ligation-dependent Probe Amplification® (MLPA®), a very robust and reliable technology for detecting large rearrangements. Mutations detected by MLPA® are confirmed by multiple quantitative PCR sequencing or CGH microarray.

Tests offered:

BRACAnalysis® sequencing and large rearrangement analysis of the BRCA1 and BRCA2 genes. This test is for people who do not have any known gene mutations in the family.

Single site BRACAnalysis®: This test is for individuals who already know they have a BRCA1 or BRCA2 gene mutation (or the family). A copy of the test results is provided to the gene family members for whom testing will be required.

Multiplex BRACAnalysis®: This test analyses the most common BRCA1 and BRCA2 gene mutations in individuals of Ashkenazi Jewish (Central/East European) ancestry. These three mutations (BRCA1: 187delAG, 538insC and 617delT) are present in up to 2.5% of individuals of Ashkenazi Jewish ancestry. These three mutations (BRCA2: 2321del3, 660del5, 112del40 and 6_7del14) are present in up to 30% of individuals of Ashkenazi Jewish descent. For individuals of Ashkenazi Jewish ancestry, testing is performed to detect these three mutations in BRCA1 and BRCA2 genes.

Approximately 10% of all mutations in high-risk patients (>30% risk for a deleterious mutation) are large rearrangements (deletions, duplications, etc.) and are usually not detectable through sequencing technologies. Myriad Genetics utilizes Multiplex Ligation-dependent Probe Amplification® (MLPA®), a very robust and reliable technology for detecting large rearrangements. Mutations detected by MLPA® are confirmed by multiple qualitative PCR sequencing or CGH microarray.

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   • Screen every patient for personal and family history of cancer and age of diagnosis
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Myriad Genetics support makes it easy

Our dedicated team of representatives and other staff can provide in-person and online assistance to help you implement BRACAnalysis® testing in your offices.

Medical Support

Myriad offers medical support with a team of highly trained medical specialists, available via phone, email, and in-person.

Practice Support

Our representatives help clinical practices in their implementation of genetic testing.

Professional Community Support

Multiple professional guidelines support genetic testing for HBOC syndrome.

<table>
<thead>
<tr>
<th>Professional Society</th>
<th>Website URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td><a href="http://www.nccn.org/professionals/physician_gls/PDF/BRCA1MDBRO/09/13/ENV1">www.nccn.org/professionals/physician_gls/PDF/BRCA1MDBRO/09/13/ENV1</a></td>
</tr>
<tr>
<td>European Society for Medical Oncology (ESMO)</td>
<td><a href="http://annonc.oxfordjournals.org/content/22/suppl_3/sqt011.full.pdf+html">http://annonc.oxfordjournals.org/content/22/suppl_3/sqt011.full.pdf+html</a></td>
</tr>
<tr>
<td>ESMO International</td>
<td><a href="http://www.esmo.org">www.esmo.org</a></td>
</tr>
<tr>
<td>American Society of Clinical Oncology (ASCO)</td>
<td><a href="http://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer">www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer</a></td>
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</table>

Technical information

BRACAnalysis® is a molecular diagnostic test for Hereditary Breast/Ovarian Cancer (HBOC) syndrome and cancer-related mutations in BRCA1 and BRCA2 genes. Genetic testing is performed by both full sequencing and large rearrangement methodologies.

- **Sequencing:** The majority of mutations in the BRCA1 and BRCA2 genes are detected through sequencing technology which is considered the gold standard for molecular diagnosis. Myriad Genetics currently uses large sequencing technology.
  - BRCA1 is located on chromosome 17 (17p13.2) and is composed of 1495 base pairs in 22 coding exons. Full sequencing is performed in both the forward and reverse directions of all coding exons and all intron-exon boundaries.
  - BRCA2 is located on chromosome 13 (13q12.3) and is composed of 23,661 base pairs in 39 coding exons. Full sequencing is performed in both the forward and reverse directions of all coding exons and all intron-exon boundaries.

- **Large rearrangements:** Approximately 19% of all mutations in high-risk patients (16% risk for a deleterious mutation) and 1% of low-risk patients (1.6% risk) are large rearrangements in the BRCA1 or BRCA2 gene (reference: Judkins). Large structural rearrangements (deletions, duplications, etc.) are usually not detectable through sequencing technologies. Myriad Genetics utilizes Multiplex Ligation-Dependent Probe Amplification (MLPA), a very robust and reliable technology for detecting large rearrangements. Mutations detected by MLPA are confirmed by multiplex quantitative PCR sequencing or CGH-microarray.

**Tests Offered:**

- BRACAnalysis® Sequencing: Full sequence analysis of the BRCA1 and BRCA2 genes. This test is for people who do not have any known genetic mutations in the family.
- Single site BRACAnalysis®: This test is for individuals who already know (through BRCA1 or BRCA2 gene mutation) if someone in the family has a deleterous mutation and will be processed to testing.
- Multiplex 1 BRACAnalysis®: This test examines the three most common (BRCA1 and BRCA2 gene mutations in individuals of Ashkenazi Jewish descent) breast cancer genes (BRCA1, BRCA2, and 617delT) present in up to 32% of individuals of Ashkenazi Jewish descent. This individual of Ashkenazi Jewish ancestry is considered to be at a significantly increased risk for both breast and ovarian cancer.

References

10. Tavtigian SV, et al. Multiplex Ligation-Dependent Probe Amplification (MLPA), a very robust and reliable technology for detecting large rearrangements. Mutations detected by MLPA are confirmed by multiplex quantitative PCR sequencing or CGH-microarray.

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