The impact of hereditary breast and ovarian cancer (HBOC) syndrome testing on patient management and your practice

Use BRAC*Analysis*® as a guide in your medical and surgical management

myriad®
WHEN DECISIONS MATTER

BRAC*Analysis*® testing benefits

FOR YOUR PATIENTS

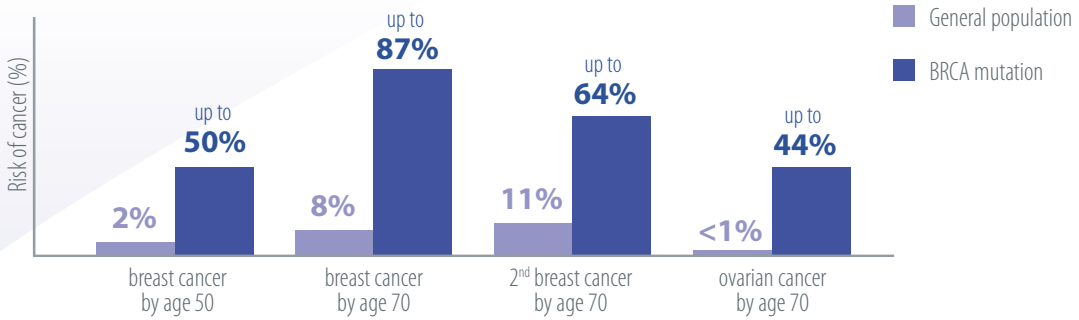
- Empower patients with knowledge to make informed surveillance, preventive, surgical, and treatment decisions.
- Provide families with useful information on inherited risks.

FOR YOUR PRACTICE

- Comply with International societal guideline recommendations.[1-5]
- Provide individualized medical management plans for your patients.

INCREASED RISK FOR PRIMARY AND SECONDARY CANCER†

Mutations dramatically increase the risk of developing cancer



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

AMONG BREAST CANCER PATIENTS:

76% of women chose to undergo BRCA mutation testing, and 79% of these women used genetic test results to aid in their surgical decision making .[6]

CHECK PERSONAL OR FAMILY HISTORY FOR THESE RED FLAGS*

- Ovarian cancer
- Breast cancer diagnosed ≤50 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
- Pancreatic cancer with an 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.[7]

* Assessment criteria based on medical society guidelines. For these individual society guidelines, go to www.myriadpro.com/guidelines.
** HBOC-associated cancers include breast, ovarian, and pancreatic cancer.

The value of test results

MAKING SENSE OF THE POSSIBLE OUTCOMES OF THE BRAC*Analysis*® TEST, AND HOW TO PROCEED WITH PATIENT CARE.

POWER OF A POSITIVE RESULT

POSITIVE FOR DELETERIOUS MUTATION

DIAGNOSIS 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:

- *Intensive surveillance initiated in the 20s, including breast MRI*
- *Preventive drug therapy*
- *Risk-reducing surgeries*

VALUE OF A NEGATIVE RESULT

NO DELETERIOUS MUTATION DETECTED

Mutation previously identified in the family

NO INCREASED CANCER RISK

Manage based on general population cancer screening recommendations

No mutation previously identified in the family

CHANCE OF HBOC SYNDROME SIGNIFICANTLY REDUCED

Manage based on negative test result and personal/family history of cancer

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

POWER OF EXPERIENCE

GENETIC VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)

MANAGE BASED ON PERSONAL/FAMILY HISTORY OF CANCER

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 patient's personal and/or family history of cancer.

RECLASSIFYING A VARIANT

When data allows a previously uncertain 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* [7] mutations.

USE CLINICAL GUIDELINES TO ADDRESS UNIQUE SURGICAL AND SURVEILLANCE NEEDS OF BRCA-POSITIVE PATIENTS

- According to NCCN relative contraindications for breast-conserving therapy requiring radiation therapy.[8] Women with a known or suspected genetic predisposition to breast cancer.
- May have higher risk of ipsilateral recurrence or contralateral cancer with breast- conserving therapy
- Prophylactic bilateral mastectomy for risk 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 HBOC patients. [1,2,4]

	Procedure	Age to begin	Frequency
Breast cancer surveillance	Breast self-exam	18 years	monthly
	Clinical breast exam	25 years	twice a year
	Mammography	25 years	yearly
	MRI	25 years	yearly
Ovarian cancer surveillance[a]	Pelvic exam	30 years in patients not electing RRBSO	twice a year
	TVUS and CA-125[b]	30 years in patients not electing RRBSO	twice a year

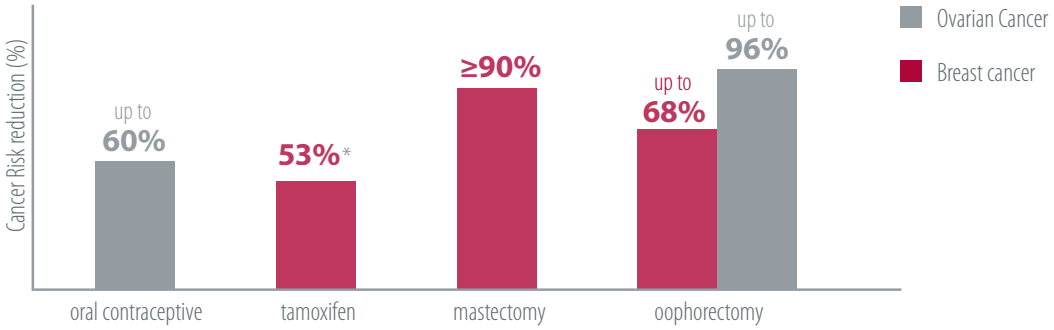
a. NCCN guidelines suggest risk-reducing salpingo-oophorectomy (RRBSO), ideally between 35 and 40 years of age, and upon ompletion of child bearing or individualized based on earliest age of onset of ovarian cancer in the family.
b. NCCN guidelines suggest patients who do not elect RRBSO consider concurrent 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.

"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 still healthy."

- Stefanie B.

MEDICAL INTERVENTION GREATLY REDUCES RISK†

Reduce risk of hereditary cancer with proven medical management



* In contralateral breast cancers.

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

"It 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."

- Jodi V.

myriad WHEN DECISIONS MATTER

Assess HBOC risk with a proven 4-step protocol

1 SCREEN

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

2 EVALUATE

- Assess for red flags
- Discuss BRAC*Analysis*® testing with appropriate patient

3 DIAGNOSE

- Order BRAC*Analysis*® 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 implement BRAC*Analysis*® 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.

Professional Society	Website URL
National Comprehensive Cancer Network Genetic/ Familial High-Risk Assessment: Breast and Ovarian [1]	www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf (login required)
European Society for Medical Oncology (ESMO)[2] BRCA in breast cancer	http://annonc.oxfordjournals.org/content/22/suppl_6/vi31.full
European Society for Medical Oncology (ESMO)[3] Primary breast cancer	http://annonc.oxfordjournals.org/content/22/suppl_6/vi12.full
American Society of Clinical Oncology (ASCO)[4,5]	http://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer

Technical information

BRAC*Analysis*® 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: 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[9] Myriad Genetics currently uses Sanger sequencing technology

- *BRCA1* is located on chromosome 17q21 and is comprised of 5,400 base pairs in 22 coding exons. Full sequencing is performed in the forward and reverse directions of all coding exons and 750 adjacent base pairs in non-coding introns. Non-coding exons 1 and 4 are not analyzed. The wild type *BRCA1* gene encodes a protein of 1863 amino acids.
- *BRCA2* is located on chromosome 13q12.3 and is comprised of 10,200 base pairs in 26 coding exons. Full sequencing is performed in the forward and reverse directions of all coding exons and 900 adjacent base pairs in non-coding introns. Non-coding exon 1 not analyzed. The wild type *BRCA2* gene encodes a protein of 3418 AAs.

Large rearrangements: Approximately 10% of all mutations in high risk patients (>30% risk for a deleterious mutation) and 7% of lower risk patients have a large rearrangement 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.

TEST OFFERINGS

BRAC*Analysis*®: 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 BRAC*Analysis*®: This test is for individuals who already know a *BRCA1* or *BRCA2* gene mutation is in the family. A copy of the test result (or name of the gene mutation) from family members who have tested positive will be required prior to testing.

Multisite 3 BRAC*Analysis*®: 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 ancestry tests negative for the three common mutations and has a significant family history, reflex testing to full BRAC*Analysis*® should be considered.

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2. *Balmaña J, et al.* BRCA *in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2011;22 (suppl 6): vi31-vi34.*
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BRAC*Analysis*®

A test for Hereditary Breast
and Ovarian Cancer (HBOC) syndrome

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