Genetic Counseling, Testing, and Management of HBOC in India: An Expert Consensus Document from Indian Society of Medical and Pediatric Oncology

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abstract

PURPOSE Hereditary breast and ovarian cancer (HBOC) syndrome is primarily characterized by mutations in the BRCA1/2 genes. There are several barriers to the implementation of genetic testing and counseling in India that may affect clinical decisions. These consensus recommendations were therefore convened as a collaborative effort to improve testing and management of HBOC in India.

DESIGN Recommendations were developed by a multidisciplinary group of experts from the Indian Society of Medical and Pediatric Oncology and some invited experts on the basis of graded evidence from the literature and using a formal Delphi process to help reach consensus. PubMed and Google Scholar databases were searched to source relevant articles.

RESULTS This consensus statement provides practical insight into identifying patients who should undergo genetic counseling and testing on the basis of assessments of family and ancestry and personal history of HBOC. It discusses the need and significance of genetic counselors and medical professionals who have the necessary expertise in genetic counseling and testing. Recommendations elucidate requirements of pretest counseling, including discussions on genetic variants of uncertain significance and risk reduction options. The group of experts recommended single-site mutation testing in families with a known mutation and next-generation sequencing coupled with multiplex ligation probe amplification for the detection of large genomic rearrangements for unknown mutations. Recommendations for surgical and lifestyle-related risk reduction approaches and management using poly (ADP-ribose) polymerase inhibitors are also detailed.

CONCLUSION With rapid strides being made in the field of genetic testing/counseling in India, more oncologists are expected to include genetic testing/counseling as part of their clinical practice. These consensus recommendations are anticipated to help homogenize genetic testing and management of HBOC in India for improved patient care.

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INTRODUCTION

Hereditary breast and ovarian cancer (HBOC) syndrome is characterized by an autosomal-dominant inheritance pattern with increased risk of early-onset breast cancer (BC) and ovarian cancer (OC) in multiple family members. HBOC syndrome is associated with 50% to 85% lifetime risk of BC and 15% to 30% risk of OC in women. Mutations in BRCA1 and BRCA2 are commonly implicated in HBOC. Founder mutations—specific mutations identified in a population with common ancestry—in BRCA1/2 have been identified in Ashkenazi Jews, French Canadians, and Icelanders, among other populations worldwide. In India, BC is the most common cancer in women as well as the most common cause of cancer-related death in women. The Indian scenario is characterized by younger median age of onset and a high incidence-to-mortality ratio compared with the West. However, the burden of BC attributable to inherited mutations is not well characterized.

With the approval of poly (ADP-ribose) polymerase (PARP) inhibitors for both germline and somatic BRCA1/2 mutations and data indicating the efficacy of platinum-based chemotherapy in gBRCA mutant cases, genetic testing has the potential to affect treatment decisions. Genetic tests improve the understanding of the risk of...
What are the current testing practices and effective approaches for advancing BRCA mutation testing and the management of hereditary breast and ovarian cancers in India?

Knowledge Generated

Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutations should undergo genetic counseling. The experts recommended single-site mutation testing in families with a known mutation and next-generation sequencing coupled with multiplex ligation probe amplification for detection of large genomic rearrangements for unknown mutations. Recommendations also include surgical and lifestyle-related risk-reduction approaches and management using poly (ADP-ribose) polymerase inhibitors.

Relevance

A growing number of oncologists in India are expected to implement genetic testing/counseling, and these consensus recommendations can be expected to standardize clinical practice for improved patient care.

Context

Key Objective

What are the current testing practices and effective approaches for advancing BRCA mutation testing and the management of hereditary breast and ovarian cancers in India?

METHODOLOGY

Recommendations were developed by a multidisciplinary group of experts using evidence from phase III randomized controlled studies, relevant prospective and retrospective studies, and clinical experience as a guide. The first meeting was organized on May 25, 2019, in Mumbai. The discussion centered on genetic counseling, methods of genetic testing, and challenges encountered during clinical practice and referrals with an Indian perspective in mind. The meeting involved extensive discussions of specific questions developed a priori by the committee chairpersons to aid the discussion, followed by voting to reach a consensus using the Delphi process.

The Expert Panel corresponded frequently through e-mail; progress on guideline development was driven primarily by committee chairpersons. All members participated in the preparation of the draft. PubMed and Google Scholar databases were searched using the following key words: “hereditary breast and ovarian cancer”; “HBOC”; “BRCA1/2 mutations”; “non-BRCA mutations”; “germline BRCA mutations”; “somatic BRCA mutations”; and “genetic testing.” Levels of evidence and grades of recommendation endorsed by the Infectious Diseases Society of America were applied.

Genetic Counseling in India: Importance and Awareness

Despite recent progress, genetic testing in HBOC remains underutilized in India. The process of genetic counseling involves an attempt by one or more appropriately trained persons to help the individual or family to:

a) Comprehend the medical facts: diagnosis and probable course of the disorder and available management options
b) Understand how heredity contributes to the disorder and the risk of recurrence in first-degree mutation carrier relatives
c) Understand the alternatives for dealing with the risk of recurrence
d) Choose a course of action according to their risk and family goals
e) Make the best possible adjustment to the disorder

Genetic counseling before testing is endorsed by many international oncology working groups. Guidelines from several countries, including Europe and Australia, advocate pretest and post-test genetic counseling for BRCA1/2 by professionals who are adequately trained in genetics and clinical oncology. In India, oncologists are often the first point of contact for these patients.
Components of HBOC Genetic Counseling

Pretest counseling. The counselor would discuss the following issues to educate patients and suggests who should be tested first in the family. The following are key components:
- Medical history and pedigree evaluation up to 3 generations
- Application of mathematical risk assessment models/qualitative criteria (eg, National Comprehensive Cancer Network [NCCN])
- Discussion of genetic testing recommendations
- Implications of genetic testing: benefits/harms
- Discussion of financial considerations
- Discussion of legal protection against genetic discrimination.18

Assessment of family history. Per the established standards, collection of complete family history should comprise a 3-generation pedigree analysis that includes information on age/year of birth for each individual, age at onset of cancer, age at death, cause of death (for deceased relatives), ethnic background of all grandparents (maternal and paternal), consanguinity, and any information on prior genetic testing, pregnancies, and half-siblings.25,26

Risk communication. Information on genetic testing results; treatment implications of pathogenic, benign variants, and variants of uncertain significance (VUS) and associated risk for patients and predictive risk among relatives should be explained. A significant increase in medical knowledge and risk perception has been reported after pregenetic testing communication via face-to-face counseling, group discussion, and written communication—for example, information booklets—that eventually helped minimize anxiety in patients after receipt of test results.27-30

Post-test counseling session. The post-test counseling session involves an assessment of understanding and recall of medical facts conveyed during counseling, change in anxiety level, severity of risk perception, reproductive plans, and satisfaction with the quality and extent of genetic counseling.18

GERMLINE BRCA TESTING

Assessment of Risk and Identifying Patients

Germline mutations in BRCA1/2 genes are regarded as high penetrance—a cancer relative risk of greater than 5—and have been characterized in several populations globally. Mutations in other non-BRCA genes, such as PALB2, TP53, CDH1, STK11, CHEK2, RAD51, and ATM, are also known to confer risk of BC and/or OC, albeit with lower frequency and penetrance31 (Tables 1 and 2).

The lifetime risk of breast and ovarian malignancies is variable, with pathogenic mutations in BRCA1 (BC: 46% to 87%; OC: 39% to 63%) and BRCA2 (BC: 38% to 84%; OC: 17% to 27%). Other cancers associated with germline

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**TABLE 1. Genes Associated With HBOC**

| Gene/Locus | Syndrome | Breast Cancer Risk, % | Mutation/Minor Allele Frequency |
|------------|----------|-----------------------|---------------------------------|
| **High-penetrance genes** |
| BRCA1 (17q21) | HBOC | 60-85 lifetime | 1/400 |
| BRCA2 (13q12.3) | HBOC | 60-85 lifetime risk | 1/400 |
| TP53 (17p13.1) | Li-Fraumeni syndrome | 50-89 by age 50 | <1/10,000 |
| PTEN (10q23.3) | Cowden syndrome | 25-50 lifetime | <1/10,000 |
| CDH1 (16q22.1) | Familial diffuse gastric cancer | RR, 6.6 | <1/10,000 |
| STK11/LKB1 (19p13.3) | Peutz Jegher syndrome | 30-50 by age 70 | <1/10,000 |
| **Moderate-penetrance genes** |
| CHEK2 (22q12.1) | Li-Fraumeni 2 syndrome | OR, 2.6 (for 100delC) | 1/100-1/200 in certain populations |
| BRIP1 (17q22) | Breast cancer | RR, 2.0 | <1/1,000 |
| ATM (11q22.3) | Ataxia telangiectasia | RR, 2.37 | 1/33-1/333 |
| PALB2 (16p12) | Breast, pancreatic, prostate cancers | RR, 2.3 | <1/1,000 |
| **Low-penetrance genes** |
| FGFR2 (10q26) | Breast cancer | OR, 1.26 | 0.38 |
| TOX3 (16q12.1) | Breast cancer | OR, 1.14 | 0.46 |
| LSPI (11p15.5) | Breast cancer | OR, 1.06 | 0.3 |
| TGFB1 (19q13.1) | Breast cancer | OR, 1.07 | 0.68 |
| MAP3K1 (5q11.2) | Breast cancer | OR, 1.13 | 0.28 |

Abbreviations: HBOC, hereditary breast and ovarian cancer; OR, odds ratio; RR, relative risk.
BRCA1/2 mutations include male BC (1% to 9%), prostate cancer (9% to 20%), pancreatic cancer (1% to 7%), and melanoma. The largest analysis of 1,010 high-risk families across India revealed BRCA mutations in 85% and non-BRCA mutations in 15% of families. Additional analysis based on age and family history showed a high prevalence of germline variants (75%) in younger patients age younger than 40 years with a first-degree family member affected with BC/OC. A recent study from North India reported a 30% prevalence of gBRCA mutation in patients with BC/OC qualifying for NCCN criteria for testing, including 5 novel mutations. A methodical review investigating the prevalence of germline variants in high-risk HBOC susceptibility genes in 1,028 patients of Indian descent with familial/early-onset/triple-negative BC or OC identified 18 BRCA1 and 16 BRCA2 variants that were not reported in the Breast Cancer Information Core or ClinVar databases. The putative Ashkenazi founder mutation BRCA1 185delAG was detected in a low proportion of patients (4.2%), the majority of whom were from South India or who were Malaysians of Indian origin. Table 3 provides a summary of deleterious germline mutations identified in Indian patients with HBOC.

Until now, our clinical practice has been to test patients who fulfill NCCN criteria for testing (Box 1); however, recent publications have emphasized that using NCCN guidelines misses many patients with both BRCA and non-BRCA mutations who would otherwise benefit.

**BOX 1. NCCN GUIDELINES 2019 FOR gBRCA RISK ASSESSMENT**

- Individual from a family with a known BRCA1/2 pathogenic/likely pathogenic variant, including such variants found on research testing
- Personal history of breast cancer (BC) plus one or more of the following:
  - Diagnosed age ≤ 45 years
  - Diagnosed age 46-50 years (an additional BC primary at any age or one or more close blood relative with BC at any age or one or more close blood relative with high-grade [Gleason score ≥ 7] prostate cancer)
  - An unknown or limited family history
  - Diagnosed age ≤ 60 years with triple-negative BC
  - Diagnosed at any age with: one or more close blood relative with BC diagnosed age ≤ 50 years; or OC, male BC, metastatic prostate cancer, or pancreatic cancer and two or more additional diagnoses of BC at any age in patient and/or close blood relatives
  - Ashkenazi Jewish ancestry
- Personal history of OC

The US Preventive Services Task Force (August 2019) recommends that primary care clinicians assess women with a personal or family history of BC, OC, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing.

**WHOM TO TEST FIRST?**

It is ideal to initiate genetic testing in a family member who is most likely to test positive for a pathogenic variant, which is usually a woman affected by early BC/OC (any age). Children should not be tested for BRCA before the age of 18 years.

**Methods of Germline BRCA Detection**

Germline genetic testing usually involves taking written informed consent for storage of biologic samples—blood sample, saliva, or cheek swab—and testing, followed by analysis of the sample for the detection of heritable germline mutations. Multigene panels using next-generation sequencing (NGS) coupled with the multiplex ligation probe amplification technique enables high-throughput genetic testing. The usual turnaround time to receive test results is 4 weeks. While selecting an NGS workflow, the following criteria should be considered to suit the genetic testing:

- a) Enrichment method: polymerase chain reaction amplification method or hybrid capture based;
- b) Sequencing chemistry: sequencing by synthesis or pH-mediated PCR; and
- c) Bioinformatic analysis

Studies examining NGS workflows for BRCA1/2 genes in HBOC samples have demonstrated excellent performance, with almost 100% sensitivity and specificity, and cost-effectiveness compared with single-site mutation testing in these genes. Two studies from India have reported that the use of multigene panel testing by NGS for germline mutations in patients with HBOC. The majority of BRCA1/2 mutations may be single-base substitution missense or
nonsense mutations. Other mutations are small insertions or deletions that result in a prematurely truncated non-functional protein. Some deleterious variants may also include splice junction alterations that lead to exon skipping or the inclusion of intronic region, resulting in a nonfunctional protein. It is important to remember that NGS can miss large genomic rearrangements, which are causal pathogenic mutations, in 5% of patients with HBOC. Some experts recommend that as multiplex ligation probe amplification technique allows for the identification of large genomic rearrangements, it should be performed in all patients who test negative by NGS who have a strong clinical suspicion of HBOC.44,45 The commonly used panels for HBOC syndrome include the following genes: ATM, BRCA1, BRCA2, BRIP1, CHEK2, RAD50, RAD51D, RAD51C, PALB2, BAARD1, P53, STK11, CDH1, MSH2, MSH6, MLH1, EPCAM, PMS2, ATM, P53, FGFR2, TOX3, LSP1, and MAP3K1.

**Interpretation of Sequencing Results**

Genetic testing helps detect sequence changes that may be benign, pathogenic, or VUS. International working groups provide guidelines for the interpretation of germline sequence variants and categorize the DNA sequence alterations qualitatively on the basis of functional evidence, family history, allele frequency data, and computational and in silico predictions (Table 4).

It is critical to note that when no deleterious germline mutation is detected in a proband, results should not be directly labeled as negative and the potential limitations of testing should be considered.44 Some possibilities include that the patient has a pathogenic variant in another gene not included in the multigene panel; that the tested gene has a sequence variant that cannot be easily detected by sequence analysis, such as large deletion; and that the patient has a sequence variant in a region, such as an intron or regulatory region of a gene, that may not be covered by the test.46

**VALIDATION OF TEST RESULT**

As results from genetic testing—for example, NGS—influence clinical treatment, validation of the test is critical.47,48 The joint consensus from the Association for Molecular Pathology

| Cancer Type | Risk in Carriers to Age 70 Years | Lifetime Risk in General Population, % |
|-------------|---------------------------------|--------------------------------------|
| Breast      | BRCA1: 55-70                    | Approximately 12                     |
|             | BRCA2: 45-70                    |                                      |
| Contralateral (opposite) breast | Up to 63 at 25 years postdiagnosis but highly age dependent | 7 at 25 years postdiagnosis |
| Ovarian     | BRCA1: Approximately 40        | Approximately 1                      |
|             | BRCA2: Approximately 15        |                                      |
| Colon       | Unclear                         | Approximately 5                     |
| Prostate    | Elevated; absolute risk not well defined | White: Approximately 14 |
| Male breast | BRCA1: 1                        | 0.1                                  |
|             | BRCA2: 8                        |                                      |
| Pancreatic  | BRCA1: Unclear                  | 1.5                                  |
|             | BRCA2: 5                        |                                      |
| Other sites | To be determined                | Varied                               |


| Study                      | Region                | Testing Method                                     | Pathogenic BRCA1/2 Mutations Identified                                      |
|---------------------------|-----------------------|---------------------------------------------------|--------------------------------------------------------------------------|
| Valarmathi et al, 2003    | New Delhi, North India| Direct sequencing                                  | BRCA1 (E1250X in exon 11; E1754X in exon 20)                               |
| Rajkumar et al, 2003      | Chennai, South India  | Heteroduplex analysis/dHPLC                        | BRCA1 (Ex12 1386 delCTCTC Stop 1389, Ex13 CGA→TGA Arginine1443 Stop), BRCA2 (Ex110 1235delCTTAA stop 1237) |
| Saxena, 2006              | New Delhi, North India| Heteroduplex analysis of PCR amplicons using exon-specific primers | BRCA1 (185delAG in exon 2; 4184del4; 3596del4 in exon 11), BRCA1 (4184del4 in exon 11) |
| Syamala et al, 2007       | Kerala, South India   | Direct sequencing                                  | BRCA2 (c.4642delAA, c.4926insGACC)                                       |
| Thirthagiri et al, 2008   | Malaysia, Indian ethnicity| dHPLC and DNA sequencing                           | BRCA1 (180 delA, 185 delAG, 5370 C>T), BRCA2 (9097 C>T)                  |
| Soumittra et al, 2009     | Chennai, South India  | PCR-dHPLC                                          | BRCA1 (c.4158_4162delCTCTCp.Ser1369SerfsX2, c.4327C>T; p.R1443X, c.1148_1149delAT; p.Asn383Arg fsX6, c.4399C>T; p.Gln1467X, c.4705_4706insTGGAAATc.p.Ile1567fsx5, c.5024_5025insT, p Thr1675Thr fsX4, c.68_69delAG; p.Glu23Val fsX16, c.66_67delTGTA; p.Leu22Ile, fsX18, c.5118_5120delAT; p.del1707Ile); BRCA2 (c.6214_6218delCTTAA.p.Ser2072Ser fsX4, c.5130_5133delTGGT.p.Tyr1693X, c.2621_2627delAAGCGTc.p. Ile873Ile fsX19) |
| Vaidyanathan et al, 2009   | South India           | Heteroduplex analysis using CSGE and direct sequencing | BRCA1 (185delAG)                                                        |
| Kang et al, 2014          | Malaysia, Indian ethnicity| PCR and Sanger sequencing                           | BRCA1 (185delAG)                                                        |

Abbreviations: CSGE, conformation-sensitive gel electrophoresis; dHPLC, denaturing high-performance liquid chromatography; PCR, polymerase chain reaction.

and College of American Pathologists recommends the validation of every detected single-nucleotide variant or indel in the coding region that results in deleterious mutations and documenting it in terms of positive percentage agreement and positive predictive value.\(^{49}\) Samples in which a deleterious variant/mutation is detected should be reconfirmed using fresh DNA extraction from a different aliquot of cells from the same patient by Sanger sequencing, a recognized gold-standard method.\(^{49}\)

**HOW TO MANAGE VUS**

VUS are genetic alterations that are usually single-base substitutions that result in a missense mutation and a different amino acid in the encoded protein. These alterations in the coding sites may be in the promoter regions, intronic regions close to exons, or may be small in-frame insertions and deletions and synonymous substitutions.\(^{50-52}\) It is estimated that more than 20,000 unique variants have been identified in the coding, splice site, and intervening sequences of BRCA1 genes.\(^{53}\) Almost 90% of BRCA1/2 mutations can be classified either as pathogenic or benign; however, approximately 10% of them cannot be classified as deleterious or neutral and are labeled as VUS. It is estimated that on complete analysis, approximately 30% to 50% of VUS might actually be pathogenic.\(^{54-56}\)

A VUS is characterized by gathering evidence, such as its co-occurrence with a deleterious mutation, cosegregation with disease in families, functional characterization with available physiochemical, cellular and biologic assays, allelic frequency in databases that document well-characterized populations, and in silico assessment. Data-sharing initiatives, like the BRCA Challenge and the Evidence-Based Network for the Interpretation of Germline Mutant Alleles, aid in the assessment of VUS. The expanding database of HBOC genetic testing results and ongoing efforts targeted at determining the pathogenicity and categorizing VUS have resulted in a 13% decline in the rate of VUS detection between 2002 and 2013.\(^{57}\)

As a result of the uncertainty of VUS, the International Agency for Research on Cancer does not recommend predictive genetic testing in at-risk relatives and emphasizes the need to treat VUS carriers as probands with no mutations. However, misinterpretation of VUS by clinicians has been reported, leading to unnecessary prophylactic surgery and patient anxiety.\(^{58}\)

**QUALITY OF GENETIC TESTING: THE BACKBONE OF CHARACTERIZING BRCA1/2 MUTATIONS**

In an oncology setting, genetic testing addresses two purposes: identifying deleterious germline mutations in families with predisposition to cancers, followed by predictive genetic testing in these high-risk families; and identifying molecular markers or signatures in the tumors for treatment and prognosis. A robust methodology/algorithm in genetic testing is extremely important for maintaining test quality. The American Association of Pathologists’ Assistants and the
College of American Pathologists have developed guidelines for NGS bioinformatics pipelines, and laboratories should follow them to reduce error rates. In addition, the guidelines emphasize the role of trained professionals to achieve optimal testing quality. Genetic testing that is based on national accreditation programs, various quality assessment programs, and participation in such schemes as the European Molecular Genetics Quality Network could help the testing laboratories maintain quality control.

**SOMATIC OR TUMOR BRCA TESTING**

Growing evidence suggests that tumors with somatically acquired BRCA1/2 pathogenic mutations respond to drugs that inhibit PARP. As mentioned in germline testing, informed consent of the participant should be obtained before testing. Testing for somatic mutations with NGS becomes a method of choice because of its sensitivity compared with Sanger sequencing. A limitation of somatic BRCA testing is DNA extraction from formalin-fixed, paraffin-embedded specimens. These samples have a variable mix of neoplastic and normal stroma cell tissue, and the quantity of DNA extracted is low and of poor quality. Furthermore, tissue preservation using formalin induces a chemical crosslinking reaction with nucleotides that results in artifactual sequence alterations and deamination of cytosine nucleotides. Use of shorter amplifiers, de-crosslinking steps, and treatment with uracil-DNA glycosylase—DNA repair enzyme—to markedly reduce the number of sequence artifacts before polymerase chain reaction amplification are steps recommended to improve the quality of extracted DNA.

The tumor content for somatic BRCA testing must be certified by a trained pathologist. DNA from the tissue sample should be extracted from a single representative block using a standardized and validated method. Known positive and negative controls should be included during testing. Somatic testing is generally recommended at 500× coverage to avoid a false-negative assessment. After testing, the bioinformatic pipeline should be able to filter out variants with 5% to 10% allele frequency on the basis of the initial tumor percentage.

The somatic testing report should include:

- a) Suitability of tumor sample for tumor content and specific testing method
- b) Number and names of genes tested (if using a multi-gene panel)
- c) Depth of coverage for each gene
- d) Details of mutation, if detected, with Human Genome Variation Society nomenclature
- e) Reference sequence of the gene
- f) Interpretation of results with reference to therapy

**Interpretation of Somatic or Tumor BRCA Result and Its Role**

Molecular signatures of homologous recombination deficiency from ovarian tumors and association with high loss of heterozygosity indicate genomic scoring and instability. Although regarded as uncommon, sporadic somatic BRCA1/2 mutations account for one third of BRCA mutations in OC and 4% to 15% of unselected triple-negative BC.

In high-grade serous OC, BRCA1/2 germline and somatic mutations are frequent (17% to 25%), with somatic mutations representing 18% to 30% of all BRCA1/2 mutations. In a sequencing study, up to 9% of patients with OC had relevant somatic mutations in homologous recombinant genes (BRCA1/2, BRIP1, CHEK2, and RAD51C). Somatic mutations were highly predictive of primary platinum sensitivity and improved overall survival.

Accumulating evidence suggests the role of somatically acquired BRCA1/2 pathogenic mutations, tumor pathology, and loss of heterozygosity as predictive biomarkers of clinical response to PARP inhibitor. In a phase II study,
patients with platinum-sensitive relapsed serous OC with positive BRCA mutations had the highest likelihood of benefiting from olaparib (median progression-free survival, 11.2 months in BRCA mutation-positive v 7.4 months in wild-type BRCA patients; hazard ratio, 0.54 [95% CI, 0.34 to 0.85]; P = .0075).69

**IMPLICATIONS OF TESTING BRCA (GERMLINE/TUMOR) MUTATIONS IN THE MANAGEMENT OF HBOC**

The presence of pathogenic or likely pathogenic mutations in BRCA1 or BRCA2 has tremendous implications for the management of patients and unaffected relatives (previvors; Box 2).

**Risk Management for the Previvor (unaffected carrier of mutation)**

**Lifestyle modifications.**

- Regular exercise and maintaining a healthy body weight
- Limiting alcohol consumption
- Avoid hormone-replacement therapy
- Encourage breast feeding

NCCN recommends that BRCA carriers be offered prophylactic bilateral mastectomy.19 In both retrospective and prospective observational studies, risk-reducing or prophylactic bilateral mastectomy decreases the incidence of BC by 90% or more in patients who are at risk for hereditary BC, with most studies focusing on BRCA mutation carriers.71-73

For BRCA1 carriers, risk-reducing bilateral salpingo-oophorectomy (rRBSO) is recommended for women who have completed childbearing and should be performed by age 35 to 40 years or individualized on the basis of age of onset of OC in the family.19 In BRCA2 carriers, this procedure can be delayed until age 40 to 45 years. rRBSO not only decreases the risk of OC in BRCA mutation carriers, but also decreases the risk of mortality.74-76 NCCN does not routinely recommend hysterectomy at the time of rRBSO and indicates that “salpingectomy alone is not the standard-of-care and is discouraged outside a clinical trial.”19

**Cancer surveillance.** For female BRCA carriers who do not wish to pursue (or would rather delay) surgical risk reduction, BC surveillance should be offered, and OC screening may be performed.19

**BC screening.** The following strategy is recommended by expert groups for women with BRCA pathogenic variants who have not undergone risk-reducing surgery and should be individualized as needed:

a) Breast awareness from 18 years of age
b) Clinical breast examination every 6 to 12 months is recommended from the age of 25 or 10 years before the youngest BC.

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**BOX 2. SUMMARY OF THE INDIAN SOCIETY OF MEDICAL AND PEDIATRIC ONCOLOGY CONSENSUS DOCUMENT ON HEREDITARY BREAST AND OVARIAN CANCER**

| Question | Recommendation | Level of Recommendation |
|----------|----------------|------------------------|
| 1. Who should undergo genetic counseling? | All clinicians should assess: Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer; or an ancestry associated BRCA1/2 gene mutations; and advise genetic counseling and, if indicated, genetic testing | VB |
| 2. Who should undergo genetic testing? | Any breast cancer (BC) diagnosed at age < 45 years | VB |
| | Any triple-negative BC age < 60 years | |
| | Any male BC | |
| | BC at any age and ≥ 1 close relative (first/second/third degree relative on same side of family) diagnosed with BC, ovarian cancer (OC), prostate, or pancreatic cancer | |
| | Any woman with OC | |
| 3. Who can perform genetic counseling? | Genetic counselors and other medical professionals (medical/surgical/radiation oncologists/breast surgeons) knowledgeable in genetic testing can provide patient education and counseling and make recommendations regarding genetic testing and arrange testing | VB |
| 4. What points should be included in pretest counseling? | Rapport building, elicitation of need and comprehension levels | VB |
| | Medical history and pedigree evaluation | |
| | Decide the best test candidate to test first | |
| | Genetic testing recommendations | |
| | Implications of genetic testing: benefits/harms | |
| | Variants of unknown significance | |
| | Financial considerations | |
| | Risk reduction options | |
| Question | Recommendation | Level of Recommendation |
|----------|----------------|------------------------|
| 4. What genetic test should be offered? | Single-site mutation testing in families with a known mutation | VB |
| For unknown mutation: | Essential: BRCA1/2 sequencing by next-generation sequencing plus multiplex ligation probe amplification (MLPA; BRCA1/2) for large genomic rearrangements (LGRs) | |
| Desirable: Multigene panel testing is representative model panel should include BRCA1; BRCA2; p53; PTEN; CDH1; PALB2; CHEK2; ATM; RAD51C; STK11; RAD51D; BRIP1; MLH1; MSH2; MSH6; and PMS2 + MLPA (BRCA1/2) for LGRs | |
| 5. What risk-reduction approaches should be offered to affected individuals? | Risk management for future cancers: | IIB |
| Contralateral prophylactic mastectomy: | | |
| Risk-reduction bilateral salpingo-oophorectomy (rrBSO): For BRCA carriers, rrBSO is recommended for women who have completed childbearing, and should be performed by age 35 to 40 years. In BRCA2 carriers, one can consider delaying this procedure until age 40 to 45 | | |
| Advanced OC with BRCA mutation: | | IA |
| Prophylactic bilateral mastectomy is not considered in these cases as the risk of death from the primary malignancy is high over the next 5 years. In these cases, nonsurgical measures and surveillance only are used for any new primary malignancy in breasts | |
| 6. What risk-reduction approaches should be offered to unaffected mutation carriers? | BRCA1/2: | |
| Lifestyle modifications: Regular exercise, maintaining healthy body weight, limiting alcohol consumption | VB |
| Avoid hormone replacement therapy, encourage breast feeding | IIB |
| Breast cancer: BRCA carriers should be offered prophylactic bilateral mastectomy; however, the final decision is based on personal preference, given that effective screening is available | IA |
| Bilateral salpingo-oophorectomy: For BRCA carriers, risk-reducing bilateral salpingo-oophorectomy is recommended for women who have completed childbearing, and should be performed by age 35 to 40 years. In BRCA2 carriers, one can consider delaying this procedure until age 40 to 45 years | IIB |
| Cancer surveillance: For female BRCA carriers who do not wish to pursue (or would rather delay) surgical risk reduction, BC surveillance should be offered, and OC screening may be performed | VB |
| Breast cancer screening: | | |
| Breast awareness from age 18 years | | |
| Clinical breast examination (CBE) every 6-12 months is recommended from the age of 25 years or 10 years before the youngest BC | | |
| Annual screening MRI (days 7-15 of menstrual cycle) should be commenced from age 25 years with the addition of annual mammography from age 35 years | | |
| OC screening: | | |
| Concurrent transvaginal ultrasound (preferably days 1-10 of menstrual cycle) and CA-125 (best performed after day 5 of menstrual cycle) every 6 months beginning at age 30 years | | |
| Before risk-reducing bilateral salpingo-oophorectomy, 6 monthly transvaginal ultrasound and measures of serum CA-125 may be considered from age 30 years; however, the limited value of these tools as an effective screening measure should be communicated to individuals | | |
| Chemoprevention: Use of tamoxifen may be considered; however, the level of evidence is weak; use tamoxifen only for BRCA2 tumors or if the first cancer was estrogen receptor positive | | |
| Surveillance in male previvors: | | |
| There are no proven risk-reducing surgical options for men | | |
| Monthly breast self-examination starting at age 35 years | | |
| Clinical breast examination every 12 months starting at age 35 years | | |
| Prostate cancer screening starting at age 45 years for BRCA2 carriers and consideration of prostate screening for BRCA1 carriers also at age 45 years | | |
c) Annual screening magnetic resonance imaging (MRI; days 7 to 15 of the menstrual cycle) should be commenced from age 25 years with the addition of annual mammography with or without tomosynthesis from age 30 years.77

d) In women younger than age 30 years, breast ultrasound can be considered if MRI is unavailable.

OC screening. For carriers who have not undergone rrBSO, we recommend OC screening. This consists of concurrent transvaginal ultrasound, preferably day 1 to 10 of the menstrual cycle, and CA-125—best performed after day 5 of the menstrual cycle—every 6 months beginning at age 30 years or 5 to 10 years before the earliest age of first diagnosis in the family. Before rrBSO, 6 monthly transvaginal ultrasound and measure of serum CA-125 may be considered from age 30 years; however, the limited value of these tools as effective screening measures should be communicated to individuals.

Chemoprevention. Use of tamoxifen may be considered; however, the level of evidence is weak.78

Prevention of other BRCA-related cancers. No evidence-based data exist. BRCA2 carriers may consider annual skin and eye examination as screening for melanoma, and annual screening for pancreatic cancer with endoscopic ultrasound or MRI/magnetic resonance cholangiopancreatography. There is no consensus when screening should commence; however, age 50 years or 10 years before the earliest diagnosed case in the family would be reasonable (Table 5).

Reproductive counseling. Pathogenic variants in many BC genes, including BRCA, are inherited in an autosomal-dominant pattern, meaning that there is a 50% chance that children of BRCA carriers will have inherited the cancer predisposition variant. Reproductive counseling of BRCA carriers includes education about prenatal diagnosis and assisted reproduction.19 One option is pre-implantation genetic diagnosis, which is used to analyze embryos—obtained by in vitro fertilization—genetically before their transfer into the uterus.

Management for Patient

Contralateral prophylactic mastectomy. Risk-reduction mastectomy is often offered to patients with or without a history of BC who carry a germline genetic mutation that...
| Gene          | Breast Cancer Risk and Management          | Ovarian Cancer Risk and Management               | Other Cancers                          |
|--------------|--------------------------------------------|-------------------------------------------------|----------------------------------------|
| **ATM**      | Increased risk                            | Potentially increased risk                      | Counsel for autosomal-recessive condition in offspring |
|              | Annual mammogram from age 40 years         | RRM, insufficient evidence                      |                                        |
| **BARD1**    | Potentially increased risk                 | Unknown                                         |                                        |
|              | RRM, insufficient evidence                 |                                                |                                        |
| **BRIP1**    | Unknown                                    | Increased risk of ovarian cancer                |                                        |
|              | RRM, insufficient evidence                 | Consider RRSO at age 45-50 years                |                                        |
| **CDH1**     | Increased risk of lobular breast cancer    | No increase                                     | Diffuse gastric cancer                 |
|              | Annual mammogram from age 30 years         | RRM, insufficient evidence                      |                                        |
| **CHEK2**    | Increased risk                            | No increase                                     | Colon                                  |
|              | Annual mammogram from age 40 years         | RRM, insufficient evidence                      |                                        |
| **NF1**      | Increased risk                            | No increase                                     | MPNST, GIST                            |
|              | Annual mammogram from age 30 years         | RRM, insufficient evidence                      |                                        |
| **NBN**      | Increased risk                            | unknown                                         |                                        |
|              | Annual mammogram from age 40 years         | RRM, insufficient evidence                      |                                        |
| **MSH2, MLH1, MSH6, PMS2, EPCAM** | Unknown or insufficient evidence | Increased risk                                  | Colon, uterus                          |
|              | Annual mammogram from age 30 years         | RRM, insufficient evidence                      |                                        |
| **PALB2**    | Increased risk                            | Unknown                                         |                                        |
|              | Annual mammogram from age 30 years         | RRM, insufficient evidence                      |                                        |
| **PTEN**     | Breast awareness from age 18 years         | Endometrial cancer: education and hysterectomy  |                                        |
|              | CBE every 6-12 months from 25 years        | Annual thyroid USG                              |                                        |
|              | MRV/mammogram from age 30 years or 5-10 years before the earliest case in the family | Colonoscopy every 5 years from age 35 years    |                                        |
|              | Discuss options of RRM                    |                                                |                                        |
| **RAD51C, RAD51D** | Unknown                                    | Increased risk of ovarian cancer                |                                        |
|              |                                            | Consider RRSO at age 45-50 years                |                                        |
| **STK11**    | Increased risk                            | Increased risk of nonepithelial ovarian cancers |                                        |
|              | Annual mammogram from age 40 years         | RRM, insufficient evidence                      |                                        |

(Continued on following page)
| Gene | Breast Cancer Risk and Management | Ovarian Cancer Risk and Management | Other Cancers |
|------|----------------------------------|----------------------------------|---------------|
| TP53 | Breast awareness from age 18 years | Annual whole-body MRI | Age 30-75 years: annual MRI + mammogram | Comprehensive physical and neurologic examination |
|      | CBE every 6-12 months from age 25 years | Annual brain MRI | Age 20-29 years: annual MRI + contrast | Colonoscopy and UGIE every 2-5 years starting at age 25 years |
|      | Age 20-29 years: annual MRI + contrast | | | |
|      | Age 30-75 years: annual MRI + mammogram | | | |
|      | RRM to be discussed | | | |

Abbreviations: CBE, clinical breast examination; GIST, GI stromal tumor; MPNST, malignant peripheral nerve sheath tumor; MRI, magnetic resonance imaging; RRM, risk-reduction mastectomy; RRSO, risk-reducing salpingo-oophorectomy; UGIE, upper GI endoscopy; USG, ultrasonography.
### TABLE 6. Results From Select Phase II and III Study of PARPi in Patients With Advanced Breast or Ovarian Cancer and BRCA1/2 Mutations

| Study Treatment | Condition | Efficacy Findings |
|-----------------|-----------|-------------------|
| Olaparib monotherapy (300 mg twice per day) vs standard single-agent therapy94 (OLYMPIAD) | Metastatic breast cancer and a germline BRCA1m | ORR: 60% (olaparib) vs 29% (standard therapy); median PFS, 7.0 months (olaparib) vs 4.2 months (standard therapy; HR, 0.58; 95% CI, 0.43 to 0.80; P < .001); DOR, 6.4 months (IQR, 2.8-9.7 months; olaparib) vs 7.1 months (IQR, 3.2-12.2 months; standard therapy) |
| Olaparib monotherapy (200 mg twice per day) vs matching placebo95 (SOLO 2) | Platinum-sensitive, relapsed high-grade serous OC with BRCA1/2m | Median PFS, 19.1 months (olaparib) vs 5.5 months (placebo; HR, 0.30; 95% CI, 0.22 to 0.41; P < .0001) |
| Niraparib monotherapy (300 mg) vs placebo96 (NOVA) | Older patients (age ≥ 70 years) with recurrent OC | In gBRCA1m subgroup: median PFS was not reached vs 3.7 months (in placebo) |
| Talazoparib monotherapy (1 mg every day) vs standard single-agent therapy87 (EMBRACA) | Advanced BC and gBRCA1/2m | Median PFS, 8.6 months (talazoparib) vs 5.6 months (standard therapy; HR, 0.54; 95% CI, 0.41 to 0.71; P < .001); ORR, 62.6% (talazoparib) vs 27.2% (standard therapy) |
| Rucaparib monotherapy (600 mg BID97 (ARIEL2) | High-grade ovarian carcinoma and a g/sBRCA1/2m | ORR, 53.8%; CR, 8.5%; PR, 45.3%; DOR, 9.2 months (95% CI, 6.6 months to 11.6 months) |
| Olaparib monotherapy (300 mg) vs placebo (SOLO 1)98 | High-grade serous or endometrioid OC, primary peritoneal cancer, or fallopian tube cancer | ORR at 3 years: 60% (olaparib) vs 27% (placebo; HR, 0.30; 95% CI, 0.23 to 0.41; P < .001) |

Abbreviations: CR, complete response; DOR, duration of response; HR, hazard ratio; IQR, interquartile range; OC, ovarian cancer; ORR, objective response rate; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PR, partial response.
confers a high risk for BC BRCA1/2, TP53, PTEN, CDH1, or STK11 mutation.\textsuperscript{79,82}

**rrBSO.** Recommendations are the same as those for pre-vivors. There are conflicting data whether rrBSO reduces the risk of BC, with many recent studies not showing any association between rrBSO and BC risk.\textsuperscript{83,85} Larger studies are needed to validate these results.

**Advanced OC with BRCA mutation.** Prophylactic bilateral mastectomy is not considered in these cases as the risk of death from the primary malignancy is high over the next 5 years.

**Medical Implications of BRCA in BC**

Olaparib is approved by the US Food and Drug Administration for patients with germline BRCA mutations and human epidermal growth factor receptor 2-negative BC previously treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic disease setting on the basis of the Olympiad trial.\textsuperscript{96}

Talazoparib is US Food and Drug Administration approved for patients with germline BRCA mutations and human epidermal growth factor receptor 2–negative locally advanced or metastatic BC on the basis of the EMBRACA trial.\textsuperscript{87}

Neoadjuvant platinum agents: Based on the GeparSixto and CALGB 40603 studies, platinum agents as neoadjuvant treatment improves pathological complete response in BRCA-positive patients. Improvement in disease-free survival was demonstrated in GeparSixto, but not in the CALGB trial.\textsuperscript{88,89}

**Medical Implications of BRCA in OC**

Olaparib, rucaparib, and niraparib have all been approved in OC for various indications (Table 6).

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This consensus statement represents the Indian Society of Medical and Pediatric Oncology expert subcommittee’s and other invited experts current thinking on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this verbatim. The treating physician is free to use an alternate mode of therapy/recommendation based on the discussions with the patient and with reference to institution, national, or international guidelines. The mention of recommendation for one particular type of testing does not constitute endorsement or recommendation for its use, but is a guidance for clinicians in complex decision making. The contributors to this document are acutely aware of the constant and continuous addition to the knowledge on the subject and in the field and the need for regular updates to this document and the fact that this needs to be living document requiring regular modification and revision.

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