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Original Article

Genetic Counselling, Testing, and Management of Hereditary Breast and Ovarian Cancer Syndrome in India: Updated Expert Consensus Recommendations from Indian Society of Medical and Pediatric Oncology

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Abstract

Introduction Hereditary breast and ovarian cancer (HBOC) is driven by mutations in BRCA1/2 and related genes. Their understanding is vital to appropriate management of such patients and at-risk families, including counselling and genetic testing. Several important recent advances have made it necessary to revise the previous recommendations we made for India in 2020.

Methods This consensus document was developed with the authors as key experts in the field. Published evidence, real-world data, and expert interpretation were used by a modified Delphi method to finalize these recommendations.

Results Detailed description and process for identifying patients at risk, doing their counselling, selecting the right molecular test, interpreting the results, and determining the optimal mode of action to attenuate risk of HOBC or its recurrence have been provided in a clear and lucid manner. Differences between germline and somatic mutations are described. Information from publicly available databases was used to fine-tune the guidelines—as more information had becomes available since the time of writing the first guidelines. Risk of various cancer types and corresponding risk reduction strategies have been explained.

Conclusion Community oncologists in India, SAARC region, and other low- and middle-income countries should use these guidelines in their clinical practice to optimize genetic counselling, molecular testing, and management of patients with HBOC.

Keywords

- hereditary cancer
- therapy
- driver mutations
- guidelines

Introduction

In India, breast cancer (BC) is still the commonest cancer in females as well as the leading cause of cancer-related death in women.[1] While the younger median age of onset reflects the population demographics (52% of Indians are below the age of 30 years), BC in Indian women has a high incidence-to-mortality ratio compared with the West.[2] It is therefore important to ascertain risk factors, high-risk biomarkers, and driver mutations to optimize management.

As the name suggests, hereditary breast and ovarian cancer (HBOC) syndrome leads to increased risk of early-onset BC and ovarian cancer (OC) in multiple family members. It usually follows an autosomal-dominant inheritance pattern.[3,4] HBOC syndrome results in higher lifetime risk of cancer in women—being 50 to 85% for BC, and 15 to 30% for OC.[5,6] Most common mutations responsible for HBOC include *BRCA1* and *BRCA2*.[7] Race and ethnicity have strong bearing in HBOC. For instance, specific mutations identified in a population sharing common ancestry (Founder mutations) first reported from the Caucasians were from Ashkenazi Jews, French Canadians, and Icelanders.[8] Similarly novel founder mutations in BRCA1, BRCA2, and MLH1 genes have been identified in India from several Maharashtrain, Gujarati, Jain, Bohri, Punjabi, Bengali, and Nepali communities[9,10] [personal communication Rajiv Sarin, 27 October 2023].

With the availability of drugs that have been proven to be useful in women with *BRCA1/2* mutations (e.g., poly (ADP-ribose) polymerase [PARP] inhibitors for both germline and somatic mutations; platinum-based chemotherapy in germline), their genetic testing is vital for optimal treatment decision making.[11] Identification of such mutations (and families at risk of HBOC) allows us to quantify their risk of future metachronous cancers as well as discuss pros and cons of appropriate surgical and/or nonsurgical prophylactic measures.[12] We can then enable families at risk to become informed previvors (a person who takes action to reduce or eliminate a genetic cancer before the cancer develops or is detected in his or her body).[13] We now know that "BRCA-ness" is also a result of mutations in several non-*BRCA* genes (e.g., *PALB2*, *CHEK2*, *ATM1, RAD51C*, and *RAD51D)* and similar preventive measures can also potentially benefit them also.[14]

The prevalence, nature, and frequency of germline mutations vary significantly—geographically and ethnically.[8,9] Their clinical significance and penetrance is also highly variable. BrCa Exchange collates data from across the world, including India, and makes them publicly available for real-time risk assessment for individual patient–related genetic mutations. In general, pathogenic genetic mutation occurs in about 10 to 15% of all patients with BC, and *BRCA1* and *BRCA2* account for almost half of the pathogenic/likely pathogenic mutations.[9,10,15,16]

While innumerable international guidelines have been published since 2010 for overall management of HBOC, almost all of them are based on the Caucasian population.[17] Our 2020 consensus document was the first to incorporate unique characteristics and needs of the Indian patients.[19]

In the intervening period, a lot of new data have been generated and our understanding of HBOC refined. It was therefore necessary to update our previous recommendations, making it more robust.

Methodology

Our multidisciplinary expert group began the revision process by re-evaluating evidence from phase III randomized controlled studies, other prospective and retrospective studies, BrCa gene mutation publications, and real-world clinical experience. Google Scholar and PubMed databases were searched with the key words: "hereditary breast and ovarian cancer"; "HBOC"; "BRCA1/2 mutations"; "germline BRCA mutations"; "somatic BRCA mutations"; "brcaness"; "non-BRCA mutations"; and "genetic testing."

The first meeting involved extensive discussions moderated by the chairperson of the committee followed by preliminary voting using the modified Delphi process.[20] Thereafter, the Expert Committee continued to discuss via e-mail and WhatsApp to fine-tune the recommendation statements. All authors participated in the preparation of the draft, multiple rounds of voting, and the approval of the final manuscript.

Recommendations (Results)

1. Genetic Counseling in India: Importance and Awareness

While our understanding has improved considerably, genetic testing in HBOC in India lags behind for several reasons, most important ones being infrastructure and finances.[21] Lack of sufficient number of trained genetic counsellors also increases the burden of the treating physician and oncologist. Where feasible, individual or family members are helped appropriately using the following principles:

- Allow them to understand the medical facts in simple terms: diagnosis, probable future course, cancer risk, and management options.
- Understand role of heredity in the risk of cancer, its risk of recurrence in patients, and first-degree relatives who are carrying the mutation(s).
- Understand how to minimize the risk of recurrence.
- Select the course of action most suitable to their individual preference and family goals.
- Understand the advantages of positive lifestyle changes.[22–25]

Pretest genetic counselling is generally recommended globally. This is also endorsed by international oncology working groups.[4,26–28] Such counselling should be done by health care professionals who are adequately trained with respect to genetic and clinical aspects of HBOC, *BRCA1* and *BRCA2*.[29,30] In India, the burden often falls on the respective oncologists.[21,31] In view of the shortage of trained and qualified staff across India, use of tele-genetic counselling is recommended. This should be carried out in compliance with the Telemedicine Practice Guidelines as published by Government of India.

Components of HBOC Genetic Counselling

(A) ***Pretest counselling***: the patient/family members should be made aware of the following key factors:

- Medical history and available pedigree evaluation of up to three generations (►**Fig. 1**).
- Objective risk estimation using mathematical risk assessment models where available and qualitative criteria as an alternate (e.g., National Comprehensive Cancer Network [NCCN] tools).
- Genetic testing methodology recommendations.
- Interpreting test reports—possible test outcomes, e.g., pathogenic variant detected, variant of uncertain significance (VUS).
- Risks, benefits, and psychosocial implications.

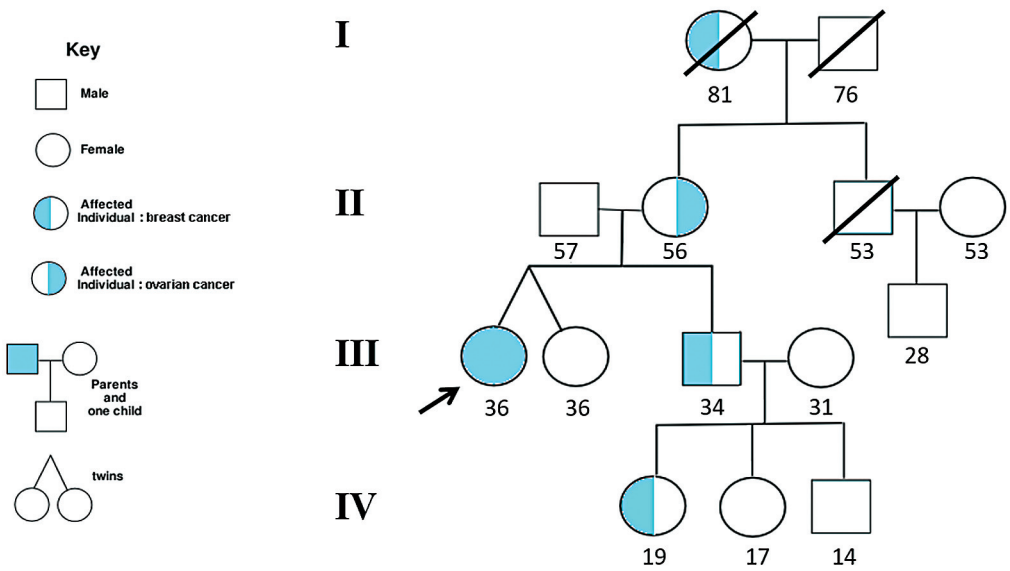

Fig. 1 Representative pedigree chart of HBOC family. HBOC, hereditary breast ovarian cancer.

- Implications of test results to other family members.
- Discussion of need to maintain confidentiality to prevent genetic discrimination.[22,24,25]

Once the pretest genetic counselling is documented, if the patient/subject allows to be subject to biological sample collection, consent is automatically implied.

Assessment of family history: while real-world limitations are well known in countries like India, attempts should be made to collect family history of three generations to prepare pedigree analysis. This should ideally include first- and second-degree relatives on both the maternal and paternal sides of the family. Details recommended are age, gender, pregnancies (if applicable), age at onset of cancer (if applicable), age at death (if applicable), cause of death (for deceased relatives), ethnic background of grandparents (maternal and paternal, if necessary), and history of consanguinity. Using this information to generate a pedigree chart gives a good visual understanding for all stake holders.[32–35]

(B)*Post-test counselling*: the key objective of this session is risk communication. Once the molecular testing report becomes available and the health care team has calculated the risk of cancers/recurrence, the same is communicated to the patient/family member as appropriate. Appropriate attention should also be given to emotional counselling. Pretest genetic counselling improves the family's journey through this process. Group discussions and use of information booklets, where available, are encouraged. This can minimize anxiety of the patients and their family members.[33–36] It is desired that all questions and doubts are answered to the satisfaction of the patient/family member during this session.[37]

2. 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*, *PTEN*, *CDH1*, *STK11*, *CHEK2*, *RAD51C*, *RAD51D*, and *ATM*, are also known to confer risk of BC and/or OC, albeit with lower frequency and penetrance[26,31,35] (►**Tables 1** and **2**).

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

Table 1 Genes associated with HBOC and their penetrance risk

Gene/locus	Syndrome	Risk	Mutation/minor allele frequency
High penetrance			
BRCA1 (17q21)	HBOC	60–85 × for BC	1/400
		15–40 × for OC	
BRCA2 (13a12.3)	HBOC	60–85 × BC	1/400
		13–23 × OC	
TP53 (17p13.1)	Li–Fraumeni	50–89 × by age 50 BC	<1/10,000
		90 × in Li–Fraumeni survivors	
PTEN (10q23.3)	Cowden	25–50 × BC	<1/10,000
CDH1 (16q22.1)	Familial diffuse gastric cancer	RR: 6.6	<1/10,000
STK11/LKB1 (19p13.3)	Peutz–Jeghers	30–50 × by age 70	<1/10,000
PALB2 (16p12)	BC, prostate Ca, pancreatic Ca	30% BC risk by age 70	<1/1,000
Moderate penetrance			
CHEK2 (22q12.1)	Li–Fraumeni 2	OR: 2.6	1/100–1/200 in some populations
BRIP1 (17q22)	BC	RR: 2.0	<1/1,000
ATM (11q22.3)	Ataxia telangiectasia	RR: 2.37	1/33–1/333
Low penetrance			
FGFR2 (10q26)	BC	OR: 1.26	0.38
TOX3 (16q12.1)	BC	OR: 1.14	0.46
LSP1 (11p15.5)	BC	OR: 1.06	0.3
TGFB1 (19q13.1)	BC	OR: 1.07	0.68
MAP3K1 (5q11.2)	BC	OR: 1.13	0.28

Abbreviations: BC, breast cancer; HBOC, hereditary breast ovarian cancer; OC, ovarian cancer; OR, odds ratio; RR, relative risk.

Table 2 Cancer risks associated with BRCA1 and BRCA2

Mutation	Lifetime risk of BC, %	Lifetime risk of OC, %
BRCA 1	50–85	35–46
BRCA 2	50–85	13–23
Cancer type	**Risk in carriers to age 70 years**	**Lifetime risk in general population, %**
Breast	BRCA1: 55–70	
	BRCA2: 45–70	
Contralateral breast	Up to 63 at 25 years post-diagnosis, but highly age-dependent	7 at 25 years post-diagnosis
Ovarian	BRCA1: ~40	~1
	BRCA2: ~15	
Colon	Unclear	~5
Prostate	Elevated; absolute risk not well defined	White: ~14
		African American: ~19
Male breast	BRCA1: 1	0.1
	BRCA2: 8	
Pancreatic	BRCA1: unclear	1.5
	BRCA2: 5	
Other sites	To be determined	Varied

Abbreviations: BC, breast cancer; OC, ovarian cancer.
Source: Adapted from Malhotra et al[19].

cancers associated with germline *BRCA1/2* mutations include male BC (1–9%), prostate cancer (9–20%), pancreatic cancer (1–7%), and melanoma.[38] The largest analysis of 1,010 high-risk families across India revealed *BRCA* mutations in 85% and non-*BRCA* mutations in 15% of families.[39] 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.[40–42] 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 (TNBC) or OC identified 18 *BRCA1* and 16 *BRCA2* variants that were not reported in the Breast Cancer Information Core or ClinVar databases.[39] 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.[40–42] In the last 5 years, several studies have been published from Indian researchers investigating the frequency of P/LP mutations in the Indian population. ►**Table 3** provides a summary of the important Indian-specific studies published till date. Most of the studies have a strong selection bias in patient enrollment and hence have reported higher frequencies.[39,43–48] However, two studies have been performed in unselected patients with BC and OC[39,43] In a predominantly North Indian population, Mittal et al have reported a frequency of 18.6% for P/LP variants, with their multigene next-generation sequencing (NGS) panel.[44] Using the NCCN 2019 criteria would have missed 11% of these mutations. This frequency is higher than those reported on unselected cases from Europe, the United States, and Africa. In their multicentric study, Gupta et al tested 239 unselected patients with OC for only BRCA1/2. They reported a prevalence of 21.4% P/LP mutations.[43] It is also important to keep in mind that NGS testing has the risk of leading to false positivity. In one study, out of all 41 samples analyzed for *BRCA1* and *BRCA2*, 5 were found with 950_951 insA (Asn319fs) at Chr13:32906565 position and 1 sample with 1032_1033 insA (Asn346fs) at Chr13:32906647, both being frame-shift mutations in *BRCA2* gene. The 950_951 insA (Asn319fs) mutation is reported as a pathogenic allele in NCBI dbSNP. On examination of IGV for all these samples, it was found that both mutations had "A" nucleotide insertion at 950 and 1032 positions in exon 10 of *BRCA2* gene. However, Sanger sequencing did not confirm these insertions.[49–53]

Clinical practice has been focused to test patients who fulfil 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.[54] At present, it is therefore uncertain whether testing for hereditary mutations is warranted beyond the standard criteria. As a rule of thumb, it is recommended to assess women with a personal or family history of BC, OC, tubal, or peritoneal cancer or those who are part of a family having known *BRCA1/2* gene mutations. Where appropriate, a familial risk assessment tool should guide whether further genetic counselling and/or genetic testing is warranted.[55]

Table 3 Pathogenic BRCA1/2 mutations identified in Indian patients

Study	Region	Tumor types	Testing method	Remarks
Valarmathi et al, 2003[118]	New Delhi, North India	Breast cancer	Direct sequencing	BRCA 1 (E1250X in exon 11; E1754X in exon 20)
Rajkumar et al, 2003[79]	Chennai, South India	Breast and ovarian cancer	Heteroduplex analysis/dHPLC	BRCA1 (Ex12 1386 delCTCTC Stop 1389, Ex13 CGA → TGA Arginine 1443 Stop), BRCA2 (Ex11O 1235delCTTAA stop 1237)
Saxena et al, 2006[119]	New Delhi, North India	Breast cancer	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[120]	Kerala, South India	Breast and ovarian cancer	Direct sequencing	BRCA2 (c.4642delAA, c.4926insGACC)
Thirthagiri et al, 2008[42]	Malaysia, Indian ethnicity	Breast cancer	dHPLC and DNA sequencing	BRCA1 (180 delA, 185 delAG, 5370 C.T), BRCA2 (9097 C. T)
Soumittra et al, 2009[121]	Chennai, South India	Breast and ovarian cancer	PCR-dHPLC	BRCA1 (c.4158_4162delCTCTC; p.Ser1369SerfsX2, c.4327C.T; p.R1443X, c.1148_1149delAT; p.Asn383Arg fsX6, c.4399C.T; p.Gln1467X, c.4705_4706insTGGAATC; p.Ile1567fsx5, c.5024_ 5025insT; p. Thr1675Thr fsX4, c.68_69delAG; p. Glu23Val fsX16, c.66_67delAG; p. Leu22Leu fsX18, c.5118_5120delAAT; p.del1707Ile); BRCA2 (c.6214_6218delCTTAA; p.Ser2072Ser fsX4, c.5130_5133delTGTA; p.Tyr1693X, c.2621_ 2627delAACTGTC; p. Ile873Ile fsX19)
Vaidyanathan et al, 2009[55]	South India	Breast and ovarian cancer	Heteroduplex analysis using CSGE and direct sequencing	BRCA1 (185delAG)
Kang et al, 2014	Malaysia, Indian ethnicity	Breast cancer	PCR and Sanger sequencing	BRCA1 (185delAG)
Mittal et al, 2022[44]	North India	Breast cancer	NGS, multigene panel with reflex MLPA	236 unselected, consecutive patients, 18.64% P/LP, 34% non-BRCA genes, 1 AJ founder mutation
Pramanik et al, 2022[45]	North India	Ovarian cancer	NGS, multigene panel with reflex MLPA	72 patients, selectively referred for genetic testing. 44% P/LP, 85% BRCA, and 15% non-BRCA
Gupta et al, 2021[43]	Pan India	Ovarian cancer	NGS, BRCA1/2	239 unselected patients, 21.4% P/LP
Kadri et al, 2021[46]	Western India	Breast and ovarian cancer	NGS, multigene panel	144 patients, selectively referred, 28% P/LP, 12% non-BRCA.
Singh et al, 2018[39]	Pan India	Breast and ovarian cancer	NGS, multigene panel	1,010 selectively referred, 30.1% P/LP, BRCA1/2 85%
Chheda et al, 2020[47]	Western India	Breast and ovarian cancer	NGS, BRCA1/2	160 women, selectively referred, 31.9% P/LP
Mehta et al, 2018[48]	North India	Breast and ovarian cancer	NGS, BRCA1/2	206 women, selectively referred, 30.6% P/LP

Abbreviations: MLPA, multiplex ligation-dependent probe amplification; NGS, next generation sequencing.

Whom to Test First?

Any woman affected by early-onset BC and/or OC should be tested first. A suspected family member who is below the age of 18 years should have testing differed till they become adults. Once an index case (proband) has been identified, testing of first-degree adult relatives is the next step. If a pathogenic variant/mutation has already been identified, single-site gene testing of the specific gene mutation is sufficient. This is called cascade testing (screening of at-risk biologic relatives of the individual who harbors a pathogenic variant).[56] Its objective is to identify asymptomatic at-risk relatives, calculate their risk, and discuss steps to reduce future morbidity and mortality from cancer (risk-reducing strategies include enhancing surveillance diagnostics, medical therapeutics, and/or surgical interventions).

Testing Methods

First-generation automated Sanger sequencing has generally been replaced by the more efficient NGS technology. It is less expensive and comprehensive genomic profiling or multigene panel testing becomes rapid. Where cost is not a significant consideration, multigene panels are being used as a first-line test for any patient suspected to have an inherited cancer syndrome.[57]

This approach is robust for detecting single-nucleotide variants (SNVs) and small insertion/deletion (indels), with high accuracy. However, this is not the case for larger genomic rearrangements (insertions/deletions) and/or copy number variants. Multiplex ligation-dependent probe amplification (MLPA) or array comparative genomic hybridization (aCGH) would have to be used to detect the same.[58] Several in silico tools make the bioinformatics part less labor-intensive and reduce turnaround time.

Based on genetic testing and interpretation, patients can be divided into three risk groups—high risk, moderate risk, and low or unknown risk (►**Table 1**).

Methods of Germline BRCA Detection

Sample for germline genetic testing could be blood, saliva, or cheek swab. As mentioned above, multigene panels using NGS enables high-throughput genetic testing with good accuracy. However such testing can be performed as follows:

- Single site.
- Founder/recurrent mutation associated with specific neoethnicity.
- Multigene/targeted panel.
- MPLA/aCGH for large genomic rearrangements/copy number variations.
- Whole exome sequencing.
- Whole genome sequencing.

While selecting a NGS workflow, the following criteria should be considered to suit the genetic testing[59–61] (Box 2):

- Design of multigene panel based on clinical utility and demand.
- Wet lab processes for enrichment of targets (hybrid capture or amplicons based capture) without compromising on sensitivity and specificity of the detection of pathogenic variants.
- Bioinformatics expertise.
- Qualified and trained personnel to interpret results.
- Reasonable turnaround time (approximately 4 weeks).

Having a reasonable turnaround time (approximately 4 weeks) helps in reducing anxiety and testing fatigue amongst patients, families, and providers.

At least three studies from India have reported the use of multigene panel testing by NGS for germline mutations in HBOC patients.[39,43–49] The majority of BRCA1/2 mutations identified are single base substitutions (missense or nonsense mutations); small insertions or deletions (result in prematurely truncated nonfunctional protein); and splice junction alterations (exon skipping or intronic inclusion, also resulting in a nonfunctional protein). In 5% of cases, there could be large genomic rearrangements which will be missed on conventional NGS testing. As mentioned above, MLPA technique or aCGH can be used in patients/families who are shown negative by NGS, but have a strong clinical suspicion of HBOC.[48,49] It is important to remember that besides BRCA1 and BRCA2, genes that need to be tested in suspected cases of HBOC syndrome includes ATM, BRIP1, CHEK2, RAD50, RAD51D, RAD51C, PALB2, BAARD1, P53, STK11, CDH1, MSH2, MSH6, MLH1, EPCAM, PMS2, ATM, PTEN, FGFR2, TOX3, LSP1, and MAP3K1.

Interpretation of Sequencing Results

International working groups have provided guidelines for the interpretation of germline sequence variants. The DNA sequence alterations are categorized qualitatively based on several factors—including functional evidence, family history, allele frequency data, computational and in silico predictions (►**Table 4**).

Failure to detect a deleterious germline mutation in a proband could be due to one or more of the following[49,62]:

- Patient has a pathogenic variant in another gene not included in the multigene panel.
- Tested gene has a sequence variant that cannot be easily detected by sequence analysis (e.g., large deletion; limitation of test methodology).
- Sequence variant in a region such as an intron or regulatory region of a gene (area not covered by the test).
- Involvement of genes not associated with known underlying phenotype.

Interpretation is facilitated by interrogating updated publicly available literature/databases (ClinVar, OMIM, BrCa Exchange, GWAS, HGMD, and SwissVar), correlation with population data, and in silico predictions of variant effect. Nonsynonymous variants' effects can be calculated using multiple algorithms such as PolyPhen-2, SIFT, Mutation Taster2, Mutation Assessor, and LRT. Only nonsynonymous and splice site variants found in the hereditary cancer gene panel should be used for clinical interpretation. Fortunately,

Table 4 Classification of mutation variants according to clinical significance (adapted from nomenclature of three international working groups)

International Agency for Research in Cancer		Clinical Molecular Genetics Society		American College of Medical Genetics	
Class	Description	Class	Description	Category	Description
5	Definitely pathogenic	1	Certainly nonpathogenic	1	Previously reported and recognized cause of the disorder
4	Likely pathogenic	2	Unlikely to be pathogenic	2	Previously unreported and is of the type that is expected to cause the disorder
3	Uncertain	3	Likely to be pathogenic	3	Previously unreported and is of the type that may or may not be causative of the disorder
2	Likely not pathogenic	4	Certainly pathogenic	4	Previously unreported and is probably not causative of disease
1	Not pathogenic			5	Previously reported and is a recognized neutral variant
				6	Previously not known or expect to be causative of disease, but is found to be associated with a clinical presentation

Source: Adapted from Malhotra et al[19].

germline BRCA testing is robust and the variants are well-curated.

Genetic Test Report

Molecular labs should transcribe their information into a report that describes the test results in a uniform manner, without using jargon, and facilitates explaining its significance to the proband and first-degree relatives. DNA change as a variant should be reported using the standard Human Genome Variation Society (HGVS) nomenclature, describing the mRNA reference sequence that was used, the nucleotide change in the cDNA as a c. and the consequent change in the amino acid and protein as a p.[63,64]

Validation of Test Result

Molecular testing laboratories should follow the joint consensus from the Association for Molecular Pathology and College of American Pathologists. They should validate every detected SNV or indel in the coding region that results in deleterious mutations and documenting it in terms of positive percentage agreement and positive predictive value.[64,65] Documenting concordance between results from a newly developed assay and a gold standard method such as Sanger sequencing is also advised. Participating in internal quality control as well as external quality assurance programs is desirable. If using the NGS for genetic testing, then validating NGS results by Sanger may not be necessary if all bioinformatic and quality parameters are controlled.[43,44,49,66]

How to Manage Variants of Uncertain Significance

VUSs are genetic alterations whose clinical significant is not yet established. They are usually single nucleotide polymorphisms—may be in the promoter regions, exons, and introns. They could also be small in frame insertions and deletions or synonymous substitutions.[64] More than 20,000 unique variants have been identified in the BRCA genes.[65] These constitute less than 10% of all mutations in BRCA1/2 (the remaining 90% have already been classified either as pathogenic or benign). The clinical implication is that once further data become available, up to 30% of current VUSs might turn out to be pathogenic.[67,68] In countries where data are still maturing, like India, up to half (30–50%) of mutations identified in BRCA1/2 genes could be VUS.[9] Data sharing initiatives like BrCa Exchange, BRCA Challenge, and Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) help in resolving the significance of VUS.[69] Such initiatives have already resulted in a 13% fall in the rate of mutations being called VUS between 2002 and 2013.[70] If the mutation is still reported as VUS, it should not be taken into consideration while arriving at risk assessment in HBOC. Unfortunately, clinicians often want to err on the side of abundant caution and factor in VUS as potentially pathogenic. Caution is advised against this because it may lead to unnecessary prophylactic medication/surgery and/or patient anxiety.[71–73]

Quality of Genetic Testing: The Backbone of Characterizing BRCA1/2 Mutations

All aspects of genetic testing need a robust quality. This includes sample collection and transport; wet lab processing; and bioinformatics. Following established standard operating procedures in genetic testing is extremely important to maintain test quality so as to avoid both false-positive and false-negative reporting (which is true for every aspect of health care management). Following guidelines developed by the American Association of Pathologists' Assistants and the College of American Pathologists for NGS bioinformatics pipelines has been shown to significantly reduce error rates.[66,74,75] National accreditation programs and quality assessment programs (e.g., EMQN [European Molecular Genetics Quality Network]) could help meet the goal of optimizing quality.

Somatic or Tumor BRCA Testing

DNA extracted from tumor tissue (freshly frozen or from the formalin fixed paraffin embedded [FFPE] blocks) is used to detect somatic mutations. The percentage of tumor cells in the sample processed for mutation analysis can determine the accuracy of the results. If the quality of DNA is compromised, that would also interfere with the test. Further, tissue preservation using formalin induces a chemical crosslinking reaction with nucleotides that results in artefactual sequence alterations and deamination of cytosine nucleotides. These features are of concern when FFPE specimens are used.[76] Use of shorter amplicons, de- crosslinking steps, and treatment with uracil-DNA glycosylase (DNA repair enzyme) are methods that can help reduce the number of sequence artefacts. Their use can improve the quality of extracted DNA.[77] Somatic NGS testing is generally recommended at 500X coverage to avoid false-negative assessment. The bioinformatic pipeline should also be set to take into consideration the percentage of tumor cells in the processed sample.

The ideal somatic mutation testing report should describe[78]:

- Suitability of tumor sample for tumor content and specific testing method.
- Number and names of genes tested (if using a multigene panel).
- Depth of coverage for each gene.
- Details of mutation (if detected) with HGVS nomenclature.
- Reference sequence of gene.
- Interpretation of results with reference to therapy.

When in doubt, somatic mutations identified using NGS may need to be confirmed by Sanger sequencing.

Significance of Somatic (Tumor) BRCA Mutations

In OCs, association with loss of heterozygosity suggests genomic scaring and instability.[73,74] Sporadic somatic BRCA1/ 2 mutations are seen in up to 33% of BRCA mutations in OC and 4 to 15% of unselected TNBC.[79–82] Amongst patients with high-grade serous OC (HGSOC), BRCA1/2 germline as well as somatic mutations are frequent (17–25%). In fact, somatic mutations have been reported in 18 to 30% of all patients with BRCA1/2 mutations. It is also interesting to note that 9% of patients with OC showed presence of somatic mutations in homologous recombinant genes (BRCA1/2, BRIP1, CHEK2, and RAD51C).[81]

Clinically, it is important to identify these because presence of somatic mutations is predictive of primary platinum sensitivity and improved overall survival.[83] Somatic BRCA1/2 pathogenic mutations and loss of heterozygosity are also predictive biomarkers for clinical response to PARP inhibitor.[83–86] Platinum-sensitive relapsed patients with serous OC and positive BRCA mutations have been shown to have the highest chance of benefiting from olaparib (median progression-free survival: 11.2 months in BRCA mutation-positive vs. 7.4 months in wild-type BRCA patients; hazard ratio: 0.54 [95% confidence interval: 0.34–0.85]; $p = 0.0075$).[87] Based on data from PAOLA-1 study, homologous recombination deficiency (HRD) testing (a composite genomic scar score) has also become an important predictive biomarker for response to PARPi.[88] Some tests developed by other laboratories that can be considered include Myriad MyChoice,[89] loss of heterozygosity, and telomeric allelic imbalance. A word of caution in interpreting their results, since different proprietary algorithms have been incorporated in these tests.[87] Thus, to ensure all eligible patients receive the benefit of PARPi therapy, it is necessary to evaluate all (somatic as well as germline) their BRCA1/2 pathogenic mutations.[90]

Somatic or Germline Testing First in Ovarian Cancer?

Somatic mutations testing is not interchangeable with germline testing. Because the bioinformatics pipeline is different, somatic testing is less sensitive. If it is used solely, a significant number (10%) of germline P/LP mutations can be missed.[91] For this reason, most guidelines, including American Society of Clinical Oncology (ASCO), recommend the use of germline testing first, and then if required, somatic testing.[92]

On the other hand, if only germline testing is carried out (on DNA extracted from blood sample), an estimated 5 to 7% of HGSOC cases who may have acquired (somatic) mutations in BRCA1/BRCA2 genes in their tumor will be missed.[50]

So another approach would be to first do tumor testing (to triage cancer genetics referrals) and then offer germline testing to the subset of HGSOC patients in whom a deleterious mutation was detected. For example, somatic P/LP variants seen in tumor specimens are common in some genes with germline implications (e.g., TP53, STK11, PTEN) and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline.[51]

Since both approaches have their limitations, current recommendation is to consider parallel testing of somatic and germline panel. This can reduce turnaround time, reduce false negativity but at the cost of double the cost. This is also recommended especially for HGSOC.[52]

European Society for Medical Oncology has recommended either approach, based on physician's choice.[53] We recommend germline testing as the first approach, followed by HRD for those with gBRCA negative.

Management of HBOC

Risk Management for the Previvor (Unaffected Carrier of Mutation)

- *Lifestyle modifications recommended are:*
  - Regular exercise and maintaining a healthy body weight.
  - Limiting alcohol consumption.
  - Avoid hormone-replacement therapy.
  - Encourage breast feeding.
- *Risk reduction surgery:* NCCN recommends that BRCA carriers be offered prophylactic bilateral mastectomy.92–94 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. For BRCA1 carriers, risk-reducing bilateral salpingo-oophorectomy (rrBSO) is recommended for women who have completed child-bearing and should be performed by age 35 to 40 years or individualized on the basis of age of onset of OC in the family.95–97 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. NCCN does not routinely recommend hysterectomy at the time of rrBSO and indicates that salpingectomy alone is not the standard of care, discouraging it outside a clinical trial.[99]

- *Cancer surveillance: for female BRCA carriers who do not wish to pursue (or would r*ather delay) surgical risk reduction, BC surveillance should be offered, and OC screening may be performed.[100]

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[100,101]:

- Breast awareness from 18 years of age.
- Clinical breast examination every 6 to 12 months is recommended from the age of 25 or 10 years before the youngest BC.
- Annual screening using 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.[78]
- Age 30 to 75 years: annual mammogram and contrast-enhanced MRI of breast (alternating every 6 months).
- >75 years: management should be considered on an individual basis.
- Male BC: breast self-examination training and education starting at 35 years. Clinical breast exam every 12 months starting at 35 years.

OC screening: 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.

- *Pharmacoprevention*: use of tamoxifen may be considered; however, the level of evidence is weak.[103] It should be used only for BRCA2 tumors or if the first cancer was estrogen receptor–positive. Its benefit is offset by risk of side effects. The dose (1–20 mg per day) and duration (2–5 years) are also not clear. If raloxifene is used instead of tamoxifen, both efficacy and toxicity are reduced.
- *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**).

Table 5 Management recommendations for other genes implicated in hereditary breast cancers

Gene	Breast cancer risk management	Ovarian cancer risk management	Other cancers
ATM	• Absolute risk 20–40% • Consider CEMRI breast from 30–35	• Potentially increased risk • RRSO, insufficient evidence	• Counsel for autosomal-recessive condition in offspring
BARD1	• Potentially increased risk • RRM insufficient evidence	• Unknown	
BRIP1	• Unknown	• Increased risk of ovarian cancer • Consider RRSO at age 45–50	
CDH1	• Increased risk of lobular cancer • Annual mammography from age of 30 years • Discuss option of RRM	• No increase	• Gastric cancer: prophylactic total gastrectomy at 20 years or 5 years earlier than the earliest case of HDGC in the family.
CHEK2	• Increased risk • Annual mammogram from age 40 years	• No increase	• Colon
NF1	• Increased risk • Annual mammogram from 40 years age • RRM insufficient evidence	• No increase	• MPNST, GIST

Table 5 (*Continued*)

Gene	Breast cancer risk management	Ovarian cancer risk management	Other cancers
NBN	• Increased risk • Annual mammogram from 40 years age • RRM insufficient evidence	• Unknown	
Lynch syndrome genes (MSH2/MSH6/MLH1/PMS2/EPCAM)	• Unknown or insufficient evidence	• Except for PMS2, the association is strong. RRSO should be discussed with the patient as evidence is limited.	• Colon, uterus
PALB2	• Absolute risk: 41–60% • Annual mammogram and breast MRI with contrast at 30 yc, • Risk reduction: discuss option of RRM • Strength of evidence of association with cancer: strong	• Absolute risk: 3–5% • Management: • Risk reduction: consider RRSO at age >45 years • Strength of evidence of association with cancer: strong	• Pancreatic cancer • Absolute risk: 5–10% • Management: screen P/LP variant carriers with a family history of pancreatic cancer
PTEN	• Breast awareness from 18 years age • CBE every 6–12 months from age of 25 years • MRI/mammography from age 30 years or 5–10 years before earlier case in family		• Endometrial cancer, education, and hysterectomy • Annual thyroid USG • Colonoscopy every 5 years from age of 35 years
RAD51C	• Absolute risk: 20–40% • Management: annual mammogram and consider breast MRI with contrast starting at age 40 years • Strength of evidence of association with cancer: strong	• Absolute risk: 10–15% • Management: risk reduction: recommend RRSO at 45–50 years • Strength of evidence of association with cancer: strong	
RAD51D	• Absolute risk: 20–40% • Management: annual mammogram and consider breast MRI with contrast starting at age 40 years • Strength of evidence of association with cancer: strong	• Absolute risk: 10–20% 10-12,63,64 • Management: risk reduction: recommend RRSO at 45–50 years • Strength of evidence of association with cancer: strong	
STK11	• Absolute risk: 32–54% • Management: screening: annual mammogram and breast MRI with contrast starting at age 30 years	• No established association	• Pancreatic cancer • Nonepithelial ovarian cancers
TP53	• Breast awareness from age of 18 years • CBE every 6–12 months from age of 25 years • Annual MRI with contrast ages 20–29 • Annual MRI + mammography ages 30–75 • RRM to be discussed		• Annual whole-body MRI • Annual brain MRI • Colonoscopy and UGIE every 2–5 years from age of 25 years • Comprehensive physical and neurological exam \follow Toronto protocol

Abbreviation: MRI, magnetic resonance imaging.

- *Reproductive counselling*: 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 (assuming that the pathogenic mutation is harbored on only one of the chromosomes of one of the parents). Reproductive counselling of BRCA carriers includes education about prenatal diagnosis and assisted reproduction.[20] One option is preimplantation genetic diagnosis, which is used to analyze embryos, obtained by in vitro fertilization, genetically before their transfer into the uterus.

Risk Management for Patients

- *Decision for breast-conserving surgery (BCS) versus B/L mastectomy*: for a patient with BC, who is technically eligible for BCS, a BRCA mutation is not a contraindication for BCS. Both BCS and mastectomy are equally recommended by ASCO guidelines.[102] Surgical management of the index malignancy (BCT vs. ipsilateral therapeutic mastectomy and contralateral risk-reducing mastectomy [CRRM]) in BRCA1/2 mutation carriers should be discussed, considering the increased risk of contralateral BC (CBC) and possible increased risk of an ipsilateral new primary BC compared with noncarriers. The risks and benefits of both approaches and reconstruction options should be weightage to her age, expectations, wishes, risk acceptance attitude, and body image preferences. For women who have a mutation in a moderate-penetrance BC susceptibility gene, mutation status alone should not determine local therapy decisions for the index tumor or CRRM. BCT should be offered to those for whom BCT is an appropriate treatment option.
- *Risk of OC*: rrBSO. Recommendations are the same as those for previvors. There are conflicting data whether rrBSO reduces the risk of BC, with many recent studies not showing any association between rrBSO and BC risk.[96,97]
- *Risk of CBC*[103,104]: for women with BC who have a BRCA1/2 mutation and who have been treated or are being treated with unilateral mastectomy, CRRM should be offered. Nipple sparing mastectomy is a reasonable option. CRRM is associated with a decreased risk of CBC; there is insufficient evidence for improved survival. The following factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy in BRCA1/2 mutation carriers: age at diagnosis (the strongest predictor of future CBC), family history of BC, overall prognosis from this or other cancers (e.g., ovarian), ability of patient to undergo appropriate breast surveillance (MRI), co-morbidities, and life expectancy.

  BRCA1/2 mutation carriers who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI. Risk-reduction mastectomy and CRRM are not advised routinely to patients with a personal history of advanced OCs, because of the increased chances of recurrence of the index ovarian malignancy.
- *Fertility preservation*: in a large analysis including 250 BRCA carriers and 578 controls, it was reported that female BRCA1 carriers had an approximately 33 percent lower anti-mullerian hormone levels relative to controls, although levels in BRCA2 carriers were not diminished. This finding may represent decreased ovarian reserve, and therefore fertility counselling may be appropriate for BRCA1 carriers, if decisions regarding chemotherapy or delayed child-bearing are being considered.[105]

Medical Implications of P/LP BRCA Mutations in BC

For patients harboring pathogenic or likely pathogenic BRCA1/2 mutation, PARPi have a role in the management of HER2-negative metastatic stages as well as select high-risk early-stage BCs (►**Table 6**).

- *Metastatic/advanced stage setting*: olaparib is recommended 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 (based on the Olympiad trial).[107]

Talazoparib is recommended for patients with germline BRCA mutations and human epidermal growth factor receptor 2–negative locally advanced or metastatic BC (based on the EMBRACA trial).[108]

- *Neoadjuvant setting*: neoadjuvant platinum chemotherapy is recommended for BRCA-positive patients (based on the GeparSixto and CALGB 40603 trials).[109,110]
- *Adjuvant setting*: one year of adjuvant olaparib is indicated after the completion of (neo)adjuvant chemotherapy and local treatment, including radiation, for patients with high-risk BC (based on the OlympiA trial).[111]

The high-risk patients are[112]:

Post-op TNBC with node-positive disease or an invasive tumor size of at least 2 cm.

Post-op TNBC who have also received neoadjuvant therapy with residual invasive cancer on histopathology (not in pathological complete response).

Hormone-positive BC with at least four involved axillary nodes.

Hormone-positive BC post-neoadjuvant therapy with residual disease and a CPS + EG score of at least 3 (CPS = clinical and pathological stage; EG = estrogen-receptor status and histologic grade).

Medical Implications of BRCA in OC

PARPi (olaparib, rucaparib, and niraparib) have been approved in OC for various indications. The broad applications are as below[88,113–116]:

- *Frontline setting*: as maintenance therapy for advanced epithelial OCs who experienced a response to frontline, platinum-based chemotherapy.
- *Relapsed/recurrent setting*: as maintenance therapy for platinum-sensitive relapsed epithelial OCs, irrespective of BRCA status, who has responded to platinum-based therapy rechallenge and who did not receive PARPi maintenance in frontline setting.

Discussion

These revised/updated consensus guidelines are recommended to be used by health care professionals in their real-world practice (changes in this version of the recommendation guidelines are highlighted in ►**Table 7** for convenience of the readers). In the absence of prospective randomized data from India, we have not made any attempt to grade or distinguish regarding the strength of the recommendations. Box 3 shows the summary of the expert group's recommendations, following which is expected to

Table 6 Results from selected PARPi studies in breast and ovarian cancer plus BRCA1/2 mutations

Study treatment (trial)	Indication	Efficacy findings
Breast		
Olaparib monotherapy (300 mg twice per day) vs. standard single agent therapy[93,106] (OLYMPIAD)	Metastatic breast cancer and gBRCA1/2m	ORR: 60% (olaparib) vs. 29% (standard therapy) Median PFS: 7.0 months (olaparib) vs. 4.2 months (standard therapy; HR: 0.58; 95% CI: 0.43–0.80; $p < 0.001$)
Talazoparib monotherapy (1 mg every day) vs. standard single agent therapy[90] (EMBRACA)	Metastatic breast cancer and gBRCA1/2m	ORR: 62.6% (talazoparib) vs. 27.2% (standard therapy) Median PFS: 8.6 months (talazoparib) vs. 5.6 months (standard therapy; HR: 0.54; 95% CI: 0.41–0.71; $p < 0.001$)
Olaparib (300 mg twice per day) vs. placebo[90] (OLYMPIA)	High-risk early breast cancer (see the text) and gBRCA1/2m	iDFS at 3 years: 86% (olaparib) vs. 77% (placebo; HR: 0.58; 95% CI: 0.41–0.82; $p < 0.001$) OS at 4 years: 89.8% (olaparib) vs. 86.4% (placebo; HR: 0.68; 98.5% CI: 0.47–0.97; $p = 0.009$)
Ovary		
Olaparib monotherapy (300 mg twice per day) vs. placebo[97] (SOLO 1)	High-grade serous or endometrioid OC, primary peritoneal cancer, or fallopian tube cancer and g/s BRCA1/2m (FRONTLINE)	PFS at 3 years: 60% (olaparib) vs. 27% (placebo; HR: 0.30; 95% CI: 0.23–0.41; $p < 0.001$)
Olaparib monotherapy (300 mg twice per day) vs. placebo[94] (SOLO 2)	Platinum-sensitive, relapsed high-grade serous or endometrioid OC, primary peritoneal cancer, or fallopian tube cancerandgBRCA1/2m	Median PFS: 19.1 months (olaparib) vs. 5.5 months (placebo; HR: 0.30; 95% CI: 0.22–0.41; $p < 0.0001$)
Niraparib monotherapy (300 mg once daily) vs. placebo[95] (NOVA)	Platinum-sensitive relapsed high-grade ovarian cancer gBRCAm cohort	Median PFS: 21 months (niraparib) vs. 5.5 months (placebo; HR: 0.27; 95% CI: 0.17–0.41; $p < 0.0001$)
Rucaparib monotherapy (600 mg twice per day)[96] (ARIEL2)	Relapsed high-grade ovarian carcinoma and a g/sBRCA1/2m	ORR: 53.8%; CR: 8.5%; PR: 45.3%; DOR: 9.2 months (95% CI: 6.6–11.6 months)
Olaparib + bevacizumab vs. placebo + bevacizumab (PAOLA-1)	1L maintenance of advanced HGSOC/endometrioid carcinoma patients who have responded to chemotherapy and bevacizumab	mPFS = 22.1 m vs. 16.6 m [PFS (HR): 0.59 (0.49–0.72)] HRD-positive and BRCA +: PFS (HR) = 0.33 (0.25–0.45) HRD-positive and BRCA −: PFS (HR) = 0.43(0.28–0.66)

Abbreviations: CI, confidence interval; HR, hazard ratio.
Note: Reference [95] to be changed - Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154–2164.

Table 7 Key highlights of the major revisions in the current HBOC article as compared to our previous publication (JGO 2020) are as follows:

1. List of non-BRCA genes updated (RAD51C and 1D)
2. Pretest counselling section added
3. Informed consent importance outlined
4. Pedigree chats with sample of the same with commonly used symbols added
5. Implications of germline BRCA and risks of germline BRCA1/2 mutations (U.S. Preventive Services Task Force recommendation added) as well as implications for management of HBOC
6. Details of how to avoid common mistakes made by labs while testing for hereditary cancer panel testing

(*Continued*)

Table 7 (*Continued*)

7. Medical Implications of BRCA in BC section including implications with respect to use of PARPi 8. New, recent Indian references added and updated in ►**Table 3** 9. Several new genes added and updated in ►**Table 5** 10. New indications and approval for use of PARPi added in ►**Table 6** 11. Appropriately, several references updated in the whole manuscript, especially in sections on Somatic/Tumor BRCA testing, BRCA, and PARPi (earlier manuscript had 98 references and the updated one has 121 references)

personalize management plan for each patient and ultimately optimize outcome. In the absence of any nationwide genetic testing policy document, our guidelines will serve as its substitute.

Conclusions

HBOC is a complex syndrome with additional insights constantly being generated from real-world experiences combined with data science developments in global publicly available databases.[117] The community oncologists in India, SAARC region, and other low- and middle-income countries are in the need of guidelines that can be impropriated easily into their clinical practice to optimize genetic counselling, molecular testing, and management of patients with HBOC. This is because the implications are far-reaching in our socioeconomic milieu. This consensus statement provides a clear picture of why to test, whom to test, how to test, when to test, which test to use, how to interpret the results, and how to discuss options with the patient and families at risk.[118–121]

HBOC ISMPO Guidelines (2023)

Box 1 Guidelines for gBRCA risk assessment (adapted from NCCN Criteria v.3 2023)

1. Personal history of breast cancer with specific features: • ≤50 years • Any age: ◊ Treatment indications – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting – To aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer ◊ Pathology/histology – Triple-negative breast cancer – Multiple primary breast cancers (synchronous or metachronous) – Lobular breast cancer with personal or family history of diffuse gastric cancer ◊ Male breast cancer ◊ Ancestry: Ashkenazi Jewish ancestry ◊ Family history – ≥1 close blood relative with ANY: ▪ breast cancer at age ≤50 ▪ male breast cancer ▪ ovarian cancer ▪ pancreatic cancer ▪ prostate cancer – ≥3 total diagnoses of breast cancer in patient and/or close blood relatives – ≥2 close blood relatives with either breast or prostate cancer (any grade)
2. Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
3. General criteria: • Individuals with any blood relative with a known P/LP variant in a cancer susceptibility gene • Individuals meeting the criteria below but who tested negative with previous limited testing • A P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline • To aid in systemic therapy and surgical decision-making • Individual who meets Li–Fraumeni syndrome (LFS) testing criteria or Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS) testing criteria or Lynch syndrome
• Family history of cancer only: • An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except for systemic therapy decision-making). • If the affected relative has pancreatic cancer or prostate cancer only, first-degree relatives should be offered testing unless indicated based on additional family history. • An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 pathogenic variant based on prior probability models (e.g., Tyrer–Cuzick, BRCAPro, CanRisk)

Box 2 Points to be considered while selecting the right lab for genetic testing:

1. Certification (e.g., NABL)
2. Participation in external quality assurance program
3. Documentation of internal quality control SOPs
4. Design of appropriate multigene panel
5. Wet lab processes for enrichment of targets (hybrid capture or amplicon-based capture) without compromising on sensitivity and specificity of the detection of pathogenic variants
6. Bioinformatic expertise
7. Qualified and trained personnel to interpret results
8. Reasonable turnaround time (approximately 4 weeks)

Box 3 Summary of the ISMPO consensus recommendation statements for HBOC (with voting by authors)

Question	Recommendation (description)	Recommendation (strength)
1. Who should undergo genetic counseling?	All clinicians should assess: • Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer. • An ancestry associated BRCA1/2 gene mutations. and advise genetic counselling and, if indicated, genetic testing	100%
2. Who should undergo genetic testing?	• Any breast cancer (BC) diagnosed at age <50 years. • Any triple-negative BC • 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	96%
3. Who can perform genetic counselling?	Genetic counsellors and other medical professionals (medical/surgical/radiation oncologists/breast surgeons) knowledgeable in genetic testing can provide patient education and counselling and make recommendations regarding genetic testing and arrange testing	**100%**
4. What points should be included in pretest counselling?	• Rapport building, • Elicitation of need and comprehension levels • 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	**100%**
5. What genetic test should be offered?	• Single-site mutation testing in families with a known mutation • 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 (a 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	**100%**
6. What risk-reduction approaches should be offered to affected individuals?	• Risk management for future cancers: – Contralateral prophylactic mastectomy: ➢ Risk-reduction mastectomy should be offered to patients with a previous history of BC who carry a germline genetic mutation in BRCA1/2 ➢ Risk-reducing bilateral salpingo-oophorectomy (rrBSO): for BRCA1 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: prophylactic bilateral mastectomy is not considered in these cases as the risk of death	**100%**

(*Continued*)

Box 3 (*Continued*)

Question	Recommendation (description)	Recommendation (strength)
	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	
7. What risk-reduction approaches should be offered to unaffected mutation carriers?	BRCA1/2: • Lifestyle modifications: regular exercise, maintaining healthy body weight, limiting alcohol consumption. • Avoid hormone replacement therapy, encourage breast feeding. • 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. • 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. • 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 • Breast cancer screening: ➢ Breast awareness from age 18 years IIA ➢ Clinical breast examination (CBE) every 6–12 months is recommended from the age of 25 years or 10 years before the youngest BC VC ➢ Annual screening MRI (days 7–15 of menstrual cycle) should be commenced from age 25 years with the addition of annual mammography from age 30 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	**100%**
8. When should poly (ADP-ribose) polymerase inhibitors be used?	➢ Olaparib, niraparib, and rucaparib are indicated for maintenance treatment in adults with recurrent epithelial OC who are in complete response (CR) or partial response (PR) after platinum-based chemotherapy (irrespective of BRCA status) ➢ In g/s P/LP BRCA-mutated OC, olaparib should be used as maintenance after a CR/PR to first-line chemotherapy and cytoreductive surgery. Niraparib is indicated in this setting irrespective of BRCA status. ➢ 1L maintenance treatment for advanced ovarian cancer in combination with bevacizumab after CR/PR to 1L platinum-based chemotherapy which is HRD+ ➢ Talazoparib is indicated for adults with deleterious or suspected gBRCA-mutated, human epidermal growth factor receptor 2–negative locally advanced or metastatic BC	**96%**

Box 3 (*Continued*)

Question	Recommendation (description)	Recommendation (strength)
	➢ Olaparib is indicated for adjuvant treatment of P/LP gBRCA HER2-negative high-risk early breast cancer in adults previously treated with NACT or adjuvant CT ➢ Olaparib is indicated for P/LP gBRCA HER2-negative metastatic breast cancer patients who have received chemotherapy in neoadjuvant/adjuvant/metastatic setting. Hormone-positive breast cancer should have been treated with prior endocrine therapy or be considered inappropriate for endocrine therapy.	

Abbreviation: CT, computed tomography.

Patient Consent

Conflict of Interest
None declared.

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