special articles

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

Hemant Malhotra, MD[1]; Pradnya Kowtal, PhD[2]; Nikita Mehra, MD, DM[3]; Raja Pramank, MD, DM[4]; Rajiv Sarin, MD[5]; Thangarajan Rajkumar, MD, DM, PhD, DSc[6]; Sudeep Gupta, MD[7]; Ajay Bapna, MD, DM[8]; Gouri Shankar Bhattacharyya, MD[9]; Sabhyata Gupta, MD[10]; Amita Maheshwari, MD[11]; Ashraf U. Mannan, PhD[12]; Ravindra Reddy Kundur, MSc, PGD[13]; Rupinder Sekhon, MD[14]; Manish Singhal, MD, DM[15]; B.K. Smruti, MD[16]; Somashekhar SP, MCh[17]; Moushumi Suryavanshi, MD[18]; and Amit Verma, MD[19]

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.

JCO Global Oncol 6:991-1008. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 21, 2020 and published at ascopubs.org/journal/go on July 6, 2020: DOI https://doi.org/10.1200/JGO.19.00381

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.[1,2] HBOC syndrome is associated with 50% to 85% lifetime risk of BC and 15% to 30% risk of OC in women.[3,4] Mutations in *BRCA1* and *BRCA2* are commonly implicated in HBOC.[5] 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.[6]

In India, BC is the most common cancer in women as well as the most common cause of cancer-related death in women.[7] The Indian scenario is characterized by younger median age of onset and a high incidence-to-mortality ratio compared with the West.[8] 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 g*BRCA* mutant cases, genetic testing has the potential to affect treatment decisions. Genetic tests improve the understanding of the risk of

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?

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.

future metachronous cancers in patients, which can be prevented by employing appropriate surgical or nonsurgical prophylactic measures.[9] Clinician and genetic counselors can prevent an almost inevitable cancer in previvors. Appropriate preventive steps are available for several non-*BRCA* genes, like *PALB2*, *CHEK2*, and *ATM1*.[10]

The prevalence of germline mutations; their relative frequencies in high-, moderate-, and low-penetrance genes; and their founder status all vary with geography and ethnicity. Pathogenic genetic mutation is estimated to occur in 10% to 15% of all patients with BC, with *BRCA1* and *BRCA2* accounting for 40% to 50% of pathogenic/likely pathogenic mutations.[11,12]

Leveraging the recent developments in the management of HBOC, more than 32 international guidelines published between 2010 and 2018 provide recommendations for genetic counseling and screening, preventive or risk reduction approaches, and systemic management of BRCA-mutated BC and OC, but all these guidelines cater to issues of Western patients.[13]

These recommendations were convened to evaluate current testing practices and referral workflows, suggest effective testing methods, and provide practical insights to advance *BRCA* mutation testing in India with the ultimate goal of improving treatment outcome and patient care.

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.[14] 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[15-18]

Genetic counseling before testing is endorsed by many international oncology working groups.[1,19-21] 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.[22,23] In India, oncologists are often the first point of contact for these patients.[18,24]

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*, *PTEN*, *CDH1*, *STK11*, *CHEK2*, *RAD51*, and *ATM*, are also known to confer risk of BC and/or OC, albeit with lower frequency and penetrance[31] (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

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
		15-40 ovarian cancer	
BRCA2 (13q12.3)	HBOC	60-85 lifetime risk	1/400
		13-23 ovarian cancer	
TP53 (17p13.1)	Li-Fraumeni syndrome	50-89 by age 50	< 1/10,000
		90 in Li-Fraumeni syndrome survivors	
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
LSP1 (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.[32] The largest analysis of 1,010 high-risk families across India[33] 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.[33] A recent study from North India reported a 30% prevalence of g*BRCA* mutation in patients with BC/OC qualifying for NCCN criteria for testing, including 5 novel mutations.[34] 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.[35] 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.[36-38] 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.[39]

BOX 1. NCCN GUIDELINES 2019 FOR g*BRCA* 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
- Personal history of male BC
- Personal history of pancreatic cancer
- Personal history of metastatic prostate cancer
- Personal history of high-grade prostate cancer (Gleason score ≥ 7) at any age with one or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or BC age < 50 years; or two or more close blood relatives with BC, or prostate cancer (any grade) at any age; or Ashkenazi Jewish ancestry
- An individual who does not meet the other criteria but with one or more 1 first- or second-degree blood relative meeting any of the above criteria

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.[40]

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 amplicon based or hybrid capture based;
b) Sequencing chemistry: sequencing by synthesis or pH mediation; 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.[41] Two studies from India have reported that the use of multigene panel testing by NGS for germline mutations in patients with HBOC.[42,43] 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 nonfunctional 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, PTEN, 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]

Interpretation of a variant for use in clinical decision making requires comprehensive knowledge of the patient's phenotype, mode of inheritance for the disease gene, mutational mechanism (eg, haplo-insufficiency, dominant negative), protein structure/function, and the strength of the gene-disease relationship. Clinically relevant mutations are annotated using published variants in the literature and a set of disease databases—ClinVar, OMIM, GWAS, HGMD, and SwissVar. Nonsynonymous variant effects are 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 are used for clinical interpretation.

The test result obtained should be transcribed into a coherent genetic testing report that describes the test results and explains its significance for the proband and first-degree relatives. DNA change as a variant should be reported using the standard Human Genome Variation Society nomenclature that describes the nucleotide change in the cDNA as a c. and the consequent change in the amino acid and protein as a p., while mentioning the cDNA reference sequence used.

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

TABLE 2. Cancer Risks Associated With *BRCA1* and *BRCA2*

Mutation	Lifetime Risk of Breast Cancer, %	Lifetime Risk of Ovarian Cancer, %
BRCA1	55-85	35-46
BRCA2	50-85	13-23
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
		African American: Approximately 19
Male breast	*BRCA1:* 1	0.1
	BRCA2: 8	
Pancreatic	*BRCA1:* Unclear	1.5
	BRCA2: 5	
Other sites	To be determined	Varied

TABLE 3. Pathogenic *BRCA1/2* Mutations Identified in Indian Patients

Study	Region	Testing Method	Pathogenic *BRCA1/2* Mutations Identified
Valarmathi et al, 2003[90]	New Delhi, North India	Direct sequencing	*BRCA 1* (E1250X in exon 11; E1754X in exon 20)
Rajkumar et al, 2003[49]	Chennai, South India	Heteroduplex analysis/dHPLC	*BRCA1* (Ex12 1386 delCTCTC Stop 1389, Ex13 CGA→TGA Arginine1443 Stop), *BRCA2* (Ex11O 1235delCTTAA stop 1237)
Saxena, 2006[91]	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[92]	Kerala, South India	Direct sequencing	*BRCA2* (c.4642delAA, c.4926insGACC)
Thirthagiri et al, 2008[37]	Malaysia, Indian ethnicity	dHPLC and DNA sequencing	*BRCA1* (180 delA, 185 delAG, 5370 C>T), *BRCA2* (9097 C>T)
Soumittra et al, 2009[93]	Chennai, South India	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[38]	South India	Heteroduplex analysis using CSGE and direct sequencing	*BRCA1* (185delAG)
Kang et al, 2014[36]	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.[47] 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 *BRCA* 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

TABLE 4. Classification of Sequence Variants by International Working Groups

International Agency for Research on Cancer		American College of Medical Genetics		Clinical Molecular Genetics Society	
Class	**Description**	**Category**	**Description**	**Class**	**Description**
5	Definitely pathogenic	1	Previously reported and is a recognized cause of the disorder	1	Certainly nonpathogenic
4	Likely pathogenic	2	Previously unreported and is of the type that is expected to cause the disorder	2	Unlikely to be pathogenic, but cannot be formally proven
3	Uncertain	3	Previously unreported and is of the type that may or may not be causative of the disorder	3	Likely to be pathogenic, but cannot be formally proven
2	Likely not pathogenic or of little clinical significance	4	Previously unreported and is probably not causative of disease	4	Certainly pathogenic
1	Not pathogenic or of no clinical significance	5	Previously reported and is a recognized neutral variant		
		6	Previously not known or expected to be causative of disease, but is found to be associated with a clinical presentation		

College of American Pathologists have developed guidelines for NGS bioinformatics pipelines, and laboratories should follow them to reduce error rates.[59] 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.[60] 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 amplicons, 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.[60,61]

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 multigene 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 scaring and instability.[62,63] 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.[64-66]

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.[67]

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.[68-70] 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.

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:	VB
	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	
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 (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	
5. What risk-reduction approaches should be offered to affected individuals?	Risk management for future cancers:	IIB
	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 *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	IIIB
	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	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.	IVC
	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	VC
	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	

Question	Recommendation	Level of Recommendation
7. When should poly (ADP-ribose) polymerase inhibitors be used?	Olaparib, niraparib, 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)	IIA
	In advanced *BRCA*-mutated OC, olaparib is indicated as a monotherapy in patients treated with 3 or more lines of chemotherapy. Rucaparib is also indicated in this setting after 2 or more lines of chemotherapy	
	In g*BRCA*-mutated OC, olaparib should be used as maintenance after a CR/PR to first-line chemotherapy and cytoreductive surgery	
	Talazoparib is indicated for adults with deleterious or suspected g*BRCA*-mutated, human epidermal growth factor receptor 2–negative locally advanced or metastatic BC	

Levels of Evidence (adapted from the Infectious Diseases Society of America–US Public Health Service Grading System)

I: Evidence from at least one large randomized controlled trial of good methodologic quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II: Small randomized trials or large randomized trials with a suspicion of bias (lower methodologic quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III: Prospective cohort studies
IV: Retrospective cohort studies or case-control studies
V: Studies without control group, case reports, and/or expert opinions

Grades of Recommendation

A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B: Strong or moderate evidence for efficacy, but with a limited clinical benefit, generally recommended
C: Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc), optional
D: Moderate evidence against efficacy or for adverse outcome, generally not recommended
E: Strong evidence against efficacy or for adverse outcome, never recommended

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 ultrasonography 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 preimplantation 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

TABLE 5. Management Recommendations for Other Genes Implicated in Hereditary Breast Cancers (level of evidence = V, expert opinion)

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	RRSO, insufficient evidence	
	RRM, insufficient evidence		
BARD1	Potentially increased risk	Unknown	
	RRM, insufficient evidence		
BRIP1	Unknown	Increased risk of ovarian cancer	
		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
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
	MRI/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)

TABLE 5. Management Recommendations for Other Genes Implicated in Hereditary Breast Cancers (level of evidence = V, expert opinion) (Continued)

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancers
TP53	Breast awareness from age 18 years		Annual whole-body MRI
	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 30-75 years: annual MRI + mammogram		Comprehensive physical and neurologic examination
	RRM to be discussed		Follow Toronto protocol

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) *v* standard single-agent therapy[94] (OLYMPIAD)	Metastatic breast cancer and a germline *BRCA*m	ORR: 60% (olaparib) *v* 29% (standard therapy); median PFS, 7.0 months (olaparib) *v* 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) *v* 7.1 months (IQR, 3.2-12.2 months; standard therapy)
Olaparib monotherapy (200 mg twice per day) *v* matching placebo[95] (SOLO 2)	Platinum-sensitive, relapsed high-grade serous OC with *BRCA1/2*m	Median PFS, 19.1 months (olaparib) *v* 5.5 months (placebo; HR, 0.30; 95% CI, 0.22 to 0.41; $P < .0001$)
Niraparib monotherapy (300 mg) *v* placebo[96] (NOVA)	Older patients (age ≥ 70 years) with recurrent OC	In gBRCAm subgroup: median PFS was not reached *v* 3.7 months (in placebo)
Talazoparib monotherapy (1 mg every day) *v* standard single-agent therapy[87] (EMBRACA)	Advanced BC and g*BRCA1/2*m	Median PFS, 8.6 months (talazoparib) *v* 5.6 months (standard therapy; HR, 0.54; 95% CI, 0.41 to 0.71; $P < .001$); ORR, 62.6% (talazoparib) *v* 27.2% (standard therapy)
Rucaparib monotherapy (600 mg BID)[97] (ARIEL2)	High-grade ovarian carcinoma and a g/s*BRCA1/2*m	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) *v* placebo (SOLO 1)[98]	High-grade serous or endometrioid OC, primary peritoneal cancer, or fallopian tube cancer	PFS at 3 years: 60% (olaparib) *v* 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.[79-82]

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.[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.[86]

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.[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.[88,89]

Medical Implications of *BRCA* in OC

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

AFFILIATIONS

[1]Department of Medical Oncology, Sri Ram Cancer Center, Mahatma Gandhi Medical College Hospital, Jaipur, India
[2]Sarin Laboratory and OIC Sanger Sequencing Facility, Advanced Centre for Treatment Research, and Education in Cancer, Navi Mumbai, India
[3]Department of Medical Oncology, Cancer Institute (WIA), Chennai, India
[4]Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India
[5]Radiation Oncology, Cancer Genetics Unit, Tata Memorial Centre and PI Sarin Laboratory, Advanced Centre for Treatment Research and Education in Cancer, Navi Mumbai, India
[6]Department of Molecular Oncology, Cancer Institute (WIA), Chennai, India
[7]Tata Memorial Centre Advanced Centre for Treatment, Research, and Education in Cancer, Navi Mumbai, India
[8]Department of Medical Oncology, Bhagwan Mahavir Cancer Hospital Research Center, Jaipur, India
[9]Fortis Hospital, Kolkata, India
[10]Department of Gynae Oncology, Medanta-The Medicity, Gurgaon, India
[11]Department of Gynecologic Oncology, Tata Memorial Centre, Mumbai, India
[12]Clinical Diagnostics, Strand Center for Genomics and Personalized Medicine, Strand Life Sciences, Bangalore, India
[13]Cancer Genetics Clinic, Tata Memorial Centre, Mumbai, India
[14]Gynae Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India
[15]Medical Oncology, Apollo Hospital, New Delhi, India
[16]Bombay Hospital and Medical Research Centre, Mumbai, India
[17]Manipal Comprehensive Cancer Center, Manipal Hospital, Bengaluru, India
[18]Molecular Diagnostics, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India
[19]Molecular Oncology and Cancer Genetics, Max Hospital, New Delhi, India

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.

CORRESPONDING AUTHOR

Hemant Malhotra, MD, Department of Medical Oncology, Sri Ram Cancer Center, Mahatma Gandhi Medical College Hospital, Jaipur C-70, Ram Marg, Tilak Nagar, Jaipur 302004, India; e-mail: drmalhotrahemant@gmail.com.

AUTHOR CONTRIBUTIONS

Conception and design: Hemant Malhotra, Pradnya Kowtal, Raja Pramanik, Rajiv Sarin, Thangarajan Rajkumar, Sudeep Gupta, Ajay Bapna, Gouri Shankar Bhattacharyya, Sabhyata Gupta, Manish Singhal, B.K. Smruti, Somashekhar S.P., Moushumi Suryavanshi, Amit Verma
Administrative support: Ravindra Reddy Kundur, Moushumi Suryavanshi, Amit Verma
Provision of study materials or patients: Thangarajan Rajkumar, Rupinder Sekhon, B.K. Smruti, Amit Verma
Collection and assembly of data: Hemant Malhotra, Rajiv Sarin, Thangarajan Rajkumar, Sudeep Gupta, Gouri Shankar Bhattacharyya, Ashraf U. Mannan, Manish Singhal, B.K. Smruti, Amit Verma
Data analysis and interpretation: Hemant Malhotra, Pradnya Kowtal, Nikita Mehra, Rajiv Sarin, Thangarajan Rajkumar, Sudeep Gupta, Ajay Bapna, Gouri Shankar Bhattacharyya, Amita Maheshwari, Ashraf U. Mannan, Ravindra Reddy Kundur, Rupinder Sekhon, Manish Singhal, Moushumi Suryavanshi, Amit Verma
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's

conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/site/misc/authors.html.
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Thangarajan Rajkumar
Consulting or Advisory Role: Serum Institute of India
Patents, Royalties, Other Intellectual Property: The Cancer Institute has signed a memorandum of understanding with HLL Life Care for transfer of technology for a cervical cancer screening kit for which we have applied for a patent (Inst)

Sudeep Gupta
Research Funding: Roche (Inst), Sanofi (Inst), Johnson & Johnson (Inst), Amgen (Inst), Celltrion (Inst), OncoStem Diagnostics (Inst), Novartis (Inst)

Gouri Shankar Bhattacharyya
Honoraria: Vicus Therapeutics, Mylan, Biocon, Cipla, Intas
Consulting or Advisory Role: Vicus Therapeutics, Mylan, Biocon, Cipla, Zuventus, OncoStem Diagnostics
Speakers' Bureau: Biocon, Novartis, Cipla, Meda, Intas, Boehringer Ingelheim, AstraZeneca, OncoStem Diagnostics
Research Funding: Vicus Therapeutics

Ashraf U. Mannan
Employment: Strand Life Sciences

Manish Singhal
Honoraria: Pfizer, AstraZeneca
Speakers' Bureau: Novartis

Amit Verma
Employment: Max Healthcare
Consulting or Advisory Role: Foundation Medicine

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors thank Priya Ganpathy, MPharm, CMPP, (SIRO Clinpharm), for medical writing assistance and Sangita Patil, PhD, CMPP, (SIRO Clinpharm), for additional editorial support. The authors gratefully acknowledge AstraZeneca for help in organizing the meeting of experts at Mumbai.

REFERENCES

1. American College of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins—Gynecology, ACOG Committee on Genetics, et al: ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol 113:957-966, 2009
2. Honrado E, Benítez J, Palacios J: The molecular pathology of hereditary breast cancer: Genetic testing and therapeutic implications. Mod Pathol 18:1305-1320, 2005
3. Ford D, Easton DF, Stratton M, et al: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 62:676-689, 1998
4. Struewing JP, Hartge P, Wacholder S, et al: The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 336:1401-1408, 1997
5. Gorodetska I, Kozeretska I, Dubrovska A: *BRCA* genes: The role in genome stability, cancer stemness and therapy resistance. J Cancer 10:2109-2127, 2019
6. Kowalewski A, Szylberg Ł, Saganek M, et al: Emerging strategies in BRCA-positive pancreatic cancer. J Cancer Res Clin Oncol 144:1503-1507, 2018
7. Ghoncheh M, Momenimovahed Z, Salehiniya H: Epidemiology, incidence and mortality of breast cancer in Asia. Asian Pac J Cancer Prev 17:47-52, 2016 (suppl 3)
8. Hortobagyi GN, de la Garza Salazar J, Pritchard K, et al: The global breast cancer burden: Variations in epidemiology and survival. Clin Breast Cancer 6:391-401, 2005
9. Rhiem K, Schmutzler R: Impact of prophylactic mastectomy in BRCA1/2 mutation carriers. Breast Care (Basel) 9:385-389, 2014
10. Marsh D, Zori R: Genetic insights into familial cancers: Update and recent discoveries. Cancer Lett 181:125-164, 2002
11. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 73:643-651, 1994
12. Peto J, Collins N, Barfoot R, et al: Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 91:943-949, 1999
13. Forbes C, Fayter D, de Kock S, et al: A systematic review of international guidelines and recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of *BRCA*-mutated breast cancer. Cancer Manag Res 11:2321-2337, 2019
14. Allen CG, Roberts M, Guan Y: Exploring predictors of genetic counseling and testing for hereditary breast and ovarian cancer: Findings from the 2015 U.S. National Health Interview Survey. J Pers Med 9:26, 2019
15. De Vries AM, de Roten Y, Meystre C, et al: Clinician characteristics, communication, and patient outcome in oncology: A systematic review. Psychooncology 23:375-381, 2014
16. Fallowfield L, Jenkins V: Effective communication skills are the key to good cancer care. Eur J Cancer 35:1592-1597, 1999
17. Jacobs C, Patch C, Michie S: Communication about genetic testing with breast and ovarian cancer patients: A scoping review. Eur J Hum Genet 27:511-524, 2019
18. Phadke SR, Pandey A, Puri RD, et al: Genetic counseling: The impact in Indian milieu. Indian J Pediatr 71:1079-1082, 2004
19. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Genetic/familial high-risk assessment—Breast, Ovarian, and pancreatic (version 1.2020). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
20. Riley BD, Culver JO, Skrzynia C, et al: Essential elements of genetic cancer risk assessment, counseling, and testing: Updated recommendations of the National Society of Genetic Counselors. J Genet Couns 21:151-161, 2012
21. Robson ME, Bradbury AR, Arun B, et al: American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 33:3660-3667, 2015
22. National Pathology Accreditation Advisory Council: Classification of Human Genetic Testing. Canberra, ACT, Australia, Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis, 2007
23. Rantanen E, Hietala M, Kristoffersson U, et al: Regulations and practices of genetic counselling in 38 European countries: The perspective of national representatives. Eur J Hum Genet 16:1208-1216, 2008

24. Darooei M, Poornima S, Salma BU, et al: Pedigree and BRCA gene analysis in breast cancer patients to identify hereditary breast and ovarian cancer syndrome to prevent morbidity and mortality of disease in Indian population. Tumour Biol 39:1010428317694303, 2017
25. Rich EC, Burke W, Heaton CJ, et al: Reconsidering the family history in primary care. J Gen Intern Med 19:273-280, 2004
26. Wood ME, Kadlubek P, Pham TH, et al: Quality of cancer family history and referral for genetic counseling and testing among oncology practices: A pilot test of quality measures as part of the American Society of Clinical Oncology Quality Oncology Practice Initiative. J Clin Oncol 32:824-829, 2014
27. Brédart A, Kop JL, De Pauw A, et al: Effect on perceived control and psychological distress of genetic knowledge in women with breast cancer receiving a BRCA1/2 test result. Breast 31:121-127, 2017
28. Mancini J, Noguès C, Adenis C, et al: Impact of an information booklet on satisfaction and decision-making about BRCA genetic testing. Eur J Cancer 42:871-881, 2006
29. Quinn VF, Meiser B, Kirk J, et al: Streamlined genetic education is effective in preparing women newly diagnosed with breast cancer for decision making about treatment-focused genetic testing: A randomized controlled noninferiority trial. Genet Med 19:448-456, 2017
30. Randall J, Butow P, Kirk J, et al: Psychological impact of genetic counselling and testing in women previously diagnosed with breast cancer. Intern Med J 31:397-405, 2001
31. National Cancer Institute: Susceptibility genes. https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq
32. Petrucelli N, Daly MB, Pal T: BRCA1- and BRCA2-associated hereditary breast and ovarian cancer, in Adam MP, Ardinger HH, Pagon RA, et al (eds): GeneReviews. Seattle, WA, University of Washington, 1993. https://www.ncbi.nlm.nih.gov/books/NBK1247/
33. Singh J, Thota N, Singh S, et al: Screening of over 1000 Indian patients with breast and/or ovarian cancer with a multi-gene panel: Prevalence of BRCA1/2 and non-BRCA mutations. Breast Cancer Res Treat 170:189-196, 2018
34. Agarwal G, Pradeep PV, Aggarwal V, et al: Spectrum of breast cancer in Asian women. World J Surg 31:1031-1040, 2007
35. Sharma-Oates A, Shaaban AM, Tomlinson I, et al: Heterogeneity of germline variants in high risk breast and ovarian cancer susceptibility genes in India. Precis Clin Med 1:75-87, 2018
36. Kang PC, Phuah SY, Sivanandan K, et al: Recurrent mutation testing of BRCA1 and BRCA2 in Asian breast cancer patients identify carriers in those with presumed low risk by family history. Breast Cancer Res Treat 144:635-642, 2014 [Erratum: Breast Cancer Res Treat 150:699-700, 2015]
37. Thirthagiri E, Lee SY, Kang P, et al: Evaluation of BRCA1 and BRCA2 mutations and risk-prediction models in a typical Asian country (Malaysia) with a relatively low incidence of breast cancer. Breast Cancer Res 10:R59, 2008
38. Vaidyanathan K, Lakhotia S, Ravishankar HM, et al: BRCA1 and BRCA2 germline mutation analysis among Indian women from south India: Identification of four novel mutations and high-frequency occurrence of 185delAG mutation. J Biosci 34:415-422, 2009
39. Finch AP, Lubinski J, Møller P, et al: Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 32:1547-1553, 2014
40. Owens DK, Davidson KW, Krist AH, et al: Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US Preventive Services Task Force recommendation statement. JAMA 322:652-665, 2019
41. Feliubadaló L, Lopez-Doriga A, Castellsagué E, et al: Next-generation sequencing meets genetic diagnostics: Development of a comprehensive workflow for the analysis of BRCA1 and BRCA2 genes. Eur J Hum Genet 21:864-870, 2013
42. Mannan AU, Singh J, Lakshmikeshava R, et al: Detection of high frequency of mutations in a breast and/or ovarian cancer cohort: Implications of embracing a multi-gene panel in molecular diagnosis in India. J Hum Genet 61:515-522, 2016
43. Rajkumar T, Meenakumari B, Mani S, et al: Targeted resequencing of 30 genes improves the detection of deleterious mutations in South Indian women with breast and/or ovarian cancers. Asian Pac J Cancer Prev 16:5211-5217, 2015
44. Borg A, Haile RW, Malone KE, et al: Characterization of BRCA1 and BRCA2 deleterious mutations and variants of unknown clinical significance in unilateral and bilateral breast cancer: The WECARE study. Hum Mutat 31:E1200-E1240, 2010
45. Sluiter MD, van Rensburg EJ: Large genomic rearrangements of the BRCA1 and BRCA2 genes: Review of the literature and report of a novel BRCA1 mutation. Breast Cancer Res Treat 125:325-349, 2011
46. Adam MP, Ardinger HH, Pagon RA, et al (eds): Appendix: Interpretation of sequence analysis results, in: GeneReviews. Seattle, WA, University of Washington, 2007
47. Jennings LJ, Arcila ME, Corless C, et al: Guidelines for validation of next-generation sequencing-based oncology panels: A joint consensus recommendation of the Association for Molecular Pathology and College of American Pathologists. J Mol Diagn 19:341-365, 2017
48. Santani A, Murrell J, Funke B, et al: Development and validation of targeted next-generation sequencing panels for detection of germline variants in inherited diseases. Arch Pathol Lab Med 141:787-797, 2017
49. Rajkumar T, Soumittra N, Nancy NK, et al: BRCA1, BRCA2 and CHEK2 (1100 del C) germline mutations in hereditary breast and ovarian cancer families in South India. Asian Pac J Cancer Prev 4:203-208, 2003
50. Nicolussi A, Belardinilli F, Mahdavian Y, et al: Next-generation sequencing of *BRCA1* and *BRCA2* genes for rapid detection of germline mutations in hereditary breast/ovarian cancer. PeerJ 7:e6661, 2019
51. Park HS, Park SJ, Kim JY, et al: Next-generation sequencing of *BRCA1/2* in breast cancer patients: Potential effects on clinical decision-making using rapid, high-accuracy genetic results. Ann Surg Treat Res 92:331-339, 2017
52. Lindor NM, Goldgar DE, Tavtigian SV, et al: BRCA1/2 sequence variants of uncertain significance: A primer for providers to assist in discussions and in medical management. Oncologist 18:518-524, 2013
53. BRCA Exchange: Summary view. https://brcaexchange.org/
54. Lindor NM, Guidugli L, Wang X, et al: A review of a multifactorial probability-based model for classification of BRCA1 and BRCA2 variants of uncertain significance (VUS). Hum Mutat 33:8-21, 2012
55. Plon SE, Eccles DM, Easton D, et al: Sequence variant classification and reporting: Recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat 29:1282-1291, 2008
56. Hofstra RM, Spurdle AB, Eccles D, et al: Tumor characteristics as an analytic tool for classifying genetic variants of uncertain clinical significance. Hum Mutat 29:1292-1303, 2008
57. Eggington JM, Bowles KR, Moyes K, et al: A comprehensive laboratory-based program for classification of variants of uncertain significance in hereditary cancer genes. Clin Genet 86:229-237, 2014
58. Zuntini R, Ferrari S, Bonora E, et al: Dealing with BRCA1/2 unclassified variants in a cancer genetics clinic: Does cosegregation analysis help? Front Genet 9:378, 2018
59. Roy S, Coldren C, Karunamurthy A, et al: Standards and guidelines for validating next-generation sequencing bioinformatics pipelines: A joint recommendation of the Association for Molecular Pathology and the College of American Pathologists. J Mol Diagn 20:4-27, 2018

60. Wallace AJ: New challenges for BRCA testing: A view from the diagnostic laboratory. Eur J Hum Genet 24:S10-S18, 2016 (suppl 1)
61. Do H, Wong SQ, Li J, et al: Reducing sequence artifacts in amplicon-based massively parallel sequencing of formalin-fixed paraffin-embedded DNA by enzymatic depletion of uracil-containing templates. Clin Chem 59:1376-1383, 2013
62. Hoppe MM, Sundar R, Tan DSP, et al: Biomarkers for homologous recombination deficiency in cancer. J Natl Cancer Inst 110:704-713, 2018
63. Neff RT, Senter L, Salani R: *BRCA* mutation in ovarian cancer: Testing, implications and treatment considerations. Ther Adv Med Oncol 9:519-531, 2017
64. Hennessy BT, Timms KM, Carey MS, et al: Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. J Clin Oncol 28:3570-3576, 2010
65. Gonzalez-Angulo AM, Timms KM, Liu S, et al: Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 17:1082-1089, 2011
66. Press JZ, De Luca A, Boyd N, et al: Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 8:17, 2008
67. Pennington KP, Walsh T, Harrell MI, et al: Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res 20:764-775, 2014
68. Ledermann J, Harter P, Gourley C: Correction to Lancet Oncol 2014; 15: 856. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 16:e158, 2015
69. Ledermann J, Harter P, Gourley C, et al: Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 15:852-861, 2014
70. Sandhu SK, Schelman WR, Wilding G, et al: The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: A phase 1 dose-escalation trial. Lancet Oncol 14:882-892, 2013
71. Hartmann LC, Schaid DJ, Woods JE, et al: Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 340:77-84, 1999
72. Meijers-Heijboer H, van Geel B, van Putten WL, et al: Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 345:159-164, 2001
73. Rebbeck TR, Friebel T, Lynch HT, et al: Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. J Clin Oncol 22:1055-1062, 2004
74. Domchek SM, Friebel TM, Singer CF, et al: Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304:967-975, 2010
75. Kauff ND, Satagopan JM, Robson ME, et al: Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 346:1609-1615, 2002
76. Rebbeck TR, Lynch HT, Neuhausen SL, et al: Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 346:1616-1622, 2002
77. Saslow D, Boetes C, Burke W, et al: American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75-89, 2007
78. King MC, Wieand S, Hale K, et al: Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 286:2251-2256, 2001
79. Carbine NE, Lostumbo L, Wallace J, et al: Risk-reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev 4:CD002748, 2018
80. Lostumbo L, Carbine NE, Wallace J: Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev 2010:CD002748, 2010
81. Pesce C, Liederbach E, Wang C, et al: Contralateral prophylactic mastectomy provides no survival benefit in young women with estrogen receptor-negative breast cancer. Ann Surg Oncol 21:3231-3239, 2014
82. Wong SM, Freedman RA, Sagara Y, et al: Growing use of contralateral prophylactic mastectomy despite no improvement in long-term survival for invasive breast cancer. Ann Surg 265:581-589, 2017
83. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, et al: Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: Revisiting the evidence for risk reduction. J Natl Cancer Inst 107:djv033, 2015
84. Kotsopoulos J, Huzarski T, Gronwald J, et al: Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 109: djw177, 2016
85. Terry MB, Daly MB, Phillips KA, et al: Risk-reducing oophorectomy and breast cancer risk across the spectrum of familial risk. J Natl Cancer Inst 111:331-334, 2019
86. Robson M, Im SA, Senkus E, et al: Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 377:523-533, 2017
87. Litton JK, Rugo HS, Ettl J, et al: Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 379:753-763, 2018
88. Sikov WM, Berry DA, Perou CM, et al: Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 33:13-21, 2015
89. von Minckwitz G, Schneeweiss A, Loibl S, et al: Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): A randomised phase 2 trial. Lancet Oncol 15:747-756, 2014
90. Valarmathi MT, A A, Deo SS, et al: BRCA1 germline mutations in Indian familial breast cancer. Hum Mutat 21:98-99, 2003
91. Saxena S, Chakraborty A, Kaushal M, et al: Contribution of germline BRCA1 and BRCA2 sequence alterations to breast cancer in Northern India. BMC Med Genet 7:75, 2006
92. Syamala V, Sreeja L, Syamala VS, et al: Novel germline mutations in BRCA2 gene among 96 hereditary breast and breast-ovarian cancer families from Kerala, South India. J Cancer Res Clin Oncol 133:867-874, 2007
93. Soumittra N, Meenakumari B, Parija T, et al: Molecular genetics analysis of hereditary breast and ovarian cancer patients in India. Hered Cancer Clin Pract 7:13, 2009
94. Robson ME, Tung N, Conte P, et al: OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 30:558-566, 2019
95. Pujade-Lauraine E, Ledermann JA, Selle F, et al: Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 18:1274-1284, 2017
96. Fabbro M, Moore KN, Dørum A, et al: Efficacy and safety of niraparib as maintenance treatment in older patients (≥ 70 years) with recurrent ovarian cancer: Results from the ENGOT-OV16/NOVA trial. Gynecol Oncol 152:560-567, 2019

97. Oza AM, Tinker AV, Oaknin A, et al: Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2. Gynecol Oncol 147:267-275, 2017
98. Moore K, Colombo N, Scambia G, et al: Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 379:2495-2505, 2018

