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REVIEW

A systematic review of international guidelines and recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of *BRCA*-mutated breast cancer

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Purpose: To conduct a systematic review of international guidelines on screening and management of patients with *BRCA*-mutated breast cancer (BC).

Methods: Major electronic databases (MEDLINE and Embase; N=8) and gray literature sources were searched (January 2007 to February 2018). Latest guideline recommendations on genetic screening, counseling, and BC treatment of *BRCA* mutation carriers were summarized. Guidelines specific to germline *BRCA* (g*BRCA*) mutation were captured where available.

Results: A total of 3,775 records were retrieved and 32 guidelines were included; Europe (n=16), USA (n=11), Canada (n=3), Australia (n=1), and Japan (n=1) were included. Across and within guidelines, genetic counseling was recommended at multiple points in the care pathway, though the format was not always clearly defined. US guidelines emphasized that *BRCA* mutation testing should occur after specialized genetic counseling; other European guidelines are less prescriptive. *BRCA* testing eligibility criteria differed, with some guidelines being less restrictive; US National Comprehensive Cancer Network (NCCN) BC guidelines specified that HER2-negative BC patients eligible for single-agent therapy are eligible for g*BRCA* testing. Fast-track *BRCA* testing is recommended in the Netherlands if treatment choice will affect survival, but in the UK only as part of clinical trials. More recent European (European School of Oncology–European Society for Medical Oncology 3rd International Consensus Guidelines for Breast Cancer in Young Women 2017, Arbeitsgemeinschaft Gynäkologische Onkologie 2017 in Germany) and US (NCCN) guidelines have updated recommendations regarding g*BRCA*-targeted poly(ADP-ribose) polymerase (PARP) inhibitor therapy in BC.

Conclusion: Regional and organizational guidelines differ for genetic screening, counseling, and treatment of patients with *BRCA*-mutated BC. Guideline harmonization would optimize identification and management of these patients.

Keywords: *BRCA1*, *BRCA2*, guidelines, systematic review, chemotherapy, PARP inhibitor

Introduction

Genetic predisposition to breast cancer (BC) may be associated with mutation in a particular gene or set of genes, including the key tumor-suppressor genes *BRCA1/2*.[1] *BRCA* mutation may be inherited (germline *BRCA* [g*BRCA*]) or arise de novo as a result of combinatorial genetic and environmental factors (somatic).[1] Specific population subgroups have been identified as having a higher proportion of individuals who carry *BRCA* mutations, including those who have been diagnosed with triple-negative breast cancer (TNBC) and those from different ethnic groups, including black populations and those of Ashkenazi Jewish

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heritage.[2–4] The majority of multiple BC cases within families, including male BC, are due to g*BRCA* mutations.[5] g*BRCA* mutation carriers have an increased lifetime risk of developing BC.[5]

Identification of *BRCA* mutation through genetic screening offers the opportunity to increase monitoring and surveillance of people for breast and other cancers, in addition to offering them prophylactic, risk-reducing interventions. Which individuals are eligible to receive *BRCA* screening varies across countries, with some testing strategies being more inclusive than others. The uptake of *BRCA* testing has also been shown to vary across populations, with genetic counseling suggested as having an influence on this.[6] Multiple Phase III randomized controlled trials have recently been published showing treatments that benefit patients with advanced BC (ABC) and g*BRCA* mutation;[7–9] specifically, platinum-based regimens and PARP inhibitors are offering new g*BRCA* mutation-targeted approaches in ABC.[10]

Prior research across international healthcare systems has suggested gaps regarding the implementation of population-based *BRCA* screening and the need to improve healthcare providers' knowledge about existing *BRCA* screening recommendations.[11,12] Strategies including specific training and the harmonization of guidelines have been recommended to increase awareness of *BRCA* screening programs in BC to enhance the guideline concordance in clinical practice.[12,13]

Given recent developments in the management of *BRCA*-mutated BC and the importance of understanding the differences in recommendations globally, a systematic literature review on the latest international guidelines was conducted to summarize recommendations regarding genetic screening, diagnosis, genetic counseling, and treatment.

Methods

This systematic review was carried out in accordance with a prespecified protocol (available from the authors on request) and methodologies recommended by the Cochrane collaboration[14] and the Centre for Reviews and Dissemination.[15] Guidelines reporting recommendations on genetic screening, diagnosis, genetic counseling, and treatment of BC with *BRCA* mutations were searched for from Europe (France, Germany, Ireland, Italy, the Netherlands, Spain, UK), North America (USA, Canada), Australia, Israel, Japan, Russia, and South Korea. Study inclusion was not limited by language, but only data that were publicly available and reported from 1 January 2007–7 February 2018 were eligible for inclusion in the review.

Extensive literature searches were undertaken and included 8 electronic databases; 17 guideline, health technology, and other resources; and 7 conference abstract collections in the geographies of interest (Supplementary material).

Two reviewers independently screened and selected guidelines for inclusion in the review, with discrepancies resolved through consensus with a third reviewer. Data were extracted from the most recent version of each included guideline, and the quality of the guidelines was assessed using the AGREE II tool.[16] A narrative summary of the guideline recommendations with accompanying evidence grades (where available) was presented according to the stage of patient care (screening, counseling, risk reduction, treatment, patient management/care, and recommendations for further research) and the target population of interest (patients with germline-specified *BRCA* mutation, men, black/African, Ashkenazi Jews, locally advanced/metastatic *BRCA* TNBC, and locally advanced/metastatic *BRCA* HR-positive/HER2-negative BC) wherever specified.

Results

Guideline selection process

A total of 3,775 titles and abstracts were retrieved from the literature searches of databases and hand-searching. From these, full papers were obtained for 114 citations. After further review, a total of 82 papers were excluded from the review. The remaining 32 papers, which are included in this review, represented 32 guidelines and were published between 2010[17] and 2018,[18] the majority (70%) within the last 3 years (2015 onward). Most were from Europe (16 guidelines) and North America (14 guidelines). Additional guidelines were identified in Australia (one guideline)[19] and Japan (one guideline).[20] A summary of the guideline selection process according to the PRISMA is given in Figure 1, and an overview summary of the included guidelines is shown in Table 1.

Summary of quality of guidelines

All 32 included guidelines were assessed using the AGREE II tool (Supplementary material). However, in many cases, poor reporting of the guidelines hampered the AGREE II assessment as it was impossible to distinguish whether guidelines were of insufficient quality or whether the methodologies were just poorly reported. In some cases, methodologies were described elsewhere, including earlier versions of guidelines, and could not be easily tracked through multiple revisions.[21,22] Where relevant, additional sources that provided information on the guideline methods were consulted and incorporated in the AGREE II assessments.[23,24]

Taking account of the potential limitations of the guidelines identified in the AGREE II assessment, overall eight of the guidelines[4,19,23–28] were recommended for use specifically in patients with *BRCA*-mutated BC. A further eight guidelines[3,21,22,29–33] were also recommended for use, but would benefit from changes to

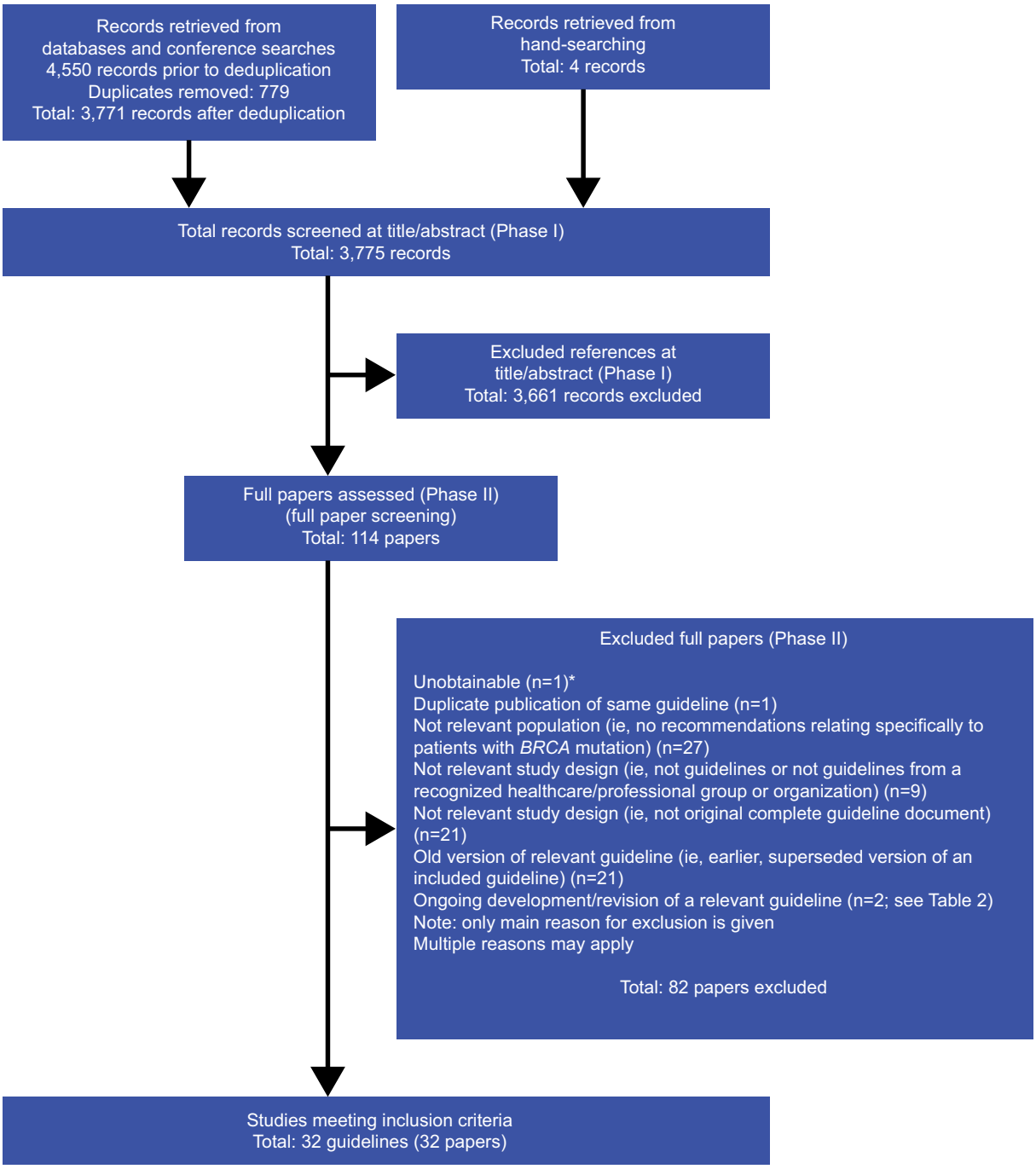

Figure 1 PRISMA flow chart.
Notes: *Unobtainable paper – not available through online sources or British Library. This paper is published in 2012 and only has two authors, with no mention of a recognized group or guideline/cancer organization. The title suggests it relates to breast cancer in general (no specific mention of *BRCA* in the keywords, title, or abstract). At full paper screening to reduce the risk of missing relevant *BRCA* recommendations, we have screened all general breast cancer guidelines. However, it is unlikely that this paper will be relevant and so its "unobtainable" status is unlikely to affect the findings of the review.

their methodologies or reporting in order to tailor them for use in patients with g*BRCA* and *BRCA*-mutated BC. Therefore, there were issues (eg, based on out-of-date evidence, a lack of clear recommendation statements, and/or poorly described methodologies) in half of the 32 included guidelines which suggested that they may be at risk of bias and potentially not appropriate for use specifically for *BRCA* patients.

Recommendations for genetic counseling

Fifteen relevant guidelines were identified as reporting recommendations on genetic counseling (Supplementary material) and were in general agreement about the importance of genetic counseling before and after *BRCA* testing, including prior to BC risk-reduction procedures (eg, mastectomy, oophorectomy). Eight were from Europe.[4,5,21,23,26,29,34] Six were

Table 1 Summary of included guidelines

Name of guideline/ organization	Country	Subgroups of interest					*BRCA* status (BC status) of populations with recommendation	Type of recommendation						
		Women only	Men only	TNBC	Ashkenazi Jews	HR+/ HER–		Genetic counseling	*BRCA* genetic screening	BC screening	BC prevention/ RR	BC treatment	Organization of care	Further research
Asia (1 guideline)														
Japanese Breast Cancer Society 2015[20]	Japan	Y	N	N	N	N	*BRCA* mutation (– BC)	N	N	Y	Y	N	N	N
Australasia (1 guideline)														
Cancer Australia 2014[19]	Australia	Y	N	N	N	N	*BRCA* mutation (+/– BC)	Y	N	N	Y	Y	N	N
North America (14 guidelines)														
Canadian Consensus Guideline 2017[28]	Canada	Y	N	N	N	N	*BRCA* mutation and familial (+ BC)	N	N	N	Y	N	N	N
Cancer Care Ontario 2012[25]	Canada	Y	N	N	N	N	*BRCA* mutation and familial (– BC)	N	N	Y	N	N	N	N
Toward Optimized Practice 2013[35]	Canada	Y	N	N	N	N	Familial risk (– BC)	Y	Y	N	N	N	N	N
ACMG and NSGC 2015[36]	USA	Y	Y	Y	Y	N	Familial risk (+ BC)	Y	N	N	N	N	N	N
ACR Screening 2017[24]	USA	Y	N	N	N	N	*BRCA* mutation (– BC)	N	N	Y	N	N	N	N
ACS/ASCO 2015[37]	USA	Y	N	N	N	N	*BRCA* mutation and familial (– BC)	Y	N	Y	N	N	N	N
ASTRO 2017[48]	USA	N	N	N	N	N	*BRCA* mutation (+ BC)	N	N	N	N	Y	N	N
NCCN Breast Cancer, Version 4.2017[40,a]	USA	Y	N	N	N	Y	*BRCA* mutation (+ BC)[b]	N	Y	N	N	Y	N	N
NCCN Genetic/ Familial High-Risk Assessment: Breast and Ovarian, Version 1.2018[3,a]	USA	Y	Y	Y	Y	N	*BRCA* mutation and familial (+/– BC)	Y	Y	Y	Y	N	Y	Y
NCCN Risk Reduction, Version 1.2018[18,a]	USA	N	N	N	N	N	*BRCA* mutation and familial (– BC)	N	Y	Y	Y	N	N	N
NCCN Breast Cancer Screening and Diagnosis, Version 1.2017[30,a]	USA	N	N	N	N	N	*BRCA* mutation (– BC)	N	N	Y	N	N	N	N
SBI and ACR 2010[17]	USA	Y	N	N	N	N	*BRCA* mutation and familial (– BC)	N	N	Y	N	N	N	N

SGO 2015[38]	USA	Y	Y	Y	Y	N	Familial risk (+/– BC)	Y	Y	N	N	N	N	N
USPSTF BRCA-Related Cancer 2013[19,c]	USA	Y	N	N	N	N	Familial risk (– BC)	Y	Y	N	N	N	N	N
Europe (16 guidelines)														
ESMO Diagnosis and Treatment 2015[34]	Europe	Y	N	N	N	N	*BRCA* mutation and familial (+ BC)	Y	N	Y	Y	N	Y	N
ESMO Prevention and Screening 2016[4]	Europe	Y	Y	N	N	N	g*BRCA* mutation (– BC)	Y	N	Y	Y	N	N	N
ESO-ESMO ABC3 2017[22,a]	Europe	N	N	Y	N	N	*BRCA* mutation (+ BC)[d]	Y	N	N	N	Y	N	N
ESO-ESMO BCY3 2017[21]	Europe	Y	N	Y	N	N	*BRCA* mutation (+ BC)	Y	Y	Y	Y	Y	Y	Y
AGO 2017[41,a]	Germany	Y	Y	Y	N	N	*BRCA* mutation and familial (+/– BC)[d]	N	Y	Y	Y	Y	N	N
AWMF Registry 2012[23]	Germany	Y	N	N	N	N	*BRCA* mutation and familial (+/– BC)	Y	N	Y	Y	Y	N	N
NCEC CG7 2015[27]	Ireland	Y	N	N	N	N	*BRCA* mutation (– BC)	N	N	N	Y	N	N	N
IKNL 2012[26]	Netherlands	Y	Y	N	N	N	*BRCA* mutation and familial (+/– BC)	Y	Y	Y	Y	N	Y	N
SEOM 2015[42]	Spain	Y	Y	Y	N	N	*BRCA* mutation and familial (+/– BC)	N	Y	Y	Y	Y	N	N
HIS 2014[43]	UK: Scotland	Y	N	N	N	N	Familial risk (+/– BC)	N	Y	Y	Y	N	N	N
ICR Protocol 1 2015[45]	UK	Y	N	N	N	N	Familial risk (– BC)	N	N	Y	Y	N	N	N
ICR Protocol 2 2017[44]	UK	N	Y	Y	N	N	Familial risk (+ BC)	N	Y	N	N	N	N	N
ICR Protocol 3 2015[46]	UK	Y	Y	N	N	N	*BRCA* mutation (– BC)	N	N	Y	Y	N	N	N
LCA 2016[29]	UK	Y	Y	Y	N	N	*BRCA* mutation and familial (+/– BC)	Y	Y	Y	Y	N	Y	N
NICE (CG14 and CG41 updates) 2017[5]	UK	Y	Y	Y	Y	N	*BRCA* mutation and familial (+/– BC)	Y	Y	Y	Y	N	Y	Y
RCR 2013[47]	UK	Y	N	N	N	N	*BRCA* mutation (+ BC)	N	N	Y	N	N	N	N

Notes: [a]Newly updated versions of these guidelines have been published since this review was carried out. Important changes in the new updated versions are summarized in the Discussion section. [b]Locally advanced/metastatic HR+ and HER2– breast cancer. [c]Guidelines are due to be updated and are currently under review. [d]Locally advanced/metastatic breast cancer.

Abbreviations: : –, negative; +, positive; ABC3, 3rd International Consensus Guidelines for Advanced Breast Cancer; ACMG, American College of Medical Genetics and Genomics; ACR, American College of Radiology; ACS, American Cancer Society; AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; BC, breast cancer; BCY3, 3rd international consensus guidelines for breast cancer in young women; CG, clinical guidance; g*BRCA*, germline *BRCA*; ESMO, European Society for Medical Oncology; ESO, European School of Oncology; Familial, familial risk factors present; HIS, Healthcare Improvement Scotland; HR, hormone receptor; ICR, Institute of Cancer Research; IKNL, Integraal Kankercentrum Nederland; LCA, London Cancer Alliance; N, no/not reported; NCCN, National Comprehensive Cancer Network; NCEC, National Clinical Effectiveness Committee; NICE, National Institute for Health and Care Excellence; NSGC, National Society of Genetic Counselors; RCR, Royal College of Radiologists; RR, risk reduction; SBI, Society of Breast Imaging; SEOM, Sociedad Española de Oncología Médica; SGO, Society of Gynecologic Oncology; TNBC, triple-negative breast cancer; USPSTF, US Preventive Services Task Force; Y, yes/reported.

from North America[3,35–39] and one from Australia.[19] Recommendations for genetic counseling were made for three main populations: those with a familial risk of BC,[3,23,38] *BRCA* carriers, and those who have BC and/or a personal history of BC.[3] A number of guidelines across the USA, Canada, and Europe agreed that predictive genetic testing should not be offered without adequate genetic counseling.[3,5,29] Recommendations from the US National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2018 guidelines[3] focused on the content and structure of genetic counseling sessions for those who had already been identified as carriers of a *BRCA* mutation and included providing information to patients regarding prophylactic interventions such as mastectomy, oophorectomy, and drug therapies, as well as advice regarding reproductive health. Similar recommendations about the content of genetic counseling sessions were also outlined in the European Society for Medical Oncology (ESMO) Prevention and Screening 2016 guidelines[4] in Europe and addressed issues of quality of life and the psychosocial impact of risk-reducing interventions.

Recommendations relating to *BRCA* testing

Four North American[3,35,38,40] and nine European[5,21,22,26,29,41–44] guidelines recommended testing for *BRCA* mutations. Table 2 summarizes the main recommendations of the included guidelines.

For individuals with BC, the Netherlands Integraal Kankercentrum Nederland (IKNL) guidelines recommended that urgent DNA testing for a *BRCA1/2* mutation be considered if it influenced the woman's choice for primary cancer treatment with regard to survival consequences.[26] Both the UK London Cancer Alliance (LCA) 2016[29] and the US NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2018[3] guidelines emphasized that genetic testing should be undertaken only after consultation and counseling by a genetics service and further personalized risk assessment. Furthermore, the NCCN[3] guideline also stressed that genetic testing should only be considered for high-risk individuals if it would affect the medical management of the tested individual and/or the individual's at-risk family members. On the other hand, the UK National Institute for Health and Care Excellence (NICE) CG164 (CG14 and CG41 updates) 2017[5] guideline made recommendations regarding *BRCA* testing in general, but recommended that the use of fast-track genetic testing within 4 weeks of BC diagnosis should only be offered as part of a clinical trial. Both the US NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2018[3] and the NICE CG164 (CG14 and CG41 updates) 2017[5] guidelines also specified certain procedures for undertaking genetic testing (full sequencing, testing in individuals who had received an allogeneic bone transplant, and the use of searchable electronic databases).

Few guidelines provided recommendations on the specific type of *BRCA* test, and guidelines usually avoided mentioning any brand by name. However, the UK NICE guidelines[5] recommended that "a search/screen for a mutation in a gene (such as *BRCA1*, *BRCA2*, or *TP53*) should aim for as close to 100% sensitivity as possible for detecting coding alterations and the whole gene(s) should be searched." The US NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2018[3] guideline emphasized the need for "comprehensive genetic testing", which included full *BRCA1/2* sequencing and testing for large genomic rearrangements. The European School of Oncology (ESO)–ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3) 2017[21] recommended that a multigene panel test be used and that practice should be guided by high-quality national or international guidelines, as commercially available multigene panels include different panels of genes.

Nine guidelines, three from North America[3,35,38] and six from Europe[5,26,29,41,42,44] made specific recommendations about genetic screening for *BRCA* mutation in men. All guidelines agreed that in unaffected individuals, the presence of male BC in the family warranted further risk assessment, genetic counseling, and possibly genetic testing. With respect to *BRCA* testing in other groups, there were no recommendations specifically relating to the black/African population, although women eligible for single-agent therapy for recurrent or metastatic HER2-negative BC were eligible for g*BRCA1/2* testing according to NCCN Breast Cancer, Version 4.2017.[40] The NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2018 also recommended *BRCA* testing where "*BRCA1/2* pathogenic mutation was detected by tumor profiling on any tumor type in the absence of germline mutation analysis."[4]

Recommendations relating to BC screening

Twenty-one guidelines made recommendations regarding BC screening in individuals at high risk of BC based on family history or a known *BRCA1/2* mutation. One of these was from Asia,[20] six were from North America,[3,17,24,25,30,37] and 13 were from Europe.[4,5,21,23,26,29,34,41–43,45–47]

Many guidelines recommended a multimodal screening approach. Six guidelines recommended a combination of annual MRI and annual mammography for women with familial risk or *BRCA* mutation and a history of BC.[3,5,29,34,37,47]

The ESMO Prevention and Screening 2016[4] guidelines stated that g*BRCA* patients should be encouraged to

Table 2 Summary of guideline recommendations relating to screening and genetic testing for *BRCA* mutations

Population	Family constellations	Action
Women with no breast cancer	**General family constellations, risk level 1:** • One first-degree female relative diagnosed with breast cancer aged ≤35 years,[35,41] <40 years,[5,26] or ≤45 years (first or second degree)[3] • One first-degree or close male relative diagnosed with breast cancer at any age[3,5,26] • Bilateral breast cancer where the first primary was diagnosed at age <50 years[35,41] in a first-degree relative;[5,26] two or more breast cancer primaries in a single relative[3,26] • Two first-degree relatives or one first-degree and one second-degree relative, diagnosed with breast cancer at any age;[5] two or more first-degree relatives with bilateral breast cancer plus another breast cancer at age <50 years[42] • Two or more individuals with breast cancer primaries (on the same side of the family) with at least one diagnosed at age ≤50 years[3,26,41,42] • One first- or second-degree relative diagnosed with breast cancer at any age and one first- or second-degree relative diagnosed with ovarian cancer at any age (one of these should be a first-degree relative)[5,41] • Three or more cases of breast and/or ovarian cancer[42] (in two or more generations), at least one diagnosed at age <50 years[35] • Three first- or second-degree relatives diagnosed with breast cancer at any age,[5,41] at least one at age <50 years[26] • Breast cancer at age <50 years and prostate cancer at age <60 years in the same branch of family[26] • Primary breast and primary ovarian cancer in the same individual (maternal or paternal),[35,41,42] in a first-degree relative[26] • Family history of (especially if diagnosed at age ≤50 years and can include multiple cancers in the same individual) breast cancer, pancreatic cancer, prostate cancer (Gleason score ≥7 or metastatic), melanoma, sarcoma (especially at age <45 years), adrenocortical carcinoma (especially in childhood), brain tumors, leukemia, diffuse gastric cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of the gastrointestinal tract,[3] glioma, or complicated patterns of multiple cancers at a young age[5]	• Referral to secondary care[5] • Further personalized risk assessment[3] • Referral to potential genetic counseling[3,26,35] and testing[42] • Genetic testing should only be considered in unaffected individuals if an appropriate affected family member is not available for testing[3] • Genetic testing should be considered in high-risk individuals if it will affect the medical management of the tested individual and/or their at-risk family members[3] • Genetic testing of family[41] • Seek advice from designated secondary care contact (if criteria for referral to secondary care are not clearly met)[5]
	Family constellations, risk level 2: • Families (maternal or paternal) with hormone receptor-negative and HER2-negative (aka, triple-negative) breast cancer[5,35] • Families (maternal or paternal) with breast or ovarian cancer[35] or personal history of pancreatic cancer[3] in a family with Ashkenazi Jewish heritage • Families (maternal or paternal) with male breast cancer[5,38,42] diagnosed at age ≤65 years[35] • Families with at least one man affected by breast cancer and one additional relative affected by breast or ovarian cancer (in one side of the family)[41] • Known *BRCA1/2* mutation in the family[3,5,35,38] • Personal history of ovarian carcinoma[3] or high-grade epithelial ovarian, tubal, or peritoneal cancer[38,42,44] • Close relative with breast cancer meeting one of the criteria for screening[38]	• Referral to specialist medical genetics services for potential genetic testing[3,5,35,38,42,44] • Further personalized risk assessment[3] • Genetic counseling[3] • Genetic testing of family[41]
Individuals (men and women) with no breast cancer	• Personal history of pancreatic cancer at any age with one or more close blood relative with ovarian carcinoma at any age or breast cancer at age ≤50 years, or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7 or metastatic) at any age,[3,38] or ovarian, tubal, or peritoneal cancer[38] • *BRCA1/2* pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis[3]	• Referral to specialist medical genetics services for potential genetic testing[3,35,38] • Further personalized risk assessment[3] • Genetic counseling[3]

(*Continued*)

Table 2 (*Continued*)

Population	Family constellations	Action
Women with breast cancer	**General family constellations, risk level 1:** • One first-degree relative with breast cancer diagnosed at age <40 years[5,29] or ≤50 years[3] • Two or three close relatives with breast cancer at any age (at least one of these a first-degree relative)[29] • Four close relatives with breast cancer at any age (at least one of these a second-degree relative)[29] • Two or more close blood relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7 or metastatic) at any age[3,38] • One or more close blood relative with ovarian carcinoma[3] or close relative with epithelial ovarian, tubal, or peritoneal cancer[38]	• Referral to secondary care (family history clinics)[5,29] • Further personalized risk assessment[3] • Genetic counseling[3] • Possibly genetic testing and management[3,38] • Seek advice from designated secondary care contact (if criteria for referral to secondary care are not clearly met)[5]
	Breast cancer characteristics: • Recurrent or metastatic HER2 breast cancer[40] • TNBC[44] diagnosed at age <40 years,[29] ≤50 years,[3,29,42] or ≤60 years[38] • TNBC if impact on management is anticipated[41] • Diagnosed at age ≤45 years[3,38,44] or ≤40 years[5,26,42] • Diagnosed at age ≤50 years with an additional breast cancer primary;[3,38] bilateral or multiple tumors in one breast with first tumor diagnosed at age <50 years[26] or ≤40 years[42] or both tumors diagnosed at age ≤60 years[44] • Bilateral breast cancer and a relative with breast cancer[5] diagnosed at age <60 years[29] • Synchronous or metachronous breast and ovarian cancer[29,42] • Diagnosed at age ≤50 years and prostate cancer at age <60 years in the same branch of the family[26] • Diagnosed at age ≤50 years with one or more close blood relative with breast cancer at any age;[3] diagnosed at age <50 years and one or more first-degree relative with breast cancer at age <50 years;[26] diagnosed at age <45 years and relative with breast cancer at age <45 years[29] • Diagnosed at age ≤50 years with one or more close relative with pancreatic cancer (Gleason score ≥7 or metastatic)[3] • Diagnosed at age ≤50 years with an unknown or limited family history[3] **Family constellations, risk level 2:** • Known *BRCA1* or *BRCA2* mutation in the family[3,29] • One first-degree relative with breast cancer diagnosed <30 years[29]/≤45 years[44] • First-degree relative with TNBC[44] • Two close relatives with breast cancer with average age at diagnosis <50 years[26,38] (at least one of these a first-degree relative)[5,29] • Three close relatives with breast cancer with an average age at diagnosis <60 years (at least one of these a first-degree relative)[29] or at any age[5] • Four close relatives with breast cancer at any age (at least one of these a first-degree relative)[29] • At least one first-degree relative with bilateral breast cancer,[29] first diagnosed at age <50 years,[5] or both diagnosed at age <60 years[44] • First-degree relative with epithelial ovarian cancer[44] or relative with ovarian cancer[5] • At least one first-degree or close relative with breast cancer or with male breast cancer[3,5,26,29,44] • At least one first-degree relative with breast cancer, with ovarian cancer,[26,29] or of Jewish ancestry[29]	• Referral to tertiary care (clinical genetics services)[29] • Referral to specialist medical genetics services for potential genetic testing[3,3,5,26,35,38,40–42,44] • Further personalized risk assessment[3] • Genetic counseling[3]

	• One first- or second-degree relative diagnosed with breast cancer at any age and one first- or second-degree relative diagnosed with ovarian cancer at any age (one of these should be a first-degree relative)[5] • At least one first-degree relative with breast cancer and Jewish ancestry[29] • Ashkenazi Jewish descent[3,38] or Jewish ancestry[5] • Family members with breast cancer and sarcoma diagnosed at age <45 years; brain, adrenocortical, or any childhood cancer; or multiple other tumor types at a young age[5,29]	
Men with no breast cancer	• Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with one or more close blood relative with ovarian carcinoma at any age or breast cancer at age ≤50 years or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7 or metastatic) at any age[3] • Personal history of metastatic prostate cancer (radiographic evidence or biopsy-proven disease)[3]	• Further personalized risk assessment[3] • Genetic counseling[3] • Possibly genetic testing and management[3]
Men with breast cancer	• Personal history of male breast cancer[3,26,44]	• Further personalized risk assessment[3] • Genetic counseling[3,26] • Possibly genetic testing and management[3,44]
	Family constellations, risk level 2: • Diagnosed with breast cancer and has relative with ovarian cancer or male breast cancer[29] • Diagnosed with breast cancer and has relatives with breast cancer and a Manchester score ≥15[29]	• *BRCA* mutation testing[29]

Abbreviation: TNBC, triple-negative breast cancer.

participate in high-risk follow-up clinics. The UK Institute of Cancer Research (ICR) Protocol 3 2015[46] emphasized that women with a *BRCA* mutation may be eligible for surveillance in research studies. The Dutch IKNL 2012[26] guideline cautioned against the elevated risk of radiation-induced tumors with mammography in young women with a *BRCA* mutation. The UK NICE (CG14 and CG41 updates) 2017[5] guideline recommended that women with a *BRCA* mutation deciding against risk-reducing mastectomy should be surveyed according to their level of risk.

Three guidelines[3,4,42] indicated that men with a *BRCA* mutation should undergo annual breast examination starting at age 35 years. However, the ESMO Prevention and Screening 2016[4] guideline commented that there was no evidence to support routine breast imaging in men. The UK ICR Protocol 3 2015[46] guideline and the German Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) 2017[41] guideline stated that no specific surveillance for men with *BRCA* mutation is recommended, other than "watchful waiting".

There were no breast screening recommendations specifically relating to black/African populations, Ashkenazi Jews, or patients with HR-positive/HER2-negative disease and TNBC.

Recommendations for the treatment of *BRCA* BC

Eight guidelines made recommendations for the treatment of individuals with *BRCA* mutation or those with a strong familial risk of developing BC. These included two pan-European guidelines,[21,22] two from Germany,[23,41] two from the USA,[40,48] one from Australia,[19] and one from Spain.[42] A summary of guideline recommendations for treatment is shown in Table 3.

None of the guidelines reported treatment pathway algorithms specific to the treatment of patients with *BRCA* BC or those with a strong familial BC risk. Two guidelines made general treatment recommendations, and each stated that indications for treatment should not be influenced by *BRCA* status (Cancer Australia 2014;[19] Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften [AWMF] Registry 2012).[23]

Three guidelines suggested platinum therapy as an option for treatment, specifically as a neoadjuvant therapy (AWMF Registry 2012),[23] especially for metastatic *BRCA*-mutated BC (Sociedad Española de Oncología Médica 2015),[42] and in young women (age <40 years) with *BRCA*-mutated BC (ESO-ESMO BCY3 2017).[21] The ESO-ESMO ABC3 2017[22] guideline stated that "carboplatin is an important treatment option with a favorable toxicity profile regardless of *BRCA*

Table 3 Guideline recommendations relating to the treatment of breast cancer in patients with *BRCA* mutation

Name of guideline/ organization	Country	Target population	Recommendation statement	Recommendation grade/ evidence level
Australasia (1 guideline)				
Cancer Australia 2014[19]	Australia	*BRCA*-mutated patients Women only	When mastectomy is offered, give women the opportunity to consider breast reconstruction either at the time of the initial surgery or as a delayed procedure	Recommended/use Expert opinion/consensus
			Base the use of neoadjuvant or adjuvant chemotherapy for women diagnosed with breast cancer with a *BRCA1/2* mutation on similar considerations for women with breast cancer not attributable to a *BRCA1/2* mutation	Recommended/use Grade C
			Base the type of neoadjuvant or adjuvant chemotherapy for women diagnosed with breast cancer with a *BRCA1/2* mutation on similar considerations for women with breast cancer not attributable to a *BRCA1/2* mutation	Recommended/use Grade C
			Base the use and type of selective estrogen receptor modulators in women diagnosed with estrogen receptor-positive breast cancer with a *BRCA1/2* mutation on similar considerations for women with breast cancer not attributable to a *BRCA1/2* mutation	Recommended/use Grade C
			Adjuvant endocrine therapy (which may include premenopausal oophorectomy/ovarian suppression) should be used when appropriate based on hormone receptor status to reduce the risk of ipsilateral and contralateral events	Recommended/use Expert opinion/consensus
		BRCA-mutated patients Women only Also for women diagnosed with breast cancer with a strong family history of breast and/or ovarian cancer and no identified *BRCA1/2* mutation	Surgical management, with or without radiotherapy, on the ipsilateral side for women diagnosed with breast cancer with a *BRCA1/2* mutation	Recommended/use Grade C
			Offer a choice of either breast-conserving treatment (breast-conserving surgery and radiotherapy) or mastectomy to women diagnosed with breast cancer with a *BRCA1/2* mutation as both are effective in terms of survival	Recommended/use Grade C
			Surgical management, with or without radiotherapy, on the ipsilateral side for women diagnosed with breast cancer with a *BRCA1/2* mutation; recommend radiotherapy after breast-conserving surgery in women diagnosed with breast cancer with a *BRCA1/2* mutation to decrease the risk of ipsilateral breast cancer (as similarly recommended to other women with breast cancer that is not attributable to a *BRCA1/2* mutation)	Recommended/use Grade C
		BRCA-mutated patients Women only Women with breast cancer and a germline *TP53* mutation	Avoid radiotherapy when possible in women with breast cancer and a germline *TP53* mutation due to possible increased second malignancy risk and other adverse effects. Mastectomy is preferable to breast conserving surgery in these women; however, offer radiotherapy if a woman chooses breast-conserving surgery or if it is indicated after mastectomy	Expert opinion/consensus
North America (2 guidelines)				
ASTRO 2017[48]	USA	*BRCA*-mutated patients All patients	Unsuitable for accelerated partial breast irradiation outside a clinical trial	Not recommended/do not use Expert opinion/consensus
NCCN Breast, Version 4.2017[40,a]	USA	*BRCA*-mutated patients HER2-negative Women only	Olaparib (PARP inhibitor) option for HER2-negative/*BRCA1/2*-positive tumors	May use/option for use NCCN category 2A

Europe (5 guidelines)				
ESO-ESMO ABC3 2017[22]	Europe	Advanced/metastatic breast cancer (*BRCA* mutated) TNBC advanced breast cancer patients	In advanced TNBC patients (regardless of *BRCA* status), previously treated with anthracyclines with or without taxanes in the neoadjuvant or adjuvant setting, carboplatin demonstrated comparable efficacy to and a more favorable toxicity profile than docetaxel and is therefore an important treatment option	Recommended/use Grade IA
			In patients with *BRCA*-associated TNBC or endocrine-resistant metastatic breast cancer previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a platinum regimen is the preferred option if not previously administered and no suitable clinical trial is available	Recommended/use Grade IA
ESO-ESMO BCY3 2017[21,a]	Europe	Advanced/metastatic breast cancer (*BRCA* mutated) Women aged <40 years	Indications of adjuvant radiation therapy are independent of *BRCA* status	Recommended/use Expert opinion/consensus
			A platinum agent should be considered in the treatment of *BRCA*-associated advanced breast cancer	Recommended/use Grade IB
		Advanced/metastatic breast cancer (g*BRCA* mutated) Women aged <40 years diagnosed with advanced breast cancer	For the time being, the type of systemic treatment of early breast cancer is independent of *BRCA* or any other constitutional genetic status	Recommended/use Expert opinion/consensus
			Olaparib monotherapy may be considered in women with advanced breast cancer harboring a g*BRCA* mutation in early lines of therapy	May use/option for use Grade IB
		Newly diagnosed breast cancer (*BRCA* mutated) Women aged <40 years	For the time being, the radiotherapy treatment of early breast cancer is independent of *BRCA* or any other constitutional genetic status, with the exception of germline *TP53* and *ATM* mutations, for which a very high risk of secondary cancers has been described after radiation therapy. Radiation therapy should be carefully discussed on an individual basis for these patients	Recommended/use Grade IB
		BRCA-mutated patients Women aged <40 years TNBC	The BCY3 panel endorses the ABC3 statement that in advanced TNBC patients (regardless of *BRCA* status), previously treated with anthracyclines with or without taxanes in the neoadjuvant or adjuvant and/or metastatic setting, carboplatin demonstrated comparable efficacy to and a more favorable toxicity profile than docetaxel, and is therefore an important treatment option	Recommended/use Grade IIB
			In patients with TNBC or *BRCA*-associated tumors, the incorporation of platinum agents increases pathological complete response (pCR) rates and may be considered when neoadjuvant chemotherapy is indicated. Data on the impact of incremental increases in pCR on long-term outcome are not conclusive. The use of platinum derivatives has potential additional impact on fertility and increased toxicity that may compromise standard duration and dosing of systemic treatment, and this needs to be clearly communicated to patients	May use/option for use Grade IIA
		BRCA-mutated patients Women aged <40 years	With respect to loco-regional treatment after neoadjuvant therapy, mutation status should be part of the individual decision-making algorithm. Sufficient time to discuss the different options and adequate psychological support should be offered given the potential long-term sequela and implications	Recommended/use Expert opinion/consensus
AGO 2017[41]	Germany	Advanced/metastatic breast cancer (*BRCA* mutated)	Individuals with *BRCA1/2*-associated breast cancer should receive systemic therapy according to sporadic breast cancer treatment	Recommended/use Grade B
		BRCA-mutated patients with breast cancer	PARP inhibitors are recommended for use in *BRCA* (*BRCA1/2*)-associated breast cancer	Recommended/use Grade D

(*Continued*)

Table 3 (*Continued*)

Name of guideline/ organization	Country	Target population	Recommendation statement	Recommendation grade/ evidence level
AWMF Registry 2012[23]	Germany	*BRCA*-mutated patients with breast cancer	The treatment of *BRCA*-associated carcinoma of the breast is based on the guideline recommendations for sporadic carcinoma of the breast	Recommended/use Expert opinion/consensus
			Therapy of *BRCA*-associated breast cancer: there are indications that platinum-containing chemotherapy may lead to better response to treatment than standard chemotherapy	May use/option for use Expert opinion/consensus
SEOM 2015[42]	Spain	*BRCA*-mutated patients	In patients with *BRCA* mutation, platinum salts might be considered in neoadjuvant setting	May use/option for use Grade IC
			In patients with *BRCA* mutation, platinum salts might be considered in the metastatic setting	May use/option for use Grade IA

Notes: [a]New updated versions of these guidelines have been published since this review was carried out. Important changes in the new updated versions are summarized in the Discussion section.
Abbreviations: ABC3, 3rd International consensus guidelines for advanced breast cancer; AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; ASTRO, American Society for Radiation Oncology; AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; BCY3, 3rd international consensus guidelines for breast cancer in young women; ESMO, European Society for Medical Oncology; ESO, European School of Oncology; g*BRCA*, germline *BRCA*; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica; TNBC, triple-negative breast cancer.

status, specifically for TNBC patients with ABC who had been previously treated with anthracyclines with or without taxanes in the neoadjuvant or adjuvant and/or metastatic setting".[22] The UK LCA 2016[29] guideline suggested that women with *BRCA1/2* mutations should be informed about the possibility of taking part in clinical trials, eg, on the therapeutic effects of PARP inhibitors in women with *BRCA* mutations and breast or ovarian cancer. Two guidelines suggested the use of olaparib as a treatment option for *BRCA*-mutated HER2-negative BC (NCCN Breast Cancer Evidence Blocks, version 4.2017)[40] and for women with g*BRCA* (age <40 years) diagnosed with ABC (ESO-ESMO BCY3 2017).[21] The AGO 2017 guidelines also recommended the use of PARP inhibitors in *BRCA* mutation (*BRCA1/2*) BC.[41]

No recommendations were made specifically about the treatment of *BRCA*-mutated BC in men, blacks/Africans, Ashkenazi Jews, and patients with HR-positive/HER2-negative BC. With respect to therapy, the European ESO-ESMO BCY3 2017[21] guidelines recommended (based on expert opinion or consensus) that the therapeutic implications of somatic *BRCA1/2* mutations in breast tumors of women aged <40 years be further explored within a research setting and not be currently applied for decision-making in routine clinical practice.

Discussion

To the best of our knowledge, this is the first systematic review to summarize international guidelines and recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of *BRCA*-mutated BC. By adhering to a rigorous systematic review methodology and focusing on guidelines published in the last 10-year period (1 January 2007 up to 16 February 2018), the quality, differences, and similarities across international guidelines regarding the management of *BRCA*-mutated BC were evaluated. Across guidelines reporting recommendations on *BRCA1/2* mutation testing and genetic counseling, there was an emphasis on the importance of genetic counseling both before and after testing in order for patients to make informed decisions about their care. Genetic counseling was identified as important prior to BC risk-reduction procedures. This is further supported by recent research suggesting a need for more innovative approaches to integrate genetic counseling into clinical practice in the modern era of increased use of multigene panel testing.[49] Genetic counseling and genetic test results should also be incorporated into management of BC patients when making decisions about the type of surgery, consideration of radiotherapy, and the value of systemic therapy in neoadju-

vant and advanced settings (including response to platinum-based chemotherapy and PARP inhibitors).[50–52]

The results of this study are limited by the inclusion dates of the systematic review. Since we carried out this review, updated guidelines have become available from the US NCCN (NCCN Breast Cancer, Version 1.2018[31] and NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2, 2019),[53] AGO (AGO 2018),[54] and ESMO (ABC4).[55] The NCCN guidelines have further broadened their recommendations regarding genetic screening criteria for *BRCA* mutation. The recommendation within the NCCN Breast Cancer Evidence Blocks, Version 4.2017,[40] that patients with "HER2-BC eligible for single-agent therapy are eligible for *BRCA1/2* testing", as identified in our review, has been strengthened in the updated NCCN Breast Cancer, Version 1.2018,[31] to recommend that *BRCA1/2* testing should be "strongly considered". The recently updated NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2019[53] recommends that "regardless of family history, some individuals with a *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment", including PARP inhibitors for metastatic HER2-BC.[53] The guidelines also state that tumor-only profiling may detect *BRCA* mutation of somatic or germline origin and that although "germline origin can sometimes be inferred with a high degree of confidence (eg, founder pathogenic/likely pathogenic variants in *BRCA1/2*), confirmatory testing is indicated for pathogenic/likely pathogenic variants with a reasonable clinical suspicion of being germline".[53] However, the guidelines emphasize that "clinically indicated germline testing is still appropriate for patients meeting testing guidelines regardless of tumor profiling results", as "the absence of reported pathogenic/likely pathogenic variants in a particular gene does not rule out the possibility of germline pathogenic/likely pathogenic variant in that gene".[53] The ESMO ABC4 guidelines state that "in the ABC setting, results from genetic testing may have therapeutic implications and should therefore be considered as early as possible" and "germline mutations in *BRCA1/2* have proven clinical utility and therapeutic impact".[55] A recent review by Tung et al also discussed the future potential utility regarding the identification of somatic or germline *BRCA* mutation in informing the optimal management of BC.[50]

Another key area of interest in the majority of guidelines in our review was the identification of appropriate individuals to undergo *BRCA1/2* mutation testing. The guidelines, regardless of geography, were in agreement that genetic testing for *BRCA* mutations should be discussed with patients and offered to those who want to undergo testing. The identification of individuals was based on familial background and personal BC (and other cancer) history. We found some differences regarding types of individuals, but there was consensus about those with key indicators, such as Ashkenazi Jewish heritage and familial/personal histories of cancer, including male BC and TNBC.

Although all guidelines advised targeting specific individuals for *BRCA* testing, recent research supports growing evidence for the expansion of *BRCA* testing to a broader range of individuals, if not to the general population.[56] Research has indicated that using the traditional familial and risk-based approach may miss a significant number of individuals with a *BRCA* mutation.[57–59] In addition, the multiple criteria and complexity of major guidelines, including those from the NCCN and the American Society of Clinical Oncology, make them difficult to use and implement systematically in real-world clinical practice. Multiple published international studies have shown that consequently, fewer patients have been offered genetic counseling and/or *BRCA* testing, even while fulfilling their respective country-specific guideline criteria.[60–62]

A recent cost-effectiveness analysis[63] of population-based mutation screening for *BRCA1/2* and other known high/moderate penetrance genes (*RAD51C*, *RAD51D*, *BRIP1*, and *PALB2*) in unselected populations of US and UK women concluded that population-based high/moderate penetrance gene (including *BRCA1/2*) testing is more cost-effective than any system of identifying individuals through clinical criteria or familial history. Compared with clinical criteria and familial history-based *BRCA1/2* testing in a decision-analytic model, population-based testing also led to increases in the number of BC cases prevented (1.86% in UK women and 1.91% in US women) and BC deaths prevented (523 per million women in the UK and 367 per million women in the USA). Other earlier research in a population of healthy Australian women[64] similarly suggested that a general population-based screening program rather than a targeted high-risk approach may be favorable.

The type of *BRCA* test will affect not only how accurate the findings are, but also how cost-effective a screening program is likely to be. A recent worldwide survey of testing laboratories found wide variations in the types of technologies used for *BRCA1/2* testing.[65] Other researchers have identified that multi-gene sequencing approaches are preferable to *BRCA1/2*-only testing for patients with BC.[66] Only three included guidelines offered recommendations on which type of *BRCA* testing to use, indicating the test should have as close to 100% sensitivity as possible and needs to

search the whole gene, including testing for large genomic rearrangements and coding alterations.[3,5,21] The ESO-ESMO BCY3 guidelines stated that "when a hereditary cancer syndrome is suspected and a mutation in *BRCA1/2* has not been identified, multigene panel testing may be considered".[21] In addition, the updated ESO-ESMO ABC4 2018[55] guidelines stated that "multigene panels, such as those obtained using next-generation sequencing (NGS) or other technology on tumor DNA have not yet proven beneficial in clinical trials for ABC, their impact on outcome remains undefined and should not be used in routine clinical practice". The ESO-ESMO ABC4 2018 guidelines[55] further indicate that for patients who are suitable to participate in clinical trials, NGS testing may be used in the context of prospective molecular triage programs for patient selection. Specific tests (as distinguished from broad mutation profiles) may play a greater role in the future as the medicines with which they are associated gain regulatory approval. Researchers have also investigated which, if any, *BRCA* genetic testing programs are ready for implementation in health care settings. A systematic review[67] assessed economic evaluations and found that cost-effectiveness was highly sensitive to the cost of *BRCA1/2* testing. As our understanding develops on how to improve screening, increased accuracy and lower pricing of tests may make screening the wider population of otherwise healthy women more cost-effective.

It should be noted that the guidelines identified in our review provided limited recommendations on the treatment options available for *BRCA* ABC, and no treatment algorithms or pathways were reported. Several guidelines suggested potential benefits from platinum therapy,[21,23,42] and the recent US NCCN Breast Cancer, Version 4.2017 guidelines also recommended the recently approved PARP inhibitor olaparib as an option for the treatment of HER2-negative, *BRCA1/2*-mutated tumors.[40] The AGO 2017 guidelines in Germany also recommended the use of PARP inhibitors for the treatment of *BRCA*-mutation associated BC.[41] The updated AGO 2018 guidelines[54] recommend the use of olaparib in patients with HER2-g*BRCA* mutation, including those who are estrogen receptor-positive and those with TNBC. The ESMO ABC4 guidelines[55] also now highlight the use of PARP inhibitors (including olaparib and talazoparib) as a "reasonable treatment option for patients with *BRCA*-associated TNBC or luminal (after progression on endocrine therapy) ABC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting)"; "the tolerability of these agents when given as monotherapy, the chemotherapy-free approach with improved quality of life makes it an attractive options for *BRCA*-related ABC".[55] Given the arrival of this new group of g*BRCA*-targeting drugs, it seems likely that all future guidelines will need to consider this as a treatment option.

With the differences in the care of patients compounded by the evolution of international guidelines across genetic screening, diagnosis, genetic counseling, and treatment of *BRCA*-mutated BC, there is a growing need to establish a translational research infrastructure[68] that aims to integrate evidence-based guidelines into clinical care while assessing the validity and utility on health outcomes among BC patients. While greater consensus and guideline harmonization across geographies would optimize the identification and management of BC patients with *BRCA* mutation, other potential barriers should also be considered. Targeted continuing medical education will be vital in improving the communication, knowledge, awareness, and guideline-concordance among clinicians and public health professionals regarding population-based *BRCA* screening.[11–13] To improve patients' experience and utility of genetic information,[69] further understanding of the potential barriers regarding patients' acceptance of *BRCA* testing, perceived undefined changes in quality of life, and unknown clinical utility is warranted.

Evidence gaps identified by the review

Given issues highlighted in this review regarding the methodologies used to develop guidelines, there is a need for future guidelines to follow recognized methodologies and use tools developed by the Grading of Recommendations Assessment, Development and Evaluation[70] working group to clearly assess and describe the strength of any recommendations. In addition, guideline reporting should adhere to the recommendations of the Reporting Tool for Practice Guidelines in Health Care (RIGHT) statement[71] and the AGREE Reporting Checklist, a tool to improve the reporting of clinical practice guidelines.[16]

In addition, the guidelines included in our review identified a number of areas where evidence was poor and/or lacking and where further research is required. Recent UK guidelines (NICE [CG14 and CG41 update] 2017)[5] highlighted that further investigations are required into the benefits and harms of creating rapid access to genetic testing for people with newly diagnosed BC, including optimum models for service delivery and organization, clinical and cost-effectiveness of such a change, uptake outcomes, and patient experience within different geographies and settings.[5] NICE also suggested research is required into which members of a multidisciplinary team should or could discuss fast-track

testing with patients and that this should form part of a trial of fast-track genetic testing in patients with familial risk and newly diagnosed BC. Additionally, among those women who are identified as *BRCA* mutation carriers, further research should compare psychosocial and clinical outcomes in women who choose or do not choose to have risk-reduction surgery.[5] ESO-ESMO BYC3 guidelines highlighted that the therapeutic implications of somatic *BRCA1/2* mutations in breast tumors in women aged <40 years should be further explored within a research setting before they can be used in routine clinical practice.[21] This is also reinforced in the ABC setting within the new ESMO ABC4 guidelines.[55] Our review also showed that there were limited recommendations (and in some cases conflicting advice across geographies) relating specifically to the care of men with g*BRCA* mutations, suggesting that this also requires further investigation and consensus.

Conclusion

This systematic review reports a broad, comprehensive summary of the latest international guideline recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of *BRCA*-mutated BC. Recent recommendations within treatment guidelines for g*BRCA* ABC highlight the promise of platinum-based chemotherapies and PARP inhibitors. Identifying individuals who carry *BRCA* mutations is therefore becoming increasingly important. Although a number of guidelines across various countries focus on identifying such high-risk individuals, the most recent guidelines adopt broader criteria regardless of family history. This supports the growing evidence within the literature suggesting that clinical criteria/family history criteria may miss individuals with *BRCA* mutations, with some indicating that *BRCA* testing should be expanded to the broader population. In order to ensure that patients are able to make a fully informed decision to undergo genetic *BRCA* testing, the guidelines also stress the importance of providing genetic counseling before and after *BRCA* testing.

Future clinical guidelines and recommendations should follow methodological guidance for their development and adhere to specific reporting tools. Current gaps within the evidence suggest that recommendations are required specifically relating to genetic screening, counseling, and treatment of black/African populations at high risk of *BRCA* mutations. In addition, greater consensus and harmonization across geographies would optimize identification and management of patients with *BRCA*-mutated BC.

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