Review

Clinical practice guidelines for *BRCA1 and BRCA2* genetic testing☆

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Abstract   BRCA1 and BRCA2 gene pathogenic variants account for most hereditary breast cancer and are increasingly used to determine eligibility for PARP inhibitor (PARPi) therapy of BRCA-related cancer. Because issues of BRCA testing in clinical practice now overlap with both preventive and therapeutic management, updated and comprehensive practice guidelines for BRCA genotyping are needed.

The integrative recommendations for BRCA testing presented here aim to (1) identify individuals who may benefit from genetic counselling and risk-reducing strategies; (2) update germline and tumour-testing indications for PARPi-approved therapies; (3) provide testing recommendations for personalised management of early and metastatic breast cancer; and (4) address the issues of rapid process and tumour analysis.

An international group of experts, including geneticists, medical and surgical oncologists, pathologists, ethicists and patient representatives, was commissioned by the French Society of Predictive and Personalised Medicine (SFMPP). The group followed a methodology based on specific formal guidelines development, including (1) evaluating the likelihood of BRCAm from a combined systematic review of the literature, risk assessment models and expert quotations, and (2) therapeutic values of BRCAm status for PARPi therapy in BRCA-related cancer and for management of early and advanced breast cancer.

These international guidelines may help clinicians comprehensively update and standardise BRCA testing practices.

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1. Introduction

BRCA1 and BRCA2 genes (BRCA) analysis is increasingly being used to detect pathogenic variants for both preventive and therapeutic issues. Several guidelines on BRCA testing are available worldwide, but recent therapeutic advances in breast cancer management and approved therapies with poly(ADP)ribose polymerase inhibitor (PARPi) agents in breast, ovarian, prostate and pancreatic cancers, as well as the specific rapid germline and tumour testing process, deserve a comprehensive and integrative update to optimise BRCA testing in clinical practice.

BRCA pathogenic or likely pathogenic variants (mutations, BRCAm) account for most identifiable hereditary breast and ovarian cancer (HBOC) syndromes. For women who carry a BRCAm, the cumulative risk for developing breast or ovarian cancer by age 70 years is 45%−66% and 11%−41%, respectively [1,2]. Validation of screening and preventive strategies in BRCAm

carriers and increased awareness of their benefit by population and healthcare providers has led to a continuous increase in BRCA testing over the last two decades [3–5]. Thus, we need to update and prioritise the main indications for BRCA testing for breast and ovarian cancer risk assessment based on a rational analysis of the likelihood of BRCAm (lBRCAm).

The major benefit of PARPi therapy for newly diagnosed ovarian cancer combined with improved progression-free survival in advanced ovarian, breast, prostate and pancreatic cancers [6,7] has prompted the development of BRCAm detection for targeted therapies. In some situations, such as ovarian cancer or prostate cancer, detecting somatic mutations has been effective for identifying PARPi-sensitive patients [8]. In breast and pancreatic cancer, only germline mutations can drive an approved PARPi treatment to date. Thus, germline BRCA (gBRCA) and tumour BRCA (tBRCA) mutational analyses are being used for selecting patients who could benefit from a PARPi. In addition, in newly diagnosed breast cancer and metastatic breast cancer, BRCAm status can also lead to a major change in management such as personalised surgery or chemotherapy regimen. These clinical decisions based on BRCAm status need to be performed quickly, guided by tumour type and disease stage. Thus, we need specific guidelines that take into account the clinical applications of BRCAm analysis, as well as tumour and fast-track testing processes.

More than 30 guidelines on BRCA testing are available worldwide [7,9,10]. In the United States, the US National Comprehensive Cancer Network [11], the American Society of Clinical Oncology [6,12] and the US Preventive Services Task Force [13] have published policy statements for genetic testing for BRCA-related cancer. Sixteen different guidelines exist in Europe [7,9,10]. However, most guidelines do not represent international consensus, differ from each other in the lBRCAm threshold retained (10% [14,15] or 5% [11]) and may not integrate the recent need for BRCA genotyping for PARPi treatment and personalised breast cancer management.

Integrated and updated guidelines would optimise and harmonise healthcare offerings of the BRCA testing and the identification of BRCAm carriers for both preventive and therapeutic purposes. Thus, we developed BRCA testing guidelines at an international level with a specific methodology of evaluating the lBRCAm for a given set of criteria. The methodology was based on a combined approach of literature review, expert evaluation and risk model assessment, taking into account newly developed PARPi agents, as well as personalised management of breast cancer.

2. Methods

2.1. Guideline development and composition of the working group

These guidelines were commissioned by the French Society of Predictive and Personalised Medicine (SFMPP) from September 2019 to June 2020, and a guideline chair was selected (supplementary data). The SFMPP is an independent non-profit learned society with public funding that aims to provide guidelines for genetic testing [16–18]. A Guideline Development Group (GDG) was selected to ensure a wide range of expertise across all relevant disciplines in different countries. Members of the GDG completed a Declaration of Conflict of Interests (CoIs) form (supplementary data), which was reviewed and vetted by the SFMPP. A scoping meeting was held on 5 October 2019 to develop key priorities and validate the methodology described below. Key questions to cover included What are the current indications for BRCA testing in clinical practice? What is the place for BRCA tumour testing and a fast-track process for personalised treatment of BRCA-related cancer? The specific guidelines process is described in supplementary data and based on published data on lBRCAm and their respective levels of evidence, evaluation of lBRCAm by risk model assessment and expert estimation, and the therapeutic value of BRCAm for managing breast cancer and treating BRCA-related cancer with PARPi agents.

The GDG consisted of a group of 48 multidisciplinary experts from Belgium, England, France, Germany, Italy, Israel, Scotland, Spain, and Switzerland, who were divided into two working subgroups: preventive and therapeutic (supplementary data). The preventive subgroup included medical geneticists and genetic counsellors, organ specialists, oncologists, surgeons, patient representatives, ethicist experts, psychologists and lawyers. The group also included a methodologist with expertise in evidence appraisal and guideline development. This group provided guidelines and ethical reflection for updating BRCA testing for preventive purposes. The therapeutic subgroup included medical, radiation and surgical oncologists; organ specialists; clinicians and molecular geneticists; pathologists; and patient representatives and provided an independent evaluation of the indication for a PARPi and personalised management of breast cancer.

Experts from the preventive and therapeutic subgroups were invited to evaluate the level of evidence and to estimate by quotation the lBRCAm independently, as described below (Tables 1a, 1b and 1c). Eight teleconference/webinar meetings were organised to develop this formal consensus and achieve expert agreement. Fourteen additional international experts (listed in

supplementary data) reviewed and proofread recommendations. The overall guideline-development process, including the funding of the work, panel formation, management of CoIs, internal and external review and organisational approval, was guided by procedures derived from the Guidelines International Network–McMaster Guideline Development Checklist [19] and was intended to meet recommendations by the Guidelines International Network [20].

2.2. Parameters evaluated

The lBRCAm for a given criterion was based on a combined approach of literature review, expert quotation and risk model assessment as defined below. The process of development of the guidelines is presented in supplementary data. Current clinical criteria for genetic testing were obtained from existing guidelines (for review, see Refs. [7,9,10]). Criteria were divided into four categories: (1) personal, (2) family or personal and family combined, and (3) theragnostic and (4) personalised management of breast cancer. Whenever possible, a given criterion was evaluated by subcategories (i.e., age at diagnosis: <35, <40, <45, <50 years, any age), and respective data on lBRCAm were collected from the literature. A theragnostic indication was defined as an approved use of PARPi in BRCA-related cancer by continental drug agencies in the United States (US Food and Drug Administration [FDA]) and Europe (European Medicines Agency [EMA]).

2.3. Literature selection process

The search strategy is given in supplementary data. The PubMed database was searched for English language studies published in English from January 1995 to May 2020 by using the following query of terms related to BRCA clinical testing: ((gene, BRCA 1[MeSH]) OR (gene, BRCA 2[MeSH]) OR (BRCA 1 gene[MeSH]) OR (BRCA 2[MeSH]) OR (BRCA1 2[MeSH]) OR (breast cancer 1 gene[Tw]) OR (breast cancer 2 gene[tw]) OR (BRCA1/2[MeSH])) AND ((genetic testing[MeSH]) OR (genetic counselling[MeSH]) OR (genetic risk[MeSH]) OR (breast cancer[MeSH]) OR (ovarian cancer[MeSH]) OR (prostate cancer[MeSH]) OR (pancreatic cancer

[MeSH]) OR (melanoma[MeSH]) OR (cholangiocarcinoma[MeSH]) OR (familial risk[Tw]) OR (prevalence[MeSH]) OR (unselected[Tw]) OR (general population[Tw]) OR (early onset[Tw]) OR (triple negative breast cancer[Tw]) OR (bilateral breast cancer[Tw]) OR (male breast cancer[Tw]) OR (founder effect[Tw]) OR (parp inhibitor[Tw]) OR (poly-adp-ribose polymerase inhibitor[Tw]) OR (polyadenosine diphosphate-ribose polymerase inhibitor[Tw]) OR (platinum sensitive[Tw]) OR (breast cancer management[Tw]) OR (rapid testing[Tw]) OR (fast testing[Tw]) OR (fast track process[Tw]) OR (tumour testing[Tw]) OR (somatic testing[Tw])) AND (English[Language]) AND ('1995/01/01'[Date - Publication]: '2020/06/20'[Date - Publication]) NOT (case reports[Publication Type]) NOT (case reports[Tiab]) NOT (mice[Tw]).

The literature search used variations and Boolean connectors of key terms. Results of database searches were supplemented with bibliographies of seminal articles or reviews and contributions from expert panel members. For guidelines, the websites of associations, colleges and learned societies listing various recommendations were also searched.

A total of 4725 results were found. From these, 603 records were retrieved, including 277 publications retained for estimating lBRCAm and 32 publications or electronic links to guidelines (Supplementary data).

Table 1a
Likelihood of BRCA1 or BRCA2 mutation.

Class	lBRCAm
A	≥10%
B	≥7.5 to <10%
C	≥5 to <7.5%
D	≥2.5 to <5%
E	<2.5%

lBRCAm, likelihood of *BRCA1 or BRCA2* pathogenic or likely pathogenic variant.

Table 1b
Level of evidence.

Level	Definition	Commentary
I	Concordant data on the lBRCAm available in level 1 publication	Level 1 publication: prospective or large retrospective studies, cohort studies with control, pooled studies
II	Data available in level 2 publication or discordant data in the literature	Level 2 publication: cohort study with non-contemporaneous control, case–control series, subgroup analysis
III	Data available in level 3 publication	Level 3 publication: case series without control, small series, series with selection bias
IV	No data available in the literature	Only model assessment of risk available

Table 1c
Grade of recommendations.

Grade	Definition	Recommendation
A	High lBRCAm (≥7.5%, supported by LOE I/II) and/or therapeutic value	Recommended
B	Moderate lBRCAm (2.5–7.5%) and no therapeutic value	Considered
C	Low lBRCAm (<2.5%) and no therapeutic value	Not routinely proposed

LOE, level of evidence.

2.4. Criteria of evaluation

Criteria for BRCA testing were obtained from existing guidelines and divided into three categories: personal criteria, family or personal and family combined criteria and therapeutic criteria. For each retained criterion, the reported lBRCAm was searched in the literature (as an independent variable or from subgroup analysis). Classes a-e were considered and corresponded to lBRCAm ≥10%, ≥7.5 to <10%, ≥5 to <7.5%, ≥2.5 to <5%, and <2.5%, respectively (Table 1a). The working group defined the level of evidence (LOE) as I, concordant data on the lBRCAm available in level 1 publications; II, data on the lBRCAm available in level 2 publications or discordant data in the literature; III, data on the lBRCAm available in level 3 publications; or IV, no data available, risk model assessments of lBRCAm (Table 1b). The level of publication was defined as 1, prospective or large retrospective studies, cohort studies with control, pooled studies; 2, cohort study with non-contemporaneous control, case–control series, subgroup analysis; or 3, case series without control, small series, series with selection bias (Table 1b).

2.5. Model estimation of lBRCAm and expert quotation

The estimation of the lBRCAm was based ideally on existing literature taking into account the level of publication defined above. In some situations, data from the literature were available from studies, including a small number of cases with possible selection bias. Subgroup analysis and model assessment of lBRCAm provided an additional estimation of the lBRCAm. In this study, we used the risk models BRCAPRO [21,22], BOADICEA [23,24], and PennII [25], and their updated versions to estimate the lBRCAm. The estimations were computed with the same fictional pedigree, representative of an average family, described and previously published [3] (also see supplementary data for 'standard' pedigree). Data are available in supplementary data.

Experts were invited to estimate the grade of lBRCAm (A-C; see below) in their field of expertise in light of data from the literature by using the a-e classification of the lBRCAm and risk model estimations. The lBRCAm for each criterion was assigned a quotation by at least three independent experts. Experts were also invited to determine the LOE and evaluate the level of publication. Discrepancies in the evaluation were discussed with the steering committee.

2.6. Theragnostic value, treatment personalisation

For PARPi, the criteria for recommendations were (1) approval by the EMA and/or FDA and (2) temporary authorisation for use in European countries and breakthrough therapy designation by the FDA. Recommendations for addressing metastatic cancer (platinum-containing regimen, PARPi, BRCA testing) were based on guidelines from the ABC global alliance in Europe (ABC4 [26], ABC5 [27]) and US ASCO guidelines [12].

2.7. Grading recommendations

Guidelines were divided into three grades: grade A, for patients for whom testing should be offered, given a high lBRCAm (≥7.5% with LOE I or II and/or established therapeutic value); grade B, for patients for whom testing should be considered, given a moderate lBRCAm (2.5–7.5%); and grade C, for patients for whom testing should not be routinely offered, given a low lBRCAm (<2.5%) (Table 1c).

In this work, the cutoff for a high lBRCAm was set at 7.5%, whereas some guidelines used a threshold of 10% (ASCO [6], NICE [15]) and others 5% (NCCN [11]). With a cutoff of 10%, most of the family criteria would not be considered at high risk (see results section) and most of the criteria analysed to give a lBRCAm of 5%–10%, so the GDG retained the intermediate cutoff of 7.5%. In some subgroups, although the lBRCAm could be above this cutoff, a grade B recommendation was attributed when the LOE was III or IV or when only one study was available.

3. Results

3.1. Single or personal criteria related to breast cancer

Personal criteria related to breast cancer, including age at disease onset, triple-negative breast cancer (TNBC) phenotype, bilaterality, male breast cancer and founder effect, have been extensively studied, and the lBRCAm are given by subgroups (Table 2a). Only three criteria featured a lBRCAm ≥7.5% with both LOE I and expert quotation of grade A: age ≤40, TNBC ≤60 and male breast cancer. The criterion 'bilateral breast cancer with first cancer at age ≤50' was also associated with lBRCAm ≥7.5%, with LOE II and expert quotation grade A. Risk model estimation is in supplementary data (Table S7a).

Age at breast cancer onset <45 or <50 years was associated with a wide range of lBRCAm depending on the study (from 1.6% to 12.2% and 4% to 12.4%, respectively). The LOE for these criteria was II and expert quotation grade B.

In women from populations with a small spectrum of founder mutation, with a founder effect (e.g., Ashkenazi, Icelandic, Polish and French-Canadian), the lBRCAm in the literature varied widely when breast cancer was diagnosed at any age. In women with Ashkenazi or Icelandic heritage, the lBRCAm was 4.5%–11.7% and 7.7%–10.3%, respectively. However, most of these studies did not reach LOE I, and the effect

of family history or age in women undergoing a genetic test could not be ruled out. lBRCAm was significantly higher when comparing subgroups of early-onset and male breast cancer with other populations (Ashkenazi heritage, 19.5%−43% and 6.4%−19.1% for early-onset and male breast cancer, respectively; Icelandic heritage, 7.7%−10.3% and 40%, respectively). For Ashkenazi women, breast cancer at age ≤50 years was associated with a lBRCAm of 8.7%−18.7% with LOE II and expert quotation grade A.

3.2. Family and combined criteria

For family and combined criteria, most available data on lBRCAm were noted in the subgroup analysis of cohort and retrospective studies. In many situations, owing to the complexity and a high number of combinations of criteria, data are lacking. The LOE was III or IV for most family or combined criteria, except for 'the number of cases of breast cancer in ≥2 relatives', with LOE II (Table 3a). Risk model estimation is in supplementary data. In several situations, models could not discriminate the specific lBRCAm with combined criteria. In women with breast cancer and a relative with grade A personal criteria (such as early-onset, male breast cancer and ovarian cancer), prediction of lBRCAm by models and expert opinion favoured a grade A recommendation for the first-degree relative and grade B recommendation for second- or third-degree relatives. For any family or combined criteria, Ashkenazi or Icelandic heritage should be taken into account because studies found an increased risk with this heritage. The lBRCAm in women with breast cancer

and a relative with prostate or pancreatic cancer varied widely by study and model, with LOE III-IV and expert estimate grade B.

3.3. Treatment personalisation of breast cancer

For women with a recent diagnosis of primary breast cancer and those with metastatic breast cancer, the knowledge of BRCA mutation status could significantly influence the medical or surgical decision-making. Table 4 summarises the situations in which rapid testing could have meaningful clinical application.

For women with primary breast cancer and high lBRCAm, the knowledge of the mutation status may be critical in the surgical options offered, specifically when the patient is a candidate for total mastectomy (uni- or bilateral) because of increased risk of a second ipsi- and/or contralateral cancer. Women with putative hereditary risk, particularly in the context of a strong family history, TNBC, young age at disease onset, or known BRCA mutation in a relative and willing to consider preventive surgery, should receive complete information delivered by a surgeon, oncologist and genetics counsellor to guide their autonomous choice. Prognostic factors of breast cancer, age, comorbidities and psychological aspects should be taken into account, as stated in currently available guidelines (NCCN [11], French Institut National du Cancer 2017 [12,28]). The working group recommended proposing the test in a rapid turnaround time after information on the benefit and risk of prophylactic surgery is given by a multidisciplinary team, including a surgeon, geneticist and medical oncologist if the patient actively opts for this

Table 2a
lBRCAm according to individual criteria related to breast cancer.

Criteria	lBRCAm[*] (%)	References	Guidelines	LOE	Quotation[*]
Age					
≤35	**6−20**	1,2,3,4,5,6,7,8,9,10,11,12	13,14,15,16,17,18	I	A
≤40	**3.8−23**	5,19,20,21,22,23,24,25,26,27,28,29,30	31,32,33,16,33,34,35	I	A
≤45	**1.6−12.2**	5,23,36,37,38,39,40	41,42,43	II	B
≤50	**4−12.4**	26,27,44,45,46,47,48	41,49,50,51	II	B
≤55	**2**	5		III	C
>50	**1.2**	52,53,54		III	C
Any age	**0.4−7.5**	55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,27,54,71,36,72,73,74,75,76,48	None	II	C
TNBC					
≤40	**23−36**	77,20,78	31,18	I	A
≤50	**7.6−27.6**	79,80,81,77,82	83,16	I	A
≤60	**11.4−16.8**	80,78	42,41,84,49,15,14,50	II	A
>60	**4.9−5.7**	80,85,78,86		II	B
Any age	**2.9−17.5**	36,87,78,82,88	43	II	B
Bilateral					
1st ≤ 40	**26.7−33.3**	25,89,90,24	16	II	A
1st ≤ 50	**9−22.7**	91,6,92	32,41,31,33,14,15	II	A
1st ≤ 60	**15.3 (<55)**	93	43,49	III	C
Any age	**6.6−34**	6,94,20,95,25,96,97,98,89,90	33,99,31,50	III	C
Male	**7.4−33**	100,101,102,103,104,105,106,107,108,109,110,111	41,32,43,99,112,31,50,18,14	I	A

* lBRCAm, likelihood to detect BRCA pathogenic of likely pathogenic variant; LOE, level of evidence; TNBC, triple-negative breast cancer.

Table 2b
lBRCAm according to founder effects.

Criteria	lBRCAm* (%)	References	Guidelines	LOE	Quotation
Ashkenazi heritage					
No cancer	**1.1—2.9**	1,2,3,4,5,6,7,8,9,10,11,12		I	C
Unselected breast cancer	**4.5—25**	13,14,15,16,17,18,19,20,21,22,23	24,25,26,27,28,29,30,31,32,33	I	B
Early onset ≤40	**19.5—43.3**	14,15,17,18,21,34,35,36		I	A
≤50	**8.7—18.7**	14,37	38	I	A
Male BC	**6.4—19.1**	37,39,40,41		I	A
Ovarian cancer	**35.7—62**	18,42,43		II	A
Icelandic heritage					
No cancer	**0.4—0.6**	44,45		II	C
Unselected BC	**7.7—10.4**	44,45,46,47,48	29	II	B
Male BC	**38—40**	46,47,49		II	A
Polish heritage					
No cancer	**0.25—0.4**	50,51		III	C
Unselected BC	**3.1**	51		III	B
BC age > 50	**8.3**	50		III	B
BC age < 50	**6—13**	52,50		III	B
TNBC	**9.9**	53		III	B
Unselected ovarian cancer	**6.3—21**	54,55,56,57,58,59		II	A
French-Canadian heritage					
No cancer	**0.2**	60,61		II	C
Unselected BC	**3.1—3.8**	60,63		II	B
BC age < 40	**13**	64		II	A
BC age < 45	**9.3**	60		III	B
BC age < 50	**4.7—5.1**	61,62		II	B
BC and FH	**45**	65		II	A
Unselected OC	**7.7—8**	66,67,68		II	A
Hungarian heritage		69,70			
BC	**3.6**			III	B
BC and FH	**18**			III	B
OC	**11**			II	A
Mexican heritage		71,72			
TNBC < 50	**23**			III	B
BC and FH	**6**			III	B

* lBRCAm, likelihood to detect BRCA pathogenic of likely pathogenic variant; LOE, level of evidence; BC, breast cancer; FH, family history; OC, ovarian cancer.

analysis. For patients with newly diagnosed breast cancer and high lBRCAm, breast conservative surgery is also an option [12]. Thus, conservative surgery and uni- or bilateral risk-reducing mastectomy should be discussed and balanced in discussion with the patient, considering the increased risk of a second cancer (ipsi- or contralateral), the physical and psychological burden of surgery and taking into account prognostic factors, age and comorbidities with respect to the autonomous choice of the patient.

For women with breast cancer at low risk of recurrence, such as age at onset >40 years and N0, T1/T2, hormone-receptor—positive (HR+), and human epidermal growth factor receptor—negative (HER2-) tumours, radiation therapy could be omitted when the patient opts for mastectomy rather than conservative surgery for preventive action. In contrast, a risk-reducing mastectomy that follows conservative surgery plus radiation therapy may negatively affect the cosmetic results and increase surgery complications.

In the metastatic setting, for patients with HER2 negative tumours requiring chemotherapy, gBRCA testing is recommended because a platinum treatment should be preferred to taxane in platinum-naive patients [12,26,27,29]. In the neoadjuvant setting, because available studies are not conclusive, the use of a platinum-containing regimen is not routinely recommended outside clinical trials (Table 4).

3.4. Theragnostic value for PARPi

The use of PARPi and the lBRCAm in breast, ovarian, prostate and pancreatic cancer are summarised in Tables 5 and 6. In ovarian cancer, the benefits of various PARPi therapies (olaparib, niraparib rucaparib, and veliparib) on progression-free survival in phase III randomised trials are highly significant and approved by the EMA and FDA (Table 5). In the absence of gBRCAm, BRCAm should be screened in any non-mucinous high-grade epithelial ovarian carcinoma at the germline and tumour level because PARPi has been found efficacious in exclusive tumour mutation, and thus, approved by drug agencies (for review, see Ref. [7]). Personal or family criteria could not

Table 3a
PBRCA in according to family and combined criteria.

Family/combined£ criteria	lBRCAm literature (%)	lBRCAm models*(%)	References	Existing guidelines	LOE	Quotation
1 case of BC with 2 cases of BC in a CR**				1,2,3,4,5,6,7,8,9,10	II	A
Any CR	3.8−10.6		11,12,13,14			
1st/1st	13	0.2−10.5	12		III	A
1st/2nd	6	0.1−7	12		III	B
2nd/2nd	4	<0.1−6	12		III	B
1 case of BC and 1 of BC in CR with one age ≤ 50	4−22		11,12,13,15,16,17,18	2,19,20,21,22,6	II	A
1st		0.2−3.8				
2nd		<0.1−3.8				
1 case of BC and bilateral BC in a CR	12.8−21 (age <50)		11,13	19 (first age <50),20,23 (both age <60)	III	A
1st		5−8				
2nd		1.1				
1 case of BC and a CR with ovarian cancer	4.3−55		11,12,13,14,15,16,18	21,20,9,23,19,24,22,2,3,25,5,6,26	II	A
1st		0.4−8				
2nd		<0.1−4.				
1 case of BC and a CR with one male BC	16.5		11	2,19,24,20,23,22,9,6,27,28	II	A
1st		1.2−14				
2nd		0.3−7				
1 case of BC and a CR with prostate cancer	13.6−19	0.1−7	29	24 (prostate age <60 and BC age <50), 2,3 (Gleason score ≥7), 4,5 (prostate age <55)	III	B
1 case of BC and a CR with pancreatic cancer	19.7−37.5	0.1−12	30,31,32,33,34	3,4, (BC age <50), 2	III	B
1 case of BC and an FDR with individual grade A criteria and no possibility for testing ***		theoretically >50% of lBRCAm of FDR			II	A
Asymptomatic person with individual grade A criteria in an FDR		theoretically 50% of lBRCAm of FDR			II	B

£ Combined, personal and family criteria; LOE, level of evidence; CR, close relative, first-degree or second-degree relative; FDR, first-degree relative; 1st/1st: two first-degree relatives; * BOADICEA, BRCAPRO, PENN II (see Table 5 bis//supplementary data); ** in the paternal or maternal side; *** death or other reason.

discriminate against women with BRCAm because up to 40% of women carrying a BRCA1 or BRCA2 mutation do not present a discernible family history or meet NCCN [11] or other testing criteria (Table 6).

For women with metastatic breast cancer, olaparib and talazoparib improved both progression-free survival and quality of life as compared with chemotherapy in two phase III randomised trials ([30,31]). Overall survival was not significantly improved in these studies [32,33]. Screening for BRCAm in the metastatic setting is recommended for any TNBC or hormone-resistant breast cancer because personal or family criteria predicting mutation are lacking in 20%−70% of patients (Table 6). In the neoadjuvant setting, PARPi agents are under investigation (ClinicalTrials.gov: NCT03499353) and are not currently recommended outside of the clinical research field.

In metastatic prostate cancer, the PARPi agents, olaparib, rucaparib, niraparib and talazoparib, were found to be effective in phase II or III trials (Table 5). Because almost 50% of BRCA cases occur in patients who do not present family criteria for testing, BRCA testing should be proposed to any person with metastatic castrate-resistant prostate cancer (Table 6). A fast track process should be proposed to patients with castration-resistant prostate cancer who have already received taxane and abiraterone or enzalutamide because a PARPi, in this case, provides a superior response as compared with other agents, given the results of clinical trials (Table 5, [34]). BRCA tumour genotyping could be proposed as a first approach if coupled with complete information on family and preventive consequences of a germline finding.

In metastatic pancreatic cancer, BRCA testing should be offered to all patients with platinum-sensitive cancer given the results of the POLO study, in which olaparib improved progression-free survival and quality of life of patients with advanced pancreatic cancer, with no disease progression at 16 weeks after platinum initiation [35,36]. Given the rapid evolution of pancreatic cancer, BRCA testing may be proposed as soon as the diagnosis is given. Family criteria could not be used to select patients for BRCA genotyping because 10%−60% of germline mutation carriers with pancreatic cancer do not fit the NCCN criteria (Table 6). Further studies are needed to evaluate whether molecular profiling at the

Table 4

Rapid BRCA testing for treatment personalisation of primary or metastatic breast cancer.

Treatment personalisation	Option	Treatment phase	Criteria for rapid testing	Personalisation	References
Putative impact on surgery for women considering preventive surgery	mastectomy versus conservative surgery	prior surgery neoadjuvant chemotherapy	age <40 TNBC high lBRCAm newly diagnosed cancer in a family with a known mutation	breast conservative surgery or radical preventive surgery (ipsilateral or bilateral). Both acceptable options.	[1] [2] [3,4,5,6,7,8]
Putative impact on radiation therapy for women considering preventive surgery	no radiation therapy versus radiation therapy	after ipsilateral or bilateral mastectomy	high lBRCAm with age >35, T1/T2, N0, HR+ and HER2-	• no PMRT if age >40, HR + Her 2-grade I/II, no LVI, pT1 pN0 • PMRT required if age <35, or pN + T3/T4 HER2+ M+ • PMRT multidisciplinary discussion if intermediate risk	[9] [2]
Putative impact on chemotherapy	platinum	neoadjuvant	no evidence of benefit	no recommendations	[2] [5] [6]
	platinum versus taxane	metastatic in platinum-naive patient	TNBC or hormone resistant	platinum-containing regimen	[10] [11,6]
Putative impact on targeted therapy	PARPi PARPi	neoadjuvant metastatic	no evidence of benefit TNBC or hormone resistant	ongoing trial olaparib, talazoparib	[12] [13,6,14,2,5]

PMRT, post-mastectomy radiation therapy; PARPi, poly(ADP)ribose polymerase inhibitor; HR+, hormone receptor-positive; TNBC, triple-negative breast cancer.

Table 5
Rapid BRCA testing process for PARPi.

Organ	State	Rapid testing	Drug	Germline or tumour BRCAm, HRD	Approval	Study/Reference
Ovary *	Maintenance (after first line)	Platinum sensitive High-grade serous	olaparib	Tumour or germline	FDA, EMA	SOLO1[1] (NCT01844986) PAOLA[2] (NCT02477644)
		Platinum sensitive High-grade serous or endometrioid	olaparib plus bevacizumab	Tumour or germline HRD	FDA, EMA	
		Platinum sensitive High-grade serous or endometrioid	niraparib	All-comers	FDA, EMA	PRIMA[3] (NCT02655016)
	Front line and maintenance	High grade serous or endometrioid	veliparib	Tumour or germline, HRD	FDA UR EMA UR	VELIA[4] (NCT02470585)
	Recurrence	Platinum sensitive High-grade serous or endometrioid	olaparib	Tumour or germline All-comers	FDA, EMA FDA, EMA	[5] (NCT00753545),[6] (NCT00753545), SOLO[7] (NCT01874353), STUDY 19[8] (NCT00753545)
		Platinum sensitive High-grade serous or endometrioid	rucaparib	All-comers	FDA, EMA	ARIEL 3[9,10] (NCT01968213), (NCT01968213)
		Platinum sensitive	niraparib	All-comers	EMA FDA	NOVA[11] (NCT01847274) QUADRA[12] (NCT02354586)
	Recurrence >2 lines	In patients intolerant to platinum	rucaparib	Tumour or germline	EMA UR	ARIEL 2 (NCT01891344)
Prostate	Metastatic	Castration resistant (who received taxane and abiraterone/enzalutamide)	olaparib	Tumour or germline, HRD	FDA EMA	PROfound[13] (NCT02987543)
			rucaparib niraparib talazoparib	Tumour or germline Tumour or germline All-comers	FDA FDA BTD NA	TRITON 2[14] (NCT02952534) GALAHAD[15] (NCT02854436) TALAPRO 1/2[16,17] (NCT03148795), (NCT03395197)
Pancreas	Metastatic Maintenance	Platinum sensitive (with no progression at 16 weeks)	olaparib	Germline	FDA, EMA	POLO[18] (NCT02184195)
Breast	Metastatic or locally advanced	TNBC or HR + HER2-hormone-resistant	olaparib talazoparib	Germline Germline	EMA FDA EMA FDA	OlympiAD[19] (NCT02000622) EMBRACA[20] (NCT01945775)

HRD, homologous recombination deficiency; BTD Breakthrough Therapy Designation; *epithelial non-mucinous non-borderline ovarian cancer, tubal or peritoneal carcinoma. UR, Under review; NA, not available.

Table 6
Likelihood of germline BRCAm in unselected BRCA-related cancer.

Site/Stage	BRCA 1 (%)	BRCA 2 (%)	BRCA 1/2 (%)	References	gBRCAm found although unmet testing criteria* (%)	References
Breast Cancer						
Any disease stage	0.2−4.1	0.8−2.5	1.6−10.7	1,2,3,4,5,6,7,8	20−77	2,9,3,4,5,6,7
Metastatic only	1.1−2.0	1.0−2.9	3.0−4.3	10,11,12	−	−
Prostate Cancer						
Any disease stage	0−1.25	1.1−4.7	1.0−5.9	13,14,15,16	37−64	15,17
Metastatic	0−1.3	4.2−9	4.2−10	13,18,19,20,21,22,23,24,25,26,27,28	44−53	22,23
Pancreatic Cancer						
Any disease stage	0−1.4	1.3−4.2	1.8−7.1	29,30,31,32,33,34,35,36,37,38,39,40	12−57	29,31,33,41,39,40
Metastatic	1.5	1.5	3−7.5	13,42,43,44	−	−
Ovarian Cancer						
Any disease stage	4−13.3	0.6−8	5.8−25.8	8,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59	8−77	48,49,47,46,55,51,56,58

gBRCAm, germline BRCA mutation; *Testing criteria vary according to the publication, NCCN criteria, family criteria, Ontario criteria, etc.; -, No data available.

time of diagnosis, including BRCAm status, would help decide the first-line chemotherapy (e.g., platinum-containing regimen).

3.5. Sequence analysis

BRCA sequence analysis should be performed and reported according to laboratory guidelines such as the American College of Medical Genetics (ACMG) standards ([37] for germline DNA sequencing [38]; for tumour DNA sequencing). For both germline and tumour DNA sequencing and interpretation of results, particular attention should be paid to coverage (at least 100% of exonic sequence and adjacent intronic sequence that may affect the splice site), read depth (at least $30\times$ for germline single nucleotide variant (SNV) DNA sequencing, at least $200\times$ for copy number variant (CNV) DNA sequencing, at least $300\times$ for tumour DNA sequencing), use of the Human Genome Variation Society (HGVS [39]) unambiguous nomenclature for variant designation, and use of well-defined variant classification. For *BRCA1 or BRCA2* germline variants, classification should be based on variant pathogenicity with respect to a hereditary cancer predisposition syndrome, such as the five-category classification of the ACMG: pathogenic, likely pathogenic, uncertain significance, likely benign, or benign [37]. Standardised terminology and definitions for describing and reporting sequence variation have been set out by the recommendations of the ENIGMA consortium (PMID: 30962250 J Med Genet. 2019 Jun; 56(6):347–357. Towards controlled terminology for reporting germline cancer susceptibility variants: an ENIGMA report Amanda B Spurdle 1, Stephanie Greville-Heygate 2, Antonis C Antoniou 3, Melissa Brown 4, Leslie Burke 4, Miguel de la Hoya 5, Susan Domchek 6, Thilo Dörk 7, Helen V Firth 8, Alvaro N Monteiro 9, Arjen Mensenkamp 10, Michael T Parsons 1, Paolo Radice 11, Mark Robson 12, Marc Tischkowitz 13, Emma Tudini 1, Clare Turnbull 14 15, Maaike Pg Vreeswijk 16, Logan C Walker 17, Sean Tavtigian 18 19, Diana M Eccles 2).

For *BRCA1* and BRCA2 somatic variants, classification should focus on their significance in clinical decision-making with respect to the therapeutic issue (i.e., the 4-category classification of the ACMG: strong clinical significance, potential clinical significance, unknown clinical significance and benign or likely benign variants) [38]. Implementation of techniques and pipelines enabling both SNV and CNV detection should be preferred, optimally by next-generation sequencing. Implementation of identity monitoring should be guaranteed. For appropriate interpretation of tumour DNA sequencing results, specific consideration should be given to the cellularity of the tumour sample ($<30\%$ considered as low cellularity and $<10\%$ very low cellularity, increasing false-negative results), variant allele fraction, and variant detection in a normal matched control DNA sample if included.

4. Guidelines bottom line

4.1. Guideline questions

What are the current indications for BRCA testing in clinical practice?

What is the place for BRCA tumour testing and a fast-track process in treatment personalisation of BRCA-related cancer?

4.2. Target population

Individuals with a personal or family risk of a BRCAm (preventive purpose).

4.3. Breast cancer patient

Patient with a diagnosis of BRCA-related cancer sensitive to PARPi agents (ovarian, breast, prostate, pancreas).

4.4. Target audience

The target audience and intended users of these guidelines are health providers involved in BRCA-related cancers, including geneticists, medical and radiation oncologists, surgeons, organ specialists such as gynaecologists, urologists and gastroenterologists, general practitioners and genetic counsellors.

4.5. Guideline aims

Establish clinical guidelines on BRCA testing to (1) identify individuals who may benefit from risk-reducing strategies, (2) update recommendations of testing for

Table 7
Grade A BRCA testing criteria.

Criteria	
Individual (BC)	Age $\leq$ 40
	Age $\leq$ 50: bilateral[£], founder effect[$]
	Age $\leq$ 60 triple negative
	Male
Family history	BC with BC in two FDR*
	BC with any of individual above criteria in a FDR**
	Any relative of a known BRCA mutation carrier
Theragnostic	Epithelial ovarian cancer***
	Metastatic HR and TN BC
	Metastatic HR prostate cancer
	Metastatic platinum-sensitive pancreatic cancer

BC, breast cancer; FDR, first-degree relative; HR, hormone resistant; £bilateral BC with one $\leq$50 years; $ Ashkenazi Jewish or Icelandic heritages; * within maternal or paternal side; ** anytime possible the affected relative would be the most relevant to test first; *** also fulfil individual preventive grade A criteria; non-mucinous, including primary peritoneal and fallopian tube; TN, triple negative.

theragnostic purposes with PARPi agents in BRCA-related cancer, (3) provide recommendations for testing for personalised management of early and metastatic breast cancer, and (4) define the place and role of a tumour testing approach and fast-track genotyping and counselling processes.

4.6. Methods

An expert panel consisting of clinical geneticists; medical, radiation and surgical oncologists; molecular geneticists; pathologists; genetic counsellors; patient representatives; ethicists; psychologists; lawyers; and methodologists developed clinical practice guideline recommendations for BRCA testing. These recommendations are based on a combined approach that included a systematic review of the medical literature, evaluation of the lBRCAm (from publications, evaluation by risk assessment models and expert opinion), the theragnostic value in BRCA-related cancer (based on treatment approval for PARPi agents in specific cancer types) and the impact of BRCAm knowledge on the management of early or advanced breast cancer. The overall guideline development process, including the funding of the work, panel formation, management of conflicts of interest, internal and external review, and organisational approval, was guided by procedures derived from the

Table 8
Grade B BRCA testing criteria.

Criteria
Individual (BC)
• Age 41-45
• TNBC age >60
• Bilateral (first after age 50)
• BC >50 with founder effect*
***Family history* or combined**
• BC with 2 cases of BC in a second- or third-degree relative
• BC with individual grade A criteria (TNBC, age ≤ 40, male, ovarian cancer) in a second- or third-degree relative
• BC and 1 case of BC in first-degree relative with one age ≤ 50
• BC and a bilateral BC in first-degree relative (first after age 50)
• BC and 1 case of prostate cancer (Gleason score ≥ 7, metastatic or age ≤ 60) in an FDR
• BC and 1 case of pancreas cancer in an FDR
• BC with association of 2 cases of prostate (Gleason score ≥ 7, metastatic or age ≤ 60 years), pancreas or melanoma cancer in a CR
• Prostate or pancreatic cancer with AJ or Icelandic heritage
• Family history[a] of pancreatic and/or prostate cancer
• Person with an FDR with one of individual grade A criteria and no possibility for testing[b]

CR, close relative; FDR, first-degree relative; If not specify BC, breast cancer any age. * founder effect: Ashkenazi Jewish or Icelandic heritages.

[a] Association of two or more of these types of cancer in a CR on maternal or paternal side.

[b] Death or other reason.

Guidelines International Network−McMaster Guideline Development Checklist [40].

4.7. Recommendations

1. Preventive
    1.1. For patients presenting a personal or family history of high lBRCAm (grade A, Table 7), *BRCA* testing should be offered after genetics information is provided and discussed with a specialist in genetics.
    1.2. For patients with moderate lBRCAm (grade B, Table 8), testing should be considered taking into account specificities of the family history and personal criteria, and issues should be discussed with the patient in a dedicated and personalised genetic consultation.
    1.3. Independently of the lBRCAm, testing should be performed in a non-directive manner, and the patient's autonomy and desire to know or to ignore the mutational status must be respected. The individual should make an informed decision with a written consent on whether they want to pursue genetic testing at the dedicated consultation.
    1.4. For patients with low lBRCAm (grade C) and for whom the mutational status does not have a proven therapeutic value, BRCA testing is not routinely recommended in clinical practice. However, the working group raised the question of the ethical issue of denying access to a BRCA genetic test for informed individuals with low lBRCAm who wish to be tested, given that up to 50% of breast cancer mutation carriers have low lBRCAm. In this situation, genetic counselling before and after the test is highly recommended. The test should be performed in a qualified laboratory fulfilling quality criteria for testing (see below). This option raises unsolved issues of cost-efficiency, medical benefit and testing reimbursement.
    1.5. Genetic counselling is highly recommended before and after a *BRCA* predictive test for a known familial mutation.
2. Breast cancer treatment personalisation
    2.1. For patients with newly diagnosed breast cancer and meeting criteria of high lBRCAm, germline testing (gBRCA) should be considered when BRCAm status could affect the management of breast cancer (Table 4). For women with heredity-associated increased risk of a second cancer, particularly in the context of a cancer-dense family history, TNBC, young age or a relative with a known BRCAm, who are willing to consider the option of risk-reducing surgery, BRCA testing should be offered as a fast-track process after receiving complete information pertaining to the possible outcome of the test. The information should be given by a multidisciplinary team, including an oncologist, surgeon and genetic counsellor, to foster an autonomous choice and optimise the oncoplastic surgical decision and sequence. Appropriately trained non-geneticists involved in breast cancer such as oncologists and surgeons could give adequate information in coordination with genetic professionals.
    2.2. For metastatic breast cancer patients requiring chemotherapy, gBRCAm testing is recommended

because platinum chemotherapy should be preferred to taxane in platinum-naive patients.

2.3. In HER2-negative metastatic breast cancer, gBRCAm testing is recommended because olaparib or talazoparib should be offered as an alternative to first-to third-line chemotherapy for women with gBRCAm.

3. PARPi

3.1. BRCA testing should be offered for PARPi theragnostic purposes to patients with HER2-negative metastatic breast and castrate-resistant prostate cancer, platinum-sensitive metastatic pancreatic cancer and newly diagnosed FIGO stage III/IV or recurrent high-grade epithelial ovarian cancer in a fast-track process after specific genetic information is provided.

3.2. For targeted therapy with PARPi agents, BRCA testing is recommended regardless of moderate or high lBRCAm criteria because 10%−75% of patients with breast, ovarian, prostate or pancreatic cancer, and gBRCAm do not fulfil these criteria (Table 6).

3.3. Epithelial ovarian cancer fulfils criteria of high lBRCAm for risk-reducing purposes and major theragnostic value. Therefore, gBRCA testing should be offered to any woman with epithelial non-borderline non-mucinous ovarian cancer at the time of diagnosis in a fast-track process. Additional tumour testing should be proposed to ovarian cancer patients who do not carry gBRCAm.

3.4. Appropriately trained non-geneticists involved in cancer care such as oncologists and surgeons could give adequate initial information in coordination with a multidisciplinary team, including geneticists.

4. Tumour testing

4.1. When tumour testing for theragnostic purposes is the preferred initial approach, the patient should be aware of inherited genetic aspects, including family and prevention issues that might emerge from genetic tumour testing, because most tumour BRCAm findings reflect a germline predisposition. Thus, genetic information and informed consent are required before any BRCA tumour testing. In case of therapeutic value, the information should be given by trained healthcare providers such as oncologists familiar with the genetic diagnosis and management of hereditary breast cancer, working in conjunction with a genetic consultation.

4.2. For appropriate interpretation of tumour DNA sequencing results, specific consideration should be given to the cellularity of tumour sample, depth of coverage, ability to detect long-scale rearrangement and variant allele fraction. Techniques and pipelines enabling both SNV and CNV detection such as next-generation sequencing should be preferred

4.3. Germline testing should be offered to any patient with an identified pathogenic or likely pathogenic tumour BRCA mutation.

4.4. Educational programs should be developed to increase the awareness and training of healthcare providers in oncology, particularly oncologists, surgeons, organ specialists and patient advocacy representatives, to improve their skills to provide adequate explanations for BRCA testing for therapeutic purposes and personalised care according to the genetic results.

5. General recommendations

5.1. Clinical decisions, including preventive issues, management of breast cancer or PARPi treatment, should be based on pathogenic or likely pathogenic variants but not variants of unknown significance (VUS).

5.2. BRCA sequence analysis should be performed and reported according to laboratory guidelines. For both germline and tumour DNA sequencing and interpretation of results, particular attention should be paid to sequence coverage (at least 100% of exonic sequence and intronic sequence adjacent to the splice site) and read coverage (at least $30\times$ for SNV and $200\times$ for CNV in germline DNA sequencing, at least $300\times$ for tumour DNA sequencing). Results should use an unambiguous nomenclature for variant designation and classification (HGVS, ACMG).

5.3. For germline or tumour BRCA genetic testing for theragnostic use, the information should be given by a clinician trained and aware of genetics, including the interpretation of results, regulations and risk-reducing strategies. The information given to the patient may include the medical implications of a positive, negative or non-informative result (i.e., VUS); the risk of transmission of genetic predisposition to offspring and family relatives (and according to regulations of certain countries in Europe, the legal obligation to transmit the information to close relatives); and the risk and benefit of risk-reducing strategies and the psychological consequences of knowing a genetic predisposition.

5. Discussion

BRCA1 and BRCA2 gene mutations account for most actionable genetic breast cancer predispositions and are increasingly used for personalised breast cancer management and PARPi therapy of BRCA-related cancer. Thus, we propose updated guidelines for *BRCA* testing. Preventive and therapeutic indications are now overlapping in many situations, as in ovarian cancer or metastatic breast cancer. Thus, BRCA testing should be considered in a global and integrative way so that healthcare providers involved in both cancer care and genetics can clarify and standardise the appropriate process and timing of BRCA testing for all patients. With this aim, we introduce a methodology of recommendations based on expert consensus, integrating published data on lBRCAm and their respective levels of evidence, evaluation of lBRCAm by risk model assessment as well as the therapeutic value of BRCAm for managing BRCA-related cancer.

Of note, epithelial ovarian cancer is the most powerful predictor of lBRCAm. Also, BRCAm in ovarian cancer offers the most actionable context for both preventive and therapeutic purposes. This point still needs to be universally communicated to healthcare providers and to professionals involved in managing ovarian cancer because recent data show a lack of testing in patients with ovarian cancer [41].

Although the burgeoning knowledge of hereditary breast and ovarian cancer (HBOC) and the development

of next-generation sequencing have prompted the use of multigene panels that include *TP53, PALB2, PTEN, CDH1,* and *STK11, BRCA1 and BRCA2* gene mutations account for the vast majority of the actionable and identifiable hereditary syndromes [42−44]. Moreover, many other actionable genes involved in HBOC (i.e. *TP53, PTEN, CDH1* and *STK11*) are often responsible for specific personal and family characteristics that differ from criteria for BRCA testing. Therefore, guidelines for BRCA testing should be clarified independently of other considerations. However, multigene panel genotyping is useful in BRCA-negative familial syndrome. Mutations of *PALB2, RAD51C* and other genes are currently under investigation to detect PARPi sensitivity but are not yet approved in BRCA-related cancer. The human recombination deficiency (HRD) that included tBRCAm and gBRCAm is approved as a predictive marker of PARPi sensitivity in ovarian cancer and studied with different approaches in other BRCA-related cancer. Further recommendations are needed for clinicians on HRD used as a predictive marker of PARPi sensitivity. Here, we focused on specific criteria that drive a clinical, non-systematic and personalised recommendation of BRCA testing for any individual with a family history or affected by BRCA-related cancer.

From abundant literature, personal parameters related to breast cancer, such as TNBC, male breast cancer, early-onset breast cancer, or bilateral breast cancer, have been identified as predictors of a high probability of harbouring *BRCA1 or BRCA2* mutations. The founder effect is another parameter that significantly increases the lBRCAm. For women with breast cancer who are of Ashkenazi or Icelandic heritage, the lBRCAm varies widely according to the study and population (from 4.5% to 25%; Table 2b). When considering subgroups of early-onset, TNBC and male breast cancer in individuals of Ashkenazi or Icelandic ethnicity, the lBRCAm is increased to more than 10%. Ashkenazi or Icelandic heritage in other situations received a grade B recommendation for testing outside these subgroups, except for Ashkenazi Jewish and Icelandic women with breast cancer diagnosed before age 50 years. Ashkenazi or Icelandic heritage in a woman with any grade B personal or family criteria should be considered for testing because this factor significantly increases the lBRCAm.

Most combined and family criteria proposed in guidelines are based on clinical studies with a low level of evidence. For most of these criteria, only subgroup analyses of studies were available, and for some, no data were available in our search. Moreover, most published data are devoted to the selection bias of women referred for genetic counselling and undergoing *BRCA* testing. In situations of combined criteria for which clinical data are lacking, a risk assessment model could provide a helpful estimate of the lBRCAm. However, as reported previously, the estimation varies widely among models [45] and may not be appropriate to discriminate some situations such as triple-negative phenotype, discrimination of risk according to relative closeness, ability to score single criteria, integrating prostate or pancreas cancer affecting relatives, etc. Because family or combined situations could not be exhaustively addressed by a literature search and/or estimates by models, lBRCAm >2.5% was assumed for some items such as 'BC with ≥2 prostate, pancreatic or melanoma cancer cases in close relatives' or 'family history of pancreatic cancer and/or prostate cancer (≥2 cancer cases in first-, second- or third-degree relatives)'. With the complexity and a high number of combinations of parameters, the evaluation of lBRCAm in each situation should be addressed and discussed in a dedicated genetic and personalised consultation.

Because of the clinical benefits of PARPi in BRCA-related cancer, the lack of timely identification of a BRCAm represents a lost opportunity for patients. Between 30% and 50% of patients with ovarian cancer or metastatic prostate, pancreatic or breast cancer do not fulfil personal or family criteria for preventive BRCA testing; thus, family history or personal criteria for testing cannot be retained to select patients who require testing. Of note, the incidence of BRCAm in metastatic prostate, pancreatic and breast cancer are in the range of grade B recommendations for testing for preventive purposes (2.5%−7.5%).

In these guidelines, when the lBRCAm is estimated at <2.5% and the mutational status does not have therapeutic value, BRCA testing is not routinely recommended in clinical practice (expert agreement). The benefit of genetic testing is not established in women whose personal or family history suggest low risk for mutations in *BRCA1 and BRCA2* genes, and the US Preventive Services Task Force found adequate evidence that this benefit is small to none (ref Task Force). However, in the study by Buchanan *et al.*, some women with *BRCA1 or BRCA2* mutation found in the UK genome projects without any personal/family criteria of testing benefitted from screening [46]. Other studies suggest that screening may be beneficial in the general population or in women with breast cancer, particularly in populations with a high rate of predominant mutations [47,48]. The cost-effectiveness of BRCA testing is also debated in the low-risk or general population [49,50]. Further studies are required to state the medical benefit and cost-effectiveness of offering BRCA testing in populations with low lBRCAm and refining this cut-off. Overall, 20%−77% of BRCAm carriers in breast cancer do not fulfil testing criteria (Table 6), so strictly limiting access to genetic testing to people with high or moderate risk criteria and denying access to those with low risk who wish to be tested is questionable. The access of a person willing to undergo the test after genetic counselling and being given appropriate

information about the benefits and risks of testing raises a host of unanswered questions in terms of ethics, regulation and economics. The Royal Marsden/ICR proposed that individuals not meeting any of the eligibility criteria could have a self-funded test. Other healthcare payers may be involved. The issue of testing low-risk individuals should be addressed in a personalised way according to the regional health regulations, funding and insurance policies. For testing low-risk patients, the working group recommended dedicated genetic consultation before and after the test, with complete information (including psychological impact, risk-reducing strategy and familial consequences of the test). Attention should be paid to the quality of the analysis, as described in our guidelines.

Genetic counselling by a genetics professional genetics is recommended before and after a genetic test for an inherited breast/ovarian cancer syndrome related to BRCA and performed for preventive purposes. For theragnostic purposes, the information should be given by a clinician (physician or surgeon) who is trained, aware of genetics regulation, comfortable with interpreting results of a genetic test, and able to give appropriate information on risk-reducing strategies. The information should include the medical implications of a positive, negative or non-informative result (e.g., VUS); the risk of transmission of the genetic predisposition allele to an offspring and other family members (and according to regulations of certain countries in Europe, the juridical obligation to transmit the information to close relatives), the risk and benefit of risk-reducing strategies, and the psychological consequence of knowing the precise risk of genetic predisposition-associated cancer. Increasing numbers of surgeons and oncologists are becoming aware of these issues, and recent publications such as the ENGAGE results show that an oncologist-led *BRCA*m testing process in ovarian cancer is feasible [51].

If tumour testing for theragnostic purposes is preferred as the initial approach, the patient should be aware of the same family and prevention issues because most of the tumour mutation findings will be related to a germline predisposition [8,17]. Therefore, informed consent and genetic information are still required before any *BRCA* tumour testing, and patients should be aware that the results may have extra-therapeutic medical issues for themselves and their relatives. We and others previously reported clinical practice considerations and schemes for managing germline findings in somatic analysis, including written informed consent and a multidisciplinary approach involving an oncologist, molecular biologist/pathologist and geneticist for germline findings [8,16,17]. At any time of the somatic analysis, a patient may have access to a consultation with a geneticist if additional information is required. These recommendations should be regularly updated according to the knowledge evolution about cancer risk, target therapies with PARPi agents or other agents, and the level of evidence.

These integrative and updated guidelines may help clinicians standardise and optimise *BRCA* testing practices for both preventive and therapeutic purposes.

Conflicts of interest

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.12.023.

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