

## Review

# Genetic counselling and testing for inherited gene mutations in newly diagnosed patients with breast cancer: a review of the existing literature and a proposed research agenda

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## Abstract

Many women newly diagnosed with breast cancer and with a strong family history of breast cancer are referred to a family cancer service for genetic counselling and for consideration of genetic testing for germline mutations in cancer predisposition genes following completion of their cancer treatment. However, there is growing evidence that mutation status may influence treatment recommendations, and that there may be benefits in having 'treatment-focused genetic counselling and testing' available shortly after cancer diagnosis. This article reviews the literature that could inform the development of treatment-focused genetic counselling and testing, including: the rationale for genetic testing to aid with treatment decisions; the potential benefits of using mutation or risk status to tailor management; the criteria that may be used to identify patients most likely to carry germline mutations; and the evidence regarding women's decision-making regarding treatment-focused genetic counselling and testing and the associated psychological impact.

It is generally recommended that women with breast cancer and a family history that includes multiple cases of breast and/or ovarian cancer across several generations should be referred to a family cancer service for genetic counselling and consideration of genetic testing for germline mutations in breast cancer predisposition genes [1,2]. (The majority of germline mutations will be in the *BRCA* genes, although a small proportion of families may also be eligible for *TP53* germline mutation screening in relation to Li Fraumeni Syndrome or *PTEN* screening if Cowden's syndrome is suspected. However, our review will focus on mutation

screening of the *BRCA* genes due to the rarity of the other syndromes and the paucity of associated evidence in terms of the implications for breast cancer management.) Most women with breast cancer and a relevant family history are referred following completion of surgery and adjuvant chemotherapy and/or radiotherapy. The resulting genetic information may provide the basis for advice regarding their personal future risk management and for risk clarification for their unaffected blood relatives [1,2]. Currently, there is usually little urgency for genetic counselling and testing as the outcomes have generally not altered or directly influenced the initial cancer management in an individual patient [3].

However, there is growing evidence that knowledge of *BRCA* mutation status or a high likelihood of a hereditary cancer syndrome may influence specific treatment recommendations [4-6]. At this time, the major contribution of a confirmed *BRCA* mutation status is to the decision between selection of a breast conserving approach or a therapeutic mastectomy with or without a contralateral risk-reducing mastectomy. In the future it may also direct the selection of adjuvant chemotherapy if agents targeted to *BRCA* mutation status, such as the poly (ADP-ribose) polymerase (PARP) inhibitors, prove effective in clinical trials. Targeted genetic counselling and testing is now increasingly being offered and used for surgical management decisions because of the very good survival from early breast cancer [7] and the technical advances in genetic testing, which mean genetic test results

ER = oestrogen receptor; PARP = poly (ADP-ribose) polymerase; RRSO = risk-reducing prophylactic salpingo-oophorectomy.

can be available within a few weeks. As the survival from early breast cancer continues to improve, the importance of considering the risk of developing a new primary breast cancer increases and may impact on the surgical management of the current cancer. Consequently, it seems likely that more women will be offered genetic counselling and testing for inherited *BRCA* mutations shortly after diagnosis and the results used to determine appropriate cancer therapy [3], primarily as it relates to the prevention of future cancer risks. Hereafter, genetic counselling and testing offered shortly after diagnosis while treatment options are being considered will be referred to as 'treatment-focused genetic counselling and testing'. Such an intervention, with all its familial considerations, occurs at a vulnerable time when the woman is coming to terms with her diagnosis and making decisions about treatment options.

Linking the results of genetic counselling and testing to subsequent patient management is likely to impact on familial cancer services by increasing the number of patients and their unaffected relatives referred for genetic counselling and testing and the need for patients to be seen soon after referral in already under-resourced services. The subsequent increase in the number of mutation-positive families and the need to provide additional psychosocial support to these women and their families will impact even further on services already struggling under personnel and funding constraints [8]. For example, in the UK almost 2,200 women under the age of 40 years (5% of all new female breast cancer cases) are diagnosed with breast cancer each year [9], and there is evidence that a significant proportion of these will have a mutation in either of the *BRCA1* or *BRCA2* genes. Inclusion of treatment-focused genetic counselling and testing will also impact on the current clinical pathways within the associated breast oncology units. Although the familial cancer clinic is recognised as part of the multidisciplinary team, its current role is more consultative in nature and adoption of treatment-focused genetic counselling and testing will mean a change to the current management protocols and established work practices.

This paper highlights the evolving role of treatment-focused genetic counselling and testing and its application to daily clinical practice and patient management. There is a growing need to develop and trial cost-effective clinical pathways for genetic counselling and testing that are responsive to the timeframes demanded in acute cancer management. There will also be a need to address and target resource allocation to best meet the broader health service needs for individual patients and their families that will arise as a direct consequence of referral for genetic counselling to help with treatment decision-making [8,10]. Clearly, innovative new service models need to be developed for the delivery of treatment-focused genetic counselling and testing to patients in already stretched busy clinics. In particular, the potential roles of health professionals who are already part of the patient's treatment team (including breast surgeons, gynaecological oncologists, radiation and medical oncologists)

in the delivery of treatment-focused genetic counselling and testing require careful consideration.

This paper reviews: the current literature regarding the potential benefits of using germline *BRCA* mutation status to tailor the management of newly diagnosed patients with breast cancer; the criteria used to identify patients most likely to carry mutations in the *BRCA* genes; and the factors that influence women's decision-making and attitudes regarding treatment-focused genetic testing as well as its potential impact on psychological adjustment and breast surgery choices. Although the focus of the literature to date has been on genetic testing for *BRCA* mutations, it is important to emphasise that it is not simply genetic testing for *BRCA* mutations that is important for directing cancer treatment. Rather, it is treatment-focused genetic counselling, which focuses on the potential impact of the personal and family history of cancer on future cancer risks and may include genetic testing for mutations in *BRCA* or other breast cancer predisposition genes, that provides the hereditary cancer risk assessment necessary to inform therapeutic choices.

The aim of this paper is to raise awareness of the increasing role of genetic counselling and testing in the therapeutic arena and to delineate and highlight the associated research priorities. The article provides the basis for the formulation of guidelines as they relate to the use of genetic counselling and testing to inform treatment in certain newly diagnosed patients with breast cancer.

### Literature search strategy

To provide guidance on the criteria that may be used to select women for treatment-focused genetic testing, we undertook a systematic literature search. Studies were included in the review if they met the following criteria: they assessed mutation frequency in women with early onset breast cancer who were unselected for family history; they were published in a peer-review journal; they were published between January 1997 and October 2008; and they were published in the English language. Both studies that recruited through hospitals as well as population-based studies were included. Studies that included women of all ages (even if they reported data on young women separately) were excluded. The CD-ROM databases PubMed (which includes MEDLINE), PsychInfo, CINAHL, and EMBASE were searched, using the following key words individually and in combination: 'breast cancer', 'early onset', 'young women', 'prevalence', 'mutation frequency', '*BRCA1*', '*BRCA2*'. Searches were conducted for key authors who published in this field. The reference lists accompanying all publications identified were examined.

### Literature research process and results

Articles that met the inclusion criteria were evaluated, and data from these articles were extracted (BM). The included articles were checked by a second reviewer to determine if

they met the inclusion criteria (KT). The literature search identified 309 references as potentially relevant. After reviewing these, 22 references were selected for detailed review (Table 1).

## **Role of *BRCA* mutation status in guiding clinical management of patients newly diagnosed with breast cancer**

### **Genetic testing and decision-making about breast cancer surgery**

Breast conserving surgery (followed by radiotherapy) is the treatment of choice for many women diagnosed with an early breast cancer. Most women with early breast cancer are cured from their disease [7], and evidence suggests there is no difference in mortality at 10 years between *BRCA* mutation carriers and non-carriers [11]. However, in women who carry a *BRCA* mutation, the risk of a recurrence or a new primary in the ipsilateral breast at 10 years is estimated to be as high as 20% to 50% [12]. The risk at 10 years for a contralateral second primary cancer is approximately 30% and is modestly greater for women diagnosed before age 50 years [13,14]. There is good evidence that contralateral risk-reducing mastectomy decreases the risk of breast cancer by up to 95% [15-19]. Therefore, as survival from early breast cancer continues to improve, consideration of the risk of developing a new primary breast cancer becomes more important if it impacts on the surgical management of the current cancer.

While the discussion so far has focused on known *BRCA* mutation carriers, it is important to emphasise that simply relying on the presence or absence of a *BRCA* mutation after a genetic test is an inadequate assessment of a woman's likely future cancer risks. A woman with breast cancer in whom a *BRCA* mutation has not been detected with current techniques may still have a significant risk of developing a new primary cancer depending on her associated family history, which, in turn, could still influence her decision regarding breast conserving surgery. Genetic counselling is an essential component of the genetic risk assessment in order to interpret the implications of a genetic test result, particularly if no mutation can be identified - an 'uninformative' result. The clinical implications of an uninformative result depend on whether or not a woman has a relevant family history of breast and/or ovarian cancer. Specifically, in a woman with a strong family history of breast and/or ovarian cancer, there is no convincing evidence that in the absence of a detectable mutation there is a substantial reduction in the chance of ipsilateral and/or contralateral breast cancer. There is some evidence that the risk of a second primary remains elevated in *BRCA1* and *BRCA2* mutation negative families, especially if the breast cancer was diagnosed early [20]. Thus, women with a relevant family history of breast and/or ovarian cancer who receive uninformative results may still reasonably consider risk-reducing surgery on the basis of their strong family history alone. It is important that the information is discussed with genetic specialists to ensure

correct interpretation of results, but also that these specialists understand that absence of a detectable mutation does not preclude a substantial risk of a further primary.

In other circumstances, specific personal and family features may mean that an uninformative test may support an assessment that it is less likely there is a hereditary syndrome, thus reducing estimates of risks for a new ipsilateral or contralateral breast cancer. In this instance, the woman can make an informed decision and reasonably elect breast conservation.

It is possible that a significant proportion of women found to have a deleterious mutation would opt for bilateral mastectomy if they had access to this information at diagnosis [21-25]. If a woman is identified as a *BRCA* mutation carrier, the mutation status can be used as a variable in the complex decision-making process regarding the use of radiotherapy and the type of surgery. The option of combining definitive and risk-reducing surgery as a unilateral or bilateral mastectomy after adjuvant therapy is completed avoids the need for additional surgery if a woman would have elected risk-reducing surgery at a later date following delayed genetic counselling with or without genetic testing [26]. Furthermore, radiation treatment, which may negatively impact on the cosmetic outcome of breast reconstructive surgery, may be able to be avoided.

The discussion so far has focused on the relative roles of breast conservation versus mastectomy, so it could be argued that treatment-focused genetic counselling and testing need not be considered at this vulnerable time if women do not want to consider a mastectomy. However, we would argue that although a woman may not want to consider a mastectomy as her first reaction to a new cancer diagnosis, if she has a suspicious family history and does not have the opportunity for a full consultation about the possible associated cancer risks, she risks not being fully informed about the pros and cons for all the treatment choices available.

### **Decision-making about risk-reducing salpingo-oophorectomy**

Women newly diagnosed with breast cancer with a *BRCA* mutation may also consider a risk-reducing salpingo-oophorectomy (RRSO) to reduce their significant associated future ovarian cancer risk [27]. RRSO has been shown to reduce the risk of ovarian cancer by between 85% [28] and 95% [29]. It also reduces the risk of subsequent breast cancer by up to 50% in *BRCA1* and *BRCA2* mutation carriers [28-31], with risk reduction being greatest for premenopausal women.

Although the cancer prevention considerations are important, the main indication for considering such surgery around the time of cancer diagnosis is because an oophorectomy is also an effective adjuvant treatment for oestrogen-receptor (ER) positive premenopausal breast cancer. Furthermore, RRSO will also permit the use of adjuvant aromatase inhibitors,

**Table 1****Mutation frequency in women with early onset breast cancer unselected for family history**

Publication	Sample	Age cut-off (years)	Sensitivity ranking of methodology <sup>a</sup>	<i>BRCA1/2</i> mutation frequency combined	<i>BRCA1/2</i> mutation frequency in women with family history	Percentage of women with <i>BRCA1/2</i> mutations without a family history <sup>b</sup>
Uhrhammer <i>et al.</i> 2008 [78], France	51 (North African) women (hospital-based)	<38	1	9.8% ( <i>BRCA1</i> only)	NA	NA
Loizidou <i>et al.</i> , 2007 [52], Cyprus	26 women (unclear whether population or hospital-based)	<40	1	23.0%	27% of women with a family history and 27% without a family history of <i>BRCA</i> (not closer specified) were <i>BRCA1/2</i> carriers	43
Choi <i>et al.</i> , 2004 [48], Korea	60 women (hospital-based)	≤40	2	15.0%	25% of women with a FDR and a SDR with br/ov ca were <i>BRCA1/2</i> carriers, compared to 13% without such a family history	78
Haffty <i>et al.</i> , 2006 [79], US	170 Caucasian (including 31 of Jewish ancestry), and 30 African-American women (hospital-based)	≤45	2	17.0%; 11% in non-Jewish Caucasian women	40% of women with a moderate to strong family history (details not specified) were <i>BRCA1/2</i> carriers compared to 10% without such a family history	47
Loman, <i>et al.</i> 2001 [43], Sweden	234 women (population-based)	<41	3	8.9%; higher in cases diagnosed <36 years (15.9%)	26% of women with at least one FDR or two FDRs or SDRs with br/ov ca were <i>BRCA1/2</i> carriers, compared to 4% without such a family history	29
Hamann <i>et al.</i> 2003 [80], Germany	91 women (hospital-based)	<41	3	5.5%	13% of women with at least 1 FDR or SDR with br/ov ca were <i>BRCA1/2</i> carriers compared to 4% without such a family history	40
Bonadona <i>et al.</i> 2005 [81], France	232 women (population-based)	<46	3	9.1%; higher in cases diagnosed <41 years (12.8%)	21% of women with at least 1 FDR or SDR with br/ov ca or with small family size, a predominantly male pedigree, or other specific cancers were <i>BRCA1/2</i> carriers, compared to 5% without the above features	33
de Sanjose <i>et al.</i> 2003 [82], Spain	136 women (population-based)	<46	3	6.8%; higher in cases diagnosed <40 years (11.6%)	10% of women with at least 1 FDR or SDR with br ca were <i>BRCA1/2</i> carriers, compared to 4% without such a family history	25
Malone <i>et al.</i> 2000 [44,83], US	203 women (population-based)	<35	3	9.4%	19% of women with at least one FDR with br ca were <i>BRCA1/2</i> carriers, compared to 1% without such a family history	16
Martinez-Ferrandis <i>et al.</i> 2003 [53], Spain	124 women (hospital-based)	<41	3	5.6%	15% of women with at least one FDR with br/ov ca or male br ca were <i>BRCA1/2</i> carriers, compared to 3% without such a family history. Frequency of carriers was higher in cases with ov ca relatives (38%) than in those without (4%)	14
Plaschke <i>et al.</i> 2000 [84], Germany	40 women (population-based)	<40	3	12.5% ( <i>BRCA2</i> only)	1 carrier (1/5, 20%) had one FDR and one SDR affected by br ca. No other family history data were provided	NA
Ho <i>et al.</i> 2000 [85], Singapore	43 women (hospital-based)	<36	3	7.0% ( <i>BRCA1</i> only)	29% of women with a family history of br/ov ca in a FDR or SDR were <i>BRCA1</i> carriers, compared to 2% without such a family history	33

Continued overleaf

**Table 1 (continued)**

<b>Mutation frequency in women with early onset breast cancer unselected for family history</b>						
Publication	Sample	Age cut-off (years)	Sensitivity ranking of methodology <sup>a</sup>	<i>BRCA1/2</i> mutation frequency combined	<i>BRCA1/2</i> mutation frequency in women with family history	Percentage of women with <i>BRCA1/2</i> mutations without a family history <sup>b</sup>
Yassae <i>et al.</i> 2002 [86], Iran	83 women (hospital-based)	<45	3/4	6.0%	29% of women with at least one relative affected by <i>br/ov</i> cancer were <i>BRCA1/2</i> carriers, compared to 1% without such a family history	20
Anglian Breast Cancer Study Group 2000 [87], UK	1,220 women (population-based)	<55	4A	2.0%; higher in cases diagnosed <35 years (12.4%)	4% of women with at least one FDR or two FDRs and/or SDRs with <i>br/ov</i> ca were <i>BRCA1/2</i> carriers, compared to 1% with no more than one SDR with <i>br/ov</i> ca	29
Hopper <i>et al.</i> 1999 [51], and Southey <i>et al.</i> 1999 [88], Australia	388 women (population-based)	<40	4A	4.6%	5% of women with a FDR or SDR with <i>br</i> ca were <i>BRCA1/2</i> carriers, compared to 5% without such a family history	61
Krainer <i>et al.</i> 1997 [89], US	73 women (non-Jewish) 39 women (Jewish; hospital-based)	≤32 ≤40	4A	14.7% 14.6%	No family history data reported	NA
Peto <i>et al.</i> 1999 [90], UK	254 women 363 women (population-based)	<36 ≥36 to ≤45	4A	5.9% 4.1%	45% of women with two or more FDR or SDR relatives affected by <i>br/ov</i> ca were <i>BRCA1/2</i> carriers, compared to 11% women with at least one FDR affected by <i>br/ov</i> ca	50
Lubinski <i>et al.</i> 2006 [91], Poland	3,472 women (hospital-based)	<51	4B	5.7% ( <i>BRCA1</i> only)	13% of women with one or more first- or second-degree relatives with <i>br</i> ca or <i>ov</i> ca were <i>BRCA1</i> carriers	43
Robson <i>et al.</i> 1998 [92], US	91 Ashkenazi women (hospital-based)	≤42	4B	33.0%	45% of women with one or more first- or second-degree relatives with <i>br</i> ca or <i>ov</i> ca were <i>BRCA1/2</i> carriers, compared to 7% of women without such a family history	10
Gershoni-Baruch <i>et al.</i> 2000 [93], Israel	91 Ashkenazi women (hospital-based)	≤42	4B	31.3%	57% of women with one or more first- or second-degree relatives with <i>br</i> ca or <i>ov</i> ca were <i>BRCA1/2</i> carriers, compared to 10% of women without such a family history	17
Tonin <i>et al.</i> 2001 [94], Canada	61 French-Canadian women (hospital-based)	≤40	4B	13.1%	19% of women with at least one first-, second- or third-degree relative with <i>br</i> ca or <i>ov</i> ca were <i>BRCA1/2</i> carriers, compared to 4% of women without such a family history	13
Lalloo <i>et al.</i> 2006 [46,90], UK	100 women of 278 (population-based); 42% deceased not tested	≤30	NA	18.0%	Mutations in <i>BRCA1/2</i> or <i>TP53</i> were identified in 49% of familial cases (that is, family history of <i>br</i> ca <65 years or <i>ov</i> ca any age or family history consistent with Li Fraumeni syndrome) and 6% of the non-familial cases	6

<sup>a</sup>Sensitivity ranking of methodology used for mutation detection, with a range of 1 (most sensitive) to 4 (least sensitive): 1, sequencing and multiplex ligation probe analysis (MLPA); 2, sequencing; 3, denaturing high performance liquid chromatography analysis (dHPLC) of all exons, or protein truncation test (PTT) of exon 11 *BRCA1* and exon 10/11 *BRCA2* plus alternative analysis of other exons; 4A, multiplex heteroduplex analysis (MHA), PTT alone (exon 11 *BRCA1* and/or exon 10/11 *BRCA2*); 4B, population specific founder mutation screen. <sup>b</sup>Having a family history' is defined as having at least one first- and/or second-degree relative with breast and/or ovarian cancer. *br/ov* ca, breast and/or ovarian cancer; FDR, first-degree relative; NA, not available; SDR, second-degree relative.



which are superior to tamoxifen but are only effective in postmenopausal women [32,33]

### **Potentially increased scope of the future uses of treatment-focused genetic counselling and testing**

There are emerging data that indicate that complete cellular loss of *BRCA1* or *BRCA2* function in *BRCA*-associated cancers confers increased resistance to agents such as taxanes [34], and that these tumours are more sensitive to DNA-damaging agents such as platinum agents [35]. It is reasonable, therefore, to speculate that the known or likely *BRCA* mutation status of a woman could influence systemic therapy decisions and choice of chemotherapy once we have more definitive data from randomised trials. Moreover, further refining of pathological techniques may allow treatment targeted at aberrant molecular pathways of the tumour, which may be related to both somatic and germline *BRCA* mutations as well as other predictive markers. There is evidence that *BRCA1*-associated breast cancers are more aggressive [36,37], and that adjuvant chemotherapy should be considered in the majority of mutation positive women, even those with small, node negative breast cancers.

As well as improvements in the understanding of the relative efficacies of conventional chemotherapy agents in the adjuvant treatment of *BRCA1* or *BRCA2* mutation carriers, novel agents such as PARP inhibitors have been developed that exploit the effect of a mutated gene in the associated cancers. The *BRCA1* and *BRCA2* genes are important for DNA double-strand break repair by homologous recombination. PARP is an enzyme involved in base excision repair, a key pathway in the repair of DNA single-strand breaks [38]. The inhibition of PARP results in the development of DNA double-strand breaks that are normally repaired through the homologous recombination pathway mediated by *BRCA1* and *BRCA2*. The *BRCA1* or *BRCA2* dysfunction occurring in cancers arising in *BRCA1* or *BRCA2* germline mutation carriers sensitises tumour cells to the inhibition of PARP enzymatic activity, resulting in chromosomal instability, cell cycle arrest and apoptosis, as these cells have no functioning copy of the *BRCA* genes. The other body cells are relatively insensitive to the effects of PARP inhibition as these cells still retain a functioning *BRCA1* or *BRCA2* gene. Consequently, the use of PARP inhibitors in *BRCA*-associated cancer has the potential for a wide therapeutic index between the effects of PARP inhibition on tumour and normal body cells [39].

Clinical trials using PARP inhibitors are underway in *BRCA*-associated cancers [40]. If successful, and if they progress into the adjuvant arena, the use of PARP inhibitor agents will increase the need to ascertain a patient's *BRCA* mutation status around the time of cancer diagnosis. The results of phase 1 and 2 studies show that PARP inhibitors are very active agents [41], and it is likely that they will be investigated in the adjuvant setting for women with early stage breast cancer within the next few years.

### **Complexity of decision-making about treatment-focused genetic counselling and testing**

There is a growing awareness of the potential benefits of understanding a woman's likely hereditary cancer risk status for the consideration of simultaneous therapeutic and contralateral risk-reducing mastectomy, better tailoring of conventional adjuvant therapies and the testing of novel agents in the adjuvant setting. There is a small window of opportunity to establish the optimal ways in which to offer treatment-focused genetic counselling and testing and to develop appropriate associated clinical pathways, in advance of a more widespread clinical demand.

The development of educational resources that support women considering genetic counselling and testing to make informed decisions as well as facilitating discussions between women and their health professionals is also critical. These resources will need to provide information for women to consider the potential advantages and disadvantages of this process. These include the added stress of undergoing genetic testing for a hereditary predisposition around the time of a breast cancer diagnosis; the implications of uninformative genetic test results; the possibility of delaying surgery for a short time while waiting for genetic testing results if there is no planned delay in definitive surgery or radiotherapy due to neoadjuvant or adjuvant chemotherapy; and the implications of this information for the wider family.

Raising the issue about the hereditary aspects of breast cancer at the time of diagnosis involves more than considering the usual pros and cons of genetic testing and, if a mutation is found, discussing the role of mastectomy as a risk-reducing strategy at some time in the future. It adds another layer of complexity to the decisions around cancer treatment when providing women with the opportunity to consider the wider issues that may affect their future survival and possible disease course rather than using the tumour staging and characteristics alone. There are a variety of management options, and this is complex information to convey at a vulnerable time, so this will require multidisciplinary input from breast surgeons, plastic surgeons, medical and radiation oncologists as well as other health professionals involved in the care of women with breast cancer outside traditional genetic counselling services. Involvement of genetic specialists in the multidisciplinary team will ensure that these issues are brought up, but also that patients are not disadvantaged by ill informed application of these genetic tests. As genetic testing becomes faster and cheaper, some clinicians might believe that testing results indicate a clear set of treatment options. It is, however, essential that the decisions that arise as a result of genetic testing be considered within the context of the priorities of treating the current cancer. Integration of a new model of genetic counselling and testing to help direct therapy may also challenge assumptions that women who are coping with a recent diagnosis of breast cancer, and are already making

multiple decisions about their treatment are not interested in, or able to cope with, additional information about their genetic risk.

### **Targeting of treatment-focused genetic testing to certain patients with newly diagnosed breast cancer**

The current costs of genetic testing and a climate of cost constraints mean that treatment-focused genetic testing will need to be targeted to the women who have a reasonable chance of being mutation carriers. How to select women appropriately is problematic. The traditional approach of only offering genetic testing to women in a potentially high-risk group based on their family history alone is being challenged as there is accumulating evidence that many women with mutations in *BRCA1* or *BRCA2* genes do not have a classic family history (Table 1) [42,43]. Other indicators are now also being considered to provide a basis for the selection for testing, such as phenotypic pathological characteristics of the tumour tissue (for example, basal-like phenotype). Treatment-focused genetic testing will be no different and case selection should include consideration of the classic features, including a strong family history of breast and/or ovarian cancer, younger age at breast cancer diagnosis, presence of bilateral breast cancer, membership in an ethnic group with a high incidence of founder mutations (for example, Ashkenazi Jewish background), in addition to the tumour tissue characteristics. The evidence available to support the adoption of such selection criteria are described briefly below.

#### **Women with a strong family history of breast and/or ovarian cancer**

There is strong evidence that the frequency of mutations in *BRCA1* or *BRCA2* genes is increased in women with a strong family history of breast and/or ovarian cancer involving multiple generations of affected blood relatives and/or those with a specific ethnicity or from certain geographical locations that are associated with known founder mutations. For example, Malone and colleagues [44] provide a summary of the literature and report that in women with extensive family histories, estimates of mutation frequency range from 20% to 50%. There is a consensus that women with strong family histories of breast and/or ovarian cancer should be offered genetic counselling and testing for mutations in the two *BRCA* genes (for example, National Breast Cancer Centre [45] and American Society of Clinical Oncology [1,46]).

However, it is also clear that many mutation carriers will be missed if the presence of a strong family history of breast cancer and/or ovarian cancer is used as the sole criterion to offer genetic testing. Table 1 provides a summary of published studies on women with early onset breast cancer who have had genetic testing for *BRCA1* and *BRCA2* mutations; it shows that the proportion of women with a *BRCA1* or *BRCA2* mutation with no family history of breast/ovarian

cancer ranges from 6% [47] to 78% [48]. The lack of a family history of breast and/or ovarian cancer can arise because of a small family size, few female relatives of an age to have developed cancer, patrilineal inheritance, low cancer penetrance and non-disclosure of relevant family cancer diagnoses due to geographic or social distance between relatives [42,49].

#### **Women with early onset breast cancer**

Table 1 also shows that the proportion of women found to have mutations in *BRCA1* or *BRCA2* genes varies considerably between studies, ranging from 2.0% to 33.0%. This variability is likely to be the result of differing populations, age selection criteria and mutation detection methods utilised. Studies vary in the extent to which they include women from ethnic backgrounds characterised by the presence of founder mutations, which will have specific population frequencies not applicable to a wider outbred population. The age selection criteria chosen for different studies also vary between under 31 to under 55 years. Finally, the diagnostic sensitivity of the methods used for the detection of *BRCA1* and *BRCA2* mutations varies [50]. Accordingly, in Table 1 the studies are ranked for sensitivity of the mutation detection method. Sensitivity estimates are based on published data only and do not take into account the operator dependence of these methodologies.

Extracting the data for women aged under 40 years from the studies in Table 1 gives a *BRCA* mutation detection rate of between 4.9% [51] and 23.0% [52]. A prior probability of mutation detection exceeding 10% [1] is generally considered sufficiently high to justify genetic testing for *BRCA* mutations through many public genetics clinics. It should be noted though that this threshold is not based on health economic analyses, and the cut-off to be used will depend on local availability of resources and ethnic mix.

#### *Women with early onset breast cancer and a family history of breast/ovarian cancer*

Several studies found that women with early onset breast cancer who have at least one first-degree or one first- and one second-degree relative with breast or ovarian cancer have higher mutation frequencies (Table 1) and may be suitable candidates for treatment-focused genetic testing. For example, Loman and colleagues [43] found that in women aged 40 years and under, 39% of women with this degree of family history carried mutations in *BRCA1* or *BRCA2*. Similarly, Martinez-Ferrandis and colleagues [53] found that even a moderate family history was a good predictor of *BRCA1* or *BRCA2* mutation status; 15.4% of women with at least one first-degree relative with breast or ovarian cancer or one case of male breast cancer were *BRCA1* or *BRCA2* mutation carriers. Laloo and colleagues [47] found an even higher rate of mutation carriers in women under the age of 31 years with a first- or second-degree relative with breast and/or ovarian cancer (44%), compared to those without such a family history.

#### *Women with early onset bilateral breast cancer*

Young women with bilateral breast cancer have a higher chance of a *BRCA* mutation than their counterparts with unilateral disease. For example, Loman and colleagues [43] found that 33% of women aged 40 and under with bilateral cancer were *BRCA1* or *BRCA2* mutation carriers.

#### *Women whose tumours have certain histological characteristics*

Tumour pathology is increasingly useful in case selection for *BRCA* genetic testing [42]. Specifically, it has been shown that *BRCA1*-associated tumours have a distinct immunohistochemical profile associated with the basal-like phenotype [42].

Lakhani and colleagues [54] showed that information on age at diagnosis, high histological grade and an ER negative receptor status provides a powerful predictor of *BRCA1* mutation status. Specifically, in women who were aged between 30 and 34 years at diagnosis, the probability of presence of a *BRCA1* mutation increased from 5% for women with all histology, to 27% for women with ER negative and grade 3 histology. The data reported by Lakhani and colleagues suggest that women aged under 35 years with ER negative breast cancers, regardless of grade, have *BRCA1* mutation frequencies much greater than 10%. Similarly, Atchley and colleagues [55] found that 34% and 8% of women diagnosed with triple negative breast cancer were *BRCA1* and *BRCA2* mutation carriers, respectively. However, the true rate of *BRCA1* mutations in ER negative or 'triple negative' (ER, progesterone receptor and HER2 negative) breast cancer cases is unknown, as there have been no studies looking at the *BRCA1* and *BRCA2* mutation prevalence in a prospectively collected population-based cohort of cases.

#### *Women with early onset breast cancer from populations with BRCA founder mutations*

Specific ethnic factors increase the likelihood of a *BRCA1* or *BRCA2* mutation in women with early onset breast cancer. For example, Abeliovich and colleagues [56] found a frequency of *BRCA1* or *BRCA2* mutations of 30% in women of Ashkenazi Jewish background who developed breast cancer under the age of 40 years. Data from Myriad Genetics clinical testing service [57] show a *BRCA1* or *BRCA2* mutation prevalence of 12% in women of Ashkenazi Jewish ancestry with breast cancer who are aged less than 50 years and who have no relevant listed family history. By contrast, the *BRCA1* or *BRCA2* mutation prevalence in women of Ashkenazi Jewish ancestry with breast cancer aged 50 and over with no relevant family history is considerably lower (4%). Founder mutations have been identified in many populations, including Swedish, Norwegian, Icelandic, Dutch, Eastern European and French Canadian to name but a few.

### **Selective testing of certain subgroups of women with early breast cancer**

In conclusion, these data suggest some specific features that may guide selection for treatment-focused genetic counselling and testing, which are summarised in Table 2.

Limited data are currently available on whether to use age 40, 45 or even 50 years as a cut-off to define the group of young women from each of the four groups described above for an offer of treatment-focused genetic testing. Hence, a meta-analysis of existing data and/or more research involving larger samples will be required to decide on optimal age cut-offs. Cost considerations are also likely to be a critical factor, and health economic analyses need to be undertaken to provide a basis for decisions on which mutation prevalence thresholds to use for an offer of treatment-focused genetic counselling and testing consistent with local resources.

### **Previous attempts at integrating treatment-focused genetic testing into clinical practice**

Several groups have demonstrated that genetic counselling and testing of newly diagnosed breast cancer patients can be integrated successfully into clinical practice [12,26,58,59]. Published reports of existing treatment-focused genetic testing programs used varying criteria for selecting patients for the offer of such genetic testing. In particular, three used a minimum of a 10% probability of carrying a *BRCA1* or *BRCA2* mutation as assessed by risk assessment models such as BRCAPRO or that of Myriad Genetics [12,58] or on the basis of data from published reports [26]. A fourth program utilised a check list with risk factors thought to be predictive of hereditary breast cancer, which incorporated both family history of breast and/or ovarian cancer as well as young age (regardless of family history) and diagnostic features (bilateral, multifocal and/or multicentric breast cancer), again regardless of family history [59].

These programs also differed in terms of which health professional recommended genetic testing; in one study women self-referred, typically following a physician recommendation [26]. In other programs, testing was offered by cancer clinic staff [12,58], or the health professional offering testing was not specified [59].

The timing of the offer of genetic testing was also variable. In one program women were offered testing before definitive surgical treatment, which was defined as either breast conserving surgery with radiation treatment, or unilateral or bilateral mastectomy; women who had undergone a lumpectomy but not yet commenced radiation therapy remained eligible for testing [26]. Similarly, Stolier and colleagues [58] report that testing results became available either during systemic therapy, or radiation therapy was delayed until results were given, while Weitzel and colleagues [12] report that genetic testing took place either immediately following biopsy, after breast conserving surgery or during chemotherapy. These authors report that definitive surgery was not delayed to accommodate genetic testing, but that radiation therapy did not take place where possible until the results from genetic testing had become available [12,26].

It should be noted that timing of genetic testing before initial surgery has also been proposed; in particular, Silva [5]



**Table 2****Features that may guide selection for treatment-focused genetic counselling and testing**

Strong family history consistent with dominantly inherited breast/ovarian cancer	Two or more first- or second-degree relatives on one side of the family plus one or more of the following features on the same side of the family <sup>a</sup> : <ul style="list-style-type: none"> <li data-bbox="716 402 1154 427">Additional relatives with breast or ovarian cancer</li> <li data-bbox="716 444 1187 470">Breast cancer diagnosed before the age of 40 years</li> <li data-bbox="716 487 922 512">Bilateral breast cancer</li> <li data-bbox="716 529 1133 555">Breast and ovarian cancer in the same woman</li> <li data-bbox="716 572 956 597">Ashkenazi Jewish ancestry</li> <li data-bbox="716 614 1000 640">Breast cancer in a male relative</li> </ul> One or more first- or second-degree relatives with breast cancer at age 45 years or younger plus another first- or second-degree relative on the same side of the family with sarcoma (bone/soft tissue) at age 45 years or younger
Young age of onset <sup>b</sup> especially in combination with:	At least one first-degree relative with breast or ovarian cancer; <i>or</i> <ul style="list-style-type: none"> <li data-bbox="638 783 873 808">Bilateral breast cancer; <i>or</i></li> <li data-bbox="638 825 1390 874">Specific ethnic group with known founder mutations, for example, Ashkenazi Jewish ancestry; <i>or</i></li> <li data-bbox="638 891 1390 940">Presence of a triple negative breast tumours (ER, progesterone receptor and HER2 negative) or their subgroup of basal-cell like tumours</li> </ul>

<sup>a</sup>National Breast Cancer Centre [96]. <sup>b</sup>The age cut-off to be used will depend on local availability of resources and the future cost of mutation detection.

advocates that genetic counselling and testing be offered during the window of time when some patients are having neoadjuvant therapy. Therefore, either neoadjuvant or adjuvant chemotherapy given prior to radiotherapy can give a useful window in which to consider treatment-focused genetic testing before definitive local surgery.

### **Women's decision-making about, and the psychological and behavioural impact of, treatment-focused genetic testing**

#### **Psychological impact of standard genetic testing for *BRCA1* and/or *BRCA2* mutations**

There is an expanding body of literature about the psychological impact of genetic testing in affected women at increased risk for hereditary breast/ovarian cancer who were offered 'standard' genetic testing for *BRCA1* and/or *BRCA2* mutations, that is, genetic testing offered in the context of genetic counselling following completion of cancer treatment, as opposed to treatment-focused genetic counselling and testing (see Schlich-Bakker and colleagues [60] and Meiser [61] for reviews). This literature indicates that the impact of genetic testing is mediated and amplified by women's former experience of cancer [61]. Women with a previous diagnosis of cancer have been found to be significantly more distressed compared to unaffected women following genetic testing [62] independently of carrier status [63]. Women for whom the gap between being diagnosed with cancer and being genetically tested was less than a year tend to report greater reductions in well-being compared to those for whom the gap was longer [64,65]. This may indicate that genetic testing around the time of diagnosis may place additional

psychological stressors on women or that women feel frustrated if they realise they might have selected an alternative therapy had they received genetic counselling prior to completion of cancer treatment. These results do not suggest that treatment-focused genetic testing should not occur, but rather that it should be provided in a supportive environment that is responsive to these wider issues.

#### **Impact of treatment-focused genetic testing for *BRCA1* and/or *BRCA2* mutations on surgery decisions**

Limited empirical data have been published that describe women's decision-making about, and the psychological and behavioural impact of, treatment-focused genetic testing in the context of a new diagnosis of breast cancer. In a key US study, Schwartz and colleagues [21,26,66,67] evaluated the impact on surgical decision-making in 194 newly diagnosed breast cancer patients who were offered testing before definitive surgery. In this study, women with a 10% prior probability of carrying a *BRCA1* or *BRCA2* mutation were offered genetic testing, and test results were made available within 2 to 3 weeks. Seventy-six percent of the study participants chose to have *BRCA1* and/or *BRCA2* testing; the decision to undergo testing was associated with physician recommendation and indecision about definitive local treatment [21]. Twenty-one percent of the women who were tested proceeded with definitive local treatment before receiving their tests results; delays in the availability of test results and low levels of anxiety were associated with the decision to proceed with definitive local treatment [21]. Schwartz and colleagues [21] also found that 48% of women who were found to carry a *BRCA1* or *BRCA2* mutation

opted for bilateral mastectomy, compared to 4% of women who declined genetic testing. These findings indicate that knowledge of a *BRCA1* or *BRCA2* mutation before definitive surgery significantly increases the number of women opting for bilateral mastectomy for both treatment and risk reduction [26,66,67]. They also suggest that the presentation of the information about genetic testing by the treating clinician is an important factor in the final decision to undertake genetic testing.

#### **Impact of contralateral risk-reducing mastectomy on psychosocial outcomes**

The study by Schwartz and colleagues [26] also found that, compared with women who chose breast conservation or unilateral mastectomy, those who chose mastectomy of the affected breast and contralateral risk-reducing mastectomy of the unaffected breast did not report diminished quality of life or decreased distress [67]. These results are consistent with findings from another study of 435 *BRCA1* or *BRCA2* carriers that assessed predictors and outcomes of the decision to undergo contralateral risk-reducing mastectomy and found no impact on distress outcomes of contralateral risk-reducing mastectomy [66]. In this latter study the decision to undergo contralateral risk-reducing mastectomy (in conjunction with mastectomy of the affected breast) following treatment-focused genetic testing was associated with an informative, mutation positive test result, higher cancer-specific distress at baseline and younger age at diagnosis [66]. Similarly, in an international cohort of women, uptake of contralateral mastectomy was found to be associated with younger age [68].

In the study by Schwartz and colleagues [26,66] women opted into the study and received extensive pre- and post-test genetic counselling; the select nature of the sample and the unique resources of the study limit the generalisability of the results to other settings [69]. Although the data reported by Schwartz and colleagues suggest few adverse psychological effects of treatment-focused genetic testing, further controlled studies in a range of different clinical settings are needed to determine definitively the psychological and behavioural impact of treatment-focused genetic testing for *BRCA1* and/or *BRCA2* mutations.

In another prospective study from The Netherlands, Schlich-Bakker and colleagues [60,70,71] assessed predictors of the decision to undergo treatment-focused testing and its psychological impact in women with breast cancer who were about to commence adjuvant radiotherapy. The psychological distress levels of 102 women who met referral criteria for genetic counselling and testing were compared to those of 182 women who did not meet such criteria. The authors report that psychological distress levels did not increase after an active approach for genetic counselling and testing [60,70]. Of importance in this setting, not having a family history of breast cancer was found to predict long-term

distress in the combined group of tested and untested women [60,70]. Of note, of the 102 patients who met referral criteria, only 57% opted to have genetic testing [71]. Sixty-four percent of the 102 women were happy with the timing of genetic testing, while 13% would have preferred an earlier, and 19% a later, approach [71].

#### **Women's attitudes and information needs regarding treatment-focused genetic testing**

A small UK study by Arden-Jones and colleagues [72] explored whether women wanted to be offered information about genetic testing close to the time of diagnosis. Thirteen women, who were ascertained through a family cancer service, were under the age of 40 and were subsequently identified as *BRCA1* or *BRCA2* mutation carriers, participated in focus groups. The majority of women expressed the view that offering genetic testing around the time of a breast cancer diagnosis might add too much stress at a time when women were confronted with multiple demands on their coping abilities. However, some women supported testing around the time of breast cancer diagnosis if it could alter treatment decisions. All agreed that there was no 'right' time for everyone, with women expressing a preference for being told that the information was available if they wanted it rather than then being offered the test at the time of their cancer diagnosis. However, a broad range of views was observed and indeed some women said they would prefer to be tested immediately following their breast cancer diagnosis.

#### **Health professionals' attitudes toward treatment-focused genetic testing of newly diagnosed women**

The study by Arden-Jones and colleagues [72] also found that health professionals involved in breast cancer care expressed concerns about informational and emotional overload caused by offering genetic testing at the time of a breast cancer diagnosis. Similar views were expressed in a recent study of 34 Australian cancer genetics practitioners that was undertaken to identify problematic or ethically contentious issues in cancer genetics consultations [73]. The latter study also highlights: the rights of women to be fully informed when making treatment decisions; the need to provide emotional support at this vulnerable time; the importance of including the genetic counsellor in the multi-disciplinary team and the impact on the delivery of cancer genetic services with increasing demand for testing [73].

#### **Potential future directions for research on the psychosocial implications of treatment-focused genetic testing**

This overview of the psychosocial literature shows that treatment-focused genetic testing for *BRCA1* and/or *BRCA2* mutations is not associated with adverse psychological and quality of life outcomes. However, these studies included almost exclusively women with a family history that indicated an increased risk for hereditary breast/ovarian cancer, and very little is known about the psychosocial impact of

treatment-focused genetic testing in women without a family history. This review also shows that very few data are currently available on: the anticipated implications of genetic testing for the patient and other family members; patient preferences in terms of timing of genetic testing information; mode of delivery of information; and preferred format and amount of information. Furthermore, no educational interventions have been developed to supplement expert advice and counselling of women considering treatment-focused genetic testing.

Given current funding constraints, the potential for routine testing in the future of newly diagnosed breast cancer patients also points to a need to develop and evaluate innovative patient education strategies as time-efficient means to supplement expert counselling provided by health professionals. Possible formats of resources include simple information sheets or more complex communication and decision aids. Communication aids may be used to facilitate and structure the discussion between the patient and the health professional and may also be tailored to the particular patient and taken home to be shared with other family members. Decision aids have been shown to improve understanding of the potential benefits and risks of different options and to assist patients to consider the personal importance of these options [74-77].

## Conclusion

There is increasing interest in treatment-focused genetic counselling and testing. This approach is not indicated for women who would not consider mastectomy or oophorectomy for cancer management because of age considerations or personal preference as they would have little to gain from an expedited genetic assessment. Currently, the main utility of a treatment-focused genetic assessment is to direct surgical therapy, but if agents targeted to *BRCA*-associated tumours move into the adjuvant arena, then the indications for treatment-focused genetic assessment will increase further.

For those women in whom knowledge of a likely hereditary cancer syndrome or mutation status might alter their cancer treatment, we suggest a stepwise approach to their genetic assessment. Specifically, women who have a strong family history or develop breast cancer diagnosed at a young age regardless of family history may benefit from a formal assessment of the likelihood of a hereditary component to their breast cancer. If possible, an analysis of a three-generation pedigree should be undertaken in conjunction with the woman's breast cancer pathology. With regard to women without a relevant family history of breast and/or ovarian cancer, there will have to be consideration of an age cut-off for testing depending on local circumstances, local ethnicities and mutation prevalence as well as financial considerations, until the cost of genetic testing substantially reduces. If genetic testing proceeds, it is essential that the results be interpreted within the context of the specific family

history so that an accurate hereditary risk assessment can be provided to the patient.

The opportunity currently exists to systematically ascertain the important clinical and psychosocial implications of genetic risk determination for hereditary breast cancer in women newly diagnosed with breast cancer, in advance of the inevitable widespread clinical implementation of treatment-focused genetic testing. Ethical practice requires confidence that information about genetic risk and testing results can be provided without damaging psychological or behavioural consequences, and that the genetic information is correctly interpreted and relayed to the patient by an appropriate multidisciplinary team. Thus, data on the acceptability of treatment-focused genetic testing for germline *BRCA1* or *BRCA2* mutations and women's associated information and communication needs are required urgently.

## Competing interests

The authors declare that they have no competing interests.

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