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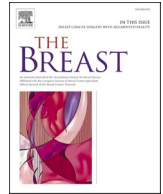
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## Does mainstream BRCA testing affect surgical decision-making in newly-diagnosed breast cancer patients?

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### ABSTRACT

**Background:** Germline pathogenic variants mutations) in the BRCA1 and BRCA2 genes cause an increased risk of breast cancer and ovarian cancer. Mainstream cancer genetic testing (MCG) was introduced for breast cancer patients in our unit in 2013. Non-geneticist clinicians have been trained to offer genetic testing during initial treatment planning. We assessed the impact of timely test results on surgical decision-making.

**Methods:** Women who had undergone mainstream genetic testing for breast cancer between September 2013 and September 2018 were identified from a prospective database. Surgical data were collected retrospectively.

**Results:** 580 eligible women had mainstream genetic testing. For 474 this was their first breast cancer diagnosis. The median age was 46 years (interquartile range (IQR) 38–57). The indications were: age  $\leq 45$  years for 233 (49%); triple negative disease for 192 women (40.5%); bilateral breast cancer age  $< 60$  for 39 (8%) and other for 72 (14%) women. The median time for test initiation to result was 18 days (IQR 15–21). 302 (64% received results before surgery. 88% of those found to have a BRCA mutation before surgery opted for bilateral mastectomy (compared to 5% with BRCA wild type). An additional 106 patients had a new diagnosis on a background of previous treatment. Of these all with a pathogenic variant chose bilateral mastectomy.

**Conclusion:** Timely BRCA gene testing influences surgeons' and patients' choice of surgery. It reassures women with a negative result and allows those with a positive result to take an active decision about the management of their future risk.

### 1. Introduction

Three to five percent of breast cancers [1] occur due to an inherited mutation in either the BRCA1 or BRCA2 gene. A BRCA gene mutation carrier has 69%–72% cumulative risk of developing breast cancer before the age of 80 years [2–4]. Although these are a small subset of breast cancer patients, the implications of an identifying a mutation are manifold and include a risk of 40–60% for developing a contralateral breast cancer [5–7]. Genetic counselling for the patient and family are crucial for those with a mutation, this also influences treatment planning for early breast cancer including type of surgery and choice of chemotherapy [8,9].

Bilateral risk-reducing mastectomy has been shown to reduce the risk of developing breast cancer by 90–100% in unaffected BRCA1 and

BRCA2 carriers [10–14]. All-cause mortality is lower in this group of women opting for bilateral risk-reducing mastectomy as compared to women under surveillance [10]. However, the role of contralateral risk-reduction mastectomy for patients with previous breast cancer remains controversial in the literature. It is difficult to estimate the impact of risk-reducing surgery in the context of the original cancer [15–18]. Available data does show a reduced incidence of contralateral cancer and improved overall survival if risk-reducing mastectomy is done, but it is difficult to conclude whether the overall survival benefit seen is true or biased due to patient selection, as healthier patients or those with less aggressive disease might be chosen for the procedure [19–22]. It is therefore imperative to explore all options to make an informed decision with all patients. This includes the role of timely genetic testing in newly-diagnosed breast cancer patients to enable clinicians to have a

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conversation with patients about their management, which will be both informed and evidence-based.

Previously, in the UK, access to genetic counselling was a rate-limiting step and eligibility for referral depended on family history. However, mainstream cancer genetics (MCG) gives the opportunity for high-risk patients to have an expedited BRCA mutation testing at an early stage of treatment planning [16]. This has been facilitated by straightforward criteria based on the patient with cancer (rather than family history), and the training of non-genetic clinicians to offer and seek consent for testing. Onward referral to geneticists is then only required for those found to carry mutations or those who have other concerning personal or family history [17]. MCG has been available in our unit since 2013.

The aim of this study was to examine the impact of rapid, early genetic testing on choice of surgical procedure, as this has not previously been explored [15]. The hypothesis was that patients with a pathogenic mutation identified through mainstream testing will have a higher rate of bilateral mastectomy. Conversely, those without pathogenic mutations are unlikely to opt for this.

## 2. Materials and methods

### 2.1. Population

Patients were offered mainstream genetic testing if they fulfilled the eligibility criteria at the time of their cancer diagnosis at our institution. Testing was based on clinical characteristics indicating a 10% likelihood of carrying a mutation. This threshold reflected the NICE Familial Breast Cancer guidance (CG 164) issued in July 2013 [18]. However, the guidance also stated that testing is cost effective at a 5% threshold but was not achievable within the prevalent model of genetics services in the UK at that time. In our unit, the combination of a local accredited laboratory which could support the MCG pathway and funding from the National Institute for Health Research (NIHR) Biomedical Research Centre allowed us to implement testing at a 5% threshold from February 2015. Patients were tested for pathogenic variants in BRCA1 and BRCA2.

The test was initiated by non-geneticist clinicians including surgeons, oncologists and senior nurses, who were trained by an online course designed for the MCG programme. The 5% threshold criteria of eligibility are summarised in Table 1 [17].

Of note, in the UK, more than 99% of women with screen-detected breast cancer have a definitive diagnosis by core biopsy before surgery [40]. This would be expected to be almost 100% in symptomatic disease. Women were not, therefore, undergoing excision biopsy as a simultaneous diagnostic and therapeutic procedure. Those who chose breast-conserving surgery did so as their definitive surgical management, knowing their breast cancer diagnosis and phenotype. Many had neoadjuvant chemotherapy for triple negative disease between diagnosis and surgery.

**Table 1**  
Mainstream cancer genetic testing criteria [17].

Mainstream Category	Eligibility Criteria
1	Patient with diagnoses of breast cancer and ovarian cancer
2	Breast cancer in patients diagnosed ≤45 years
3	Two primary breast cancers, both diagnosed in patient ≤60 years
4	Triple negative breast cancer at any age
5	Male breast cancer
6	Breast cancer plus parent, child or sibling meeting any of the above (MCGplus)

\*MCG – mainstream cancer genetics.

### 2.2. Data Collection

A prospective database was maintained to capture all women undergoing MCG testing. Retrospective surgical data was added for women who were tested via this pathway between September 2013 and September 2018. Male patients were excluded. The information collected included test initiation and result date, initial preference for surgical procedure (both surgeon’s and patient’s) if documented, final surgical plan and influence of test result on eventual surgical procedure.

### 2.3. Statistical analysis

Descriptive statistics were used to characterize the study population and examine the pattern of surgical procedure selection with respect to timing of surgery.

## 3. Results

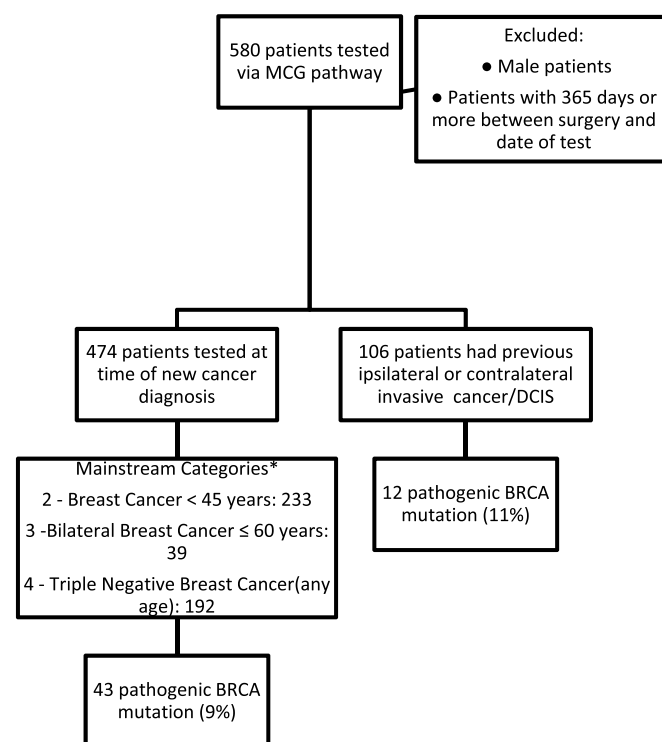
During the study period 580 patients were tested for BRCA1 and BRCA2 gene mutations in the MCG pathway. For 474 women this was at the time of their first diagnosis of breast cancer (invasive or DCIS). 106 patients had a previous history of ipsilateral or contralateral cancer or in situ disease and were excluded from the subsequent analysis of surgical decision-making. Fig. 1 illustrates how the patients were selected for final data analysis.

\*72 patients were tested at the clinician’s discretion. Some women fulfilled more than one criterion e.g., age less than 45 years and a triple negative cancer, see Fig. 2.

## 4. Newly diagnosed patients

### 4.1. Demographics and indications for testing

The median age at the time of diagnosis was 46 years (IQR 38–57). The median time taken for the result was 18 calendar days (IQR 15–21). Of the 474 patients, 49% were 45 years or younger and 8% had bilateral



**Fig. 1.** Flow diagram of patient selection in the study.

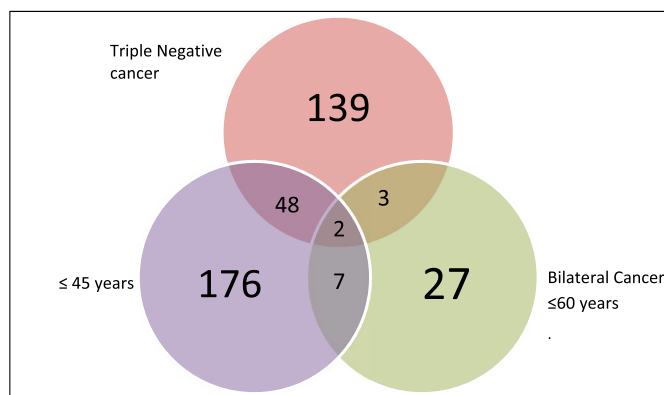


Fig. 2. Venn diagram showing distribution of patients across the three main testing indications.

breast cancer at the age of ≤60 years. 40% had triple negative breast cancer. There was overlap between the groups as 2 (0.4%) women younger than 45 years had bilateral and triple negative breast disease and 50 (11%) were young women with triple negative breast cancer (Fig. 2).

#### 4.2. Test results

43 of the 474 women (9%) women were found to have a pathogenic mutation in BRCA1 or BRCA2 (17/43,39% and 26/43,60% respectively). These data include the 72 women tested at the clinician's discretion who did not meet the standard mainstream criteria. Fig. 3 shows the distribution of the mutation carriers by indication for test.

#### 4.3. Impact of test results on surgical decision

Three hundred and two of 474 patients (64%) received their BRCA test results before surgery. The influence of timing of test results and subsequent surgical procedures is described in various groups, summarised in Tables 2–4.

#### 4.4. Group 1: BRCA mutation carrier patients who had test results before the surgery (n = 24)

Twenty-one out of 24 BRCA mutation carriers (88%) who knew their result before surgery opted for bilateral mastectomy. Sixteen of these twenty-one women had initially planned a breast-conserving operation or unilateral mastectomy.

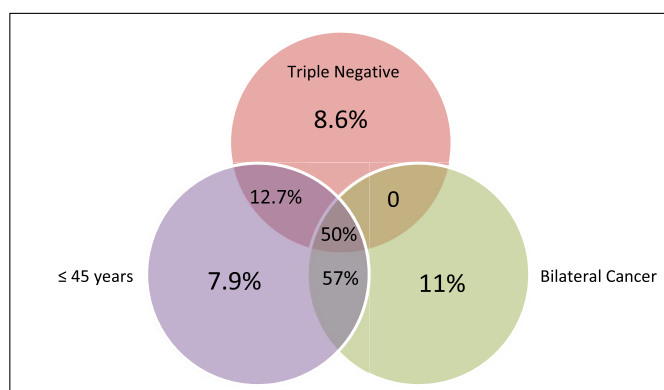


Fig. 3. Percentage BRCA1/2 mutation carriers by indication for testing.

Table 2  
Definitive surgery in relation to mainstream results.

	Primary Surgery According to Mainstream Results			
	Results Before Surgery (n = 302)		Results After Surgery (n = 172)	
	Group 1 BRCA mutation (n = 25)	Group 2 BRCA wild type (n = 277)	Group 3 BRCA mutation (n = 19)	Group 4 BRCA wild type (n = 153)
BCS	1 (4%) <sup>a</sup>	167 (60%)	15 (79%)	117 (76.5%)
Bilateral Mastectomy	22 (88%)	15 (5.4%)	1 (5%)	3 (2%)
Unilateral Mastectomy	2 (8%)	95 (34.2%)	3 (16%)	33 (21.6%)
Reconstruction	24/24 (100%)	89/110 (80%)	2/4 (50%)	26/36 (72%)

<sup>a</sup> Treated for ovarian cancer 2015, in remission at time of breast cancer treatment (2018). During breast cancer imaging incidental adrenal mass requiring further investigation was found. Therefore, it was decided to treat current cancer with BCS and plan further more extensive surgery at a later date.

Table 3  
Impact of BRCA results on surgical decision-making.

BRCA test result before surgery (n = 302)	Bilateral Mastectomy (n = 36)	Unilateral Mastectomy/Breast Conservation (n = 266)
<b>Pathogenic variant</b>	21	3
<b>Wild type</b>	15	263

Fisher's exact test - P < 0.0001.

Table 4  
Impact of timing of pathogenic variant in BRCA gene on extent of surgery.

BRCA test showed pathogenic variant (n = 43)	Bilateral Mastectomy (n = 22)	Unilateral Mastectomy/Breast Conservation (n = 21)
<b>Before surgery</b>	21	3
<b>After surgery</b>	1	18

Fisher's exact test - P < 0.0001.

#### 4.5. Group 2: BRCA wild type patients who had test results available before surgery (n = 278)

Ninety-five percent of the patients in this group (263/278) who learned that they did not have a BRCA mutation before surgery had unilateral surgery (60% breast conservation, 34% mastectomy). Only 15 (5%) of this group underwent bilateral mastectomy, of whom 4 had bilateral cancer at the time of diagnosis. A small minority (11 out of 278 women) proceeded with contralateral prophylactic mastectomy by personal choice, mostly influenced by family history. The median Manchester score for those who opted for bilateral mastectomy without bilateral disease (n = 11) was 9 (IQR 8–16).

#### 4.6. Group 3: BRCA mutation carriers who had surgery before the test results (n = 19)

Seven of the 19 carriers (39%) whose status was not known until after surgery returned for further surgery in form of contralateral risk-reducing mastectomy. The procedures they had before and following BRCA result are shown in Table 5. Despite not being able to influence their initial surgery, the additional procedures were undertaken before radiotherapy.

The remaining 11 patients opted for surveillance instead of further surgery. All of these patients opted for monitoring alone as personal choice after careful consideration of all options available to them during discussions in separate surgery and genetics clinics. It is possible that

**Table 5**  
Further surgical intervention in Group 3.

First Surgery	Further Ipsilateral Surgery	Contralateral Side	Interval between procedures (months)	RT	Reconstruction
BCS	SSM	SSM	7	No	DIEP
BCS	SSM	SSM	7	No	None
BCS	None	BCS*	6	No*	N/A
BCS	SSM	SSM/NSM	1	No	Implant
BCS	Simple	Simple	6	No	None
BCS	SSM	SSM	51	No	Implant
BCS	Simple	Simple	4	No	None
UNSM	None	SSM	8	No	Implant

RT – Radiotherapy; \*This patient had an incidental diagnosis of DCIS after contralateral symmetrisation surgery. She was then tested positive for BRCA genes and opted for no further surgery. SSM = skin-sparing mastectomy (with reconstruction); simple = simple mastectomy; NSM = skin and nipple-sparing mastectomy; UNSM = unilateral NSM.

these women opted for breast conserving surgery and had no intention of adjusting that decision, hence proceeded to surgery before the test result but since 8 of 19 had further surgery at that stage, we can hypothesise that had the result been available sooner, they might have chosen bilateral mastectomy as their definitive surgery. Furthermore, during a median follow-up of 45 months (IQR 17–52), 2 additional women have undergone contralateral risk-reducing mastectomy. Both of these patients had had implant-based reconstruction, without prior radiotherapy.

One patient's test result was available on the day of surgery. She was found to have mutation in BRCA2 gene. Her test result could not influence her decision about her surgical procedure. However, afterwards she opted for screening instead of further surgery. She later developed metastases and died.

#### 4.7. Group 4: BRCA wild type patients who had surgery before the test results ( $n = 153$ )

77% of these patients had breast-conserving surgery and 21.6% underwent unilateral mastectomy. 3 (2%) had bilateral mastectomy for bilateral disease at the time of initial diagnosis. Although all three of these patients had disease amenable to breast conservation on one side, they opted for bilateral mastectomy. Two chose bilateral simple mastectomy and one had implant-based reconstruction.

#### 4.8. Patients with a previous history of breast cancer ( $n = 106$ )

This group was different from the women newly diagnosed with breast cancer as they had previously undergone surgery (and sometimes radiotherapy) for ipsilateral or contralateral disease. This experience represents an additional factor in their decision-making.

The median age at diagnosis with the current episode of disease was 59 years (IQR 51–67). 27% (29/106) had triple negative breast cancer, 11% (12/106) were found to have a BRCA gene mutation, 50% (6/12) being a BRCA 1 mutation.

68 (64%) of these patients had their BRCA test result before their surgery and 8 (11.7%) carried a BRCA mutation. All of the latter opted for completion and/or risk-reduction surgery. Of 60 patients who had a BRCA wild type result before surgery, 22 (37%) had breast-conserving surgery, 35 (58%) had unilateral mastectomy. Only 3 (5%) women of this cohort opted for bilateral mastectomy despite having had previous ipsilateral or contralateral surgery for breast cancer in the past.

## 5. Discussion

This is the first European study to report on the impact of rapid access to genetic test results on surgical decision-making in women with

breast cancer. In concordance with the published literature [9,19], in the group of women who had a germline BRCA gene mutation the frequency of bilateral mastectomy is higher than breast conservation ( $p < 0.00001$ ). The difference in bilateral mastectomy rates by test result is much greater in women receiving their result before surgery than in a prospective study by Schwartz et al. In that study, now more than 16 years old, of 194 newly diagnosed breast cancer patients, only 48% of BRCA1/2 mutation carriers opted for bilateral mastectomy while as many as 24% of non-mutation carriers chose this [9]. In our study the rates were 88% and 5% respectively.

The key impact is in the timing of receiving these results: We have shown a significant difference in bilateral mastectomy rate between patients who had their BRCA test result before and after the surgery ( $p < 0.0001$ ). Similar results have been demonstrated by Armstrong et al. that more women who tested positive for BRCA mutation pre-operatively chose bilateral mastectomy as compared to women who had positive results after surgery [39]. In 2003 Weitzel et al. reported that women who underwent BRCA gene testing after their initial surgery showed regret at the lost opportunity of choosing a more proactive procedure for themselves [19]. In our cohort of patients, 47% of women who were found to carry a BRCA mutation after their initial procedure opted for further risk-reduction surgery. None of these women had radiotherapy prior to further surgery, thereby avoiding limiting their reconstructive options and avoiding issues of delayed wound healing and excessive implant failure rates following radiotherapy.

Risk-reducing surgery in breast cancer patients, both familial and sporadic in origin, reduces the risk of contralateral breast cancer as shown by Herrinton and Peralta et al. [20,21] However, the literature on impact of prophylactic mastectomy on overall and breast cancer-specific survival is conflicting. Fifteen years ago, Van Sprundel et al. demonstrated in a retrospective study that prophylactic mastectomy did not confer a significant overall survival benefit [22]. More recently, Valachis showed no difference in breast cancer-specific survival between BRCA carriers who had risk-reducing mastectomy and those who did not (HR 0.78, 95%CI 0.44–1.39) [23] and the prospective POSH study reported by Copson et al. revealed similar results, where immediate risk-reducing mastectomy was not associated with improved survival [24]. However, a meta-analysis by Li et al. has shown all-cause mortality being significantly lower in patients who have contralateral prophylactic surgery [25]. Not only the survival data is debatable, the choice of surgery for gene mutation carriers with regards to in breast recurrence is worthy of discussion. Pierce et al. has shown no significant ipsilateral recurrence difference in mutation carriers who had breast-conserving surgery and radiotherapy versus non carriers [26].

Despite this, simultaneous risk-reduction surgery in women newly-diagnosed with cancer who have a timely BRCA mutation carrier result has several potential advantages:

- 1) With ever-improving survival from a primary cancer [27], the risk of future development of contralateral disease has greater impact. In addition to survival implications there is morbidity associated with ongoing screening, investigation and treatment of any subsequent cancers and this should be taken into consideration.
- 2) Many women who choose bilateral mastectomy rather than breast conservation will avoid radiotherapy, unless their disease indicates the need for post-mastectomy radiotherapy.
- 3) If a woman undergoes breast-conserving surgery and radiotherapy before genetic testing, the radiotherapy limits reconstructive options as implant reconstruction in an irradiated field carries additional risks.
- 4) Autologous reconstruction in the form of DIEP flap can only be done as a single procedure because of the abdominal tissue harvest, so the decision for bilateral surgery is best taken pre-operatively. Many surgeons feel that symmetry is easier to obtain in implant reconstruction when both breasts are removed and reconstructed in the same operation.

For the healthcare system as well as for patients potentially a greater advantage of timely genetic test results is the reassurance provided to women who were found before surgery not to carry a BRCA mutation. They could proceed to breast conservation or unilateral mastectomy with confidence in their decision. In our study the rate of breast-conserving surgery was 60% and unilateral mastectomy was 34% (group II) while only 5% underwent bilateral mastectomy, markedly different from the 34% rate of bilateral mastectomy in women advised of a negative test result before surgery in Armstrong's paper. A similar rate was seen in women who had genetic testing at the time of a second breast cancer diagnosis, of whom only 5% chose bilateral mastectomy. Timely genetic testing may help limit the rise in demand for contralateral mastectomy (which carries its own risks) in those whose risk is insufficient to warrant it. King et al. and Tuttle et al. showed significant increases in risk-reducing mastectomy rates in the USA over time and reported on the various factors that may be driving this trend. Both have emphasised that decision-making for risk-reduction surgery should be optimised by appropriate risk assessment and patient education [28,29]. Leff et al. proposed a multidisciplinary approach and use of risk assessment tools to guide the decision-making process to avoid unnecessary surgery [30,31].

Incorporating genetic testing in the initial treatment planning in newly-diagnosed breast cancer patients could also have negative implications for all women. The majority of women will receive a result showing no mutation and be reassured [32,33]. For some, a pathogenic mutation will burden them with an additional complex decision at the time of an already anxiety-provoking diagnosis. There is a risk it could lead to a hasty decision for bilateral mastectomy [34,35] to conform with treatment target dates, though many women were undergoing neoadjuvant chemotherapy and had time to deeply consider their options. In our study, 11 of 18 patients who carried a BRCA mutation and learned of it after unilateral surgery, did not opt for further operations and preferred surveillance. None of them had an excision biopsy prior to their index operation. This is in concordance with the UK breast screening report 2020–2021, where 99% of women had pre-operative diagnosis [40]. It is not clear whether this suggests that when the decision is taken at a less emotionally-charged phase of life women are less likely to choose bilateral mastectomy, or that the psychological barrier of returning to the patient role and seeking a second surgical procedure is sufficient to affect decision-making. The number of women in this group was small, limiting our ability to interpret this. One woman in this group under surveillance developed metastatic disease that proved to be fatal. She had her results available on the day of surgery, hence not influencing her initial choice of surgery.

For the provider, the discussion of genetic testing adds little to the time taken for a surgical consultation, especially as it addresses a question often raised by patients themselves. The opportunity to discuss and seek consent through the mainstream pathway avoids delay inherent in referral to a separate genetics team and allows the genetics team to focus on women with a positive result thereby offering an efficient service to those who most need it. Provision of bilateral surgery is efficient in terms of bed occupancy and operating theatre time. However, payment structures for multiple procedures during a single anaesthetic mean that system-level efficiency is often not matched by cost-effectiveness for the provider.

Although our data have limitations, being a retrospective and single centre study, the information may also be useful for policy makers [18, 36]. Currently, in the UK, the criteria for genetic testing are narrower and still predominantly based on family history to standardise national test delivery. Sun et al. have shown that unselected genetic testing (including BRCA and PALB2) has better chances of detecting genetic variants, as compared to currently-used criteria based on prior likelihood of mutation [36]. Our study provides evidence that timely genetic testing has a wider impact on the management of breast cancer patients. With the advent of personalized medicine, it becomes even more relevant to be guided by risk assessment including genetic testing while

planning treatments for cancer patients [37]. Tuttle et al. have recommended recent recommendations for availability of genetic testing for all breast cancer patients as it will improve patient centred care in terms of tailored therapy regimen and follow-up [38]. However, there are limitations to the available published data and there are no randomised controlled trials assessing the benefit of contralateral mastectomy, the timing of genetic testing, psychological impact, or outcome of breast conservation in this group of patients. Therefore, consultations must convey the balance between risk of recurrence from the primary, risk of a contralateral breast cancer, the risks and efficacy of additional surgery, and the effects of adjuvant treatment and risk-reducing bilateral salpingo-oophorectomy [23].

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## Ethics approval

Approved by Clinical Research and Development Department at The Royal Marsden NHS Foundation Trust with reference number SE471.

## Author statement

Concept – CR,AG,ZK,JR; Design – CR,AG,JR,ZK,QA; Supervision – JR,ZK; Materials – JR; Data Collection and/or Processing –; QA,MM, CR; Analysis and/or Interpretation - QA; Literature Search –; QA, JR; Writing Manuscript – QA,JR; Critical Reviews - QA,CR,MM,AG,ZK,JR.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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