

## REVIEW

# Finding all *BRCA* pathogenic mutation carriers: best practice models

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Identifying germline *BRCA* pathogenic mutations in patients with ovarian or breast cancer is a crucial component in the medical management of affected patients. Furthermore, the relatives of affected patients can be offered genetic testing. Relatives who test positive for a germline *BRCA* pathogenic mutation can take appropriate action to prevent cancer or have cancer diagnosed as early as possible for better treatment options. The recent discovery that *BRCA* pathogenic mutation status can inform treatment decisions in patients with ovarian cancer has led to an increased demand for *BRCA* testing, with testing taking place earlier in the patient care pathway. New approaches to genetic counselling may be required to meet this greater demand for *BRCA* testing. This review discusses the need for best practices for genetic counselling and *BRCA* testing; it examines the challenges facing current practice and looks at adapted models of genetic counselling.

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## INTRODUCTION

It is well established that individuals carrying a germline *BRCA1* or *BRCA2* pathogenic mutation have an elevated lifetime risk of developing ovarian cancer (40% and 18% by age of 70 years for *BRCA1* and *BRCA2*, respectively) or breast cancer (57% and 49% by age of 70 years for *BRCA1* and *BRCA2*, respectively).<sup>1</sup> Prospective cancer-risk data from the EMBRACE study in the UK show similar numbers; average cumulative risk of ovarian cancer by age of 70 years in *BRCA1* and *BRCA2* pathogenic mutation carriers is 59% and 17%, respectively; and 60% and 55%, respectively, for breast cancer.<sup>2</sup> Although guidelines differ between countries and regions, genetic testing is used predominantly to determine the *BRCA* pathogenic mutation status and assess the cancer risk in patients with a high probability of an inherited predisposition, which is currently based in particular on a family history for breast and ovarian cancer or, for instance, Jewish ancestry.<sup>3–6</sup> Pathogenic mutation carriers are offered regular surveillance and/or prophylactic mastectomies or prophylactic salpingo-oophorectomies, which have been shown to reduce the risk of developing cancer.<sup>7,8</sup>

In view of the elevated lifetime risk of developing ovarian or breast cancer associated with germline *BRCA* pathogenic mutations, it is important that relatives of those patients who developed ovarian or breast cancer because of a germline *BRCA* pathogenic mutation are offered germline *BRCA* testing. Those relatives who are confirmed as carrying a germline *BRCA* pathogenic mutation can then take appropriate action in order to prevent cancer or have cancer diagnosed as early as possible for better treatment options.

Recent studies have reported that patients with ovarian cancer who carry a *BRCA* pathogenic mutation have longer survival rates, a favourable response to platinum-based chemotherapy and may demonstrate sensitivity to novel treatments such as inhibitors of poly(ADP)-ribose polymerase (PARP), which target the DNA repair pathway that is defective in the tumour cells of carriers.<sup>9–12</sup> By focussing on family history while selecting patients eligible for *BRCA*

testing, 15–44% of women with ovarian cancer, who are *BRCA* pathogenic mutation carriers but appear to have no family risk factors, are missed.<sup>9,13–16</sup> With the prospect of targeted treatment options on the horizon and the high prevalence of *BRCA* pathogenic mutations among patients with ovarian cancer, there is a case for expanding genetic testing to all women with ovarian cancer regardless of family history and to screen not only for germline *BRCA* pathogenic mutations in this setting but also for somatic *BRCA* pathogenic mutations.<sup>9,17</sup>

*BRCA* testing guidelines vary considerably between countries, but there is an evolving trend to look beyond family cancer history. For instance, the National Comprehensive Cancer Network, the American Congress of Obstetricians and Gynecologists and the revised Dutch guidelines recommend *BRCA* genetic testing for patients with ovarian cancer, irrespective of family history, and the Scottish Intercollegiate Guidelines Network guideline 135 recommends offering *BRCA* genetic testing to all women with non-mucinous ovarian cancer or fallopian tube cancer, irrespective of family history; however, other guidelines, including the European Society for Medical Oncology clinical practice guidelines and some country-specific guidelines, rely on family history of breast cancer and/or ovarian cancer.<sup>4–6,18,19</sup>

Undeniably, this increase in demand for *BRCA* testing will have an impact on the current genetic testing process. Current practice in many countries requires face-to-face counselling with a qualified genetic counsellor or a clinical geneticist both before and after *BRCA* testing.<sup>3,5</sup> One could argue that there will be a need for more genetic professionals in order to cope with increasing demands, but new approaches for delivering genetic counselling can also be explored.

This review gives an overview of alternative procedures for genetic counselling and testing of patients at risk of hereditary breast and ovarian cancer, with a focus on patients with ovarian cancer. On the basis of these examples and the experienced advantages and disadvantages, a novel best practice model for patients with ovarian cancer is proposed, to ensure that patients and relatives receive consistency

of care and that sequence variants are interpreted and managed appropriately.<sup>20</sup>

### The effect of new treatment options on the existing *BRCA* testing process

Utilising *BRCA* testing to inform treatment selection is likely to add greater complexity to the existing testing process (Figure 1). Early and rapid *BRCA* testing has already been introduced in the workflow of many centres for newly diagnosed women with breast cancer who have characteristics of an inherited predisposition, in order to inform surgical decisions (eg, bilateral mastectomy).<sup>21</sup> Because of the implications of test results on patients and their families (ie, raised cancer risk), current practice in many countries requires face-to-face counselling with a qualified genetics counsellor both before and following *BRCA* testing.<sup>22</sup> As genetic testing may take place early in routine patient care in order to guide management decisions, the content and timing of genetic counselling is likely to change in the future.<sup>23</sup>

As models of genetic counselling evolve, a multidisciplinary team of professionals, including clinical geneticists, gynaecologists, surgeons, radiotherapists and medical oncologists will be increasingly involved in the process.<sup>23</sup> Any future model of *BRCA* testing and genetic counselling will need to address a range of issues that arise in genetic counselling. For example, broader cancer gene testing may lead to a higher probability of identifying a ‘variant of unknown significance’ rather than a known pathogenic mutation, which requires careful interpretation and sensitive explanation by a clinical geneticist.<sup>24,25</sup> In addition, clinicians need to be aware of the different clinical consequences of a somatic versus a germline pathogenic *BRCA* mutation. Furthermore, if a negative *BRCA* result is received, other less frequent genetic causes of cancer predisposition need to be considered.

The effect of genetic testing reaches beyond the patient with cancer and affects the entire family. Not only are there consequences for relatives once a pathogenic *BRCA* mutation is found but also when no such mutation is found, as the relative may still have a high familial risk for cancer and the need for cancer prevention. Currently, the majority of oncologists are not accustomed to calculating and communicating cancer risks for relatives.<sup>26</sup> The information provided to patients and their relatives needs to be consistent among all members of the multidisciplinary team and a clinical geneticist must be part of this team. Importantly, professionals involved in *BRCA*

testing need to be aware of the psychological consequences of *BRCA* genetic testing, which may result in distress during the testing process and/or after carrier status is identified.<sup>27–29</sup>

### MODELS OF GERMLINE *BRCA* TESTING

Research is currently being undertaken on novel approaches to *BRCA* testing and genetic counselling.<sup>24,30–32</sup> These alternative processes may act as a guide to optimal practice as the demand for access to genetic counsellors and clinical geneticists increases. The following section outlines four approaches to genetic counselling and discusses the associated issues and benefits of each in the context of current practice.

#### Current practice: the Huntington protocol

Because of the potentially far-reaching implications of *BRCA* susceptibility testing, a lighter version of the ‘Huntington protocol’ was adopted for the counselling of unaffected individuals who wanted to determine whether they had inherited a familial pathogenic mutation in *BRCA*.<sup>22</sup> Predictive testing is generally offered solely to adults at risk, who have had the appropriate counselling, are fully informed and wish to proceed.<sup>22</sup> The guidelines recommend that individuals who undergo predictive testing are seen for two to four counselling sessions, spread over a 3-month period, before disclosure of the test results.<sup>22</sup> If a pathogenic mutation is found, counselling must be offered to the family and others involved.

The pre-test counselling sessions allow for advance consideration of medical options and the impact that test results may have on the individual as well as on family members, while post-test counselling provides a valuable opportunity for health-care providers to interpret test results and to decide whether additional genetic testing is needed. For instance, in women with ovarian cancer and a family history for colorectal cancer, analysis of the mismatch repair genes may reveal Lynch syndrome. Another item in the post-counselling is to emphasise the importance of continuing regular preventive activities for the patient and for relatives if indicated.<sup>33</sup> For example, if a patient receives a negative *BRCA* test result, a personalised and intensified breast surveillance protocol in agreement with increased familial cancer risk as calculated from the exact family history is often advised for specific female relatives. Therefore, relatives may benefit from cancer prevention both in cases of a pathogenic mutation in *BRCA* or in cases of a positive family history hinting at a high familial cancer risk.

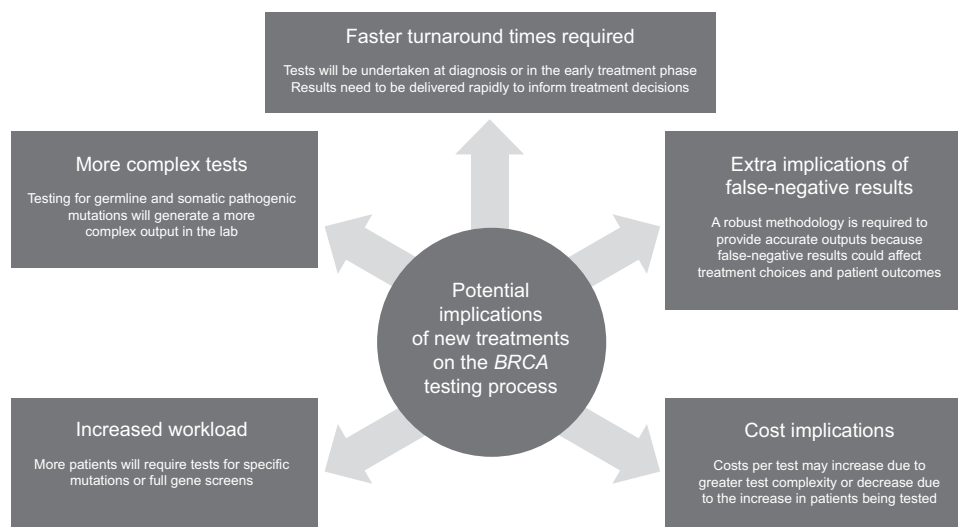


Figure 1 New treatment options will have an impact on existing *BRCA* testing processes.

Although there are local or national variations of this process, the universal characteristic is the need for at least one pre-test counselling session with a genetic counsellor or a clinical geneticist. The strength of this approach is the face-to-face contact with a health-care professional who is specifically trained in discussing the medical and psychological implications of genetic testing; however, this approach may no longer be possible in the era of treatment-based genetic counselling, which demands faster turnaround times.<sup>23</sup>

### The 'DNA-direct' model (The Netherlands)

The 'DNA-direct' model is a telephone-based genetic counselling model for patients with breast cancer. It is a novel approach that replaces the initial consultation with a telephone call (to provide information, not counselling) and written and digital information, which is sent home with the patient; face-to-face counselling is offered only after *BRCA* testing, where the counsellor discloses the DNA results and delivers customised advice to the patient (Figure 2).<sup>32</sup>

The aim of this process is to eliminate extraneous information, which is not applicable to the individual patient, and to provide patients with the information they desire in a quick and patient-centric manner.<sup>32</sup>

In a study of 161 eligible patients with breast cancer, patients chose either the DNA-direct approach or a traditional DNA-intake approach. The DNA-intake approach offered pre-test face-to-face genetic counselling. The patients who chose the DNA-direct approach received an information package, which included an information letter, a link to a website and access to a short educational movie about hereditary breast cancer and DNA-testing. An appointment for a personal consultation to disclose the results was set for 8 weeks after DNA-testing commenced.<sup>32</sup> The fact that patients were not randomised between the two methods of counselling enabled the researchers to measure the percentage of patients that opted for the DNA-direct approach. This study design however introduced a bias and does not allow a thorough comparison between the two approaches.

Overall, 59% of patients chose the DNA-direct approach, of whom 89% were satisfied and would choose DNA-direct again (including 6/8 carriers of a pathogenic *BRCA* mutation). The self-reported reasons for choosing the DNA-direct or the DNA-intake approach can be seen in Figure 3.<sup>32</sup>

Patient characteristics differed significantly between the approaches (Figure 3). Participants who had previously received information about personal consequences of hereditary breast cancer, or used websites for breast cancer information, were more likely to choose DNA-direct.<sup>32</sup> Those who had received information about genetics in general or who experienced higher decisional conflict were more likely to choose DNA-intake.

General distress and heredity-specific distress scored lower in the DNA-direct group than the DNA-intake group both at baseline and at

follow-up 2 weeks after *BRCA* result disclosure.<sup>32</sup> Quality of life, breast cancer worry, risk perception for hereditary breast cancer and second breast cancer did not differ between DNA-direct versus DNA-intake or over time. *BRCA* pathogenic mutation detection rate was equal between procedures at 8%. Processing time (triage call to patient *BRCA* result disclosure) was reduced by 1 month with the DNA-direct (70 days) versus the DNA-intake (103 days;  $P=0.002$ ) approach.<sup>32</sup> The total duration of face-to-face contact time was diminished from 60 to 30 min (unpublished data). It is worth noting that processing times are health-system dependent and may vary elsewhere.<sup>32</sup>

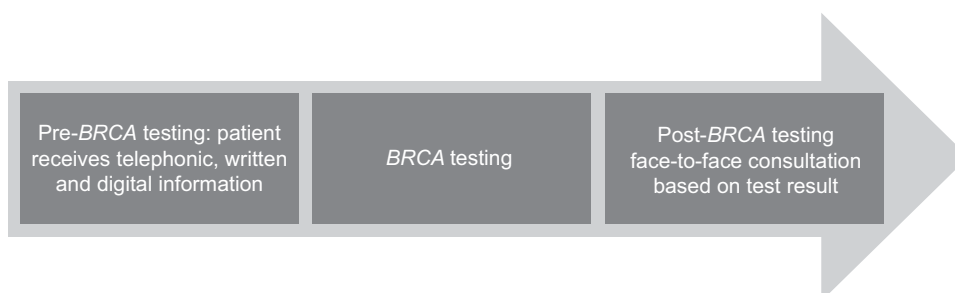
The authors concluded that before *BRCA* testing, more patients with breast cancer preferred replacing a face-to-face consultation with a trained genetic counsellor by a home information package including telephone, written and digital information. The majority of patients were strongly to moderately satisfied with the procedure without increased distress compared with the face-to-face intake approach.<sup>32</sup> Benefits attributed to the DNA-direct approach included the ability to review information at home without having to attend additional hospital/clinic appointments and perceived faster turnaround times; however, this approach may not be suited to all patients. The authors suggest that it may be most appropriate for patients who match the overall profile of DNA-direct participants – more highly educated and better informed patients, who are more certain of genetic testing and show less distress.<sup>32</sup>

### Telephone-based counselling model (USA)

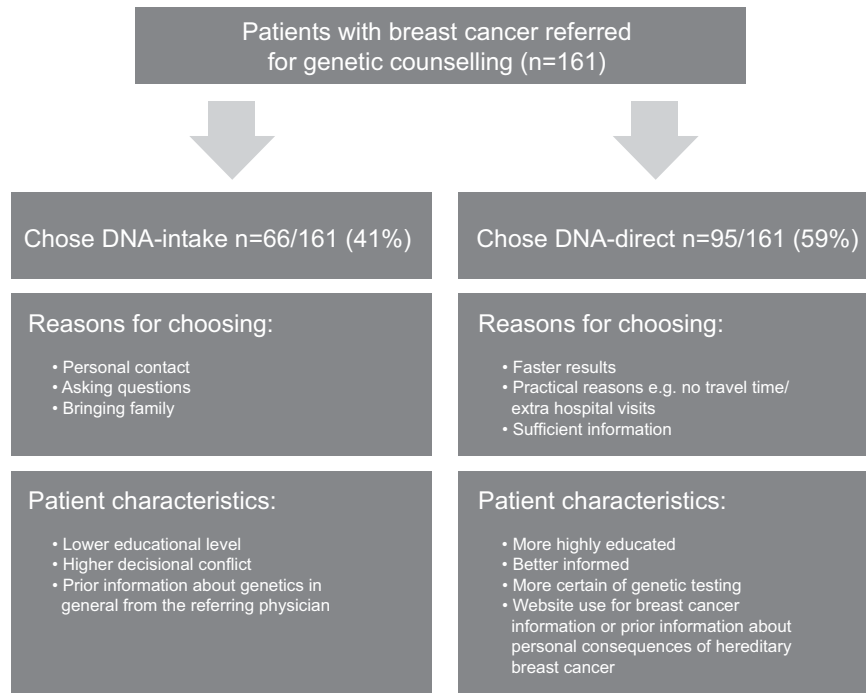
The telephone-based counselling model was made for healthy relatives or patients after successful breast or ovarian cancer treatment. Genetic counselling offered via telephone has the potential to broaden the reach and accessibility of *BRCA1/BRCA2* testing – especially in rural areas or where there is limited access to genetic counselling resources – and to reduce costs (Figure 4).<sup>31</sup>

A study by Schwartz *et al.*<sup>31</sup> compared telephone delivery of *BRCA* genetic counselling with in-person delivery. Women aged 21–85 years, who did not have newly diagnosed or metastatic cancer and who lived within a study site catchment area, were randomly assigned to usual care or telephone counselling. Usual care participants received in-person pre- and post-test counselling while telephone counselling participants completed all counselling by telephone. Telephone counselling was non-inferior to usual care on all primary outcomes (Figure 5).

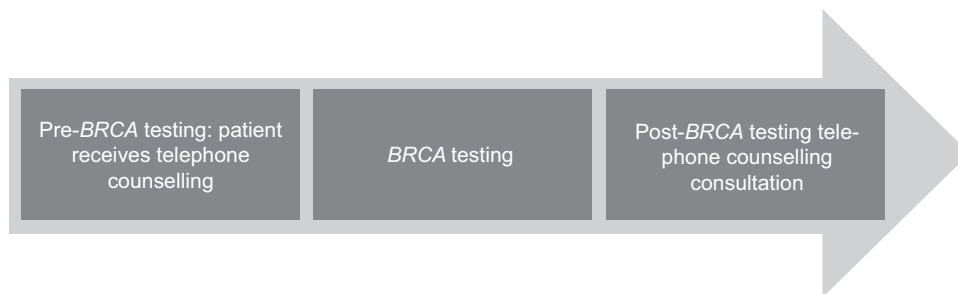
One area where telephone counselling was not equivalent to usual care was on *BRCA* test uptake: 84% of patients randomised to telephone counselling went on to have a *BRCA* test compared with 90% following usual care. Patients receiving usual care could supply a DNA sample directly after their counselling session, whereas telephone-counselled patients had to travel to a clinic to provide a sample. Moreover, the time between the telephone counselling session and



**Figure 2** The DNA-direct approach for patients with breast cancer to genetic counselling.



**Figure 3** Patient characteristics and their reasons for choosing DNA-intake or DNA-direct approaches.



**Figure 4** The telephone-based counselling model for healthy relatives or patients after successful breast cancer treatment.

attending the clinic may have provided time for deliberation and reconsideration, leading patients to forgo testing.

The outcome of this study might have been influenced by the fact that ‘direct-to-consumer’ genetic testing is offered by numerous companies in the USA and therefore is more common practice than in other countries. Especially in Europe, this is not common practice. In our opinion, it is important to note that telephone counselling may not be appropriate for newly diagnosed patients with cancer or patients with metastatic cancer, for whom the reassurance of face-to-face guidance is important.

#### Royal Marsden testing model (UK)

At the Royal Marsden Hospital in London a new mainstreaming model for *BRCA* testing in patients with ovarian cancer has been implemented.<sup>34</sup> This pathway requires non-geneticists to undertake online training and follow clear protocols that delineate the patient pathway and the approval process (Figure 6).

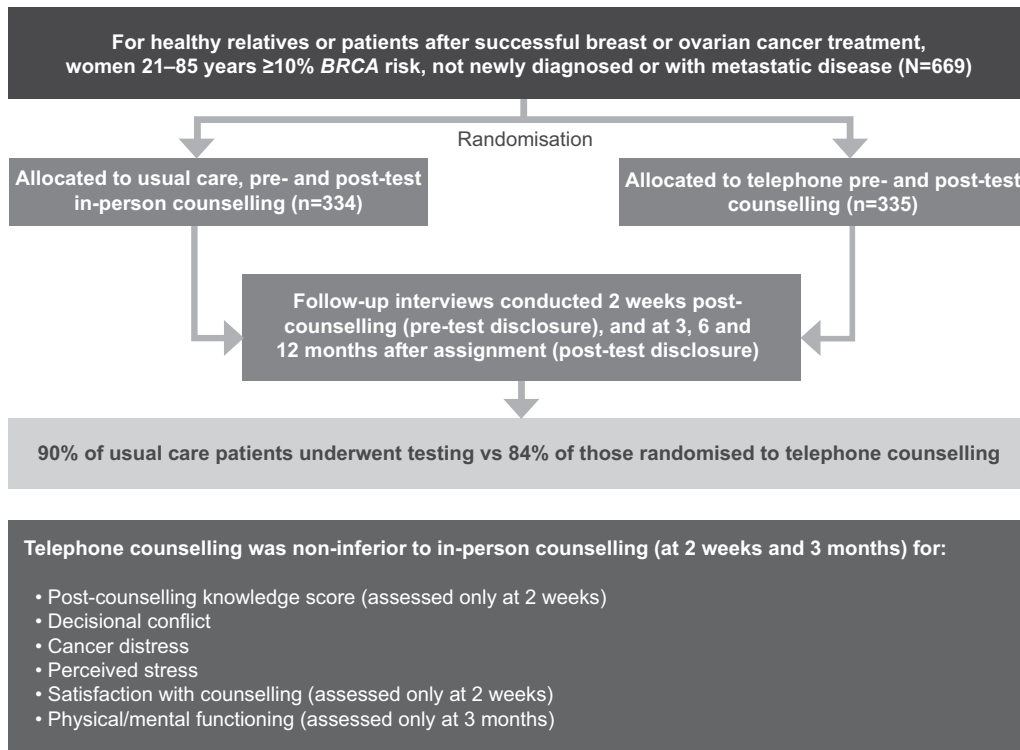
This approach aims to bring gene testing to the patient through their existing oncology appointments. Trained members of the oncology team manage the pre-test consultation; however, patients are referred to the Cancer Genetics Unit if more detailed discussions are required. Any patient found to carry a pathogenic mutation is seen

by a geneticist in the Cancer Genetics Unit; those with normal results are referred to the Cancer Genetics Unit only if requested by the patient.

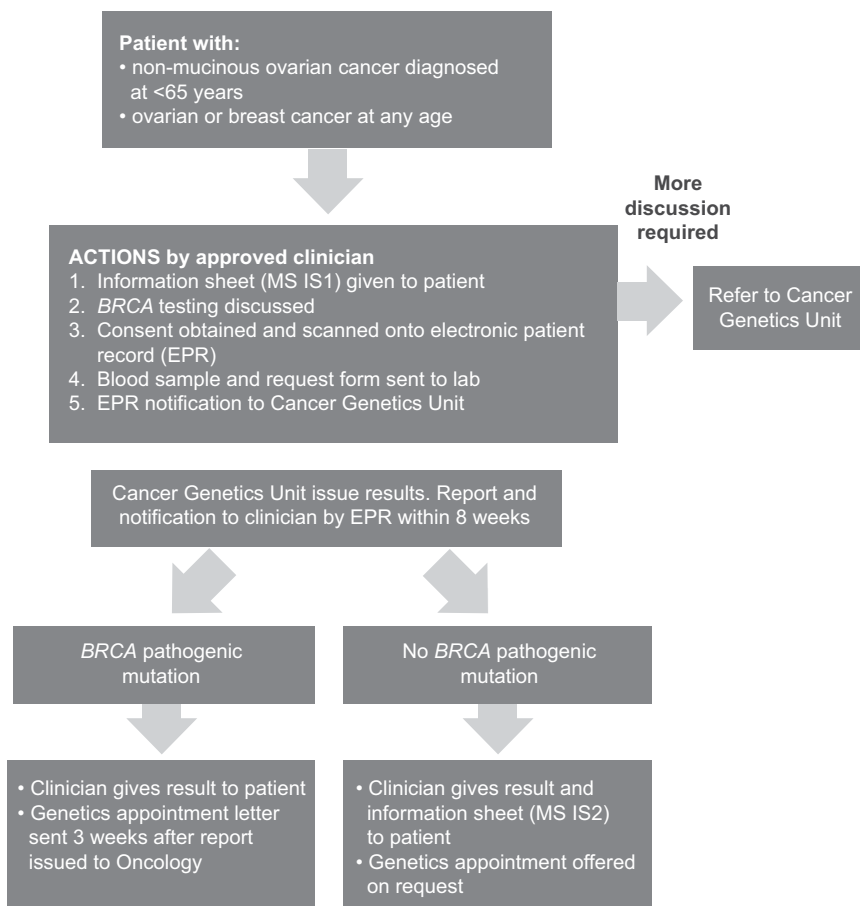
In a pilot from July to December 2013, 119 women with either non-mucinous ovarian cancer diagnosed at <65 years or ovarian or breast cancer at any age were tested.<sup>34</sup> No patients requested additional Cancer Genetics Unit input before the test. Among the 119 women tested, 20 patients (17%) carried a pathogenic mutation (*BRCA1* *n* = 8, *BRCA2* *n* = 12). Of those with a pathogenic mutation, 60% were assessed as having no family history of breast and/or ovarian cancer. Nine of the carriers of a pathogenic mutation had an immediate change in management due to *BRCA* status. It should be noted that data on family history from this study were not validated or checked and no data are available on uptake of *BRCA* cascade testing in relatives.

#### SOMATIC (TUMOUR) PATHOGENIC MUTATIONS IN *BRCA*: IS THERE A CASE FOR TESTING PRIOR TO GERMLINE TESTING?

Although research has demonstrated that germline pathogenic mutations in *BRCA1/BRCA2* in ovarian cancer can deregulate homologous recombination (HR), and thereby increase a patient’s sensitivity to platinum-based chemotherapy and possibly to treatment with PARP



**Figure 5** Telephone counselling was non-inferior to usual care on all primary outcomes.



**Figure 6** The Royal Marsden *BRCA* testing model.<sup>31</sup>

inhibitors, few studies have investigated the potential impact of somatic sequence variants on *BRCA* function.<sup>9–12</sup>

A recently published study has demonstrated that germline and somatic pathogenic mutations in HR genes (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *FAM175A*, *MRE11A*, *NBN*, *PALB2*, *RAD51C* and *RAD51D*) occur in ~31% of patients with serous or non-serous ovarian cancer.<sup>12</sup> Of these, 75% of germline HR mutations and 71% of somatic HR mutations were in *BRCA*.<sup>12</sup> Patients with a germline or somatic HR pathogenic mutation were more sensitive to primary platinum chemotherapy and experienced improved overall survival (66 months, germline HR mutation; 59 months, somatic HR mutation; and 41 months, no HR mutation) compared with patients with no HR pathogenic mutations.<sup>12</sup>

The role of somatic pathogenic *BRCA* mutations in platinum-based chemotherapy sensitivity, and their potential role in PARP inhibitor sensitivity, suggests that the number of women with ovarian cancer who might benefit from these treatments is greater than predicted by the frequency of germline pathogenic mutations.<sup>10</sup> Consequently, there is a possible case for the inclusion of somatic pathogenic mutation testing in the *BRCA* testing process.

The ‘Nijmegen tumour analysis plan’ is one such proposed genetic counselling pathway that includes *BRCA* testing of ovarian tumour samples from newly diagnosed patients with ovarian cancer as a means of pre-screening for germline *BRCA* testing. The benefit of this plan is twofold. First, this allows more effective recognition of patients who may benefit from PARP inhibitor treatments. Second, and equally important, these patients are also eligible for germline *BRCA*-analysis to determine hereditary cancer risks in their relatives, who may benefit from cancer-prevention measures. Half of the tumour *BRCA* pathogenic mutations are accompanied by a germline *BRCA* pathogenic mutation.<sup>35</sup> Therefore, the use of tumour *BRCA* testing as a pre-screen

for germline *BRCA* testing would reduce the number of patients referred for genetic counselling and increase the pathogenic mutation detection rate of germline *BRCA* testing from 12 to 50%. We are aware that tumour *BRCA* testing poses several challenges for laboratories, which are discussed in the accompanying article by Andrew Wallace (*New challenges for BRCA testing: a view from the diagnostic laboratory*).

### SUMMARY OF *BRCA* TESTING AND COUNSELLING MODELS

It is possible that future *BRCA* testing and counselling models will incorporate different elements of those models described above. In Figure 7, a hypothetical *BRCA* testing model is described for a broader ovarian cancer population that keeps the patient and their relatives well informed of the test consequences throughout the process. In this model, all newly diagnosed patients with epithelial ovarian cancer receive an initial *BRCA* test of tumour samples guided by a gynaecologist. For those patients testing positive for a *BRCA* tumour pathogenic mutation with or without a positive family history of cancer, a clinical geneticist would provide counselling before germline *BRCA* testing. On the basis of patient preferences, this could be via telephone with additional educational resources provided in the form of written and digital information. Following germline *BRCA* testing, all patients would be provided with face-to-face genetic counselling with a clinical geneticist. Patients who test negative for a *BRCA* tumour pathogenic mutation but have a positive family history of cancer would also be referred for genetic counselling.

There is still some ambiguity amongst national and society guidelines on the universal approach of *BRCA* testing for all newly diagnosed patients with ovarian cancer, with several still having a requirement of a pre-test probability threshold to be met before genetic testing is offered.<sup>36</sup> Arguments for having a pre-test probability threshold are generally based on the cost implications and potential overload to

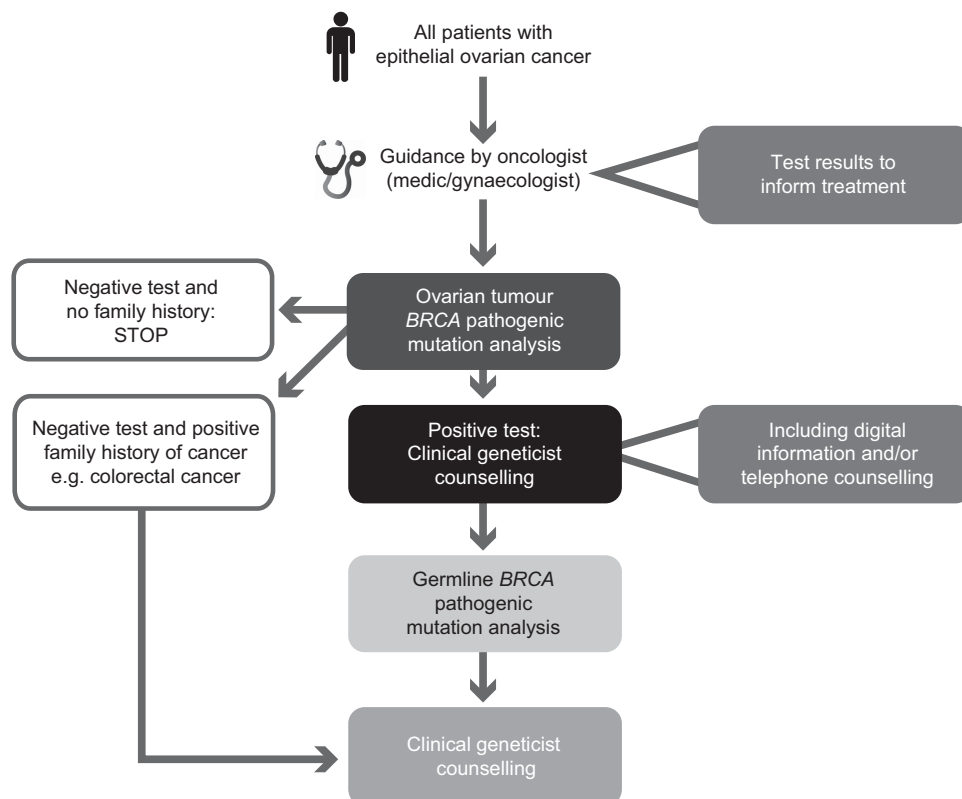


Figure 7 Summary *BRCA* testing and counselling model for a broad ovarian cancer population.

existing health-care infrastructure and services.<sup>36</sup> There will also be some patients who will not choose to have genetic testing performed due to ethical/religious beliefs or comorbidities such as psychological conditions.

## THE IMPORTANCE OF EDUCATION AND THE MANAGEMENT OF PATIENT PREFERENCES IN THE GENETIC COUNSELLING PROCESS

Educating women and their families on the consequences of genetic testing so that they can make an informed decision about whether to proceed is a central tenet of the genetic counselling process. In most women, this can be achieved successfully through face-to-face or telephone-based consultations with clinical geneticists, or at home via printed and digital media.<sup>24,30–32</sup>

Patients at risk of a hereditary predisposition are likely to prefer information that is specific to their familial risk of cancer and the treatment or prophylactic options available to them over general information on genetics.<sup>37</sup> Providing personalised information as early as possible and reducing the long period of uncertainty during the genetic diagnostic process may prove helpful.<sup>32</sup>

Studies have consistently reported high levels of inaccurate risk perception in women at high risk, even after counselling.<sup>38</sup> Therefore, health-care professionals involved in the genetic counselling process must be adequately trained to ensure that genetic test results are correctly interpreted and the potential consequences of those results are clearly and consistently communicated to the patient.

A single approach to genetic counselling may not be appropriate for all patients. Although the majority of patients are comfortable with receiving pre-test information via telephone, print or digital media, others express a preference for the personal contact of a face-to-face consultation with a clinical geneticist.<sup>32,39</sup> Determining patient preferences early in the genetic counselling process, and ensuring that the process is flexible enough to accommodate a range of preferences, will ensure that both the needs of the patient and of her relatives are adequately met.<sup>23</sup>

## CONCLUSIONS

In many countries, genetic counselling before *BRCA* testing is carried out face-to-face by a qualified genetic counsellor or a clinical geneticist. Germline *BRCA* testing without prior face-to-face genetic counselling could be considered for selected patients who are adequately informed by their oncologist together with telephone, digital or written information from a clinical geneticist. This could include all patients with ovarian cancer and breast cancer patients with a positive family history of breast or ovarian cancer.

There is a general consensus that after a positive *BRCA* test result or in cases of highly suggestive family history for hereditary cancer, face-to-face counselling with a clinical geneticist is important in order to discuss the consequences of the results for the patient and other family members, as well as to explain complex test results and other hereditary causes of cancer. Evidence suggests that there is a case for extending genetic testing to all patients with ovarian cancer; the inclusion of genetic testing for somatic pathogenic mutations may also prove valuable. In the era of personalised care and treatment-based genetic counselling these approaches may form the basis of optimising future workflow.

## CONFLICT OF INTEREST

NH has received payments for consulting and speaker services from AstraZeneca and has attended advisory boards for AstraZeneca. She has also received grant support from AstraZeneca. MCJJ has declared no conflicts.

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