Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients

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Abstract (maximum 250 words)
Traditionally, *BRCA* genetic testing has been undertaken to identify patients and family members at future risk of developing cancer and patients have been referred for testing based on family history. However, the now recognised risk of ovarian carcinoma (OC) patients, even those with no known family history, harbouring a mutation in *BRCA1/2*, together with the first poly adenosine diphosphate [ADP] ribose polymerase inhibitor (PARPi; olaparib [Lynparza™]) being licensed for the treatment of *BRCA*-mutated OC, has led to reconsideration of referral criteria for OC patients. Provided here is a review of the existing data and guidelines in the European Union, relating to recommendations, as well as considerations, for the referral of OC patients for *BRCA* genetic testing. Based on this review of newly updated guidance and up-to-date evidence, the following is recommended: all patients with invasive epithelial OC (excluding borderline or mucinous), including those with fallopian tube and peritoneal cancers, should be considered as candidates for referral for *BRCA* genetic testing, irrespective of age; genetic testing should ideally be offered at diagnosis, although patients can be referred at any stage; retrospective testing should be offered to patients in long-term follow-up because of the implications for family members and individual future breast cancer risk; and germline *BRCA* testing of a blood/saliva sample should initially be conducted and, if negative, tumour tissue should be tested (to identify non-germline [somatic] *BRCA* PARPi therapy candidates).

**Highlights** *(max 85 characters, including spaces, per bullet point):*

- **Offer** *BRCA* genetic testing to all invasive epithelial OC patients (excluding borderline and mucinous cancers)
- **Testing** should be irrespective of age
- **Ideally** offer testing at diagnosis, although patients can be referred at any stage
- **Retrospective** testing should be offered to patients in long-term follow-up
- **Tumour** testing should be considered in non-germline-mutated patients

**Keywords:** ovarian cancer, *BRCA1*, *BRCA2*, PARPi, guidelines, genetic testing

**Introduction**
Ovarian cancer (OC) is the fifth most common cancer in European women; estimated 65,500 cases and 42,700 deaths annually [1]. Germline mutations in *BRCA1* and *BRCA2* (tumour suppressor genes) incur an increased risk of breast cancer (BC) and/or OC and, to a lesser extent, other cancers [2,3]. The general population's lifetime risk of developing OC is 1.5% [4], compared with 40–60% and 11–30% for women with *BRCA1* and *BRCA2* germline mutations, respectively [5]. Approximately 6–25% of OC patients have a *BRCA1/BRCA2* germline mutation [4], and a further 5–11% have a somatic mutation [5,6].

Identification of *BRCA*-mutated OC patients is important to identify those at further cancer risk, at-risk family members and for individual treatment decisions, as germline/somatic *BRCA*-mutated OCs are associated with improved response to platinum-based chemotherapy (OC standard-of-care) and long-term prognosis than non-*BRCA*-associated OCs [2,7]. Furthermore, in 2015, the first poly adenosine diphosphate [ADP] ribose polymerase inhibitor (PARPi; olaparib [Lynparza™]) was licensed in Europe for *BRCA*-mutated (germline/somatic) high-grade serous OC (HGSO) treatment [8]. Thus, *BRCA* genetic analysis is now also important to identify PARPi therapy candidates.

Despite up to 25% of OCs harbouring a *BRCA1/2* germline mutation [4], >40% of mutation carriers have no known family history of BC/OC [4,10]. Traditionally, *BRCA* genetic testing referral was based on family history, thus likely to miss many OC *BRCA* carriers. In light of the now recognised high incidence of *BRCA* mutations in OCs, recently updated guidelines have extended testing beyond those with a family history. For example, the European Society of Medical Oncology (ESMO) *BRCA* testing guidelines, 2011 update, recommend testing based on family history and estimated mutation risk [11], whereas international guidelines by the National Comprehensive Cancer Network [12], 2015 update, recommend *BRCA* testing in all invasive OC patients and the Society of Gynaecological Oncology guidelines [13], 2014 update, recommend testing all patients with epithelial ovarian, tubal and peritoneal cancers (Table 1). OC *BRCA* testing guidelines have recently been updated in many European countries, representing a shift away from family-history-based testing towards OC histology based recommendations, reflecting the need to identify patients for treatment decisions and patient’s lack of accurate family history. The published/open-access guidelines available for *BRCA* testing in OC patients are summarised in Table 1 [11–25].

The referral criteria differ between these published guidelines due, mostly, to guideline publication timing and understanding OC patients’ mutation risk at that time, along with considered local practicalities of excluding/including minority patient groups with a low mutational risk. Furthermore, many institutions have established practices not stipulated in their national guidelines; for example, the Royal Marsden Hospital (UK) and the Leuven Cancer institute (Belgium, EU) test all ovarian (fallopian tube and primary peritoneal), non-
mucinous cancer patients for germline BRCA mutations. The aim of this manuscript is to review the existing data/guidelines and provide an updated opinion on recommendations and considerations for the referral of OC patients for BRCA genetic testing.

**Referral criteria for BRCA testing in OC patients**

In unselected population studies, BRCA mutations are most frequently associated with high-grade serous OC (HGSOC) (17%) and to a lesser extent with low-grade serous carcinoma [26]; 1–13% of other homologies also harbour BRCA mutations (Table 2; [8, 26–30]). Based on this evidence, and in line with recently updated guidance, it is recommend that OC patients with invasive epithelial OC (excluding borderline and mucinous), including fallopian tube and peritoneal cancers, irrespective of age, are considered for referred for BRCA genetic testing; non-epithelial cancers that should also be excluded include germ cell and sex cord–stromal tumours.

The decision to exclude pure borderline and mucinous OCs is based on the lack of association between BRCA mutations and these histologies (Table 2). However, some institutions may choose to include mucinous tumours because BRCA mutations have been reported in mucinous tumours [31], and including the relatively few patients with this histology would not significantly impact upon the testing services burden.

Retrospective testing is also recommended for patients in long-term follow-up because of family member implications and BC risk in disease free germline BRCA-mutated OC patients. Patients with stage 1 OC often receive care under a general gynaecologist and may not be seen by a medical or gynaecological oncologist. Therefore, it is important to alert all clinicians treating OC of the importance of identifying patients meeting current BRCA testing referral criteria. Ideally, pathologists could include a statement for clinicians to be aware that patients with invasive non-mucinous/borderline epithelial OC may harbour a germline BRCA mutation in OC-related pathology reports, although this may have regulatory implications in some countries due to third party sharing of genetic information, e.g. insurance companies.

**BRCA genetic testing recommendations**

Ideally, to eliminate follow-up loss and for treatment implications previously stated, patients should be offered genetic testing at diagnosis, as this information is helpful for patient management. However, if this does not occur, patients can be referred at any stage during the patient pathway; Figure 1 is a proposed algorithm, devised during a consensus meeting held in Europe with European experts.
BRCA analysis differs from other genetic tests for cancer treatment decisions, e.g. RAS or epidermal growth factor receptor, because an identified OC BRCA1/2 pathogenic mutation is likely to be a somatic event in \(~15–20\%) of cases and a germline event in the remaining \(80–85\%) [8]. Thus, patients need to be informed about the implications of the result, both for themselves and family members. Genetic counselling is a requirement (by law in many countries) prior to patients undergoing testing. Traditionally, this counselling has been delivered by trained geneticists/genetic counsellors at specialised genetic/family cancer centres. However, due to the increasing demand for BRCA testing services, new models for delivery of genetic counselling have been developed and their use has increased in recent years. For example, in the UK, The Royal Marsden NHS Foundation Trust/Institute of Cancer Research has developed a system to support the implementation of BRCA testing in routine oncology appointments. In this Mainstreaming Cancer Genetics (MCG) programme, members of the oncology team undergo online training to enable them to deliver initial genetic counselling to women for whom BRCA testing is recommended. All patients have the option of seeing a trained geneticist/genetic counsellor prior to deciding on whether to proceed with testing and are followed up by a trained geneticist/genetic counsellor if found to harbour a mutation [10]. As of 2015, 300 women had gone through this MCG programme; a survey (n=105) found 99\% were happy with their decision to undertake the test and 97\% were satisfied to have had the test organised via the oncology department. As part of this initiative, gynaec-oncology clinical nurse specialists, as well as doctors have counselled and consented patients for germline BRCA testing; nurses consented 36\% of patients in oncology clinics and thus far, feedback has been positive [32]. This programme is being further evaluated in a larger study (ENGAGE study), which is assessing this model at 30 sites in the USA, Italy and Spain. ENGAGE aims to include \(~400\) patients with epithelial ovarian, fallopian tube or primary peritoneal cancer (https://clinicaltrials.gov/ct2/show/NCT02406235). Preliminary results of the European arm are anticipated towards the end of 2016. Details and resources for the MCG programme are freely available at: https://mcgprogramme.com/brcatesting/. Further information on different methods to deliver genetic counselling can be found on the European Society of Gynaecological Oncology eAcademy platform http://eacademy.esgo.org/esgo/. Pre-test telephone interviews with genetic counsellors have also been evaluated in patients referred for BRCA testing. In a randomised non-inferiority trial, telephone counselling was found to be non-inferior to in-person counselling for knowledge, perceived stress and patient satisfaction [33]. Following receipt of genetic counselling, patients must also provide their written informed consent prior to testing.

**Sample type (blood/tumour tissue)**
Olaparib is licensed for OC patients with either germline or somatic BRCA mutations. The limited data available support the hypothesis that somatic BRCA-mutated OCs respond equally to PARPi as germline-mutated [7,8], although further studies are needed to confirm this. Methods also need to be validated for the identification of BRCA mutations in fixed tissue samples; such primary surgery samples are the most readily available to utilise for testing. There is some evidence supporting the stability of both somatic and germline BRCA mutations between samples taken during initial surgery and following relapse [34]; however, further studies are required, and mutations may not always remain stable during disease progression. For these reasons, for the time being, germline testing of a blood/saliva sample is recommended in the first instance, followed by consideration to test tumour tissue upon obtaining a negative result (Table 3). However, ultimately, it may be both logical and cost-effective to test OC tumour samples for BRCA mutations first, and then, if positive, go on to confirm if mutations are germline or somatic by testing a blood/saliva sample because of the cost implications of testing all patients for germline mutations and then repeat testing all who obtain a negative result, in order to identify the further 5–7% of patients who may potentially benefit from PARPi therapy. In addition, in the near future, it is expected that not only patients with somatic BRCA mutations but also patients with a proven tumour homologous recombination deficiency might be candidates for PARPis [35].

**Turnaround times / technical**

Ideally, results of BRCA genetic testing should be available within 4–8 weeks, if required for treatment decisions. Further technical recommendations for BRCA testing are outlined in Table 3.

**Conclusions**

Worldwide studies have highlighted that BRCA mutations among OC patients are more frequent than previously thought. This together with the licensing of the first PARPi therapy for BRCA-associated OC (with further drugs in this class likely to be licensed soon) has led to a change in the rationale for BRCA testing criteria. Referral criteria, previously based on family cancer history and designed to identify those at risk of future cancers, are being changed to identify those who may benefit from treatment and those at risk who lack a known family history and who may benefit from future preventative strategies.

BRCA testing differs from other tumour treatment decision genetic tests because OC BRCA mutations are likely to be germline, with individual and family member implications beyond current treatment. Thus, information, genetic counselling and written informed consent are
required prior to \textit{BRCA} testing. Although originally initiated to reduce waiting times and save costs, initial genetic counselling by trained medical staff, in close collaboration with medical geneticists, is now being adopted by many institutions because it has been found to work well and to be at least as well accepted by patients as classical genetic counselling.

The published guidance on \textit{BRCA} testing in OC patients differs in various recommendations because of differences in understanding at the time of publishing, highlighting that ideally guidelines should be re-evaluated, and updated if necessary, at least every 2 years. Following a review of newly updated guidance and up-to-date evidence, the following is recommended: all OC patients with invasive epithelial OC (excluding borderline and mucinous), including fallopian tube and peritoneal cancers, should be considered for referred for \textit{BRCA} genetic testing, irrespective of age; genetic testing should ideally be offered at diagnosis, although patients can be referred at any stage; retrospective testing should be offered to long-term follow-up patients because of family member implications and individual future BC risk; and germline \textit{BRCA} testing of a blood/saliva sample should initially be conducted and, if negative, a tumour tissue sample tested to identify non-germline \textit{BRCA} PARPi therapy candidates (Figure 1, Table 3).

OC genetics understanding is evolving: genes other than \textit{BRCA1} and \textit{BRCA2} have been associated with OC development, and loss of other genes involved in homologous DNA recombination is thought to potentially confer PARPi response \cite{5,26}. Furthermore, genomic scar tests, which identify signs of homologous recombination deficiency, are being evaluated to identify further PARPi-responsive patients \cite{5}. However, scar assays do not preclude the requirement for \textit{BRCA} testing because of the need to identify individuals and family members at risk of future cancers. In the future, studies exploring the effect of PARPi treatment on somatic \textit{BRCA} mutations will also be of interest.

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References


Table 1. Summary of international and individual published guidance on *BRCA* mutation testing of OC patients

<table>
<thead>
<tr>
<th>Country</th>
<th>Year published</th>
<th>Criterial for referral for testing</th>
<th>Testing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Based on family history</td>
<td>Based on patient characteristics</td>
</tr>
<tr>
<td>ESMO [11]</td>
<td>2011</td>
<td>≥3 BCs and/or OCs in the family (at least 1 &lt;50 yrs)</td>
<td>BC and OC in the same patient</td>
</tr>
<tr>
<td>NCCN [12]</td>
<td>2015</td>
<td>≥1 invasive primary OC</td>
<td>Invasive OC</td>
</tr>
<tr>
<td>SGO [13]</td>
<td>2014</td>
<td>≥1 invasive primary OC</td>
<td>Epithelial ovarian, tubal and peritoneal cancers</td>
</tr>
<tr>
<td>Austria [14]</td>
<td>2015</td>
<td>1 BC &lt;35 yrs 2 BCs ≥1 &lt;50 yrs 3 BCs &lt;60 yrs 1 BC + 1 OC 2 OCs 1 male BC</td>
<td>Epithelial OC</td>
</tr>
<tr>
<td>Belgium [15]</td>
<td>2015</td>
<td>NA to OC patients</td>
<td>NA to OC patients</td>
</tr>
<tr>
<td>Czech Republic [16]</td>
<td>2015</td>
<td>≥3 BCs any age ≥2 BCs 1≤ 50 yrs or 2 ≤60 yrs</td>
<td>Bilateral BC BC ≤50 yrs BC and pancreatic cancer Male BC</td>
</tr>
<tr>
<td>Finland [17]</td>
<td>2012</td>
<td>≥1 BC</td>
<td>OC with 1 close relative with OC OC and BC</td>
</tr>
<tr>
<td>Country</td>
<td>Year</td>
<td>Family History</td>
<td>Age of Diagnosis</td>
</tr>
<tr>
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<td>------------------</td>
</tr>
<tr>
<td>France [18]</td>
<td>2016</td>
<td>Low-grade OC, tubal or primary carcinoma regardless age at diagnosis with BC or OC</td>
<td>Any age + 1st degree relative (or 2nd degree if male 1st degree)</td>
</tr>
<tr>
<td>Germany [19]</td>
<td>2013</td>
<td>3 BCs 2 BCs 1 &lt;51 yrs 1 BC and 1 OC 2 OCs 1 male BC</td>
<td>Bilateral BC BC &lt;36 yrs</td>
</tr>
<tr>
<td>Italy [20]</td>
<td>2015</td>
<td>Genetic family history (old guidelines)</td>
<td>BC and OC OC &lt;45 yrs</td>
</tr>
<tr>
<td>Netherlands [21]</td>
<td>2015</td>
<td>All epithelial OC (including fallopian)</td>
<td>–</td>
</tr>
<tr>
<td>Portugal [22]</td>
<td>2013</td>
<td>–</td>
<td>BC and OC (other multi/multiple tumours)</td>
</tr>
<tr>
<td>Spain [23]</td>
<td>2016</td>
<td>1 BC and 1 OC 2 OC OC &lt;40 yrs</td>
<td>–</td>
</tr>
<tr>
<td>Scotland [24]</td>
<td>2013</td>
<td>Family history of BC and/or OC, colon cancer</td>
<td>–</td>
</tr>
<tr>
<td>UK [25]</td>
<td>2015</td>
<td>4 BCs 3 BCs &lt;60 yrs 2 BCs &lt;50 yrs OC and BC &lt;50 yrs OC and 2 BCs &lt;60 yrs 2 OCs Bilateral BC &lt;50 yrs Male BC and ≥1 BCs &lt;60 yrs</td>
<td>–</td>
</tr>
</tbody>
</table>

BC, breast cancer; OC, ovarian cancer; HGSOC, high-grade serous ovarian cancer; HG, high grade; TNBC, triple-negative breast cancer

*Criteria likely to be included in 2016 update of guidelines*
Table 2. Percentage of ovarian cancer patients, by histology, with germline BRCA1 or BRCA2 mutations in different published studies of populations with unknown BRCA1/2 status

<table>
<thead>
<tr>
<th>Study</th>
<th>Serous %</th>
<th>Mucinous %</th>
<th>Endometrioid %</th>
<th>Clear cell %</th>
<th>Undifferentiated %</th>
<th>Other/unspecific %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alsop 2012 [9]</td>
<td>16.6</td>
<td>0</td>
<td>8.4</td>
<td>6.3</td>
<td>–</td>
<td>8.2</td>
</tr>
<tr>
<td>(N=1001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobi 2007 [27]</td>
<td>10.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(N=85)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Malander 2004 [28]</td>
<td>7.6</td>
<td>0</td>
<td>13.0</td>
<td>12.5</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>(N=161)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norquist 2015 [26]</td>
<td>16 (HGS)</td>
<td>0</td>
<td>8.8</td>
<td>6.9</td>
<td>–</td>
<td>53.5</td>
</tr>
<tr>
<td>(N=1915)</td>
<td>5.6 (LGS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soegaard 2008 [29]</td>
<td>5.5</td>
<td>0</td>
<td>5.4</td>
<td>9.1</td>
<td>12.5</td>
<td>10.0</td>
</tr>
<tr>
<td>(N=445)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risch 2001 [30]</td>
<td>16.4</td>
<td>0</td>
<td>4.3</td>
<td>0</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>(N=649)</td>
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</tbody>
</table>

HGS, high-grade serous; LGS, low-grade serous
Table 3. Summary of *BRCA* testing recommendations for OC patients

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of testing</td>
<td>At diagnosis</td>
</tr>
<tr>
<td></td>
<td>Or if not undertaken at diagnosis at any stage during the patient pathway</td>
</tr>
<tr>
<td></td>
<td>Retrospective testing should be offered to patients in long-term follow-up because of the implications for other family members and the future risk of breast cancer in the individual patient</td>
</tr>
<tr>
<td>Patients to refer for testing</td>
<td>All OC patients with invasive epithelial OC (excluding borderline and mucinous), including fallopian tube and peritoneal cancers, irrespective of age</td>
</tr>
<tr>
<td>Genetic counselling requirements</td>
<td>Some form of genetic counselling together with written informed consent are required prior to patients undergoing testing</td>
</tr>
<tr>
<td>Sample type</td>
<td>Germline testing of a blood/saliva sample for <em>BRCA</em> mutations should be conducted in the first instance, followed by testing of tumour tissue if a negative result is obtained (to identify those suitable for PARPi therapy who are not germline carriers of a <em>BRCA</em> mutation)</td>
</tr>
<tr>
<td>Technical</td>
<td>Full gene analysis, not just hot spots, should be undertaken, including rearrangements and deletions</td>
</tr>
<tr>
<td></td>
<td>Certified labs should be used for analyses with quality control in place (European Molecular Genetics Quality Network or equivalent)</td>
</tr>
<tr>
<td></td>
<td>Next-generation sequencing should be used for tumour testing</td>
</tr>
<tr>
<td>Turnaround times</td>
<td>4–8 weeks</td>
</tr>
</tbody>
</table>
Figure 1. The *BRCA* genetic testing patient journey in ovarian cancer

Ovarian cancer diagnosis → Refer for *BRCA* testing → Genetic counselling (by geneticist/genetic counsellor or trained MDT member) – written informed consent obtained → Germline *BRCA* analysis undertaken → Result available 4–8 weeks

1st-line chemotherapy → Relapse → 2nd-line chemotherapy → PARPi maintenance therapy

Germline *BRCA* positive (including VUS)* → Genetic counselling for patient and family members (by geneticist/genetic counsellor)

Germline *BRCA* negative** → Test tumour sample for somatic *BRCA* mutations

Somatic *BRCA* mutation positive → Somatic *BRCA* mutation negative (or positive with VUS)

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* VUS, variants of uncertain significance
** Patients with VUS should still be referred for genetic counselling, but will not be eligible for PARPi therapy
** If family history is suspicious of a hereditary cancer syndrome offer referral to genetic counselling