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

Authors:

Ignace Vergote,[1] Susana Banerjee,[2] Anne-Marie Gerdes,[3] Christi van Asperen,[4] Christian Marth,[5] Fatima Vaz,[6] Isabelle Ray-Coquard,[7] Dominique Stoppa-Lyonnet,[8] Antonio Gonzalez-Martin,[9] Jalid Sehouli,[10] Nicoletta Colombo[11]

[1]Leuven Cancer Institute, KU Leuven, Belgium, European Union

[2]The Royal Marsden NHS Foundation Trust, London, UK

[3]Department of Clinical Genetics, Copenhagen University Hospital, Denmark

[4]Department of Clinical Genetics, Leiden University Medical Center, Netherlands

[5]Innsbruck Medical University, Austria

[6]Portuguese Institute of Oncology, Lisbon,Portugal

[7]Department of Medical Oncology, CRLCC Léon Bérard, University Claude Bernard Lyon, France

[8] Institut Curie, Department of Tumour Biology, Paris, France; Institut Curie, INSERM U830, Paris, France; Université Paris Descartes, Sorbonne Paris Cité, France

[9]MD Anderson Cancer Center Madrid, Spain

[10]Charité University of Medicine Berlin, Germany

[11]University of Milan-Bicocca and European Institute of Oncology, Italy

Corresponding author: Professor Ignace Vergote, Leuven Cancer Institute
KU Leuven, Belgium. Tel: +32/16344207; E-mail: ignace.vergote@uzleuven.be

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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, gynae-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 *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 *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 *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 *BRCA* testing of a blood/saliva sample should initially be conducted and, if negative, a tumour tissue sample tested to identify non-germline *BRCA* PARPi therapy candidates (Figure 1, Table 3).

OC genetics understanding is evolving: genes other than *BRCA1* and *BRCA2* have been associated with OC development, and loss of other genes involved in homologous DNA recombination is thought to potentially confer PARPi response [5,26]. Furthermore, genomic scar tests, which identify signs of homologous recombination deficiency, are being evaluated to identify further PARPi-responsive patients [5]. However, scar assays do not preclude the requirement for *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 *BRCA* mutations will also be of interest.

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References

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–1403.

[2] Zhong Q, Peng HL, Zhao X, Zhang L, Hwang WT. Effects of BRCA1- and BRCA2-related mutations on ovarian and breast cancer survival: a meta-analysis. Clin Cancer Res 2015;21:211–220.

[3] Shu CA, Pike MC, Jotwani AR, Friebel TM, Soslow RA, et al. Uterine Cancer After Risk-Reducing Salpingo-oophorectomy Without Hysterectomy in Women With BRCA Mutations. JAMA Oncol. 2016 Jun 30.

[4] Eccles DM, Balmaña J, Clune J, et al. Selecting patients with ovarian cancer for germline *BRCA* mutation testing: findings from guidelines and a systematic literature review. Adv Therapy 2016;33:129–150.

[5] Moschetta M. George A, Kaye SB, Banerjee S. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. Annal of Oncology 2016:00:1–7.

[6] Hahnen E, Baumann KH, Heimbach A, Reuss A, Jackisch C, Hauke J, et al. Prevalence of somatic mutations in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR-1 study). J Clin Oncol 2016;34(suppl); abstr 5544

[7] Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube and peritoneal carcinomas. Clin Cancer Res 2014;20:764–775.

[8] Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in randomised phase 2 trial. Lancet Oncol 2015;15:852–861.

[9] Alsop K, Fereday S, Meldrum C, et al. *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30:2654–2663.

[10] George A, Riddell D, Seal S, Talukdar S, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016 Jul 13;6:29506. doi: 10.1038/srep29506.

[11] Balmaña J, Diez O, Rubio I, Castiglione M, on behalf of the ESMO Guidelines Working Group. BRCA in breast cancer: ESMO clinical practice guidelines. Annal Oncol 2010;21(Suppl 5):v20–v22

[12] NCCN. Genetic/familial high-risk assessment: Breast and Ovarian. Version 2.2015. NCCN.org. Available at:

http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf (accessed June 2016)

[13] SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer 2014 (https://www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer/) (accessed June 2016)

[14] Marth C, Hubalek M, Petru E, et al. AGO Austria recommendations for genetic testing of patients with ovarian cancer. Wiener Klinische Wochenschrift 2015;127:652–654

[15] Claes K, Denys H, Huizing M, et al. Therapy-orienting testing of BRCA1 and BRCA2 germline mutations in women with ovarian cancer. Belg J Med Oncol 2015;9:65–70

[16] Foretová L, Macháčková E, Palácová M, Navrátilová M, Svoboda M, Petráková K. [Recommended Extension of Indication Criteria for Genetic Testing of BRCA1 and BRCA2 Mutations in Hereditary Breast and Ovarian Cancer Syndrome]. Klin Onkol 2016;29(Suppl 1):S9–S13.

[17] Care Guidelines. Ovarian Cancer. 2012 Available at: http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00035

[18] http://www.arcagy.org/arcagy-organisation-et-recherche/

[19] http://www.ago-online.de/fileadmin/downloads/leitlinien/ovar/S3-Ovarialkarzinom-OL-Langversion.pdf

[20] Pinto C, Bella MA, Capoluongo E, Carrera P, Clemente C, Colombo N, et al. Recommendations for the implementation of BRCA testing in the care and treatment pathways of ovarian cancer patients. Future Oncol. 2016 May 31. [Epub ahead of print]

[21] http://www.oncoline.nl/erfelijk-en-familiair-ovariumcarcinoom

[22] http://www.ipolisboa.min-saude.pt/Default.aspx?Tag=CONTENT&ContentId=9296”Llort G, Chirivella I,

[23] Morales R, et al. SEOM clinical guidelines in hereditary breast and ovarian cancer. Clin Transl Oncol 2015;17:956–61.

[24] Scottish Intercollegiate Guidelines Network (SIGN). Management of epithelial ovarian cancer. Edinburgh: SIGN; 2013. (SIGN publication no. 135). [November 2013]. Available from URL: http://www.sign.ac.uk

[25] NHS England. Clinical commissioning policy: genetic testing for BRCA1 and BRCA2 mutations. 2015; Available at: https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/brca-policy.pdf

[26] Norquist BM, Harrell MI, Brady MF, et al. Inherited mutations in women with ovarian carcinoma. JAMA Oncol. 2015;1–9. doi: 10.1001/jamaoncol.2015.5495. [Epub ahead of print]

[27] Jacobi CE, van Ierland Y, van Asperen CJ, et al. Prediction of BRCA1/2 mutation status in patients with ovarian cancer from a hospital based cohort. Genet Med 2007;9:173–179.

[28] Malander S, Ridderheim M, Måsbäck A, et al. One in 10 ovarian cancer patients carry germ line *BRCA1* or *BRCA2* mutations: results of a prospective study in Southern Sweden. Eur J Cancer 2004;40:422–428

[29] Soegaard M, Kjaer SK, Cox M, et al. *BRCA1* and *BRCA2* mutation prevalence and clinical characteristics of a population-based series of ovarian cancer cases from Denmark. Clin Cancer Rev 2008;14:3761–3767.

[30] Risch HA, McLaughlin JR, Cole DE, et al. Population *BRCA1* and *BRCA2* mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 2006;98:1694–1706.

[31] Candido-dos-Reis FJ, Song H, Goode EL, et al. Germline mutation in BRCA1 or BRCA2 and ten-year survival for women diagnosed with epithelial ovarian cancer. Clin Cancer Res 2015;21:652–657.

[32] Percival N, George A, Gyertson J, et al. The integration of BRCA testing into oncology clinics. Br J Nurs 2016;25:690–4.

[33] Schwartz MD, Valdimarsottir HB, Peshkin BN, et al. Randomized noninferitority trial of telephone versus in-person genetic counselling for hereditary breast and ovarian cancer. J Clin Oncol 2014;32:18–26.

[34] Lambrechts S, Smeets D, Moisse M, et al. Genetic heterogeneity after first-line chemotherapy in high-grade serous ovarian cancer. Eur J Cancer 2016;53:51–64.

[35] Kristeleit R, Swisher E, Oza A, et al. Final results of ARIEL2 (Part 1): a phase 2 trial to prospectively identify ovarian cancer (OC) responders to rucaparib using tumor genetic analysis. Eur Cancer Congr 2015;51:s531

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

		Criterial for referral for testing				Testing recommendations		
	Year published	**Based on family history**	**Based on patient characteristics**	**Based on risk**	**Based on histology**	**Type of sample**	**Timing of testing**	**Turnaround time of tests**
ESMO [11]	2011	≥3 BCs and/or OCs in the family (at least 1 <50 yrs)	BC and OC in the same patient BC and OC in the same patient	10–20% chance of finding a mutation (predictive models)	–	–	–	–
NCCN [12]	2015	≥1 invasive primary OC	Invasive OC	No recommendations	-	–	–	–
SGO [13]	2014	≥1 invasive primary OC	Epithelial ovarian, tubal and peritoneal cancers	No recommendations	–	–	–	–
Austria [14]	2015	1 BC <35 yrs 2 BCs ≥1 <50 yrs 3 BCs <60 yrs 1 BC + 1 OC 2 OCs 1 male BC	Epithelial OC	Not defined	TNBC <60 yrs	Blood (quality control testing of tumour)	At diagnosis At recurrence	*Not defined*
Belgium [15]	2015	NA to OC patients	NA to OC patients	No recommendations	All HGSOC	First blood and if negative tumour	During 1st-line therapy	Institution dependent; use fast track for treatment decisions
Czech Republic [16]	2015	≥3 BCs any age ≥2 BCs 1≤ 50 yrs or 2 ≤60 yrs	Bilateral BC BC ≤50 yrs BC and pancreatic cancer Male BC	–	All patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer regardless of the age at diagnosis TNBC ≤60 yrs	–	–	Within 3 months for therapy decisions
Finland [17]	2012	≥1 BC	OC with 1 close relative with OC OC and BC	–	–	–	–	–

France [18]	2016	Low-grade OC, tubal or primary carcinoma any age + 1st degree relative (or 2nd degree if male 1st degree) with BC or OC regardless age at diagnosis	OC, tubal or primary peritoneal carcinoma, any age, regardless of family history if HG (serous, endometrioid, clear cell, carcinosarcoma) or if affected with BC	-	OC, tubal or primary peritoneal carcinoma, any age if HG (serous, endometrioid, clear cell, carcinosarcoma)	Blood in 1st-line Blood & tumour in sensitive relapsed patients	At diagnosis	4–6 months in 1st-line 4–8 weeks for sensitive relapsed patients
Germany [19]	2013	3 BCs 2 BCs 1 <51 yrs 1 BC and 1 OC 2 OCs 1 male BC	BC and OC Bilateral BC BC <36 yrs	Risk based on family history	*HGSOC (for therapy decisions)*	Blood or tumour, or both	At diagnosis or if risk factors present	10–14 days
Italy [20]	2015	Genetic family history (old guidelines)	BC and OC OC <45 yrs	>10% risk	All non-mucinous, non-borderline	Blood or tumour	At diagnosis	*Not indicated*
Netherlands [21]	2015		All epithelial OC *(including fallopian)*	–	All excluding borderline	No recommendation	No recommendation	*No recommendation*
Portugal [22]	2013	–	BC and OC (other multi-multiple tumours)	≥10% risk (BRCAPRO)	HGSOC	Blood	At diagnosis/ during primary treatment	1–6 months
Spain [23]	2016	1 BC and 1 OC 2 OC OC <40 yrs			Epithelial OC (fallopian cancer or primary peritoneal cancer), HG for the histologic subtypes HGSOC, clear cell, endometrioid, undifferentiated and carcinosarcoma	Blood, if negative perform tumour testing for therapeutic purposes	At diagnosis or time of relapse in platinum-sensitive patients	Within 4 months
Scotland [24]	2013	Family history of BC and/or OC, colon cancer	–	>10% risk	Non-mucinous OC, fallopian tube cancer	–	–	–

UK [25]	2015	4 BCs 3 BCs <60 yrs 2 BCs <50 yrs OC and BC <50 yrs OC and 2 BCs <60 yrs 2 OCs Bilateral BC <50 yrs Male BC and ≥1 BCs <60 yrs	–	>10% risk	–	Blood	–	–

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

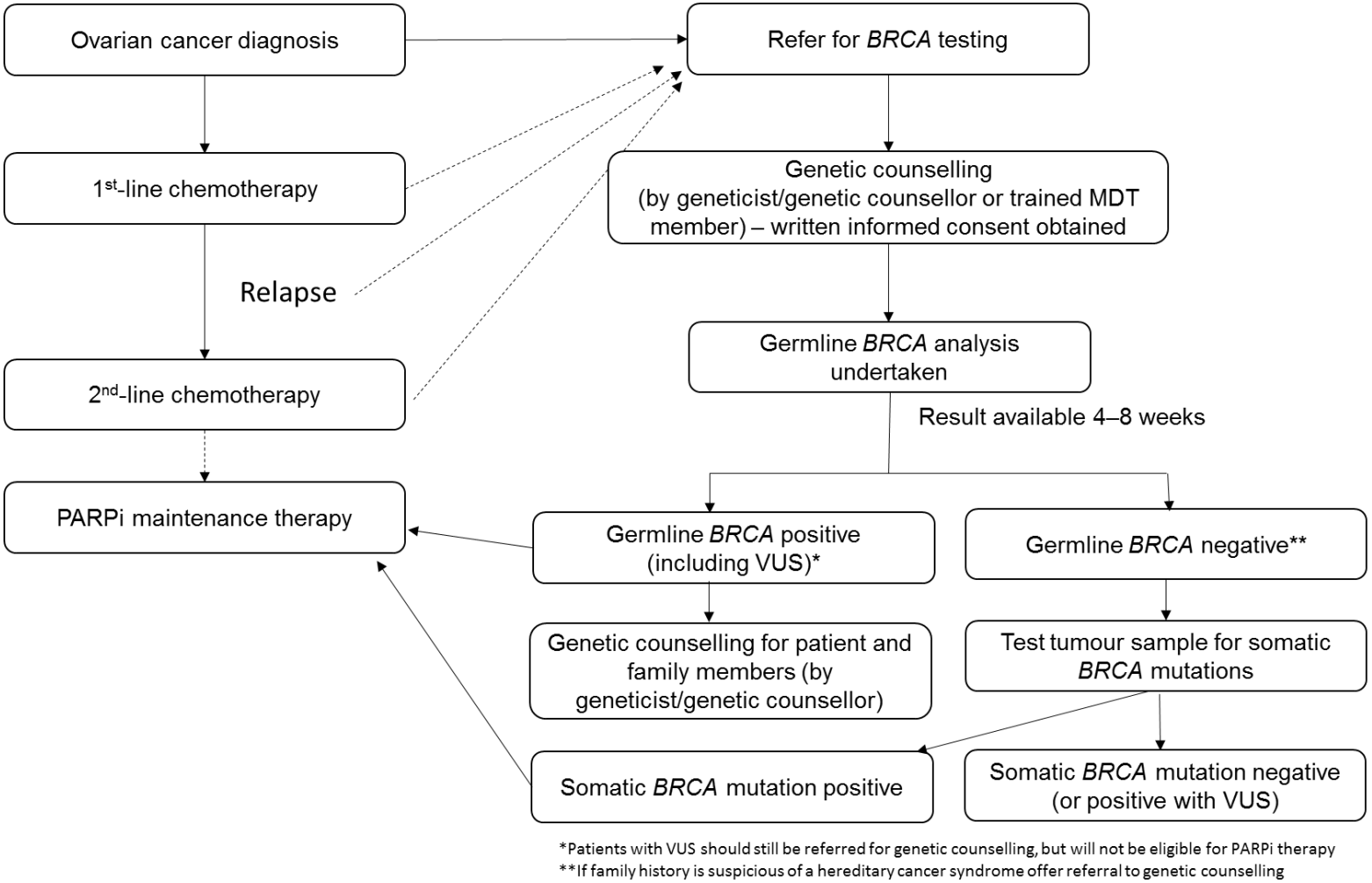
Study	Serous %	Mucinous %	Endometrioid %	Clear cell %	Undifferentiated %	Other/unspecified %
Alsop 2012 [9] (N=1001)	16.6	0	8.4	6.3	–	8.2
Jacobi 2007 [27] (N=85)	10.8	0	0	0	0	0
Malander 2004 [28] (N=161)	7.6	0	13.0	12.5	–	0
Norquist 2015 [26] (N=1915)	16 (HGS) 5.6 (LGS)	0	8.8	6.9	–	53.5
Soegaard 2008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

HGS, high-grade serous; LGS, low-grade serous

Table 3. Summary of *BRCA* testing recommendations for OC patients

Criteria	Recommendation
Timing of testing	At diagnosis Or if not undertaken at diagnosis at any stage during the patient pathway 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
Patients to refer for testing	All OC patients with invasive epithelial OC (excluding borderline and mucinous), including fallopian tube and peritoneal cancers, irrespective of age
Genetic counselling requirements	Some form of genetic counselling together with written informed consent are required prior to patients undergoing testing
Sample type	Germline testing of a blood/saliva sample for *BRCA* 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 *BRCA* mutation)
Technical	Full gene analysis, not just hot spots, should be undertaken, including rearrangements and deletions Certified labs should be used for analyses with quality control in place (European Molecular Genetics Quality Network or equivalent) Next-generation sequencing should be used for tumour testing
Turnaround times	4–8 weeks

Figure 1. The *BRCA* genetic testing patient journey in ovarian cancer



VUS, variants of uncertain significance