British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for germline and tumor testing for *BRCA*1/2 variants in ovarian cancer in the United Kingdom

Sudha Sundar ,[1,2] Ranjit Manchanda ,[3] Charlie Gourley,[4] Angela George,[5] Andrew Wallace,[6] Janos Balega,[1] Sarah Williams,[7] Yvonne Wallis,[8] Richard Edmondson,[9] Shibani Nicum,[10] Jonathan Frost,[11] Ayoma Attygalle,[12] Christina Fotopoulou ,[13] Rebecca Bowen,[11] Dani Bell,[14] Ketankumar Gajjar,[15] Bruce Ramsay,[16] Nicholas J Wood,[17] Sadaf Ghaem-Maghami,[18] Tracie Miles,[19] Raji Ganesan[20]

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For numbered affiliations see end of article.

Correspondence to
Professor Sudha Sundar, Pan-Birmingham Gynaecological Cancer Centre, Birmingham B152TT, UK; sudha.sundar@nhs.net

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ABSTRACT

The British Gynecological Cancer Society and the British Association of Gynecological Pathologists established a multidisciplinary consensus group comprising experts in surgical gynecological oncology, medical oncology, genetics, and laboratory science, and clinical nurse specialists to identify the optimal pathways to *BRCA* germline and tumor testing in patients with ovarian cancer in routine clinical practice. In particular, the group explored models of consent, quality standards identified at pathology laboratories, and experience and data from pioneering cancer centers. The group liaised with representatives from ovarian cancer charities to also identify patient perspectives that would be important to implementation. Recommendations from these consensus group deliberations are presented in this manuscript.

INTRODUCTION

Pathogenic germline *BRCA*1/2 variants play a key role in the etiology of epithelial ovarian cancer. Recent studies showing the prevalence of pathogenic *BRCA* germline mutations in patients with high-grade serous ovarian cancer of 13–15% as well as the recognition of the clinically significant role of therapeutic poly-ADP ribose polymerase (PARP) inhibition in *BRCA* deficient tumors have led to an expansion in demand for germline *BRCA* testing.[1–6] The Cancer Genome Atlas (TCGA) identified somatic and germline *BRCA* pathogenic variants in around 22% of high-grade serous ovarian cancers.[7]

To manage this increased demand and ensure timely access to testing early on in the patient care pathway, models of delivery using surgeons, oncologists or clinical nurse specialists to 'mainstream' germline testing have been developed in many centers. In these models, cancer clinicians counsel and offer germline *BRCA* testing to all patients with ovarian cancer and only patients with pathogenic variants or variants of uncertain significance are referred to genetics services.

Different models have been developed across the UK with variable testing criteria, availability and access.[4 8 9] Some models restrict testing to defined histological criteria (high-grade serous or endometrioid), others restrict testing to age groups (under 70 years). However, there is considerable variability in implementation of mainstream germline *BRCA* testing worldwide with some centers still relying on individual clinicians referring patients to regional genetics centers and approximately 30% of eligible patients not being offered testing.[10]

Until 2018, the evidence base for maintenance PARP inhibition strategies was restricted to women with relapsed ovarian cancer. However, following publication of the SOLO-1 trial, the evidence for benefit has been shown in the first-line setting with women with *BRCA*-deficient advanced stage IIIC/IV ovarian cancer having significantly longer progression-free survival with maintenance olaparib compared with placebo.[11]

There are currently two methods by which *BRCA* testing may be undertaken, each of which detects slightly different pathogenic variants due to the pathogenesis of the mutations and the limitations of the analytical techniques. *Germline testing* is undertaken on blood samples and will detect inherited pathogenic variants, including the large duplications or deletions which are not reliably detected on tumor testing. Thus, germline testing results have implications for family members. *Tumor testing* involves extracting DNA from the ovarian tumor and testing it for pathogenic variants. Approximately two-thirds of the mutations detected in tumors will be of *germline* (inherited) origin, however nearly one-third will be *somatic* (tumor only, not inherited) mutations. Therefore, tumor testing results may have implications for family members in some but not all instances.

Crucially, PARP inhibition increases progression-free survival in patients with somatic *BRCA* mutation.[11] Therefore, patients and clinicians need as much information as possible to guide treatment choices in the first-line setting.

Thus, there is an urgent clinical need to clearly identify women whose tumors contain deleterious *BRCA* mutations early in their ovarian cancer treatment journey to maximize the population of women afforded the opportunity of PARP inhibitor treatment on completion of first-line chemotherapy. Additionally, unselected germline testing identifies approximately 50% more women whose families may benefit from predictive testing and subsequent screening and prevention in unaffected individuals.[12]

Implementing these tests into routine practice at first-line treatment of ovarian cancer requires careful consideration of issues around scheduling of tests, the timing of testing in relation to first-line therapy, counseling of patients, costs involved, sample management processes, quality controls and audit trails. This guidance document evaluates the underlying evidence and sets out recommendations for implementation in clinical practice in the United Kingdom.

DETECTION OF DIFFERENT DNA VARIANTS IN GERMLINE TESTING

Next generation sequencing based technologies are used for detection of *BRCA* 'point mutations' (single nucleotide variants or small insertion/deletion variants typically <40 bp in size) in both blood (germline) and tumor samples. Although pathogenic large genomic rearrangements can be detected in germline samples using next generation sequencing, the algorithms show reduced sensitivity for smaller, single exon large genomic rearrangements. Consequently, pathogenic large genomic rearrangements in *BRCA* are typically detected in clinical laboratories using multiplex ligation dependent probe amplification in blood samples. However, multiplex ligation dependent probe amplification has a high analytical failure rate in formalin fixed paraffin embedded derived tumor DNA due to poor DNA quality and genomic instability present in many ovarian tumors and is consequently not routinely employed.

SCHEDULING OF GERMLINE AND TUMOR BRCA TESTING

The consensus group carefully reviewed the emerging evidence summarized below to formulate its recommendation on scheduling of testing.

Evidence from the SIGNPOST Study

A concomitant/parallel panel germline and tumor genetic testing pathway for all high-grade non-mucinous epithelial ovarian cancers was initially introduced at Barts Health (North East London Cancer Network) in 2016. This involved an initial period of training of clinical staff (surgeons, medical oncologists, clinical nurse specialists) and design of patient information materials and was undertaken within the SIGNPOST (Systematlc GeNetic Testing for Personalized Ovarian Cancer Therapy) study (ISRCTN 16988857). Germline testing included testing for *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*. Tumor testing was undertaken for *BRCA1* and *BRCA2* genes. Both germline testing and tumor testing were done in parallel they were offered prospectively and retrospectively to those with a pre-existing diagnosis.

Pathogenic variant rates identified in the SIGNPOST study were consistent with those previously reported in the literature. Critically, this study shows that 10% of *BRCA* mutation carriers (individuals with large genomic rearrangements) would not have been identified without concomitant parallel testing for both germline and somatic mutations (personal communication, Professor Manchanda, unpublished data).

Evidence from Imperial College Healthcare NHS Trust and the Royal Marsden Hospital

At Imperial College Healthcare NHS Trust, parallel germline and tumor BRCA genetic testing is offered to all eligible patients with ovarian cancer. At initial presentation, the cancer team talk with the patient about the pathways and the possibility of genetic testing and its implications. If consent is obtained, germline and tumor tests are requested from the gynecological oncology clinic.

The Royal Marsden Hospital initiated mainstream germline *BRCA* testing in 2012 for all patients with non-mucinous ovarian cancer through the oncology teams as standard of care. Subsequently, reflex tumor testing was introduced for all patients with high-grade serous ovarian cancer. Currently, the data (unpublished) from The Royal Marsden Hospital have identified 9% of patients with pathogenic variants present only in the tumor, and 15% of patients with germline pathogenic variants that were not detected during tumor testing. All of the germline pathogenic variants represent large genomic rearrangements (duplications or deletions) that are not reliably detectable during tumor BRCA testing due to DNA fragmentation.

Evidence from Public Health England

Data from Public Health England show that as of the end of February 2020, from a total of 17 384 pathogenic *BRCA* variants reported by all labs in England, 1830 were large genomic rearrangements (personal communication, Fiona McRonald, Program Manager, Molecular, Genomic and Research Data National Disease Registration, Public Health England; see Figure 1). However, it is widely accepted in England that there are several 'hotspots' for large genomic rearrangements, which also coincide with less access to testing. Thus, the true proportion of large genomic rearrangements in this population may be closer to 15–17% of pathogenic variants. This finding would be consistent with data from the Manchester and Royal Marsden labs (unpublished).

In England, given the above results, parallel testing would be the most effective strategy and would avoid missing a proportion of patients (around 10%), as tumor testing alone using 'next generation sequencing' technology is likely to miss the proportion of patients with germline pathogenic large genomic rearrangements of *BRCA*. Conversely, germline testing alone will miss a proportion of patients with only somatic variants in *BRCA*. Ongoing studies in Scotland will provide information for local populations.

Each health system will need to establish baseline rates to determine whether sequential testing or parallel testing is optimal for their patient groups. For patients in whom there are limited data about ethnicity, such as those from South Asian populations (https://academic.oup.com/pcm/article/1/2/75/5106037), parallel testing will be particularly important.

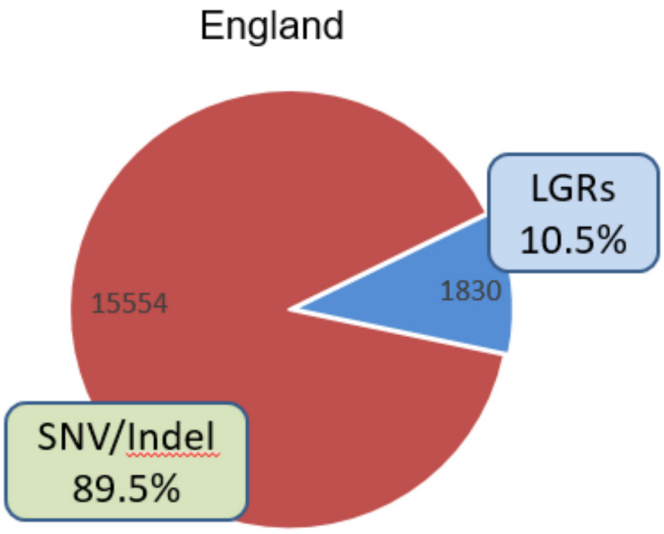

Figure 1 Proportion of germline pathogenic variants from patients with hereditary breast and ovarian cancer that are large genomic rearrangements. indel, insertion or deletion; LGR, large genomic rearrangement; SNV:,single nucleotide variant.

TIMING OF BRCA TESTING IN RELATION TO FIRST-LINE TREATMENT

The consensus group reflected on two issues. First, to preserve patient choice and autonomy in making an informed decision; and second, the crucial utility of knowledge of *BRCA* status in decisions about neoadjuvant, adjuvant or maintenance treatment in first-line settings. The consensus group also had discussions with ovarian cancer charities representing patient perspectives. The consensus group agreed that preserving patient choice in timing of testing was key. However, discussions around *BRCA* testing should start at the earliest available opportunity in a patient's cancer diagnosis journey.

In the ideal scenario, early testing at the time of diagnosis of ovarian cancer is vital so that *BRCA* status is available when it is clinically most relevant to the patient and should factor in the local turnaround time for testing and the potential need for genetic counseling. It is recognized that patients may feel ready to undergo testing at different points in their cancer journey. Counseling and consenting can be carried out by a trained gynecological oncologist, the referring gynecologist with expertise in gynecological oncology (cancer unit lead in the UK), an oncologist or adequately trained clinicians (clinical nurse specialist). Some patients may need to access the genetics service for pre-test counseling and this should be supported where possible.

Initial Consultation

BRCA tumor testing can be discussed with patients who present with a high clinical suspicion of ovarian cancer (carcinomatosis on CT scan with CA125/CEA ratio >25) at initial presentation to a referring gynecologist (cancer unit lead in the UK) or gynecological oncologist, prior to confirmatory histological or cytological diagnosis.

Consultation Before Primary Cytoreductive Surgery

As part of the counseling and consenting for primary cytoreductive surgery, informed consent should be sought for tumor *BRCA* mutation testing; this can be in the form of a verbal discussion which is documented. Although undertaken by some centers (and considered good practice), currently tumor testing does not necessitate written consent in the UK. Information on whether the patient has provided or declined consent for tumor testing should be communicated with the pathology team receiving the surgical specimens after primary cytoreductive surgery, by being recorded in the pathology request form or communicated via other means. This will enable a streamlined process wherein the pathology team can identify the representative tumor block (or slides) and arrange transfer of the specimen to the genomic laboratory hub once a diagnosis of high-grade serous carcinoma or high-grade endometrioid cancer of tubo-ovarian or peritoneal origin is confirmed.

Consultation after Primary Cytoreductive Surgery

If the pathology of the surgery reveals non-mucinous high-grade epithelial ovarian cancer, the patient should be counseled about germline *BRCA* mutation testing and written consent must be obtained. If consenting for tumor *BRCA* mutation testing was not obtained prior to surgery, this should be done and the nominated pathologist should be informed.

Consultation before Biopsy in Patients Planned to Receive Neoadjuvant Chemotherapy

If the patient is not suitable for primary cytoreductive surgery (or in cases of diagnostic uncertainty), counseling about tumor *BRCA* testing should be performed before the image guided biopsy or diagnostic laparoscopy. Informed consent should be obtained either in the form of a verbal discussion which is documented or through a formal consent form. Whether the patient has provided or declined consent for tumor testing should be recorded in the pathology request form after biopsy or conveyed to the pathologist by other means (electronic records, letter or email).

Special Considerations

Imaging-Guided Biopsy

In order to obtain an adequate amount of chemotherapy naïve tissue, extra cores of tumor tissue should be obtained for the purpose of successful tumor *BRCA* mutation testing; this must be recorded in the histopathology request form. Experience from the BRITROC study suggests that imaging-guided biopsy using an 18-gage needle and two passes are feasible and acceptable to patients and results in adequate tissue sampling.[13] If the pre-chemotherapy biopsy does not yield an adequate tissue sample for *BRCA* testing, tumor testing should be reconsidered from the interval debulking surgery specimens in patients with negative germline testing. As the success rate of tumor sequencing from post-chemotherapy specimens is lower (impaired DNA yield) compared with chemotherapy naïve tissue, maximum effort should be made to obtain an adequate amount of tissue during pretreatment biopsy. If debulking surgery is not performed after neoadjuvant chemotherapy, repeat imaging-guided biopsy for tumor testing should be considered.

Diagnostic Laparoscopy

Adequate biopsy should be taken to provide the genetic laboratories with a sufficient amount of tissue for tumor testing.

Table 1 Summary of testing of BRCA genes in ovarian cancer in the UK

	Germline testing	Tumor testing
Indications	All non-mucinous epithelial high-grade ovarian cancer, all stages.	High-grade serous ovarian cancer, FIGO stages III and IV* High-grade endometrioid ovarian cancer,†‡ FIGO stages III and IV*
Timing of test	Patient choice Offer from as early in the journey as possible	Patient choice Offer from as early in the journey as possible
Sequence of testing	Parallel testing	Parallel testing
Information provided and consent	Written information on the implications for patient and family is provided and written consent is obtained	Written information on the implications for patient and family is provided and the verbal consenting process is documented in the notes

*Tumour testing is confined to patients with advanced stage ovarian cancer as current evidence of benefit from PARP inhibition is confined to stage III and IV disease.
†Current criteria for *BRCA* testing in the national test directory for England allows germline testing in all stage, non-mucinous epithelial ovarian cancer and tumour testing for somatic mutations in advanced stage, high-grade serous ovarian cancer alone (Clinical indication IDs: R207 and R208 rare and inherited disease directory). https://www.england.nhs.uk/publication/national-genomic-test-directories/ However, evidence supports testing in high-grade endometrioid cancer as well.
‡Current testing in England is confined to *BRCA1/2* genes only. It is likely that in the future, additional genes such as RAD51C, RAD51D, BRIP1 will be included as evidence accumulates.

Ascites Cytology (in rare cases where tissue cannot be obtained)
Ascitic fluid should be sent to the pathology laboratory to obtain a tumor cell-rich block. A summary of indications, timing, sequence of testing and the consent process is given in Table 1.

PATHOLOGY: TISSUE HANDLING AND PATHWAYS FOR TUMOR BRCA TESTING

Mutation testing relies on detecting a mutant allele in a background of wild type alleles. It is important that adequate numbers of malignant cells are available to provide DNA for the test. Therefore, maximizing the tissue available in a diagnostic biopsy is of paramount importance. Any biopsy done with suspicion of tubo-ovarian cancer must be sampled in at least two blocks. One block (with lower volume of tumor) should have an H&E (hematoxylin and eosin) stain with a confirmatory panel of PAX8, WT1, ER and p53. In the context of morphology, PAX8 positive, WT1 positive, ER positive and p53 mutation/aberrant staining (https://www.thebagp.org/download/bagp-ukneqas-project-p53-interpretation-guide-2016/) is confirmatory of tubal/ovarian high-grade serous carcinoma. When there is diagnostic uncertainty, in order to preserve tissue, the case should be sent to a cancer center for review before further tissue is used for immunohistochemistry. The second block should have an H&E stain to confirm the presence of malignancy. This is the tissue that needs to be sent to the nominated pathologists. In resection specimens, the reporting pathologist should send one block of primary or metastatic carcinoma containing maximum viable and well fixed tumor with its H&E-stained slide to the designated pathologist. The cellblock from cytology received with suspicion of ovarian cancer should be sent to the pathologist if confirmatory of tubal or ovarian high-grade serous carcinoma.

Pathology teams and clinical teams should jointly establish pathways for communication of requests for tumor testing. This communication should clearly document patient consent for testing. The nominated pathologist should mark tumor areas on the H&E-stained slide and estimate tumor volume. The tissue (as required by the genomic laboratory hub), marked slide and completed form are sent to the genomic laboratory hub. This should be recorded securely and, where possible, this record should be accessible to the clinical team. When the result is received, it should be added to the initial pathology report as a supplementary or upload report on the patient's electronic record. Please see online supplemental file 1 for further details.

GENOMIC LABORATORY HUB CONSIDERATIONS

The NHS Genomic Laboratory Hub network has limited capacity to undertake assessment of pathology samples for adequacy for somatic *BRCA* analysis from patients with ovarian cancer. Their specialist expertise is the analysis of nucleic acids. It is the primary responsibility of the pathology laboratory holding the tissue sample to undertake an assessment of the adequacy of tissue samples for tumor *BRCA* analysis; this should include an assessment of the neoplastic cell content of the sample. It is recommended that the neoplastic cell content of samples should be at least twice the limit of detection of the assay used. For next generation sequencing based assays, the typical minimum neoplastic cell content for reliable detection of pathogenic variants is 20%. Formalin fixed paraffin embedded samples with less than 20% neoplastic cell content and regions of higher neoplastic cell content may be 'rescued' by macrodissection in the genomic laboratory. Macrodissection by the referring pathologist should, therefore, be considered for any samples where the neoplastic cell content is less than the minimum recommended by the genomics laboratory. A clearly marked H&E-stained guide slide with areas of neoplasia ringed using an indelible marker should be sent along with unstained slide mounted sections. The H&E guide slide should be derived from a serial section next to the sections sent for genomic analysis. Tissue morphology can change as successive sections are cut from the block and a neighboring section mitigates against macrodissecting an inappropriate region of the tissue section.

Table 2 Classes of variants[14 15]

Variant description	Variant class	Probability of being pathogenic	Clinical recommendations (germline or somatic)	Other recommendations for germline variants
Pathogenic	5	>0.99	May be eligible for *BRCA* specific treatments for example, PARPi	Follow high-risk management guidelines Referral to clinical genetics Predictive testing in family members
Likely Pathogenic	4	0.95–0.99	May be eligible for *BRCA* specific treatments for example, PARPi	Unaffected family members carrying the familial variant should follow high-risk management guidelines
Variant of Uncertain Significance (VUS)	3	0.05–0.949	No clinical implication	Presence of variant should **not** be used to influence clinical management No predictive testing Kept under review by genetics as a small proportion may get reclassified to pathogenic or likely pathogenic in the future
Likely Benign or Likely Not Pathogenic	2	0.001–0.049	No clinical implication	Presence of variant should **not** be used to influence clinical management No predictive testing Do not refer to clinical genetics
Benign or Not Pathogenic	1	<0.001	No clinical implication	

Genomic target test turnaround times for genomic laboratory hubs in England are set by National Health Service England. The key turnaround times appropriate for ovarian cancer are 21 calendar days for tumor *BRCA* analysis and 42 calendar days for germline *BRCA* analysis. Genomic laboratories are expected to meet these turnarounds in at least 90% of cases.

CONSENT ISSUES

With the roll-out of the NHS Genomic Medicine Service, patients across England gain equity of access to genomic testing for the first time, including whole genome sequencing for certain rare diseases and cancers. Healthcare professionals will need to be equipped to obtain patient consent for these tests, and provide the information and support required

To support this roll-out, the Genomics Education Program has developed a competency framework that identifies eight areas of proficiency to facilitate obtaining patient consent for genomic tests (https://www.genomicseducation.hee.nhs.uk/consent-a-competency-framework/). This framework is intended as a cross-professional guide for best practice and has been designed around four categories of healthcare professionals based on their training and experience with genomics. The competency framework can be used by individual healthcare professionals as a guide to help them identify their learning needs. For educators, the framework provides a mechanism to recognize the training needs of health professional groups, and to structure training so that consent conversations about genomic testing can be delivered consistently across different specialties. In addition, the competencies can be used to evaluate how consent is being obtained in different practice areas to enhance the delivery of genomic medicine.

Crucially, with the new framework, consent is rightly seen as a process whereby an 'offer' is made, adequate information provided and discussions to enable informed choice by patients are provided. Until the 'patient choice' forms are readily available in the UK (as detailed in the Genomics Education Program), the current consent forms can be used and adapted to indicate if a patient has provided consent for somatic, germline or combination (parallel) testing. The patient notes must record that the discussion about opting to have a BRCA test has taken place over different points in the diagnostic or treatment work up. The consenting process should comply with General Medical Council standards (https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent).

In all cases, high quality, culturally appropriate information must be provided to patients so that they can make an informed decision. Please see online supplemental appendix 2–4 for template letters.

Box 1 Patients perspectives on BRCA testing

- Variation in provision of BRCA testing across the UK is a cause for concern and this should be minimized.
- BRCA testing should be offered to all patients where treatment options exist that would be influenced by this knowledge, even when patients have missed an initial opportunity to be tested.
- Whilst the offer for testing should be made as early as possible, different patients may be ready to be tested at different points in their cancer journey and this should be recognized by treating teams. Testing should be undertaken at an appropriate time in a patient's journey.
- Results of tests should be made available in time to impact chemotherapy options.
- It is important to recognise that information on genetic testing is valuable to to both patients and family members.
- Providing adequate time for informed consent and decision making.
- Appropriate pre-test counselling should be offered to all patients. Providing information in a culturally sensitive manner keeping in mind socio-cultural issues relevant to ethnic minorities.

RECORDING OF BRCA STATUS AND MULTIDISCIPLINARY TEAM MEETING OUTPUTS

Consistency of terminology is important to avoid confusion. For instance, use of the term 'BRCA positive' should be avoided as it can be interpreted to mean the diametric opposite of the positive presence of a mutation or the positive presence of protein. To avoid confusion, the following terms should therefore be used: germline variant—a variant detected in the blood sample; tumor variant—a variant detected in the tumor; importantly, without reference to the blood sample, a tumor variant could be either germline or somatic; and somatic variant—a pathogenic variant detected in the tumor sample which is not present in the blood sample; to define a somatic variant therefore requires that both blood and tumor samples have been analyzed.

For ease of recording, a common notation is to use a prefix to define the type of variant described and a suffix to describe the result. Using these notations, g, t and s are used to describe germline, tumor and somatic, respectively. Additionally, m, vus and wt are used to describe pathogenic or likely-pathogenic variant (mutation), variant of unknown significance and wild type, respectively. For example, gBRCA1m would describe a germline variant (pathogenic or likely pathogenic variant) of BRCA1, in contrast to sBRCA2wt which would describe a somatic wild type (no pathogenic variant) BRCA2. For more information on classes of variant, see Table 2.

PATIENT PERSPECTIVES

Conversations with gynecological cancer charities have highlighted issues of concern and importance for patients that need to be considered when implementing *BRCA* testing. Critically, patients should feel reassured that the timing of *BRCA* testing is their decision as patients may feel ready to undergo testing at different points in their journey. High quality, culturally appropriate information is vital to this; see Box 1.

Box 2 Recommendations for BRCA testing in ovarian cancer the UK (seeonline supplemental file 5)

General

- Parallel tumour and germline testing for BRCA1 and BRCA2 is superior to either germline alone, tumour alone or sequential testing strategies.
- Robust processes should be in place to ensure results of BRCA testing are recorded, with the correct nomenclature, in the patient's clinical and laboratory records and that the patient is informed of the result.
- Patients with positive test results should be referred to clinical genetics for post-test counselling and facilitation of predictive testing in family members.
- The classification of BRCA variants is under constant review; and variants previously considered VUSs might be reclassified as pathogenic or non-pathogenic variants as the analytical process improves. Therefore, consideration should be given to VUS review at the time of disease recurrence if initial testing was done at diagnosis and if knowledge of BRCA 1/2 status will change management.

Consent

- High quality, culturally appropriate information must be provided to patients so they can make an informed decision. Consenting should be carried out according to standards set up by General Medical Council, UK. Consenting for BRCA1/2 testing can be undertaken by any appropriately trained healthcare professional. For tumour testing, it is recognized that this consent may be verbal and documented in the patient records; for germline testing written consent should be undertaken.
- Where BRCA1/2 testing has been discussed with the patient, this should be documented in the clinical records.

Tumour BRCA Testing

- Testing for tumour BRCA1/2 can be discussed with patients either prior to or after biopsy for suspected high-grade serous ovarian cancer.
- Tumour testing alone should not be relied upon for exclusion of a clinically relevant BRCA1/2 mutation. LGRs may be missed on tumour testing alone but identified by germline testing.
- If tumour testing is to be undertaken on a radiological biopsy then additional cores should be taken to ensure sufficient tissue for analysis.
- If a diagnostic result is not obtained from an initial tissue biopsy then additional tissue should be analysed at the time of interval debulking surgery. If a diagnostic result is not obtained from an initial tissue biopsy and the patient is not undergoing debulking surgery then an additional tissue biopsy for BRCA testing alone should be considered, if the result would change management.
- It should be noted that as funding arrangements for oncological treatments change the absolute requirement for BRCA1/2 tumour testing might change.

Germline Testing

- Germline testing should be offered to patients as early as possible at diagnosis and not delayed.
- Low-grade serous tumours do not require BRCA1/2 testing when the diagnosis has been confirmed by a specialist gynaecological cancer histopathologist.

Audit standards

- Percentage of patients eligible for germline testing who underwent testing – Target 100%.
- Percentage of patients eligible for tumour testing who underwent testing - Target 100%.
- Percentages of specimens sent for tumour testing where analysis did not yield a diagnostic result – Target 0%.
- Turnaround times for tumour BRCA analysis - Target 21 calendar days.
- Turnaround times for germline BRCA analysis - Target 42 calendar days.
- Exclusions: patients who choose not to undergo BRCA testing or patients where it is not clinically appropriate.

CONCLUSIONS

Germline testing has significant implications for patients, in terms of therapy choices, but also for their families in terms of risk management and the development of additional tumors. Tumor *BRCA* testing identifies an additional subgroup of women who have benefit from PARP inhibitors. Recommendations for testing are summarized in Box 2. It remains of critical importance to stratify patients and identify those who do not have a *BRCA* (germline/somatic) pathogenic variant as this group of women are least likely to benefit from PARP inhibitors and should therefore be considered for studies of novel therapies or combinations going forward. Additionally, family members who have a pathogenic or likely pathogenic variant can opt for a range of interventions such as reproductive choices, prenatal genetic diagnosis, planning a family, risk reduction surgery, screening or chemoprevention to minimize their ovarian cancer and breast cancer risk.

Author affiliations
[1]Gynaecological Oncology, Pan-Birmingham Gynaecological Cancer Centre, Birmingham, UK
[2]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK
[3]Gynaecological Oncology, Barts Health NHS Trust, Barts Cancer Institute, London, UK
[4]University of Edinburgh Cancer Research UK Centre, Edinburgh, UK
[5]Royal Marsden Hospital NHS Trust, London, UK
[6]Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester, UK
[7]University Hospital Birmingham Foundation NHS Trust, Birmingham, UK
[8]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
[9]University of Manchester, Manchester, UK
[10]Oxford University Hospitals NHS Trust, Oxford, UK
[11]Royal United Hospitals Bath NHS Foundation Trust, Bath, UK
[12]Pathology, Royal Marsden NHS Foundation Trust, London, UK
[13]Gynaecologic Oncology, Imperial Hospitals NHS trust, London, UK
[14]Macmillan Cancer Support, London, UK
[15]Nottingham University Hospitals NHS Trust, Nottingham, UK
[16]Peterborough City Hospital, Peterborough, UK
[17]Obstetrics and Gynaecology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK
[18]Imperial College London, London, UK
[19]Gynaecological Oncology, Royal United Hospitals, Bath, UK
[20]Birmingham Women's and Children's NHS Trust, Birmingham, UK

Twitter Sudha Sundar @sundar_sudha and Ranjit Manchanda @ProfManchanda

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ORCID iDs
Sudha Sundar http://orcid.org/0000-0002-5843-3015
Ranjit Manchanda http://orcid.org/0000-0003-3381-5057
Christina Fotopoulou http://orcid.org/0000-0001-6375-9645

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Tumour BRCA (tBRCA) guidelines for pathologists are extrapolated from recommendations for HER-2 testing. There are no published studies on pathology protocols and result outcomes in tBRCA testing. This guidance is based on general principles and author experience.

Tubo-ovarian cancer and BRCA

The frequency of *BRCA1* and *BRCA2* germ-line pathogenic variations (mutations) in women with tubo-ovarian cancer is variably quoted. If all tubo-ovarian cancers are taken into consideration, the stated frequency is 10 – 15%. *[Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, Friedlander M, Fox S, Bowtell D, Mitchell G. 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 Jul 20;30(21):2654-63. doi: 10.1200/JCO.2011.39.8545.]*. When somatic mutations are included, this figure rises to 20% or greater. *[Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. Eur J Cancer. 2016;60:49-58. doi:10.1016/j.ejca.2016.03.005]*.

Recombinant DNA Repair

Recombination occurs when two molecules of DNA exchange pieces of genetic material with each other. This must be accurate in order to maintain genetic integrity. The most notable example of recombination is in meiosis resulting in creation of gametes that contain new combinations of parental genes. Throughout life, the DNA undergoes damage. There are six major DNA repair pathways in humans. These include base excision repair, nucleotide excision repair, single strand break repair, homologous recombination (HR) repair, non-homologous end joining and mismatch repair. *[Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009;461(7267):1071-1078. doi:10.1038/nature 08467]*. The HR pathway consist of a set of related sub-pathways that utilize DNA strand invasion and template-directed DNA repair synthesis to effect a high-fidelity repair of damaged DNA.

Recombinant DNA repair and BRCA pathogenic variants

The HR pathway involves the coordinated interactions of many proteins including BRCA1 and BRCA2 and other proteins such as RAD51 and proteins of the Fanconi anaemia pathway. Alterations of the BRCA1 and BRCA2 genes may occur as a germline abnormality, but may also occur through mechanisms such as somatic mutations and epigenetic silencing. *[Moschetta M, George A, Kaye SB, Banerjee S. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. Ann Oncol. 2016;27(8):1449-1455.]* Deficiency in HR is a target for Poly(ADP-ribose) polymerase (PARP) inhibitors.

Germline mutations vs somatic mutations

Germline mutations are inherited mutations and are present in every cell of the body. Somatic mutations are non-inheritable mutations that are found only in tumour cells. Upto 6-7% of high grade serous tubo-ovarian carcinomas have somatic BRCA1/2 mutations. tBRCA and somatic BRCA are not synonymous. BRCA mutations in tumour cells reflects both germline and somatic mutations.

Testing for BRCA pathogenic variants (mutations)

Germline testing is generally done using blood. tBRCA testing is done mostly by using formalin fixed paraffin embedded (FFPE) tissue from the carcinoma. Cytology samples, rarely, can also be used.

Reasons for tBRCA testing

PARP inhibitors inhibit DNA repair pathways and cause apoptosis/death of cancer cells, especially in HR-deficient cells. tBRCA testing is important to identify this subgroup of patients. Tumours harbouring BRCA1/2 mutations (detected by tBRCA testing) in the tumour, irrespective of germline or somatic, are also associated with better response to platinum-based chemotherapy. tBRCA abnormalities due to germline BRCA mutations have additional implications in identifying BRCA germline mutation carriers.

Role of the pathologist

The pathologist plays an important role in selection of the test sample and is the member of the multidisciplinary team who has access to pre-test and post-test pathways and is pivotal in establishing standard operating procedures, audit of the process and institution of change if needed.

Understanding pre-analytic variables

The process of acquiring tissue starts with tissue collection by the clinician as a diagnostic or resection sample. Warm ischemia time is the time from the interruption of the blood supply to the tumour to the excision of the tissue specimen. This is followed the cold ischaemia time which is the time taken to transfer the surgical specimen into the fixative. The length of this time influences the levels of gene expression and is an important factor. The cold ischaemia time is less for small samples acquired at inpatient or outpatient settings.

Once in the specimen container, the tissue is penetrated by the fixative before the actual process of fixation starts. This is a problem particularly with large specimens such as ovarian tumours. *[Goldstein NS Hewitt SM, Taylor CR, Yaziji H, Hicks DG Recommendations for Improved Standardization of Immunohistochemistry." Applied Immunohistochemistry & Molecular Morphology 15 (2007): 124-133].*

The fixative of choice is 10% neutral buffered formalin. Formalin should only be used for upto 24 h after dilution to 4% w/v. After 24 hours, polymerisation starts and a stable ph and 4% concentration gets affected. Formalin penetrates tissue at around 1 mm/hour. A minimum of 6 hours of formalin fixation is required, complete tissue fixation requires up to 24 hours. Prolonged fixation (arbitrarily designated as beyond 36 hours) is a possible cause for test failure and should be averted wherever possible. Fixation over the weekend, especially of small biopsies, should be avoided.

Laboratory processes

Sections should be cut under conditions (clean microtome etc) that avoid cross contamination from other specimens.

Appropriate numbers of air dried, mounted, unstained, non coverslipped sections should be sent.

For cytology specimens, It is essential that cells and tissue fragments from the cytology samples are processed into agar/cell blocks, formalin-fixed and paraffin embedded and then undergo an assessment process as per tissue samples.

The request forms

Requests for tBRCA testing can be made by managing clinicians, nurse specialists, multidisciplinary teams or pathologists. This is a local decision. In all scenarios, patient consent needs to confirmed and documented.

At the time of writing these guidelines, the BRCA form testing form (Astra Zeneca) can be downloaded from

https://medicines.astrazeneca.co.uk/content/dam/multibrand/uk/en/resources/lynparza/tbrca-testing/0715-test-request-form-Manchester.pdf

https://medicines.astrazeneca.co.uk/content/dam/multibrand/uk/en/resources/lynparza/tbrca-testing/0715-test-request-form-Royal-Marsden.pdf

The results should be requested to generic pathology and generic clinical emails.

Choosing material for testing

In England, tBRCA testing is advised for high grade serous carcinomas and in Scotland tBRCA testing is advised for high grade serous and endometrioid carcinomas. The diagnosis is made in several settings. The pathologist or advanced practitioner dealing with the specimen may not be a specialist in gynaecological pathology. This guideline advises the following in order to conserve the maximum amount of tissue for tBRCA test.

Biopsy of suspected tuboovarian carcinoma:

· Cores blocked separately (at least 2 blocks)

· H&E on both blocks to confirm cancer

· One block (preferably the one with less tissue/tumour) for confirmatory IHC

· IHC to confirm high grade serous carcinoma (PAX8+ve, WT1 +ve, ER +ve. p53 mutation/aberrant) (https://www.thebagp.org/download/bagp-uknegas-project-p53-interpretation-guide-2016/) *If there is diagnostic uncertainty, in order to preserve tissue for testing, further immunostains should not be done. The available material should be sent to Cancer Centre for review and diagnosis.*

· Tissue/blocks, H&E and immunostained slides should be sent to nominated pathologist.

Resection specimen from known high grade tuboovarian serous carcinoma:

· Reporting pathologist should send block/tissue from primary or metastatic carcinoma containing maximum viable and well-fixed tumour and its H&E stained slide to nominated pathologist

Cell block from fluid sample (pleural effusion or ascites) in suspected tuboovarian carcinoma:

· H&E to confirm cancer

· Minimal IHC to confirm high grade serous carcinoma (PAX8+ve, WT1 +ve, ER +ve. p53 mutation/aberrant)

· Block, H&E and IHC slides sent to nominated pathologist.

Sending material for testing

Nominated pathologist/s mark tumour areas on H&E slide and estimates tumour volume within the whole section and within the marked areas. As a guidance, the marked areas should contain at least 20% tumour cells.

The tissue block, the marked slide and the completed form are sent to the appropriate genetic laboratory hub.

Recording the report

When the result is received, it should be added (in full) to the initial pathology report as a supplementary. Wherever possible, the pathologist should enable including the result in the MDT and patient records and make the result accessible to the managing clinician. Local pathways should be followed

Audit

We recommend that there should be mechanisms in place to document preanalytic variables, laboratory processes and tumour content prospectively to enable audit of these parameters.

University Hospitals Bristol and Weston NHS Foundation Trust

Receiving a BRCA1 and BRCA2 test result that identifies an alteration

Information sheet for patients with cancer

You had a *BRCA1* and *BRCA2* gene test because of your diagnosis of cancer.

The test result has shown that you have a pathogenic variant (alteration) in either the *BRCA1* or *BRCA2* gene. This was found in your cancer sample as well as your blood sample.

BRCA1 or *BRCA2* alterations result in increased risks of breast, ovarian and prostate cancer, and occasionally other cancers. Therefore, this result provides an explanation for why you developed cancer.

This result has implications for your future health and potentially for your relatives. A referral has been made for you to the Clinical Genetics team discuss these issues further.

At your Genetics appointment you will be able discuss your future risks of cancer and your options for cancer screening and measures to reduce the risk of cancer. The potential implications for relatives will also be discussed. The processes by which your relatives can be referred themselves to decide if they wish to have testing will be explained.

If you have not heard from the Genetics team with an appointment date in the next 4 weeks, please contact them on 0117 342 5107 to check the progress of your referral.

Your cancer team will discuss with you if this result has implications for your cancer treatment and/or follow-up.

If you have any further questions in relation to your ongoing cancer treatment, please contact your cancer team on [local contact details].

University Hospitals Bristol and Weston NHS Foundation Trust

Receiving a BRCA1 and BRCA2 test result that identifies an alteration in your cancer

Information sheet for patients with cancer

You had a *BRCA1* and *BRCA2* gene test because of your diagnosis of cancer.

The test result has shown that you have a pathogenic variant (alteration) in either the *BRCA1* or *BRCA2* gene in your cancer sample. This alteration was not found in your blood sample.

What does this result mean for me?

Your cancer team will discuss with you if this result has implications for your cancer treatment and/or follow-up. Because this alteration was not found in your blood sample, it does not have implications for your risks of other cancers.

If you have a strong family history of breast and/or ovarian cancer, or a strong family history of other cancers, or if you developed cancer at an unusually young age, it may be helpful to look into things further. The cancer team will discuss this with you and, if appropriate, refer you for further assessment by the Clinical Genetics team.

Very occasionally alterations in other genes can be involved in causing breast or ovarian cancer. Also new discoveries are being made all the time. In the years to come if you would like to find out if any further genetic testing is available, please discuss this with your GP, who could refer you to the genetics team, if appropriate.

What does this result mean for my relatives?

This result is good news for your relatives, as it means they are less likely to be at a high increased risk of developing breast and/or ovarian cancer themselves because it was not found in your blood sample. You may wish to share this result with them.

There is currently no known effective form of ovarian screening. If a woman has more than one relative with ovarian cancer, removal of the ovaries is sometimes considered.
All women are eligible to have mammograms from 47 years in the National Breast Screening Programme. Depending on the family history, some women may be eligible for mammograms from 40 years.
If this is the case in your family, please discuss this further with your cancer team.

If any of your relatives wish to discuss their own risks of cancer further, they should speak with their GP who can refer them for further discussions at their local Family History screening clinic.

If you have any further questions, please contact your cancer team on [local contact details].

Genetic Testing of *BRCA1* and *BRCA2* in a person with ovarian cancer

St George's University Hospitals NHS
NHS Foundation Trust

Cancer in the general population

Cancer is a common condition which will affect up to 1 in 2 people in the general population in their lifetime. In the UK around 2 in 100 (2%) women develop ovarian cancer. The majority (85 out of 100, or 85%) of ovarian cancer cases are due to a combination of increasing age, environmental, lifestyle, and low risk genetic factors.

Why am I being offered a genetic test?

You have been given this leaflet because you have been diagnosed with ovarian cancer. Genetic testing of your tumour will help your oncologist plan the best treatment for you. Genetic testing of your blood may help guide your future care and provide you with information on future cancer risk. It may also give us information to help your relatives to manage their future cancer risk.

What are genes?

Genes are our cells' instruction manuals. We each have around 20,000 pairs of genes which are present in almost every single cell of our bodies. Our genes tell our cells how to function normally. Different genes have different roles in the body. The genetic test we are offering you looks to see if there are changes in two genes associated with ovarian cancer.

What are cancer-causing genetic variants called?

Many different words are used to describe cancer-causing genetic changes. "Mutation," "disease-causing alteration or variant," "pathogenic mutation," or "pathogenic variant" are all terms you may come across. We will use the term "pathogenic variant" to describe a variant in a gene which is known to cause cancer.

How do changes in genes cause cancer?

Most of the time cancer-causing genetic changes are found ONLY in the cancer cells (in the tumour). In this case the changes are called "***somatic*** pathogenic variants".

A smaller number of women with ovarian cancer have inherited a genetic change which means they are more at risk of cancer. This is a called a "***constitutional*** or ***germline*** pathogenic variant".

Which genes are associated with ovarian cancer?

The two main genes we test for in ovarian cancer are called *BRCA1* and *BRCA2*. We all have two copies of these genes, as we inherit one copy from each of our parents. We can look at the *BRCA1* and *BRCA2* genes in the ovarian cancer cells (the tumour) to see if there is a ***somatic*** pathogenic variant. To see if this variant is also present in other cells in the body we can also look at the *BRCA1* and *BRCA2* genes in the blood cells. If the variant is also present in the blood cells this means it is an inherited ***germline*** pathogenic variant.

How do we test for genetic variants?

There are two tests to look for genetic changes that may have contributed to you developing cancer.

1. Tumour testing to look for ***somatic*** variants. Your oncologist will send a sample of your tumour onto a specialist laboratory to test it for variants in *BRCA1* and *BRCA2*. These results will take around 5 weeks to be reported.

2. A blood test to look for ***germline*** variants. Your treating team will take a blood sample from you and ask you to sign a consent form to have this sample stored. A member of the genetics team will contact you to explain more about testing your blood sample for variants in *BRCA1* and *BRCA2*. The results may take around 6-8 weeks to be reported.

What are the outcomes of testing? (1)

1. Somatic testing (from your tumour)

a) A *BRCA1* or *BRCA2* pathogenic variant is detected in your tumour sample which we know is associated with ovarian cancer. Your oncologist may use this information to guide your treatment. We would need to check to see if the variant is also present in your blood sample.

b) No BRCA1 or BRCA2 pathogenic variant is detected in your tumour sample. In this case it would be unlikely that your cancer was caused by a BRCA pathogenic variant. We would still check your blood test results to confirm this.

Sundar S, *et al. Int J Gynecol Cancer* 2021;0:1–7. doi: 10.1136/ijgc-2020-002112

What are the outcomes of testing? (2)

1. Germline testing (from your blood sample)

(a) A BRCA1 or BRCA2 pathogenic variant is detected in your blood sample which we know is associated with ovarian cancer. This is often called being a "BRCA carrier." This will likely explain why you developed cancer.

In this case you would meet with a member of the genetics team to discuss what this means for your future management and for your relatives. We know that germline BRCA carriers are at increased risk of breast cancer as well as ovarian cancer. Although treating your ovarian cancer takes priority, we can also assess your future breast cancer risk and offer personally tailored advice about managing this risk.

The chance that a first degree relative (parent/sibling/child) of a person with a pathogenic variant will also carry that variant is 1 in 2 (50%). We can support families to share this information with relatives so they can be tested.

(b) No BRCA1 or BRCA2 pathogenic variant is detected in your blood sample. In this case it would be less likely that your cancer was due to an inherited condition. You will still have a full review of your personal and family history to check no further genetic testing or screening is needed.

(c) A Variant of Uncertain Significance is detected (VUS). In rare cases we may identify a *BRCA1* or *BRCA2* variant, but we do not know if it is affecting the way the gene is working to cause cancer. This is known as a 'variant of unknown significance.' Most of these are likely to be harmless and we would usually manage you as if you had no variant identified. Sometimes we may wish to perform additional tests to clarify the significance of the variant which we will discuss with you. As our knowledge about genetic variation increases, we may decide this variant is pathogenic or harmless and change your management if needed.

How will finding a pathogenic variant in *BRCA1* or *BRCA2* affect my treatment?

Your oncologist may use this information to help decide the best treatment for your cancer. In particular, they may suggest prescribing a medication called a PARP Inhibitor. PARP Inhibitors have been shown to improve response to cancer treatment in BRCA carriers.

What can be done if I decide not to undergo testing?

If you do not have either tumour or blood testing, your oncologist will not be able to use the test information in your treatment plan and Genetics would make a risk assessment for family members based on the family history alone.

Sometimes, although someone does not wish to pursue a blood test at that time, they may decide to have a blood sample stored for either their own future use or for that of their family members. This is something we can discuss with you. You could still have your tumour tested to help make decisions about your treatment if you wish.

Family history information

The genetics team will take a family history to make sure we have offered you all the tests you need. They will also use this information to give screening advice in the family, even if a genetic test is negative. You can fill out your family history information in advance of your appointment at ***www.fhqs.org*** or by scanning the QR code below.

Websites for further Information

Breast awareness (Macmillan):
http://www.macmillan.org.uk/Cancerinformation/Testsscreening/Breastscreening/Breastawareness.aspx

Ovarian symptoms (Ovarian Cancer National Alliance):
http://www.ovariancancer.org/about-ovarian-cancer/symptoms/

Details regarding your test

- Date of test:
- Contact person:
- Results expected:

To provide feedback on this leaflet please go to ***https://www.surveymonkey.co.uk/r/DHX7HQN***

2019

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British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for germline and tumour testing for *BRCA*1/2 variants in ovarian cancer in the United Kingdom

Sudha Sundar, Ranjit Manchanda, Charlie Gourley, Angela George, Andrew Wallace, Janos Balega, Sarah Williams, Yvonne Wallis, Richard Edmondson, Shibani Nicum, Jonathan Frost, Ayoma Attygalle, Christina Fotopoulou, Rebecca Bowen, Dani Bell, Ketan Gajjar, Bruce Ramsay, Nick Wood, Sadaf Ghaem-Maghami, Tracie Miles, Raji Ganesan

Key message 1 - BRCA mutations can develop in two ways

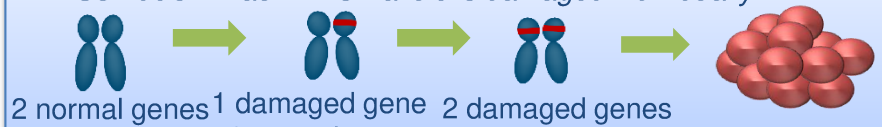
In hereditary cancer, one damaged gene is inherited

Germline – *One damaged BRCA allele is inherited*

accounts for ~ 15 % HGSOC

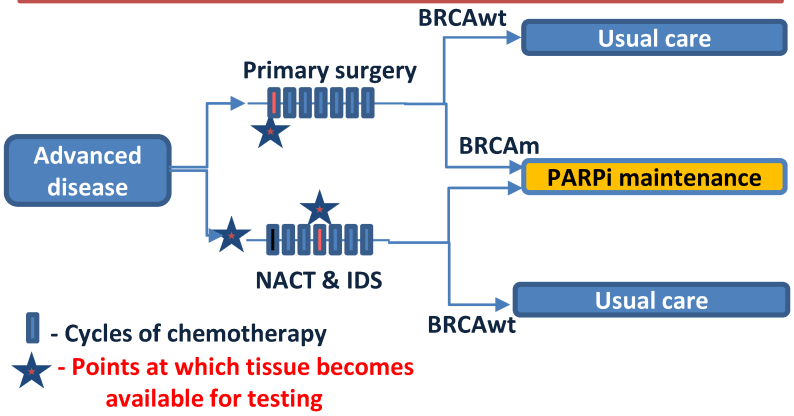
In sporadic cancer, each gene is damaged individually

Somatic - *Each BRCA allele is damaged individually*



accounts for ~7% HGSOC

Key message 2 – Tumour tissue for testing available at different points in pathway (★)but offer at the earliest point in treatment when possible



Key message 3 – Tumour testing cannot distinguish between somatic and germline mutation.

gBRCA testing (blood sample)

All inherited pathogenic variants can be detected, including large duplications/deletions (~10%) which are not reliably detectable in tumour samples

Results can inform of increased cancer risk in relatives and contribute to decisions on prophylactic measures

tBRCA testing (FFPE ovarian tumour sample)

Identifies ~50% more patients eligible to receive PARP inhibitors (~ 7% sBRCAm and ~15% gBRCAm) than germline testing alone, as it detects both variants (however tBRCA testing cannot distinguish between these mutations)

Key message 4 – We advise both germline and tumour BRCA testing to be done in parallel.

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