British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for genetic testing in epithelial ovarian cancer in the United Kingdom

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Table of Contents

1. Introduction 4
   1.1. Rationale for parallel genetic testing in epithelial ovarian cancer 4
   1.2. Mainstreamed germline genetic testing 4
   1.3. This consensus guidance update 5
2. Timing of genetic testing in relation to first-line treatment 5
   2.1. At Initial consultation before histological diagnosis 6
   2.2. Consultation before primary cytoreductive surgery 6
   2.3. Consultation before neoadjuvant chemotherapy or further investigations 6
   2.4. Consultation after upfront debulking surgery or diagnostic biopsies 6
   2.5. Patients with recurrent ovarian cancer 7
3. Special considerations in the following clinical scenarios: 7
   3.1. Imaging-guided biopsy (IGB) 7
      3.1.1. Patient and treatment factors 7
      3.1.2. Site of image-guided biopsy 7
      3.1.3. Other technical considerations 8
      3.1.4. Safety of multiple IGB cores 8
      3.1.5. Multidisciplinary decision-making 8
   3.2. Diagnostic laparoscopy 9
      3.2.1. Indications 9
      3.2.2. Technical considerations 9
   3.3. Ascites cytology (in cases where tissue cannot be obtained) 9
4. Summary of genetic testing in ovarian cancer 10

4.1. Parallel genetic testing for patients newly diagnosed with EOC 10
5. The role of unit leads 11
6. The role of cancer nurse specialists 12
7. Pathology - guidance on tissue handling and pathways for tumour *BRCA* testing 13
7.1. General principles: 13
7.2. Sample handling 13
7.2.1. Biopsies 13
7.2.2. Resection specimens 14
7.2.3. Ascites and other cytology samples 14
8. Genomic Laboratory Hub considerations 14
9. Consent issues 15
9.1. Mode of consent and reflex tumour testing 15
9.2. The consent process and consent forms 16
10. Recording of genetic testing results 17
10.1. Information to be recorded in clinical notes 17
10.2. Five classes of variants 17
11. Changes on the horizon 18
11.1. Whole-Genome Sequencing and alternative HRD testing 18
11.2. *BRCA1/2*-mutant tumours with incongruous mutational signature scores 18
12. Continual professional development 19
13. Patient and public involvement 19
13.1. Mainstreaming 19
13.2. Co-production 19
14. Audit and governance 20
15. Conclusions 20
16. Recommendations 20
16.1. General 20
16.2. Consent 21
16.3. Tumour Testing 21
16.4. Germline Testing 22
16.5. Audit standards 22
17. Acknowledgements 22

18. References _____23

Appendix 1: Co-produced written patient information on parallel genetic testing- an example_____27

Appendix 2: Consent form for parallel genetic testing- an example _____27

Appendix 3: Description and person specifications of gynaecological genomics clinical lead and administrative support roles _____27

Appendix 4: Questions for patient group discussions and result summaries _____27

Appendix 5: A proposed Whole Genome Sequencing pathway_____27

1. Introduction

Genetic aberrations play key roles in the pathogenesis of epithelial ovarian cancer (EOC), with prognostic and predictive values in patients affected with the disease. As the role of poly (ADP-ribose) polymerase (PARP) inhibitors are established in the treatment of advanced EOC in first-line setting [1-4] and their access are often dependent on *BRCA1/2* mutational and tumour homologous recombination defect (HRD) status, parallel genetic testing is now part of the standard of care in patients diagnosed with EOC.

1.1. Rationale for parallel genetic testing in epithelial ovarian cancer

The Cancer Genome Atlas (TCGA) identified somatic and germline *BRCA1/2* pathogenic variants in ~22% of high-grade serous ovarian cancers.[5] There are currently two methods by which genetic testing, such as *BRCA* testing, is undertaken, each detects slightly different pathogenic variants due to the pathogenesis of these variants and the limitations of the analytical techniques:

- **Germline testing** is undertaken on blood or saliva samples and will detect inherited pathogenic variants, including the large duplications/deletions which are not reliably detectable on testing of tumour tissue. Germline testing results carry implications for family members.
- **Testing of tumour tissue** (referred as tumour testing in this document) involves extracting DNA from the tumour and testing for pathogenic variants. A tumour variant should only be described as 'somatic' if germline DNA has also been tested and is wild type.

Depending on the population tested, around half to two-thirds of the variants detected in tumours will be of germline (inherited) origin.[6] Therefore, results of tumour testing may have implications for family members. Tumour testing also provides the opportunity to simultaneously test for HRD status.

Patients with a germline and tumour *BRCA* variant have longest progression-free and overall survival followed by those who are have HR repair defects (without *BRCA* variant /wild type *BRCA*) detected within the tumour.[1-3, 7, 8] Early knowledge of the tumour *BRCA*/HRD status facilitates and improves informed treatment choices for patients and clinicians in the first-line setting.

1.2. Mainstreamed germline genetic testing

The prevalence of pathogenic *BRCA* germline mutations in patients with high-grade serous ovarian cancer (HGSOC) were reported to be 13-15%.[8-13] Unselected germline testing

identifies around 50% more patients with germline pathological variants than when germline testing was offered based on family history.[14, 15] The asymptomatic individuals in these families could benefit from predictive testing and subsequent risk reduction management.

To manage this increased demand and ensure timely access to testing early in the care pathway, models of delivery involving surgeons, oncologists or clinical nurse specialists to "mainstream" germline testing have been developed in centres across the UK, improving the uptake and reducing the time to genetic results.[11, 13, 15, 16] In these models, the clinical care teams for cancer treatments counsel and offer germline testing to all patients with a diagnosis of EOC; only patients who are found to have pathogenic variants or variants of uncertain significance (VUS) are referred to clinical genetics services. Some mainstream models restrict testing to defined histological criteria (e.g., high-grade serous or endometrioid), others restrict testing to age groups (e.g., under 70 years) resulting in considerable variability and around 30% of eligible patients not being offered testing.[17]

1.3. This consensus guidance update

Incorporating *BRCA* and HRD testing and other emerging genetic tests into routine practice in newly diagnosed EOC requires careful consideration of the scheduling of tests, timing of testing in relation to first-line therapy, counselling of patients, costs, sample management processes, quality controls and audit trails.

The British Gynaecological Cancer Society (BGCS) and the British Association of Gynaecological Pathologists (BAGP) established a multidisciplinary consensus group comprising of experts in surgical gynaecological oncology, medical oncology, genetics, scientists and clinical nurse specialists to identify the optimal pathways to implement genetic testing into routine clinical practice. In particular, the group explored models of consent, quality standards within pathology and genetic testing laboratories. The group liaised with representatives from charities and patient groups to identify and address patient perspectives prior to implementation. Recommendations and suggested resources from this consensus group have informed this update to the guideline document first published in 2021,[18] and are presented below.

2. Timing of genetic testing in relation to first-line treatment

The consensus group reflected on issues related to the utility of knowledge of genetic status in treatment decisions in the first-line setting, including patient choice and consent (see Section 9 on Consent). Discussion around genetic testing should start at the earliest available opportunity in a patient's cancer journey, with recognition that patients may be ready to offer their consent at different time points. When appropriate, samples can be taken and stored with consent.

To ensure results are available when they are clinically relevant to treatment options, genetic testing should ideally be performed as near to the time of diagnosis as possible. Local turnaround time for testing and the need for counselling for germline testing

should be considered during clinical pathway development (see Section 12 on Continuing Professional Development [CPD]).

Counselling and consenting can be carried out by any members of the clinical team with appropriate training, which may include surgical oncologists in secondary and tertiary settings, medical oncologists, and cancer nurse specialists. In a small proportion of patients, the involvement of clinical genetics services for pre-test counselling is beneficial and should be supported.

We present possible points of testing in a patient's journey.

2.1. At Initial consultation before histological diagnosis

Genetic testing can be discussed with patients who present with a high clinical suspicion of EOC (e.g. carcinomatosis on imaging, CA125:CEA ratio >25[19, 20]) at initial presentation to a cancer unit gynaecologist or gynaecological oncologist, prior to confirmatory histological or cytological diagnosis (e.g. before the imaging-guided biopsy or diagnostic laparoscopy).

2.2. Consultation before primary cytoreductive surgery

Informed consent for genetic testing, if not previously obtained, should be sought during the counselling and consenting for primary (upfront) cytoreductive surgery (CRS).

In hospitals without an established reflex tumour testing pathway, information on whether the patient has provided consent for tumour testing should be communicated to the pathology team receiving the surgical specimens after CRS via locally agreed methods (e.g., recorded on the request forms or via email to the pathology team). This will enable timely transfer of the specimens to the laboratory performing the genetic testing.

2.3. Consultation before neoadjuvant chemotherapy or further investigations

Informed consent for genetic testing, if not previously obtained, should be sought from patients who are not suitable for upfront debulking surgery (or in cases of diagnostic uncertainty) before the commencement of neoadjuvant chemotherapy (or further investigations). In some cases, further biopsies may be needed for tumour testing.

This group often involves different members of the multidisciplinary team, including interventional radiologists, gynaecology cancer unit leads and non-gynaecological oncology services (e.g., acute oncology service and other specialties who may be the first contact for patients with ovarian cancer). Each clinical care team is advised to establish robust pathways with the relevant multidisciplinary teams to facilitate genetic testing.

2.4. Consultation after upfront debulking surgery or diagnostic biopsies

Informed consent for relevant genetic testing, if not previously obtained, should be sought when a patient is presented with the histological diagnosis of high-grade EOC (see Section 4).

Written consent must be obtained for germline testing (see Section 4). If a patient is not ready to offer their consent for germline genetic testing, a two-step process could be offered (i.e., consent for taking and storing a blood sample initially, and consent for testing later).

2.5. Patients with recurrent ovarian cancer

At the time of this update, patients with recurrent EOC are eligible to be tested for tumour *BRCA1/2* but not HRD testing.

This consensus group also recommends, if germline testing has not been performed previously, it should be offered to patients presenting with recurrence, to inform clinical management and support cascade testing.

3. Special considerations in the following clinical scenarios:

3.1. Imaging-guided biopsy (IGB)

3.1.1. Patient and treatment factors

Biopsies obtained post-chemotherapy can have a lower content of cancer cells and provide a lower DNA yield when compared with chemotherapy naïve tissue.[21] In patients who are not suitable for primary CRS, the initial diagnostic IGB can be used, not only for histological diagnosis, but also tumour genetic testing. Therefore, every attempt should be made to ensure enough tissue is obtained at the initial biopsy for tumour genetic testing.

If the pre-chemotherapy biopsy does not yield an adequate tissue sample for *BRCA*/ HRD testing, tumour testing should be considered from the interval CRS specimens in patients with negative germline testing. If CRS is not performed after neoadjuvant chemotherapy, repeat IGB for tumour testing should be considered.

3.1.2. Site of image-guided biopsy

The commonest sites for biopsy include the peritoneal/omental disease, lymph nodes and pelvic masses.[22] The site of biopsy should be decided by an experienced radiologist, taking into consideration the most accessible tissue and lowest risk to the patient. Percutaneous biopsy of a pelvic mass in a presumed stage I ovarian cancer is not recommended due to the risk of peritoneal spill and up-staging.

Patients with micronodular or low volume peritoneal disease may not have a clear soft tissue deposit to target at biopsy, which makes IGB more challenging and anecdotally less likely to produce diagnostic tumour yield for HRD testing. This cohort of patients was excluded from analysis in the BriTROC study.[23] No other large studies have analysed the optimal technique for this cohort. Given the DNA yield required for histology and genetic testing, the methods to obtain biopsies in this group (i.e., percutaneous versus laparoscopic biopsies) should be carefully considered with the multidisciplinary team.

3.1.3. Other technical considerations

Evidence from the BriTROC study has shown that the DNA yield was higher in IGB samples obtained using 14G or 16G biopsy needles, when compared with 18G biopsy needles (2.86 µg for 14G/16G needles 0.89 µg for 18G needles).[23]

The number of biopsy cores required will depend upon the number of tests requested. For an estimated 90% whole genome sequencing (WGS) success rate, the processing laboratory requires 50 mm^3 of tissue (of which at least 30% is lesional). This equates to 45 mm length of tissue using a 16G needle, or 80 mm with an 18G needle. Therefore, if both diagnostic histology and tumour genetic testing are required, more cores will be required – typically more than five passes with a 16G needle. Audit data from the Royal United Hospitals (RUH) in Bath demonstrated that all samples where five to six cores were acquired had diagnostic tumour yield for HRD testing (unpublished local audit data).

A co-axial needle technique should be considered to improve patient comfort during the procedure, particularly when multiple cores are required.

3.1.4. Safety of multiple IGB cores

The safety of multiple IGB cores from peritoneum and omentum has been examined. In the BriTROC trial,[23] complications were reported in three of 125 patients (2.4%) post-biopsy. These included pain (two patients) and haemorrhage (one patient after a liver biopsy)- all Clavien-Dindo[24] Grade II complications. Similarly, data from Cambridge University Hospitals (CUH) of ultrasound guided biopsies from omental, peritoneal and abdominal masses (performed between February 2021 - October 2022) demonstrated that 97% of biopsies were performed with 14G or 16G biopsy needles (unpublished local audit data). All four reported complications (4/70; 5.7%) were mild Clavien-Dindo Grade I complications, including bleeding or haematoma (3/70; 4.3%), and pain (1/70; 1.4%). The operator should consider the risks and benefits including the site of biopsy, degree of vascularity and patient comfort during the procedure.

3.1.5. Multidisciplinary decision-making

Ideally biopsy decisions should be discussed within the MDT, with recommendations from the radiology MDT representative on a patient's suitability for IGB, including optimal biopsy site and choice of imaging modality.

However, not all gynae-subspecialty radiologists perform interventional procedures, and not all interventional radiologists have knowledge of gynaeoncological imaging. Therefore, adequate education and good communication between all radiologists involved in this pathway is essential. This will allow the most appropriate triage of patients into those amenable to IGB versus laparoscopic biopsies (see Section 3.2). All parties should understand the requirements and importance of tumour genetic testing in patients with ovarian cancer, especially the amount of tissue required to ensure adequate DNA yield.

3.2. Diagnostic laparoscopy

3.2.1. Indications

Diagnostic laparoscopy should be considered for tissue diagnosis, if image guided biopsy is not technically possible before treatment commencement. As discussed above, adequate quality and quantity of tissue is required for tumour genetic testing.

3.2.2. Technical considerations

Laparoscopy in possible peritoneal carcinomatosis is a high-risk procedure and should be undertaken by adequately experienced surgeons.

In the presence of peritoneal carcinomatosis, direct vision entry using Hasson technique or optical trocar is preferred. Blind laparoscopic entry techniques, such as Veress needle entry should be avoided if possible, or performed with ultrasound guidance, to reduce the risk of bowel injury.

The risk of developing port site metastases after performing diagnostic laparoscopy on patients with peritoneal carcinomatosis can be as high as 50%.[25] Whilst port site metastases in the midline can be easily resected during laparotomy, the resection of lateral port site metastases may prove to be more complex, with the risk of complications, such as hernia formation. Therefore, midline port placement is preferred and the use of lateral ports should be avoided on balance. However, disease distribution may favour alternative port placement to reduce the risk of the procedure. After obtaining the laparoscopic biopsy, it is advisable to retrieve the specimen in a specimen bag, or directly through a laparoscopic port cannula through the umbilical port, to reduce the risk of port site metastasis.

The aim of the biopsy is to obtain tumour tissue with adequate size and quality. To achieve this, biopsy from necrotic tumour masses or from superficial fibrotic plaques should be avoided, as these may not yield sufficient amount of viable tumour cells for genomics analysis. The thermal damage of monopolar scissors and other energy devices should be taken into account when deciding on how much tissue should be removed.

The combined use of a 30-degree and zero-degree laparoscopes may improve access and enhance the assessment of secluded sites, such as perihepatic peritoneal reflections, the spleen and the lesser sac. It is good practice to obtain images or videos to support decision-making based on the extent of disease and resectability. When diagnostic laparoscopy fails, mini-laparotomy to obtain tissues for diagnosis should be considered to avoid treatment delay.

3.3. Ascites cytology (in cases where tissue cannot be obtained)

When tissue cannot be obtained, ascites is an alternative source for genetic testing. It can be processed into formalin-fixed paraffin-embedded (FFPE) or fresh frozen cell blocks for diagnostic and genetic testing with good correlation with tumour tissues.[26-28] Maximising efforts to obtain adequate amounts of ascites during pre-treatment sampling is crucial for

achieving adequate DNA yield. Considerations for ascites handling is further considered in Section 5.1.

4. Summary of genetic testing in ovarian cancer

High-grade EOC includes high-grade serous, clear cell, endometrioid, carcinosarcoma and mucinous histology. Both germline and tumour testing should be offered in parallel after the diagnosis of high-grade EOC, apart from those diagnosed with mucinous EOC. Patients diagnosed with mucinous EOC are eligible for tumour testing, but not germline testing.

The available tests and their eligibility criteria are updated within the NHS England National Genomic Test Directory (updated annually).[29] The current indications of HRD testing are linked to potential therapeutic options (i.e., in advance disease), which may also evolve when new evidence emerges.

At the time of writing, the relevant germline gene panels for patients with ovarian cancer are R207 (inherited ovarian cancer without breast cancer, this test targets *BRCA1*, *BRCA2*, *BRIP1*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *RAD51C* and *RAD51D*) and R208 (inherited breast cancer and ovarian cancer, this test targets *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C* and *RAD51D*).[30] Recent analysis including data from multiple UK centers has demonstrated cost-effectiveness of unselected panel germline testing over *BRCA* testing alone (personal communication, Professor Manchanda).

Women diagnosed with high-grade ovarian carcinoma can be tested for tumour variants in *BRCA1/2*.[31, 32] All cases of advanced high-grade EOC potentially eligible for first-line maintenance therapy with bevacizumab and olaparib can undergo tumour DNA testing for mutational signatures of HRD.[33] The Myriad Genetics MyChoice® Plus HRD companion diagnostic test is based on the combined results of the Genomic Instability Score (GIS) and the tumour *BRCA* status; alternatives to this test are on track to be established in the United Kingdom by mid-2024.

The NHS test directory is expanding rapidly, allowing pathologists to test tumour tissues for diagnostic and theranostic variants that are specific to rarer ovarian cancer types.[34-36]

This consensus group supports reflex tumour testing with an established pathway set up locally to manage test results. This strategy is accepted in other cancer types and would avoid delay in formulating subsequent treatment plans (See Section 6 for explanation of this update), with options to opt out and requests for more information accommodated.

4.1. Parallel genetic testing for patients newly diagnosed with EOC

Please refer to Section 2 for further details on the timing of genetic testing and for patients with recurrent disease who have not been tested at initial diagnosis.

	Germline testing	Tumour testing
Indications – histologic type	Offer to all patients with high-grade EOC (excluding mucinous carcinomas)	Offer to all patients with high-grade EOC (no exclusions)
Indications-stage	All stages	Stages III and IV*
Timing of test	Offer from as early in a patient's journey as possible. If the patient wants time to consider further, offer storage for DNA banking.	At the time of histological diagnosis
Sequence of testing	Parallel testing	Parallel testing
Information provided to patient	**Mandatory** written information on the implications for patients and their family.	**Good practice** to have written information regarding test including implications for treatment and germline testing if test results relevant.
Consent	Written consent to be obtained, if mandated by the testing laboratory. If a patient declines testing this should be documented.	Reflex theranostic tumour testing with an established pathway set up locally to manage test results. Opt-out option maybe provided according to local protocol.

*Tumour testing for *BRCA* mutations could be performed in Stage I-II disease, although this does not currently influence standard-of-care treatment choices in first-line settings.
**Some devolved nations in the United Kingdom already have established national reflex theranostic tumour testing strategy.

5. The role of unit leads

Patients with ovarian cancer often have complex cancer pathways, seeing a multitude of different clinicians across different locations. This makes maintaining oversight of their pathway and continuity of care a particular challenge. Cancer unit leads have an important role in the genetic testing pathways and are primarily involved in three main ways:

- Introducing the concept of germline and tumour testing at an early and appropriate point in the patient journey;
- Where appropriately trained, taking consent for germline and tumour testing, depending on agreed local pathways (see Section 12 on Continuing Professional Development);
- Communicate whether tests have been performed and their results to patients, the linked cancer centres, primary care teams, medical oncologists and clinical geneticists. This is a particularly important aspect.

Cancer unit leads should ensure there are robust processes in place for the tracking of patients through their cancer journeys, to ensure the appropriate tests are offered at the right time and the results are made available to the appropriate parties in a timely manner. There should be a failsafe mechanism in place to ensure patients diagnosed with germline pathological variants are identified and referred appropriately. Where somatic testing has taken place at the cancer centre, there should be an agreed process whereby these results are made available to the local MDTs and treating oncologists.

6. The role of cancer nurse specialists

As genomics now moves from niche to necessity, cancer nurse specialists (CNSs) are well-placed to support mainstream parallel genetic testing as part of a holistic care package. In many clinical teams, CNSs already obtain consent for parallel genetic testing from a significant proportion of patients, whilst evidence also supports the feasibility of nurse-led services for genetic testing.[14, 37-39] Therefore, it is crucial to involve CNSs when locally agreed genetic testing pathways are being developed, as they are an integral part of their implementation.

Training clinical care team members, including CNSs, to deliver point-of-care parallel genetic testing (often described as mainstreaming) during diagnostic work-up is essential. Moreover, the cross-speciality Clinical Pathway Initiative, which facilitates the mapping of clinical pathways to the required competencies, could support CPD (see Section 12 on CPD).

Adoption of broader mainstream genetic testing responsibilities by CNSs will need workforce task analysis and evolution of role descriptions to include genomic literacy in the skill set. This work is currently being undertaken as part of the nursing and midwifery strategy in process by the NHS Genomic Medicine Service. When seeking for support, lead CNSs should consider the roles of CNSs in other hereditary cancer syndromes (e.g., Lynch syndrome) relevant to gynaecological oncology to encourage prioritisation of resources.

7. Pathology - guidance on tissue handling and pathways for tumour *BRCA* testing

7.1. General principles:

Genomic testing requires adequate amounts of nucleic acid for testing. In general, irrespective of cell type and size, a cell contains approximately 6-7 pg of DNA and 20 pg of RNA. The amount of tumour nucleic acid is, therefore, directly correlated with the amount of tumour cells present in the sample. The aim of the pathology pathway is to assess cellularity and preserve the tumour cell content in the sample sent for genomic testing.

The cellularity of a sample is dependent on the amount of tissue available and sample handling. The former is dependent on the sample acquisition. The latter can be influenced by pathology pathways.

Pathology pathways should concentrate on minimising ischaemic time by immediate fixation in formalin. The larger specimens should be opened as soon as possible in order to allow formalin to penetrate adequately. Inadequate fixation affects immunohistochemistry and impacts diagnosis whilst excessive fixation degrades nucleic acid. Ideal fixation times range between six and 24 hours.

7.2. Sample handling

HRD testing is done on FFPE (formalin fixed paraffin embedded) tissue. This is the conventional and commonest method of handling of tissue in pathology laboratories.

7.2.1. Biopsies

A biopsy received from a patient with clinical suspicion or diagnosis of tubo-ovarian cancer must be sampled in at least two blocks. One block should have an H&E stain with a confirmatory panel of PAX8, WT1, ER and p53. In the context of morphology, PAX8 positive, WT1 positive, ER positive and p53 aberrant staining[40] is confirmatory for tubal/ovarian high-grade serous carcinoma. Other high-grade carcinomas may need further testing. In order to preserve tissue, if there is diagnostic uncertainty, the case should be sent to a Cancer Centre for review before further tissue sections are taken for immunohistochemistry. This allows conservation of maximum amount of tumour for testing.

The other block should have an H&E stain to confirm presence of tumour. Once a diagnosis of high-grade carcinoma is made the pathologist should mark the tumour in the H&E slide avoiding areas of necrosis, assess cellularity (low, medium, high) and estimate percentage of tumour (<20% or more than >20%). It is desirable that a further estimate is done on samples with greater than 20% content.

7.2.2. Resection specimens

The reporting pathologist should routinely record the details of one or two blocks containing maximum viable and well-fixed tumour on the report. This record should include site of tumour (e.g., ovary, omentum, peritoneum), as well as cellularity and tumour content.

7.2.3. Ascites and other cytology samples

If ascites is taken for diagnostic and genetic testing purposes, in the absence of histology, a large volume (>200 ml) of ascites should be sent to the pathology laboratory to obtain a tumour cell-rich FFPE and/or fresh frozen block.[9, 41, 42]

If paracentesis is being performed to obtain a sample for diagnostic purposes, then at least 200 ml of the aspirate should be sent to the laboratory. If ascitic drainage is being undertaken for symptom relief then a drainage bag with a tap on the bottom of the bag should be used to allow the sediment to be taken off for analysis, after the ascites has been drained and allowed to settle. This will optimise the ability of the pathologist to obtain a tumour cell-rich FFPE block.

For genetic testing, a locally agreed pathway to enable direct transfer of specimens to the cytology laboratory is needed for timely processing of the sample to maximise DNA yield and quality. Ideally, samples should be transferred and stored on ice or at 4°C before processing. FFPE cytoblock should be prepared and handled as a biopsy.

8. Genomic Laboratory Hub considerations

In England, parallel genetic testing is performed by one of seven NHS GLHs, commissioned by NHS England to deliver genomic testing as outlined in the National Genomic Test Directory (~650,000 tests annually).[29] GLHs are consolidated laboratory networks with defined geographies that operate as part of the NHS Genomics Medicine Service. The aim of the GLH network is to provide a comprehensive and standardised genomic testing service using the latest technology and bioinformatics to ensure equity of access and meet the growing clinical demands.

Genetic testing for patients with EOC is a core genetic test within the rare disease test directory performed by all GLHs to meet the high demand and short turnaround times (See section 4). Routine diagnostic referrals should be delivered within 42 calendar days whilst urgent inherited and tumour tests are currently mandated to be delivered within 21 calendar days.

The volume of genetic test requests related to ovarian cancer has been increasing over the last decade with mainstreaming and availability of targeted therapies. For example, the proportion of diagnostic referrals related to ovarian cancer (R207 and R208) in a typical GLH now constitutes more than 80% of all core inherited cancer diagnostic referrals (data from Central and South GLH, May 2023). Further increase is expected, with all GLHs being expected to deliver technologies capable of detecting HRD within 2024. These tests are

more complex than traditional NGS panel tests, requiring significant investment for bioinformatics processing and data storage. Short turnaround time is also a significant challenge, hence the introduction of one-stop tests such as large cancer panels designed specifically to call a diverse range of variants, including single nucleotide variants (SNVs), small indels as well as copy number variants (CNVs). The GLH network also works closely with national cancer interpretation working groups to standardise the increasing complexity of variant interpretation and evolving gene-specific understanding and guidelines.

9. Consent issues

9.1. Mode of consent and reflex tumour testing

Germline testing should be performed following written informed consent with the patient by a trained member of staff, including careful discussion about the test, its implications and possible outcomes for patients and the family. Written information should be provided. The consent discussions and outcomes should be documented in clinical notes. When patients decline testing, this should be clearly documented.

In view of the now established reflex tumour testing pathway in endometrial and other cancers, the consensus group explored the potential of recommending reflex tumour testing in ovarian cancer. The initial guidance recommended verbal consent for tumour testing as a good practice point due to the high likelihood of pathological germline variants after the detection of pathological *BRCA* variants in the tumours (approximately 7 in 10).[18] The consensus group also acknowledged the likely availability of alternative clinical tests for HRD and other predictive tumour biomarkers or characteristics to guide patient management in the future. Discussions also emphasised the importance of robust local pathways and identification of the responsible care team to manage any reflex tumour testing results. This is particularly pertinent when pathogenic variants are identified in the tumours without documented parallel germline testing results, to ensure germline testing is offered to affected patients.

Furthermore, we consulted three patient groups (n=33 people, ranging from 5 to 22 in each group) in different parts of the UK (Cambridge, Birmingham and London) on the acceptability of reflex tumour testing (See Appendix 4). The current pathway of verbal consent and the new proposed pathway of reflex tumour testing without formal consent were discussed with their pros and cons. There was a high level of support (32/33; 97%) for the principle of reflex tumour testing amongst patients with ovarian cancer to allow timely and appropriate treatments to be delivered. Patients also highlighted the need to tailor the amount and complexity of information presented at diagnosis to avoid information overload and support those who wanted to know more. Appropriate written and/or multimedia information and signposting could address this.

We also consulted different ovarian cancer charities in the United Kingdom to ascertain their views on reflex tumour testing. Most charities were supportive of the principle of reflex tumour testing with clear information, an opt out option and clear

signposting for patients who want to speak to a health professional for more information about tumour testing.

Following deliberations, the consensus group concluded that the implementation of reflex tumour testing should be supported. Clear pathways are also needed for the management of tumour testing results, including when pathogenic or likely pathogenic variants are identified. A good practice point would be to provide appropriate patient information before reflex testing, often before a definitive diagnosis of cancer, to provide an opportunity to opt out and an option to speak to a health professional from the cancer team. Information provided should explain the tumour testing process and the associated risks, possible results and their implications.

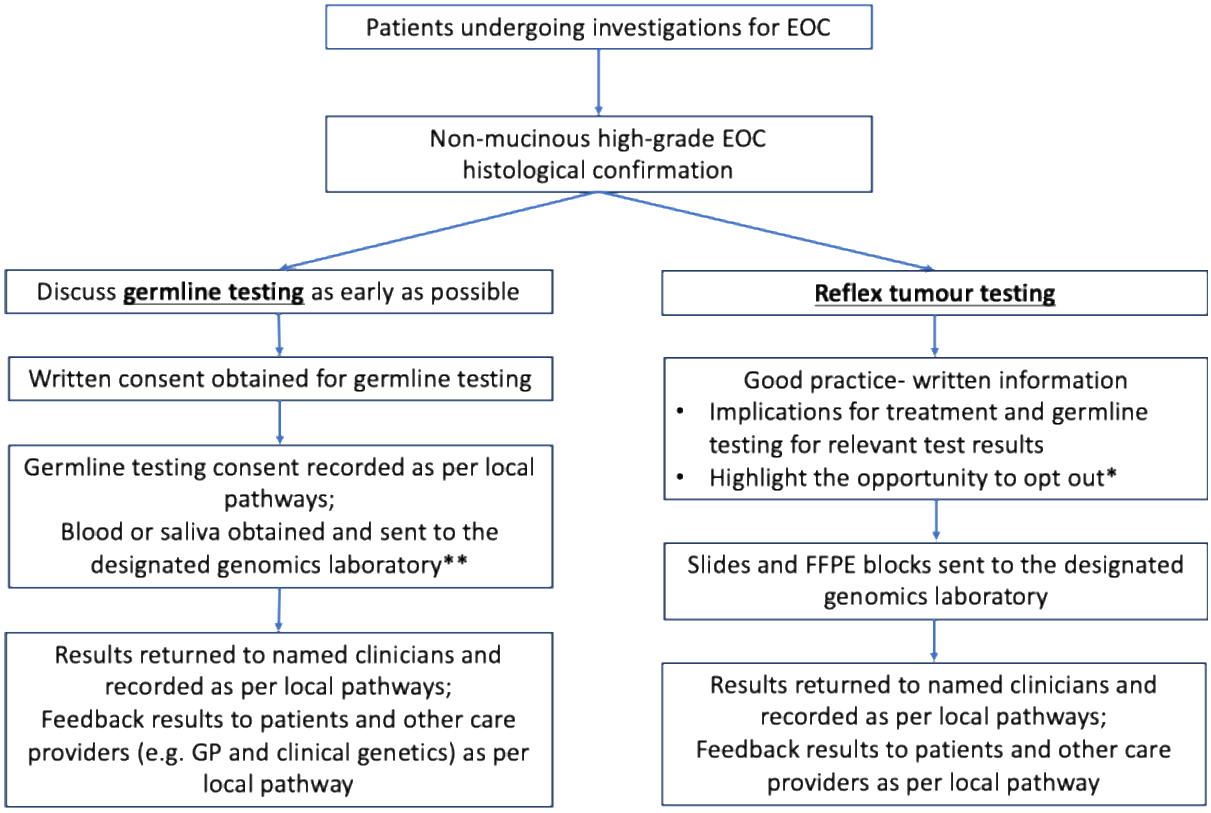

*Figure 1: Suggested consent process for parallel genetic testing for patients diagnosed with non-mucinous EOC. *Whole Genome Sequencing of tumours is an exception as it requires fresh or fresh frozen tissues and explicit patient consent. **Consent for blood or saliva samples to be stored for delayed germline testing can be considered if it is more acceptable to the patient to provide their germline genetic testing consent later. FFPE= Formalin-Fixed Paraffin-Embedded.*

9.2. The consent process and consent forms

The consent process, for germline testing and in units without a reflex tumour testing pathway, could be undertaken remotely, via telephone or video call, by appropriately trained staff. There should be clear documentation of discussion points in patient records, and followed up with relevant patient information leaflets provided via electronic or postal mail. Examples of a best practice patient information leaflet and a template of a combined record of discussion with patients and consent form can be found in

Appendix 1 and 2, respectively. The consent process should comply with GMC standards for consent.[43]

In all cases, high quality, culturally appropriate information must be provided to patients so they can make an informed decision. Please see Section 13.2 and Appendix 1 for examples.

10. Recording of genetic testing results

The results of the genetic test should be communicated to the clinical care team by the testing laboratory, and clearly recorded in an easily accessible and identifiable part of the patient's medical record. There should be consistency of terminology when recording genetic tests results to avoid confusion.

Teams should ensure that there are robust pathways in place to ensure that the results of testing are communicated with the patient, and onward referrals are made if required. Considerations should be given to the use of standard letters and/or MDT proforma to standardise documentation of tumour and germline genetic test results.

10.1. Information to be recorded in clinical notes

The minimum information that should be recorded in a patient's notes include whether germline or tumour DNA was tested, which genes were tested, and whether a variant was detected.

If a germline or tumour variant is detected, it should be reported in the patient's medical record as either pathogenic, likely pathogenic, or a variant of uncertain significance (VUS). Ambiguous terms, such as 'deleterious mutation' and 'suspected deleterious mutation', should be avoided.

If the genetic test has failed, this should be recorded in the patient's notes, especially in those cases where testing was performed on a diagnostic biopsy sample. If genetic testing failed on a diagnostic biopsy sample, repeat testing should be performed on a sample taken from cytoreductive surgery, where available.

10.2. Five classes of variants

Variant class; Description[44, 45]	**Pathogenic probability**	**Recommendations for germline variants**
5; Pathogenic	>0.99	Referral to clinical genetics Cascade testing in family members Follow high-risk management guidelines
4; Likely Pathogenic	0.95-0.99	

3; Variant of Uncertain Significance (VUS)	0.05-0.949	**Presence of variant should not be used to influence clinical management** Kept under review by genetics as a small proportion may get reclassified to pathogenic or likely pathogenic in the future
2; Likely Benign or Likely Not Pathogenic	0.001-0.049	**Presence of variant should not be used to influence clinical management** No predictive testing Do not refer to clinical genetics
1; Benign or Not Pathogenic	<0.001	

11. Changes on the horizon

The consensus group identified key potential advances on the horizon that would impact on the genetic testing pathways.

11.1. Whole-Genome Sequencing and alternative HRD testing

In addition to patients who have exhausted standards of care testing and treatment, whole genome sequencing (WGS) of germline and tumour DNA for all high-grade serous ovarian cancer has recently been included in the NHS National Genomic Test Directory in March 2022. Though the test requires fresh tissue samples, it is able to provide comprehensive information on germline and tumour variants, as well as HRD status.

The initial real-world data highlighted the potential of WGS to provide HRD evaluation, histotype refinement, and personalised medicine optimisation (personal communication, Professor Brenton). The development of an improved HRD assay could enhance the ability to identify patients most likely to benefit from targeted therapies.

Integrating WGS testing and improving HRD assays have the potential to improve the accuracy of diagnoses, better-inform treatment decisions, and improve patient outcomes. The potential benefits of WGS to advancing personalised medicine should also be balanced against implementation challenges to establish a scalable fresh tissue pathway (Appendix 5).

11.2. *BRCA1/2*-mutant tumours with incongruous mutational signature scores

Approximately 10% of high-grade epithelial ovarian cancers that contain a tumour *BRCA1/2* variant will have a mutational signature score consistent with an HRD-negative tumour.[33] The biological mechanism underlying this genotype is unknown. Possible explanations include mono-allelic loss-of-function *BRCA1/2* variants that are purely somatic, *BRCA1/2* reversion variants that restore the open reading frame of a germline mutant allele, or, more rarely, patients with mosaic germline *BRCA1/2* variants and intra-tumoral heterogeneity in homologous recombination repair.[46-48] The absence of a HRD mutational

signature in *BRCA1/2*-mutant tumours might lead to poorer responses to PARPi. Thus, those patients with this atypical genotype will require close surveillance during PARPi treatment.

12. Continual professional development

Healthcare professionals should be equipped to deliver equitable clinical genetic testing services. Training is needed to facilitate the consent process and feedback of results.

The Genetics Education Programme (GEP) is a cross-professional competency framework, developed in consultation with healthcare professionals, professional bodies and medical Royal Colleges, to ensure the objectives of the training is standardised.[49] The framework can support the identification of learning needs by individuals and planning of structured training and evaluations by educators.

Adequate time should be allocated to train appropriate staff to undertake the consent process. For example, completing the free online genomics education programme developed by Health Education England (https://www.e-lfh.org.uk/programmes/genomics-in-the-nhs/).

Multiple organisations, such as the British Society for Genomic Medicine, UK Cancer Genetics Group, and Cancer Variant Interpretation Group-UK (CanVIG UK), regularly host high-quality upskilling events, including national multidisciplinary team meetings, consensus meetings and “Lunch and Learn” webinars.

13. Patient and public involvement (PPI)

13.1. Mainstreaming

Mainstreaming genetic testing at the diagnosis of high-grade EOC is now standard of care. This includes parallel germline and tumour testing. We have consistently engaged with patient representatives, support groups and cancer charities in the development and implementation of pathways for genetic testing. PPI work has also included the development of patient facing materials, consent process, implementation strategies as well as input into the development and support of clinical trials. PPI work has highlighted important issues to be considered while developing genetic testing pathways. These include availability of the tests, equitable access for ethnic minorities and underserved groups (e.g., appropriate patient-facing information to cater for a diverse population and different accessibility needs), and consideration for psychological and wellbeing support around the time of genetic testing.

13.2. Co-production

Co-production is a term that describes working together with diverse stakeholders, with different levels of experience and understanding, and of differing values, in equal partnership and for mutual benefits and solutions. This egalitarian and trust-building approach is increasingly embraced by public services and research funders to reduce health inequality.[50] Health disparities in genetics and ovarian cancer care are well-recognised.[51-53] The publicly-funded IMPROVE-UK quality improvement awards led by BGCS and Ovarian

Cancer Action highlighted the positive impact of patient involvement and co-production in clinical care delivery in the context of ovarian cancer. A multimedia, multilingual information package, co-produced with a diverse group of patients, developed from one of the IMPROVE-UK awards, has been included in this guidance (https://ovarian.org.uk/demo-uk/). The consensus group encourages the use of co-production approaches for future quality improvement initiatives, with any lessons learned and achieved outcomes reported and made available in public domains.[50]

14. Audit and governance

Clinical genetic testing for cancer is undergoing a period of transformation. It is crucial for individual departments to establish robust clinical pathways. Moreover, involvement from all stakeholders in different sectors, including patients and regional genetic laboratories, during pathway developments are crucial to maintain and improve the quality of genetic testing services.

Prospective audit infrastructures to evaluate the standards recommended in Section 16 should be encouraged. To support the cross-disciplinary nature of genetic testing pathways, the use of novel quality improvement techniques, such as data linkage of routinely collected clinical data and statistical process control tools (https://www.england.nhs.uk/statistical-process-control-tool/) should be consider to minimise the resources required.

15. Conclusions

Genetic testing is now an established standard of care for patients diagnosed with non-mucinous EOC. Despite the effort to mainstream genetic testing in the past decade, the fast-changing indications and provision of genetic testing has posed continual challenges on its implementation. These challenges are accentuated by the complex diagnostic and treatment pathways for ovarian cancer. This multidisciplinary professional consensus group has worked with patient groups and national ovarian cancer charities to update this consensus guideline, which aims to support timely and equitable delivery of clinical genetic testing for patients with ovarian cancer.

16. Recommendations

16.1. General

- Parallel tumour and germline genetic testing are superior to either germline testing alone, tumour testing alone or sequential testing strategies.
- Robust processes should be in place to ensure the results of tumour and germline testing are recorded, with the correct nomenclature, in the patient's clinical and laboratory records.

- Tumour and germline genetic testing results should be routinely recorded in multi-disciplinary team (also known as tumour board) meeting summaries.
- Robust process should be in place to ensure patients are informed of their results and referred to clinical genetics when appropriate.
- Variants previously considered VUSs might be reclassified as pathogenic/likely-pathogenic variants or downgraded to benign/likely benign as the analytical process improves. At the time of disease recurrence, VUS review should be considered, especially if reclassification would change immediate management.
- The identification of a named staff member to promote the implementation of the relevant genetic testing pathways for EOC and liaise with different other clinical service initiatives (e.g., Lynch Syndrome testing implementation and modernisation of nurse specialist workplans) should be encouraged.

16.2. Consent

- High quality, culturally appropriate information must be provided to patients so they can make an informed decision.
- Consent to germline testing should be taken by clinicians, specialist nurses or appropriately trained healthcare professionals to support valid consent. This can be in both secondary and tertiary settings.
- Any discussions with patients about genetic testing should be documented in clinical records.
- For germline testing written consent should be undertaken.
- Clinical care teams should establish local pathways for obtaining consent, transmitting this information to pathologists and managing test results.

16.3. Tumour Testing

- Tumour testing alone should not be relied upon for exclusion of all clinically relevant pathological variants, as some pathological variants may be missed by tumour testing alone.
- Reflex tumour testing with robust mechanisms to feedback results and the possibility to opt out before the tumour test was performed should be supported.
- Adequate amount of tumour tissues should be taken during diagnostic procedures (e.g., five or more cores with a 16G needle during image-guided biopsies) to ensure all required molecular and pathological investigations can be completed.
- A co-axial needle technique should be considered to improve patient comfort during image-guided biopsies.
- If diagnostic specimens do not yield successful results, additional tissues should be obtained for tumour testing at the time of cytoreductive surgery. When no surgery is planned, additional tumour tissue biopsy for genetic testing should be considered, if the result would change management.
- For patients with recurrent EOC and no previous tumour testing results, tumour testing should be performed, if the results would inform management. This could be performed on the tumour specimen at diagnosis if histological confirmation of recurrence is not clinically indicated. Additional tumour tissue biopsy for genetic testing should only be considered if the results would change management.
- The indications and panels for tumour genetic testing should be reviewed regularly and updated with funding arrangements for the tests and oncological treatments.

16.4. Germline Testing

- Germline testing should be offered to patients as early as possible at diagnosis and not delayed.
- Offering to store genetic material for testing later should be considered when patients initially decline or require more time to consider their consent for testing.
- Patients diagnosed with low-grade serous tumours do not require germline genetic testing when the diagnosis has been confirmed by a specialist gynaecological cancer histopathologist.

16.5. Audit standards

- To support service improvement, audit pathways to evaluate the uptake of cascade testing and factors associated with poor uptake should be established.
- Percentage of all patients with tubo-ovarian/primary peritoneal high grade non-mucinous carcinoma eligible for germline testing were offered the test- Target 95%
- Percentage of the results of parallel genetic testing documented in the multidisciplinary team discussion summaries- Target 95%
- Percentage of patients who underwent germline testing with the denominator of those eligible for germline testing and chose to accept testing- Target 95%
- Percentage of patients who underwent tumour testing with the denominator of those eligible for tumour testing - Target 95%
- Percentages of specimens sent for tumour testing where analysis did not yield a diagnostic result should be regularly audited to promote continuing improvement of the tumour molecular diagnostic pathways (see Section 3)
- Percentage of patients underwent germline testing received their results- Target 100%
- Percentage of patients appropriately referred to clinical genetics (e.g., when diagnostic germline testing identified pathological variant)- Target 95%
- Turnaround times for tumour analysis - Target 21 calendar days
- Turnaround times for germline analysis - Target 42 calendar days

- Exclusions: patients who choose not to undergo genetic testing or patients where it is not clinically appropriate

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Appendix 1: Co-produced written patient information on parallel genetic testing- an example

Link

Appendix 2: Consent form for parallel genetic testing- an example

Link

Appendix 3: Description and person specifications of gynaecological genomics clinical lead and administrative support roles

Link

Appendix 4: Questions for patient group discussions and result summaries

Link

Appendix 5: A proposed Whole Genome Sequencing pathway

Link