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

Elaine YL Leung ,[1] Shibani Nicum,[2] Jo Morrison,[3,4] James D Brenton,[5] Ionut-Gabriel Funingana,[5] Robert D Morgan ,[6,7] Sadaf Ghaem-Maghami,[8] Tracie Miles,[9] Ranjit Manchanda ,[10,11] Rebecca Bowen,[12] Adrian Andreou,[12] Will Loughborough,[12] Susan Freeman,[13] Ketan Gajjar,[14] Sarah Coleridge,[14,15] Mercedes Jimenez-Linan,[16] Janos Balega,[17] Jonathan Frost,[12] Amy Keightley,[18] Yvonne Wallis,[19] Sudha Sundar,[1,17] Raji Ganesan[19]

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For numbered affiliations see end of article.

Correspondence to
Dr Elaine YL Leung, Institute of Cancer and Genomics Sciences, University of Birmingham, Birmingham, UK; e.leung@bham.ac.uk

Dr Raji Ganesan; r.ganesan@nhs.net

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ABSTRACT

Standard of care genetic testing has undergone significant changes in recent years. The British Gynecological Cancer Society and the British Association of Gynecological Pathologists (BGCS/BAGP) has re-assembled a multidisciplinary expert consensus group to update the previous guidance with the latest standard of care for germline and tumor testing in patients with ovarian cancer. For the first time, the BGCS/BAGP guideline group has incorporated a patient advisor at the initial consensus group meeting. We have used patient focused groups to inform discussions related to reflex tumor testing – a key change in this updated guidance. This report summarizes recommendations from our consensus group deliberations and audit standards to support continual quality improvement in routine clinical settings.

INTRODUCTION

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

RATIONALE FOR PARALLEL GENETIC TESTING IN EPITHELIAL OVARIAN CANCER

The Cancer Genome Atlas 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 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 large duplications/deletions which are not reliably detectable on testing of tumor tissue. Germline testing results carry implications for family members.
- Testing of tumor tissue (referred as tumor testing in this document) involves extracting DNA from the tumor and testing for pathogenic variants. A tumor 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 *BRCA* variants detected in tumors will be of germline (inherited) origin.[6] Therefore, results of tumor testing may have implications for family members. Tumor testing also provides the opportunity to simultaneously test for HRD status.

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

MAINSTREAM GERMLINE GENETIC TESTING

The prevalence of pathogenic *BRCA* germline mutations in patients with high-grade serous ovarian cancer were reported to be 13–15%.[8–10] Unselected germline testing identifies around 50% more patients with germline pathological variants than when germline testing was offered based on family history.[11 12] 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 centers across the UK, improving the uptake and reducing the time to genetic results.[9 10 12 13] In these models, the clinical care teams for cancer treatments counsel and offer germline testing to all patients with a diagnosis of epithelial ovarian cancer; only patients who are found to have pathogenic variants or variants of uncertain significance are referred to clinical genetics services. Some mainstream models restrict testing to defined histological criteria (eg, high-grade serous or endometrioid), others restrict testing to age groups (eg, under 70 years) resulting in considerable variability and around 30% of eligible patients not being offered testing.[14]

THIS CONSENSUS GUIDANCE UPDATE

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

The British Gynecological Cancer Society (BGCS) and the British Association of Gynecological Pathologists (BAGP) established a multidisciplinary consensus group consisting of experts in surgical gynecologic oncology, medical oncology, genetics, radiology, pathology, 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. Before implementation the group liaised with representatives from charities and patient groups to identify and address patient perspectives. Recommendations and suggested resources from this consensus group have informed this update to the guideline document first published in 2021,[15] and they are presented below.

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 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 counseling for germline testing should be considered during clinical pathway development (see section on Continuing Professional Development).

Counseling 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 counseling is beneficial and should be supported.

The possible points of testing in a patient's journey are:

At Initial Consultation Before Histological Diagnosis

Genetic testing can be discussed with patients who present with a high clinical suspicion of epithelial ovarian cancer (eg, carcinomatosis on imaging, CA125:CEA ratio>25[16 17]) at initial presentation to a cancer unit gynecologist or gynecologic oncologist, before confirmatory histological or cytological diagnosis (eg, before the imaging-guided biopsy or diagnostic laparoscopy).

Consultation Before Primary Cytoreductive Surgery

Informed consent for genetic testing, if not previously obtained, should be sought during the counseling and consenting for primary (upfront) cytoreductive surgery. In hospitals without an established reflex tumor testing pathway, information on whether the patient has provided consent for tumor testing should be communicated to the pathology team receiving the surgical specimens after cytoreductive surgery via locally agreed methods (eg, 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.

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 tumor testing.

This group often involves different members of the multidisciplinary team, including interventional radiologists, gynecology cancer unit leads and non-gynecologic oncology services (eg, 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.

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 epithelial ovarian cancer (Table 1).

Written consent should be obtained for germline testing (Table 1). If a patient is not ready to offer their consent for germline genetic testing, a two-step process could be offered (ie, consent for taking and storing a blood sample initially, and consent for testing later).

Patients with Recurrent Ovarian Cancer

At the time of this update, patients with recurrent epithelial ovarian cancer are eligible to be tested for tumor *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.

Table 1 A summary of recommended genetic testing in ovarian cancer

	Germline testing	Tumor testing
Indications – histologic type	Offer to all patients with EOC	Offer to all patients with high-grade EOC
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 tumor testing with an established pathway set up locally to manage test results.† Opt-out option may be provided according to local protocol.

*Tumor 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 an established national reflex theranostic tumor testing strategy.
EOC, epithelial ovarian cancer.

SPECIAL CONSIDERATIONS IN THE FOLLOWING CLINICAL SCENARIOS

Image-guided Biopsy

Technical Considerations

Every attempt should be made to ensure enough tissue is obtained at the initial biopsy for tumor genetic testing. The most common sites for biopsy include the peritoneal/omental disease, lymph nodes and pelvic masses,[18] and should be decided by an experienced radiologist supported by a multidisciplinary tumor board to balance between tissue accessibility and procedural risks. 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.

Biopsies obtained post-chemotherapy can have a lower content of cancer cells and provide a lower DNA yield when compared with chemotherapy naïve tissue.[19] Evidence from the BriTROC study has shown that the DNA yield was higher in image-guided biopsy samples obtained using 14G or 16G biopsy needles, when compared with 18G biopsy needles (2.86 µg for 14G/16G needles and 0.89 µg for 18G needles).[20]

The number of biopsy cores required will depend on the number of tests requested. For an estimated 90% whole genome sequencing success rate, the processing laboratory requires 50 mm3 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 tumor genetic testing are required, more cores will be required – typically more than five passes with a 16G needle.

Safety of Multiple Image-guided Biopsy Cores

Multiple image-guided biopsy cores from peritoneum and omentum is safe. In the BriTROC trial,[20] complications were reported in three of 125 patients (2.4%) post-biopsy. These included pain (two patients) and hemorrhage (one patient after a liver biopsy) – all Clavien-Dindo[21] Grade II complications. A co-axial needle technique should be considered to improve patient comfort during the procedure, particularly when multiple cores are required.

Diagnostic laparoscopy

Indications

If image guided biopsy is not technically possible before treatment commencement, diagnostic laparoscopy should be considered for tissue diagnosis and to obtain adequate quality and quantity of tissue required for tumor genetic testing.

Technical Considerations

Laparoscopy in possible peritoneal carcinomatosis is a high-risk procedure and should be undertaken by adequately experienced surgeons and appropriate entry technique to reduce the risk of visceral injury. The risk of developing port site metastases after performing diagnostic laparoscopy on patients with peritoneal carcinomatosis can be as high as 50%.[22] While 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 favor 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 tumor tissue with adequate size and quality. To achieve this, biopsy from necrotic tumor masses or from superficial fibrotic plaques should be avoided, as these may not yield enough viable tumor cells for genomics analysis. The

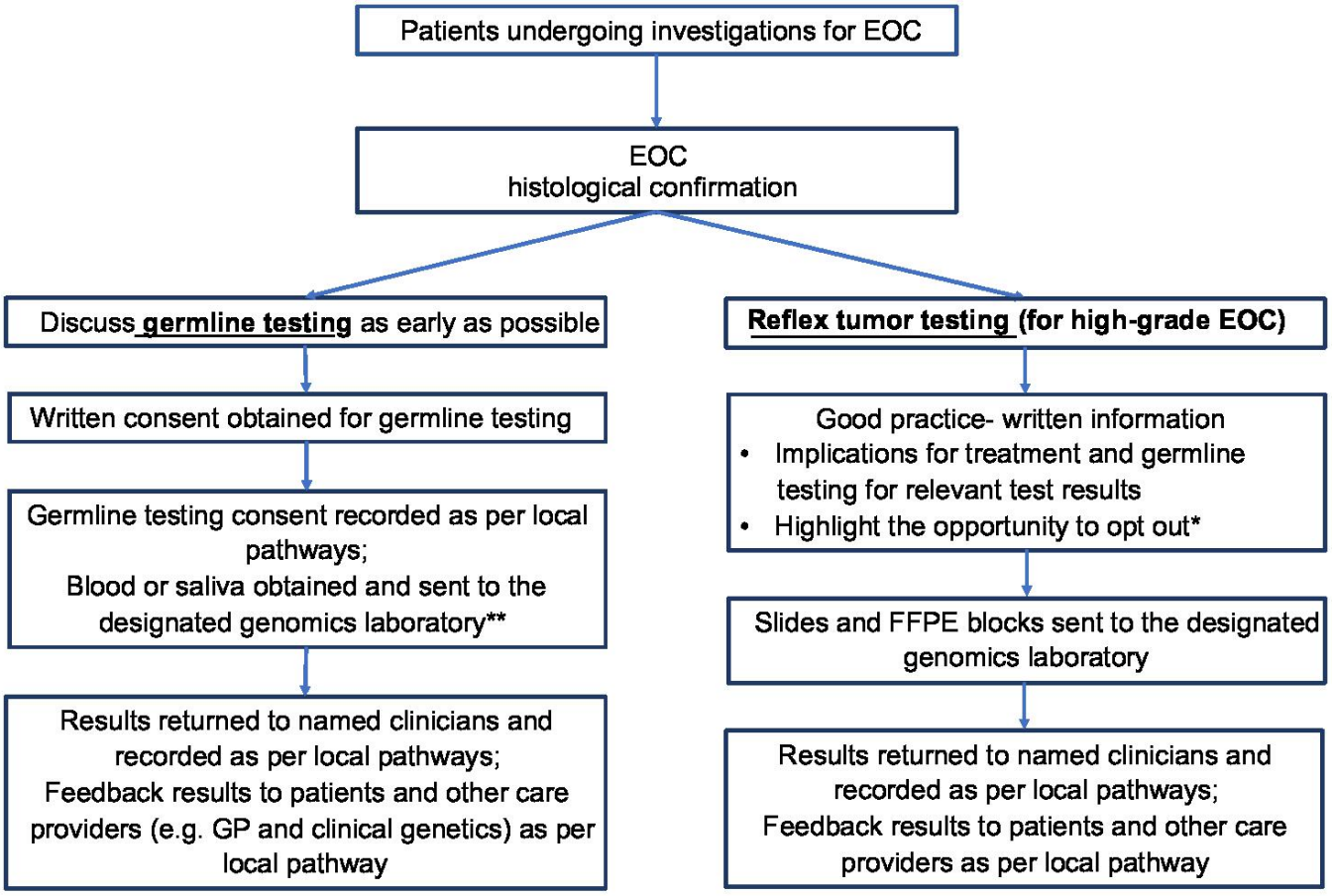

Figure 1 Suggested consent process for parallel genetic testing for patients diagnosed with EOC. FFPE=Formalin-Fixed Paraffin-Embedded.*Whole Genome Sequencing of tumors is an exception as it requires fresh or fresh frozen tissues and explicit patient consent. **Consent for blood or saliva samples to 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.

thermal damage of monopolar scissors and other energy devices should be considered when deciding how much tissue should be removed. When diagnostic laparoscopy fails, mini-laparotomy to obtain tissues for diagnosis and genetic testing should be considered to avoid treatment delay.

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 or fresh frozen cell blocks for diagnostic and genetic testing with good correlation with tumor tissues.[23–25] Maximizing efforts to obtain adequate amounts of ascites during pre-treatment sampling is crucial for achieving adequate DNA yield (also see the section on ascites and other cytology samples).

SUMMARY OF GENETIC TESTING IN OVARIAN CANCER

This consensus group supports reflex tumor 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 (elaborated in the consent issues section), with options to opt out and requests for more information accommodated (Figure 1 and Table 1).

High-grade epithelial ovarian cancer includes high-grade serous, clear cell, endometrioid, carcinosarcoma and mucinous histology. Both germline and tumor testing should be offered in parallel after the diagnosis of high-grade epithelial ovarian cancer. To align with the recently published guidance by the National Institute for Health and Care Excellence, all patients with invasive epithelial ovarian cancer should be offered germline testing.[26]

The available tests and their eligibility criteria are updated annually within the NHS England National Genomic Test Directory.[27] The current indications of HRD testing are linked to potential therapeutic options (ie, in advanced 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 panel targets *BRCA1*, *BRCA2*, *BRIP1*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *RAD51C* and *RAD51D*) and R208 (inherited breast cancer and ovarian cancer, this panel targets *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C* and *RAD51D*).[28] Recent analysis including data from multiple UK centers has demonstrated cost-effectiveness of unselected panel germline testing over *BRCA* testing alone.[29]

Patients diagnosed with high-grade ovarian carcinoma can be tested for tumor variants in *BRCA1/2*.[6 30] All cases of advanced high-grade epithelial ovarian cancer potentially eligible for first-line

Table 2 Five classes of variants and associated recommendations[42 43]

Variant class; Description	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	

Box 1 Recommended audit standards

Standards related to the uptake of testing

⇒ To support service improvement, establish audit pathways to evaluate the uptake of cascade testing and factors associated with poor uptake.

⇒ Percentage of all patients with tubo-ovarian/primary peritoneal epithelial ovarian carcinoma eligible for germline testing were offered the test – Recommended target 95%.

⇒ Percentage of the results of parallel genetic testing documented in the multidisciplinary team discussion summaries – Recommended target 95%.

⇒ Percentage of patients who underwent germline testing with the denominator of those eligible for germline testing and chose to accept testing – Recommended target 95%.

⇒ Percentage of patients who underwent tumor testing with the denominator of those eligible for tumor testing – Recommended target 95%.

Standards related to the processing of specimens

⇒ Percentages of specimens sent for tumor testing where analysis did not yield a diagnostic result should be regularly audited to promote continuing improvement of the tumor molecular diagnostic pathways.

⇒ Turnaround times for tumor analysis – Target 21 calendar days.

⇒ Turnaround times for germline analysis – Target 42 calendar days.

Standards related to the feedback of results and ongoing management

⇒ Percentage of patients who underwent germline testing and received their results – Target 100%.

⇒ Percentage of patients appropriately referred to clinical genetics (eg, when diagnostic germline testing identified pathological variant) – Target 95%.

Exclusions: patients who choose not to undergo genetic testing or patients for whom it is not clinically appropriate.

maintenance therapy with bevacizumab and olaparib can undergo tumor DNA testing for mutational signatures of HRD.[31] Similar to other health systems, alternatives to the Myriad Genetics MyChoice Plus HRD companion diagnostic test, which is based on the combined results of the Genomic Instability Score and the tumor *BRCA* status, have begun rolling out in 2024 in the United Kingdom.

The NHS test directory is expanding rapidly, allowing pathologists to offer tumor and germline testing for diagnostic and theranostic variants that are specific to rarer ovarian cancer types.[26 32 33]

THE ROLE OF GYNECOLOGISTS WORKING OUTSIDE TERTIARY CANCER CENTERS

Patients with ovarian cancer often have complex cancer pathways, interacting with a multitude of different clinical teams across different locations. Gynecologists working with outside specialist cancer centers are involved in the initial diagnostic pathway and have an important role in the genetic testing pathways. They are involved in three main ways:

- Introducing the concept of germline and tumor testing at an early point in the patient journey
- Where appropriately trained, taking consent for germline and tumor testing, depending on agreed local pathways (see the section on continuing professional development).
- Communicate whether tests have been performed, and ensure results are available to the linked cancer centers, primary care teams, medical oncologists and clinical geneticists.

There should be a fail-safe mechanism in place to ensure patients diagnosed with germline pathological variants are identified and referred appropriately. Where tumor testing has taken place at the cancer center, there should be an agreed process whereby these results are made available to the treating oncologists.

THE ROLE OF CANCER NURSE SPECIALISTS

As genomics now moves from niche to normality, cancer nurse specialists are well-placed to support mainstream parallel genetic testing as part of a holistic care package. In many clinical teams, cancer nurse specialists already obtain consent for parallel genetic testing from a significant proportion of patients, while evidence also supports the feasibility of nurse-led services for genetic testing.[11 34–36] Therefore, it is crucial to involve cancer nurse specialists when locally agreed genetic testing pathways are being developed, as they are an integral part of their implementation.

Training clinical care team members, including cancer nurse specialists, to deliver point-of-care parallel genetic testing (often described as mainstreaming) during diagnostic work-up is essential. Workforce task analysis and evolution of role descriptions to include genomic literacy in the skill set of this group will accelerate the adoption of broader nurse-led mainstream genetic testing. When seeking support, nursing leaders should consider the roles of cancer nurse specialists in other hereditary cancer syndromes (eg, Lynch syndrome) relevant to gynecological oncology to encourage

Box 2 Summary recommendations of this consensus guidance

General

⇒ Parallel tumor and germline genetic testing are superior to either germline testing alone, tumor testing alone or sequential testing strategies.

⇒ Results of tumor and germline testing are recorded, with the correct nomenclature, in the patient's clinical and laboratory records.

⇒ Robust local pathways should be established for obtaining consent, feedback results to patients, pathologists and clinical care teams, as well as managing test results and onward referrals to clinical genetics when appropriate.

⇒ Variants previously considered: Variants of Uncertain Significance (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 relevant epithelial ovarian cancer genetic testing pathway implementation and liaise with different other clinical service initiatives should be encouraged.

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 appropriately trained healthcare professionals in both secondary and tertiary settings.

⇒ Discussions with patients about genetic testing should be documented in clinical records.

⇒ For germline testing, written consent should be undertaken.

Tumor Testing

⇒ Tumor testing alone should not be relied on for exclusion of all clinically relevant pathological variants, as some pathological variants may be missed by tumor testing alone.

⇒ Reflex tumor testing with robust mechanisms to feedback results and the possibility to opt out before the tumor test is performed should be supported.

⇒ Adequate amount of tumor tissues should be taken during diagnostic procedures (eg, five or more cores with a 16G needle during image-guided biopsies) to ensure all required 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 tumor testing at the time of cytoreductive surgery. When no surgery is planned, additional tumor tissue biopsy for genetic testing should be considered, if the result would change management.

⇒ For patients with recurrent epithelial ovarian cancer and no previous tumor testing results, tumor testing should be performed, if the results would inform management. This could be performed on the tumor specimen at diagnosis if histological confirmation of recurrence is not clinically indicated. Additional tumor tissue biopsy for genetic testing can be considered if the results would change management.

⇒ The indications and panels for tumor genetic testing should be reviewed regularly and updated with funding arrangements for the tests and oncological treatments.

Continued

Box 2 Continued

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, confirmed by a specialist gynecologic cancer histopathologist, do not require germline genetic testing.

prioritization and pooling of resources to improving genetic testing after cancer diagnosis.

PATHOLOGY – GUIDANCE ON TISSUE HANDLING AND PATHWAYS FOR TUMOR *BRCA* TESTING

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 tumor nucleic acid is, therefore, directly correlated with the amount of tumor cells present in the sample. The aim of the pathology pathway is to preserve tumor, confirm diagnosis, assess cellularity, send the tissue for genomic testing and integrate/communicate the results.

Sample Handling

HRD testing is done on formalin fixed paraffin embedded tissue.

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 a Hematoxylin and eosin (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[37] 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 tertiary cancer center for review before further tissue sections are taken for immunohistochemistry. This allows conservation of maximum amount of tumor for testing. The other block should have an H&E stain to confirm the presence of tumor and assess cellularity and the content of tumor cells. A tumor content of >20% is desirable for genomic testing.

Resection Specimens

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

Ascites and other Cytology Samples

When a biopsy to obtain tissue is not possible, ascites can be taken for diagnostic and genomic testing purposes. Ascitic fluid should be sent to the pathology laboratory to obtain a tumor cell-rich formalin

fixed paraffin embedded tissue.[38–40] Such cytoblocks should be prepared and handled as a biopsy.

GENOMIC LABORATORY HUB (GLH) CONSIDERATIONS

In England, parallel genetic testing is performed by one of seven NHS Genomic Laboratory Hubs, commissioned by NHS England to deliver genomic testing as outlined in the National Genomic Test Directory (~650 000 tests annually).[27] Genomic Laboratory Hubs are consolidated laboratory networks with defined geographies that operate as part of the NHS Genomics Medicine Service. The aim of the network is to provide a comprehensive and standardized genomic testing service using the latest technology and bioinformatics to ensure equity of access and meet the growing clinical demands.

Germline genetic testing for patients with epithelial ovarian cancer is a core test within the rare disease test directory and is performed by all Genomic Laboratory Hubs to meet the high demand and short turnaround times. Genomic testing for tissue samples is a part of the cancer test directory. For example, the proportion of germline testing referrals related to ovarian cancer (R207 and R208) in a typical Genomic Laboratory Hub now constitutes more than 80% of all core inherited cancer diagnostic referrals (data from Central and South GLH, May 2023). Routine diagnostic referrals should be delivered within 42 calendar days while urgent inherited and tumor tests are currently mandated to be delivered within 21 calendar days.

CONSENT ISSUES

Mode of Consent and Reflex Tumor 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 tumor testing pathway in endometrial and other cancers, the consensus group explored the potential of recommending reflex tumor testing in ovarian cancer. The initial guidance[15] recommended verbal consent for tumor testing as a good practice point due to the high likelihood of pathological germline variants after the detection of pathological *BRCA* variants in the tumors (approximately 7 in 10). The consensus group also acknowledged the likely availability of alternative clinical tests for HRD and other predictive tumor biomarkers or characteristics to guide patient management in the future. Discussions also emphasized the importance of robust local pathways and identification of the responsible care team to manage any reflex tumor testing results. This is particularly pertinent when pathogenic variants are identified in the tumors 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 tumor testing (See online supplemental document 4). The current pathway of verbal consent and the new proposed pathway of reflex tumor testing without formal consent were discussed, including their pros and cons. There was a high level of support (32/33; 97%) for the principle of reflex tumor testing among 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 to 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 tumor testing. Most charities were supportive of the principle of reflex tumor testing with clear information, an option to opt out and clear signposting for patients who want to speak to a health professional for more information about tumor testing. Following deliberations, the consensus group concluded that the implementation of reflex tumor testing should be supported. Clear pathways are also needed for the management of tumor 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 tumor testing process and the associated risks, possible results and their implications.

The Consent Process and Consent Forms

The consent process (Figure 1), for germline testing and in units without a reflex tumor 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 this should be followed-up with relevant patient information leaflets provided via electronic or postal mail. Examples of a best practice patient information leaflet, a template of a combined record of discussion with patients, and consent form can be found in online supplemental document 1 and 2, respectively. The consent process should comply with General Medical Council standards for consent.[41]

In all cases, high quality, culturally appropriate information must be provided to patients so they can make an informed decision (see the section on patient and public involvement and online supplemental document 1).

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 test 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 tumor board proforma to standardize documentation of tumor and germline genetic test results.

Information to be Recorded in Clinical Notes

The minimum information that should be recorded in a patient's notes include whether germline or tumor DNA was tested, which genes were tested, and whether a variant[42 43] was detected (Table 2). If a germline or tumor variant is detected, it should be reported in the patient's medical record as either pathogenic, likely pathogenic, or a variant of uncertain

significance. 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.

CHANGES ON THE HORIZON

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

Whole Genome Sequencing and Alternative HRD Assays

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

Integrating whole genome sequencing 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 whole genome sequencing to advancing personalized medicine should also be balanced against implementation challenges to establish a scalable fresh tissue pathway (online supplemental document 5).

BRCA1/2-mutant Tumors with Incongruous Mutational Signature Scores

Approximately 10% of high-grade epithelial ovarian cancers that contain a tumor *BRCA1/2* variant will have a mutational signature score consistent with an HRD-negative tumor.[31] 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.[44–46] The absence of a HRD mutational signature in *BRCA1/2*-mutant tumors might lead to poorer responses to PARP inhibitors. Thus, those patients with this atypical genotype will require close surveillance during treatment with PARP inhibitors.

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. Adequate time should be allocated to train appropriate staff to undertake the consent process.

The Genetics Education Program 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 standardized.[47] The framework can support the identification of learning needs by individuals and planning of structured training and evaluations by educators.

Multiple organizations, such as the British Society for Genomic Medicine, UK Cancer Genetics Group, and Cancer Variant Interpretation Group-UK (CanVIG UK), regularly host high-quality events, including national multidisciplinary team meetings and webinars to improve skills.

PATIENT AND PUBLIC INVOLVEMENT (PPI)

Co-production with patients and the public in shared partnership for mutual benefits and solutions is crucial to identify and address issues related to the genetic testing pathways. This includes the availability and equitable access to these tests, especially for ethnic minorities and underserved groups.[48–50] This work highlighted the acceptability of mainstream and reflex testing, with consideration of well-being support around the time of testing. The publicly-funded IMPROVE-UK quality improvement awards led by BGCS and Ovarian Cancer Action highlighted the positive impact of PPI in the context of ovarian cancer genetic testing (online supplemental document 1 and https://ovarian.org.uk/demo-uk/).

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 (Box 1) 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, should be considered to minimize the resources required.

CONCLUSIONS

Genetic testing is now an established standard of care for patients diagnosed with epithelial ovarian cancer. 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 (summarized in Box 2), which aims to support timely and equitable delivery of clinical genetic testing for patients with ovarian cancer.

Author affiliations
[1]Department of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom
[2]University College London, London, UK
[3]Musgrove Park Hospital Grace Centre, Taunton, UK
[4]Faculty of Health and Life Sciences, University of Exeter, Exeter, UK
[5]CRUK Cambridge Centre, Cambridge, United Kingdom
[6]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK
[7]Division of Cancer Science, The University of Manchester Faculty of Biology Medicine and Health, Manchester, UK
[8]Imperial College London, London, UK
[9]The Department of Gynaeoncology, Royal United Hospital Bath NHS Trust, Bath, UK
[10]Wolfson Institute of Population Health, Queen Mary, University of London, London, United Kingdom
[11]Gynaeoncology, Barts Health NHS Trust, London, United Kingdom
[12]Royal United Hospitals Bath NHS Foundation Trust, Bath, United Kingdom

[13]Department of Radiology, Addenbrooke's Hospital, Cambridge, UK
[14]Nottingham University Hospitals NHS Trust, Nottingham, UK
[15]Gynaeoncology, Royal Devon University Healthcare NHS Foundation Trust, Exeter, United Kingdom
[16]Gynaecological oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[17]Pan-Bimringham Gynaecological Cancer Centre, Birmingham City Hospital, Birmingham, UK
[18]Great Western Hospitals NHS Foundation Trust, Swindon, UK
[19]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

X Elaine YL Leung @elaineleung, Ranjit Manchanda @ProfManchanda, Will Loughborough @LoughboroughW and Sudha Sundar @sundar_sudha

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Contributors Project administration: EYLL, RG, SS. Conceptualization and methodology: EYLL, RG, SS. Investigation, Data curation, Formal Analysis and Visualisation: EYLL, IGF, SN, JM, RM. Supervision: RG, SS. Writing – original draft: EYLL, JM, JDB, IGF, RM, SGM, TM, RM, RB, AA, WB, SF, KG, SC, MJL, JB, JF, AK, YW, RG. Writing – review and editing: EYLL, RG and all authors reviewed and approved the paper.

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ORCID iDs
Elaine YL Leung http://orcid.org/0000-0001-9748-7270
Robert D Morgan http://orcid.org/0000-0003-0612-0954
Ranjit Manchanda http://orcid.org/0000-0003-3381-5057

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