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

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1. Introduction

Pathogenic or likely-pathogenic (henceforth called pathogenic) germline *BRCA*1/2 variants (aka mutations) play a key role in the pathogenesis of epithelial ovarian cancer. In the pre-PARP inhibitor era, germline testing to identify pathogenic *BRCA* variants was driven by a positive family history of certain cancers and offered benefits to individual patients and wider family members in terms of future reproductive, cancer prevention and surveillance strategies.

Recent studies showing the prevalence of pathogenic *BRCA* germline mutations in patients with high-grade serous ovarian cancer of 13-15% as well as the recognition of the clinically significant role of therapeutic PARP inhibition in *BRCA* deficient tumours has led to an expansion in demand for germline *BRCA* testing. (Alsop et al, 2012; Zhang et al, 2019; Pal et al 2005; Rust et al 2018; Gourley et al 2019) The Cancer Genome Atlas (TCGA) identified somatic and germline *BRCA* pathogenic variants in ~22% of high-grade serous ovarian cancers (TCGA 2011).

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

Different models have developed across the UK with variable testing criteria, availability and access. (George A et al 2015; Plaskocinska I 2016; Rust et al 2018*)*. Some 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). However, there is considerable variability in implementation of mainstream germline *BRCA* testing worldwide with some centres still relying on individual clinicians referring patients to regional genetics centres and around 30% of eligible patients not being offered testing. (Kurian et al, 2019)

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

1.1 Rationale for tumour *BRCA* testing

There are currently two methods by which *BRCA* testing may be undertaken, each of which detects slightly different pathogenic variants due to the pathogenesis of the mutations and the limitations of the analytical techniques. ***Germline testing*** is undertaken on blood samples and will detect inherited pathogenic variants, including the large duplications/deletions which are not reliably detectable on tumour testing. Thus, germline testing results carries implications for family members. ***Tumour testing*** involves extracting DNA from the ovarian tumour and subjected to test for pathogenic variants. Around two-third of the mutations detected in tumour will be of *germline* (inherited) origin, however about one-third will be found to be *somatic* (tumour only – not inherited) mutations. Therefore, tumour testing results may have implications for family members in some, but not all instances.

Crucially, PARP inhibition increases progression-free survival in patients with somatic *BRCA* mutation. Therefore, patients and clinicians need as much information as possible to guide treatment choices in the first-line setting. For instance, knowledge of *BRCA* status at diagnosis may sway a decision to use PARP inhibitor e.g., olaparib rather than bevacizumab for a patient presenting with Stage 4 ovarian cancer.

Thus, there is an urgent clinical need to clearly identify women whose tumours contain deleterious *BRCA* mutations early in their ovarian cancer treatment journey to maximize the population of women afforded the opportunity of PARP inhibitor treatment upon completion of first-line chemotherapy. Additionally, unselected germline testing identifies around 50% more women whose families can benefit from predictive testing and subsequent screening and prevention in unaffected individuals. (George A et al, 2016)

Implementing these tests into routine practice at first-line treatment of ovarian cancer requires careful consideration of issues around scheduling of both tests, the timing of testing in relation to first-line therapy, counselling of patients, costs involved, 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 experts in surgical gynaecological oncology, medical oncology, genetics, laboratory science and clinical nurse specialists to identify the optimal pathways to *BRCA* testing in routine clinical practice. In particular, the group explored models of consent, quality standards identified at pathology, laboratory and experience/data from pathfinder centres. The group liaised with representatives from ovarian cancer charities to also identify patient perspectives that would be important to implementation. Recommendations from this consensus group deliberations are presented below.

2. Current testing offer and what is changing in NHS England

Throughout 2018 and 2019, there has been a national reorganization of genomic testing throughout England, leading to the formation of seven geographical regions, each with one hub laboratory co-ordinating germline testing (inherited), and tumour testing to evaluate somatic (non-inherited) variants. These hub laboratories are referred to as Genomic Laboratory Hubs (GLH's). To ensure equity of access, NHS England have also produced the first national test directories, which provide a list of approved tests for each disease type (e.g. ovarian cancer), and the criteria the patients must meet to access testing. Patients that meet the criteria can access centrally funded testing without local variation. The test directories also denote which specialties will be allowed to request testing for patients (e.g. oncology, gynaecology, clinical genetics). At the current time, the devolved nations are exempt from these criteria, although it is envisaged some may implement the test directories at a later date. The directories will be updated on an annual basis, with details on the process by which clinicians can request tests be added to the test directory, or request criteria be expanded to be released.

Each GLH has an educational lead, and clinical leads for cancer and rare disease, who are developing resources for clinicians and patients. They will also be responsible for determining any local education required for clinicians to undertake testing. Work is ongoing on a national patient choice module for consenting for germline and somatic mutations, but currently consent will be obtained using existing local consent forms.

3. Technical considerations for the detection of different classes of DNA variants in germline testing

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

4. Scheduling of germline and tumour *BRCA* testing: a summary of current evidence

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

4.1 Evidence from the SIGNPOST study

A concomitant/parallel panel germline and tumour genetic testing pathway for all high-grade non-mucinous EOC was initially introduced at Barts Health (North East London Cancer Network) in 2016. This involved an initial period of training of clinical staff (surgeons, medical oncologists, CNS), design of patient information materials and was undertaken within the

SIGNPOST (SystematIc GeNetic Testing for Personalised Ovarian Cancer Therapy) study (ISRCTN 16988857). Information sheets were translated into a local language (Bengali) to facilitate consent for the ethnic minority population in East London. Germline testing included testing for *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1*. Tumour testing was undertaken for *BRCA1* and *BRCA2* genes. Both germline and tumour testing was done in parallel. This was offered both prospectively and retrospectively to those with a pre-existing diagnosis.

Consent and testing was implemented across two sites treating patients: Barts Health Hospital and Queens (Barking Havering & Redbridge) Hospital. Patients were introduced to the concept of genetic testing at the initial visit by the clinical staff, but the precise time point of consent varied depending on clinical and patient context (determined by treating clinician). Pre-test counselling and written consent was undertaken at the same time for both tumour and germline testing. All members of the clinical team, including gynae oncology surgeons, medical oncologists and clinical nurse specialists could offer this to patients, provided they had completed the initial training. Results were provided by the treating clinician. Individuals identified with pathogenic and likely-pathogenic germline variants were subsequently referred to clinical genetics for further post-test counselling and predictive testing for family members. PARP inhibitor treatment was made available to somatic and germline carriers identified as per national guidelines www.nice.org.uk/guidance/ta598. Unaffected relatives who were identified as carriers were managed through a dedicated gynaecological cancer precision prevention service and established high-risk breast cancer pathway.

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

4.2 Evidence from Imperial College Healthcare NHS trust and the Royal Marsden Hospital

At Imperial College Healthcare NHS trust, parallel germline and tumour BRCA genetic testing is offered to all eligible ovarian cancer patients. The cancer team discuss the pathways and possibility of genetic testing and its implications with the patient at initial presentation. If consent is obtained, germline tests are requested from the gynaecological oncology clinic. The results are usually available in 1-2 months, so informed decisions about the optimal systemic adjuvant treatment for the patients can be made. Patients with germline BRCA mutations are referred to clinical genetics for counselling.

Tumour testing is also performed at diagnosis, if tissue is available for any patients who would be eligible for PARP-inhibitor treatment. This is currently carried out via the pharma funding scheme and samples are sent to the Royal Marsden Hospital. In addition, if a patient presents with platinum sensitive relapsed disease and the germline *BRCA* status is unknown or negative, tissue samples are sent for tumour testing (sampled at image-guided biopsy conducted at relapse or secondary debulking surgery).

The Royal Marsden Hospital initiated mainstream germline *BRCA* testing in 2012 for all patients with non-mucinous ovarian cancer through the oncology teams as standard of care. Subsequently, reflex tumour testing was introduced for all patients with high-grade serous

ovarian cancer. Once the pathologists confirm the diagnosis, tumour sample is sent directly to the lab for tumour *BRCA* testing. Patients are advised that this testing will be undertaken as part of routine histopathology assessment on either their diagnostic biopsy or surgical resection specimen. In parallel, all non-mucinous ovarian cancer patients receive information on *BRCA* germline testing at their first oncology appointment and are formally consented for germline testing if they choose to proceed (this is generally within their first 2-3 oncology appointments). Those found to have a pathogenic variant on germline testing are referred to clinical genetics for further counselling and family testing.

Currently, the data (unpublished) from The Royal Marsden Hospital has identified 9% of patients with pathogenic variants present only in the tumour; and 15% of patients with germline pathogenic variants that were not detected in the tumour testing. All of the latter represent large genomic rearrangements (duplications or deletions) that are not reliably detectable during tumour BRCA testing due to DNA fragmentation.

4.3 Evidence from Public Health England

Data from Public Health England shows that as of end of February 2020, from a total of 17384 pathogenic *BRCA* variants reported by all labs in England, 1830 were large genomic rearrangements (LGR). (Personal communication from Fiona McRonald, Programme Manager, Molecular, Genomic and Research Data National Disease Registration, PHE)

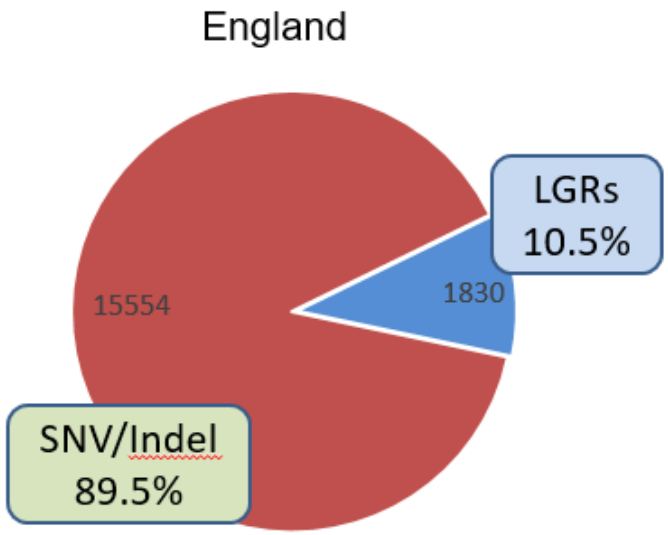


Figure 1: Proportion of germline pathogenic variants from hereditary Breast and Ovarian cancer patients that are large genomic re-arrangements. (*LGR:* large genomic rearrangement, *SNV:* single nucleotide variant, *Indel:* insertion or deletion)

However, it is widely accepted in England, that there are several 'hotspots' for large genomic rearrangements, which also coincide with less access to testing, thus, the true proportion of LGRs in this population may be closer to 15-17% of pathogenic variants. This would be consistent with data from the Manchester and Royal Marsden labs (unpublished).

In England, given above results, a parallel testing would be the most effective strategy and would avoid missing a proportion of patients (roughly 10%), as tumour testing alone using 'next generation sequencing' technology is likely to miss the proportion of patients with germline pathogenic LGRs of *BRCA*. Conversely, germline testing alone will miss a proportion of patients with only somatic variants in *BRCA.*

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

5. Situation in the devolved nations

Mainstreaming of germline *BRCA* sequencing was instituted in Edinburgh in November 2012, with the rest of Scotland moving to germline mainstreaming in 2013. Testing all ovarian cancer patients regardless of family history, increased the detection of germline mutation carriers 5-fold with 13% of patients being found to harbour a mutation. Additionally, *RAD51C* and *RAD51D* germline testing was performed in patients not found to have a *BRCA1* or *BRCA2* mutation, with a mutation rate of around 1% combined (Rust K et al 2018). Following Scottish Medicines Consortium (SMC) approval of first-line olaparib, Scotland moved in November 2019 to a model where medical oncologists continued to consent non-mucinous ovarian cancer patients for germline sequencing (albeit with a panel of genes; *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *MLH1*, *MSH2* and *MSH6*) with parallel tumour testing of *BRCA1* and *BRCA2* for patients with high-grade serous or high-grade endometrioid ovarian cancer stage III or stage IV. This pilot project will provide an assessment of the false negative rate from germline/tumour testing in the Scottish population.

In Wales, germline and tumour *BRCA1* and *BRCA2* sequencing is currently performed on all newly diagnosed high-grade ovarian cancer patients. In Northern Ireland, all stage III or stage IV high-grade serous or high-grade endometrioid ovarian cancer patients undergo germline and tumour testing of *BRCA1* and *BRCA2*. In all of the devolved nations, germline testing (and some tumour testing depending upon local PARP inhibitor access rules) is offered in the relapsed disease setting to patients who did not receive testing at diagnosis The main expected development is a move to routine/ reflex tumour testing of eligible ovarian cancer cases. Currently of all the devolved nations, only the West of Scotland offer this, with clinicians in the East of Scotland, Wales and Northern Ireland needing to request block retrieval on a case by case basis. Once the rate of false negative testing for these populations is known, decisions regarding whether to move to sequencing tumour material alone in the first instance (plus perhaps germline MLPA) can be made.

6. Timing of *BRCA* testing in relation to first-line treatment

The consensus group reflected on two issues in this section; the first to preserve patient choice and autonomy in making an informed decision, the second the crucial utility of knowledge of *BRCA* status in decisions for neoadjuvant/adjuvant/maintenance treatments at first-line

settings. The consensus group also had discussions with ovarian cancer charities representing patient perspectives.

The consensus group agreed that preserving patient choice in timing of testing was key. However, discussions around *BRCA* testing can start taking place at the earliest available opportunity in a patient's cancer diagnosis journey.

In the ideal scenario, earliest testing at the time of diagnosis of ovarian cancer is vital so that *BRCA* status is available when it is clinically most relevant to the patient and should factor in the local turnaround time for testing and the potential need for genetic counselling. It is recognized that patients may feel ready to undergo testing at different points in their cancer journey. The counselling and consenting should be carried out by trained gynaecological oncologist, cancer unit gynaecologist, oncologist or adequately trained clinician (e.g. CNS). Some patients may need to access the genetics service for pre-test counselling and this should be supported where possible.

Here, we present possible points of testing in a patient's journey.

6.1 At Initial consultation

BRCA tumour testing can be discussed with patients who present with a high clinical suspicion of ovarian cancer (e.g., carcinomatosis on CT scan with CA125/CEA ratio >25) at initial presentation to a cancer unit gynaecologist or gynaecological oncologist, prior to confirmatory histological or cytological diagnosis.

6.2 Consultation before upfront debulking surgery

As part of the counselling and consenting for upfront primary debulking surgery, informed consent should be sought for tumour *BRCA* mutation testing; this can be in the form of a verbal discussion which is documented in notes. Although undertaken by some centres (and considered good practice), currently tumour testing does not necessitate written consent.

Information on whether the patient has provided or declined consent for tumour testing should be communicated with the pathology team receiving the surgical specimens after debulking surgery, by being recorded in the pathology request form or communicated via other means. This will enable a streamlined process wherein the pathology team can identify the representative tumour block (or slides) and arrange transfer of the specimen to the GLH once a diagnosis of high-grade serous carcinoma or high-grade endometrioid cancer of tubo-ovarian or peritoneal origin is confirmed.

6.3 Consultation after upfront debulking surgery

If the pathology of the debulking surgery reveals non-mucinous high-grade epithelial ovarian cancer, the patient should be counselled about germline *BRCA* mutation testing and written consent must be obtained.

If consenting for tumour *BRCA* mutation testing was not obtained prior to surgery, this should be done now and the nominated pathologist should be informed.

6.4 In patients planned to receive neoadjuvant chemotherapy: consultation before biopsy

If the patient is not suitable for upfront debulking surgery (or in cases of diagnostic uncertainty) counselling about tumour *BRCA* testing should be carried out before the imaging-guided biopsy or diagnostic laparoscopy. Informed consent should be obtained either in the form of a verbal discussion which is documented in notes or through a formal consent form. The fact whether the patient has provided or declined consent for tumour testing should be recorded in the pathology request form after biopsy or conveyed to the pathologist by other means (e.g., electronic records, letter or email).

It is advised for each gynaecology cancer units to arrange robust internal pathways with the interventional radiologists, gynaecology cancer unit leads, gynaecological oncologists and pathologists.

Special consideration should be given in the following clinical scenarios:

6.5 Imaging-guided biopsy

In order to obtain adequate amount of chemotherapy naïve tissue, extra cores of tumour tissue should be obtained for the purpose of successful tumour *BRCA* mutation testing. This must be recorded in the histopathology request form which is usually filled by the diagnosing clinician. Experience from the BRITROC study suggests that image guided biopsy using an 18 gauge needle and 2 passes are feasible and acceptable to patients and results in good tissue sampling. (Goranova et al, 2017), if the pre-chemotherapy biopsy does not yield adequate tissue sample for *BRCA* testing, tumour testing should be reconsidered from the interval debulking surgery specimens in patients with negative germline testing. As the success rate of tumour sequencing from post chemotherapy specimens is lower (impaired DNA yield) compared to chemotherapy naïve tissue, maximum attempt should be made to obtain adequate amount of tissue during pre-treatment biopsy. If debulking surgery is not performed after neoadjuvant chemotherapy, repeat imaging-guided biopsy for tumour testing should be considered.

6.6 Diagnostic laparoscopy

Adequate biopsy should be taken to provide the GLH with sufficient amount of tissue for tumour testing.

6.7 Ascites cytology (in rare cases where tissue cannot be obtained)

large amount of ascites should be sent to the pathology laboratory to obtain a tumour cell-rich block.

6.8 Summary of testing for BRCA1/2

	Germline testing	Tumour testing
Indications	All non-mucinous epithelial high-grade ovarian cancer, all stages.	High-grade serous ovarian cancer, FIGO stages III and IV[3]. High-grade endometrioid ovarian cancer[1] [2], FIGO stages III and IV[3]
Timing of test	Patient choice Offer from as early in the journey as possible	Patient choice Offer from as early in the journey as possible
Sequence of testing	Parallel testing	Parallel testing
Information provided and consent	Written information on the implications for patient and family is provided and written consent is obtained	Written information on the implications for patient and family is provided and the verbal consenting process is documented in the notes

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

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

For additional details, please read enclosed Pathology appendix.

7.1 Tissue handling

Biopsy – any biopsy received with suspicion 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 context of morphology, PAX8 +ve, WT1 +ve, ER +ve and p53 mutation/aberrant staining (https://www.thebagp.org/download/bagp-ukneqas-project-p53-interpretation-guide-2016/) is confirmatory for tubal/ovarian high-grade serous carcinoma. The other block should have an H&E stain to confirm presence of malignancy. All blocks and the H&E and immunostained slides should be sent to the nominated pathologist. *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.*

Resection - the reporting pathologist should send one block of primary or metastatic carcinoma containing maximum viable and well-fixed tumour with its H&E stained slide to the nominated pathologist.

Cytology – Cellblock from cytology received with suspicion of ovarian cancer should be sent to nominated pathologist if confirmatory of tubal/ovarian high-grade serous carcinoma. Block should have an H&E stain with a confirmatory panel of PAX8, WT1, ER and p53 immunostains. In context of morphology, PAX8 +ve, WT1 +ve, ER +ve and p53 mutation/aberrant staining (https://www.thebagp.org/download/bagp-ukneqas-project-p53-interpretation-guide-2016/) is confirmatory for tubal/ovarian high-grade serous carcinoma.

7.2 Pathways

- Pathology teams and clinical teams should jointly establish pathways for communication of requests for tumour testing. This communication should clearly include the information that the implications of tumour genetic testing have been discussed with the patient, the patient has agreed to this testing and this has been documented.

- The nominated pathologist marks tumour areas on H&E slide and estimated tumour volume. The tissue, marked slide and completed form are sent to the GLH. This should be recorded securely and where possible, this record should be accessible to relevant clinical team.

- When result received, the result should be added to the initial pathology report as a supplementary and/or upload report on electronic patient record.

8. Genomic Laboratory Hub considerations

The NHS genomic laboratory hub network (GLH) has limited capacity to undertake assessment of pathology samples for adequacy for somatic *BRCA* analysis from ovarian cancer patients. Their specialist expertise is the analysis of nucleic acids. It is the primary responsibility of the pathology laboratory holding the tissue sample to undertake an assessment of the adequacy of tissue samples for tumour *BRCA* analysis. This should include an assessment of the neoplastic cell content of the sample. It is recommended that the neoplastic cell content of samples should be at least twice the limit of detection of the assay used. For NGS based assays,

the typical minimum neoplastic cell content for reliable detection of pathogenic variants is 20%. Formalin fixed paraffin embedded (FFPE) samples with less than 20% neoplastic cell content and regions of higher neoplastic cell content can be 'rescued' by macrodissection in the genomic laboratory. Macrodissection by the referring pathologist should, therefore, be considered for any samples where the neoplastic cell content is less than the minimum recommended by the genomics laboratory. A clearly marked H&E stained guide slide with areas of neoplasia ringed using an indelible marker should be sent along with unstained slide mounted sections. The H&E guide slide should be derived from a serial section next to the sections sent for genomic analysis. Tissue morphology can change as successive sections are cut from the block and a neighbouring section mitigates against macrodissecting an inappropriate region of the tissue section.

Genomic target test turnaround times for GLHs in England are set by NHSE. The key turnaround times appropriate to ovarian cancer are 21 calendar days for tumour *BRCA* analysis and 42 calendar days for germline *BRCA* analysis. Genomic laboratories are expected to meet these in at least 90% of the cases.

9. Consent issues

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

To support this, the Genomics Education Programme (GEP) has developed a competency framework that identifies eight areas of proficiency to facilitate and consent patients to genomic tests. https://www.genomicseducation.hee.nhs.uk/consent-a-competency-framework/. It is intended as a cross-professional guide for best practice and has been designed around four categories of healthcare professionals based on their training and experience with genomics.

Crucially, with the new framework, consent is rightly seen as a process whereby an 'offer' is made, adequate information provided and discussions to enable informed choice by patients are provided.

9.1 Using the framework

The competency framework can be used by individual healthcare professionals as a guide to help them identify their learning needs. For educators, the framework provides a mechanism to recognise the training needs of health professional groups, and to structure training so that consent conversations about genomic testing can be delivered consistently across different specialties. In addition, the competencies can be used to evaluate how consent is being facilitated in different practice areas to enhance the delivery of genomic medicine.

The consent competency framework was developed in consultation with healthcare professionals, professional bodies and medical Royal Colleges. It will continue to be reviewed on a regular basis, and feedback is welcomed. You can view the framework here.

9.2 Consent Forms

Until the 'patient choice' forms are readily available in the UK (as detailed in the GEP), the current consent forms can be used and adapted to indicate if a patient has provided consent for somatic/germline/or combination (parallel) testing. It must be recorded in the patient notes that the discussion about opting to have a BRCA test has taken place over different points in the diagnostic/treatment work up. The consenting process should comply with GMC standards. (https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent)

The new Genomics Medicine Service Alliance (GMSA) will have genomics counsellor and nursing lead who will jointly work with the Genomic Laboratory Hub (GLH) education lead to support the training and development of Genomic Champions. These posts will be funded by Macmillan (2 per each alliance), their role in essence will be to cascade train nurses to counsel and consent for genomic testing.

In all cases, high quality, culturally appropriate information must be provided to patients so they can make an informed decision. Please see Appendix 2,3,4 for template letters

10. Recording of *BRCA* status

Consistency of terminology is important to avoid confusion. For instance, use of the term "BRCA positive" should be avoided as it can be interpreted to mean the diametric opposites of the positive presence of a mutation or the positive presence of protein.

To avoid confusion the following terms should therefore be used:

Germline variant – a variant detected in the blood sample.

Tumour variant – a variant detected in the tumour. Importantly, without reference to the blood sample a tumour variant could be either germline or somatic.

Somatic variant – a pathogenic variant detected in the tumour sample which is not present in the blood sample. To define a somatic variant therefore requires that both a blood and a tumour sample have been analysed.

For ease of recording a common notation is to use a prefix to define the type of variant described and a suffix to describe the result.

Using these notations, g, t, s are used to describe germline, tumour and somatic, respectively. Additionally, m, vus & wt are used to describe pathogenic or likely-pathogenic variant (mutation), variant of unknown significance and wild type respectively.

For example, gBRCA1m would describe a germline variant (pathogenic or likely-pathogenic variant) of BRCA1, in contrast to sBRCA2wt which would describe a somatic wild type (no pathogenic variant) BRCA2.

10.1 Five classes of variants have been described

(Table-1). (Eccles et al, 2015; Plan et al 2008)

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

11. Changes on horizon

The consensus group identified potential advances on the horizon that would impact on *BRCA* testing pathways. These will be important to factor in as they near implementation in routine clinical practice.

Testing for homologous recombination deficiency

Currently homologous recombination deficiency (HRD) testing is only available via commercial assays. The National Cancer Research Institute (NCRI) Gynaecological Cancer Group is part of a Europe-wide collaboration, led by the French GINECO group to develop an academic validated HRD assay. Currently, HRD assays are associated with poor sensitivity and specificity.

PARP inhibitors – current indications and recent changes

First-line therapy:

Olaparib is licensed, and available via the Cancer Drugs Fund (CDF) in the UK, in the front line setting as maintenance therapy for women who have a pathogenic BRCA variant. Olaparib in combination with Bevazucimab, has been shown to provide progression-free survival benefit, which was substantial in patients with HRD-positive tumours, including those without a BRCA mutation. Niraparib has recently been granted fast track FDA approval as a maintenance therapy in women with advanced ovarian cancer who have responded to first-line platinum therapy. Whilst not currently licensed in Europe, Niraparib is temporarily available via an expanded access scheme in the UK (April 2020) for women who do not have other maintenance treatment options.

Relapsed Platinum Sensitive Ovarian Cancer:

In relapsed ovarian disease PARP inhibitors (Olaparib, Niraparib, Rucaparib) are licensed as maintenance therapy (following platinum based chemotherapy) for women who have platinum sensitive relapsed ovarian cancer and are available via the CDF/NICE.

12. Patient perspectives

Conversations with gynaecological cancer charities have highlighted the following issues of concern and importance for patients that need to be considered when implementing *BRCA* testing.

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

13. Conclusions

Germline testing has significant implications for patients, in terms of therapy choices, but also for their families in terms of risk management and the development of additional tumours. Tumour *BRCA* testing identifies an additional subgroup of women who have benefit from PARP

inhibitors. It remains of critical importance to stratify patients and identify those who do not have a *BRCA* (germline/somatic) pathogenic variant as this group of women are least likely to benefit from PARP inhibitors and should therefore be considered for studies of novel therapies/combinations going forward. Such a strategy will ensure that we continue to develop a personalized therapeutic approach for our patients. Additionally, family members who have a pathogenic/likely pathogenic variant can opt for a range of interventions such as reproductive choices, prenatal genetic diagnosis, planning a family, risk reduction surgery, screening or chemo-prevention to minimize their ovarian cancer and breast cancer risk.

14. Recommendations

General

- Parallel tumour and germline testing for *BRCA*1 and *BRCA2* is superior to either germline alone, tumour alone or sequential testing strategies
- Robust processes should be in place to ensure results of *BRCA* testing are recorded, with the correct nomenclature, in the patient's clinical and laboratory records and that the patient is informed of the result.
- Patients with positive test results should be referred to clinical genetics for post-test counselling and facilitation of predictive testing in family members.

- The classification of *BRCA* variants is under constant review; and variants previously considered VUSs might be reclassified as pathogenic or non-pathogenic variants as the analytical process improves. Therefore, consideration should be given to VUS review at the time of disease recurrence if initial testing was done at diagnosis and if knowledge of *BRCA* 1/2 status will change management.

Consent

- High quality, culturally appropriate information must be provided to patients so they can make an informed decision. Consenting should be carried out according to standards set up by GMC. Consenting for *BRCA*1/2 testing can be undertaken by any appropriately trained healthcare professional. For tumour testing, it is recognized that this consent may be verbal and documented in the patient records; for germline testing written consent should be undertaken.
- Where *BRCA*1/2 testing has been discussed with the patient, this should be documented in the clinical records.

Tumour *BRCA* Testing

- Testing for tumour *BRCA*1/2 can be discussed with patients either prior to or after biopsy for suspected high-grade serous ovarian cancer.
- Tumour testing alone should not be relied upon for exclusion of a clinically relevant *BRCA*1/2 mutation. LGRs may be missed on tumour testing alone but identified by germline testing.
- If tumour testing is to be undertaken on a radiological biopsy then additional cores should be taken to ensure sufficient tissue for analysis.

- If a diagnostic result is not obtained from an initial tissue biopsy then additional tissue should be analysed at the time of interval debulking surgery. If a diagnostic result is not obtained from an initial tissue biopsy and the patient is not undergoing debulking surgery then an additional tissue biopsy for *BRCA* testing alone should be considered, if the result would change management.
- It should be noted that as funding arrangements for oncological treatments change the absolute requirement for *BRCA*1/2 tumour testing might change.

Germline Testing

- Germline testing should be offered to patients as early as possible at diagnosis and not delayed.
- Low-grade serous tumours do not require *BRCA*1/2 testing when the diagnosis has been confirmed by a specialist gynaecological cancer histopathologist.

Audit standards

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

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