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

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

1-Institute of Cancer and Genomic Sciences, University of Birmingham
2- Pan Birmingham Gynaecological Cancer Centre, City Hospital, Birmingham
3- Barts Cancer Institute, London
4- Edinburgh Cancer Research UK Centre, University of Edinburgh
5- The Royal Marsden NHS Foundation Trust, London
6- St Mary's Hospital, Manchester
7-University Hospital Birmingham Foundation NHS Trust, Birmingham
8-Birmingham Women's Hospital, Birmingham
9-Division of Cancer Sciences, University of Manchester, Manchester
10-Division of Medical Oncology, Oxford Radcliffe NHS Hospitals.
11-Royal United Hospital Bath NHS Trust, Bath
12- Imperial Hospitals NHS trust
13- Macmillan Charity, UK
14-Nottingham Hospitals NHS Trust
15- Peterborough City Hospital, Peterborough.
16-Lancashire Teaching Hospitals, Preston
All authors based in UK.

Authors for correspondence

Professor Sudha Sundar
Institute of Cancer and Genomic Sciences
University of Birmingham
s.s.sundar@bham.ac.uk

Dr Raji Ganesan
Consultant in Gynaecological Pathology
Birmingham Women's Hospital
r.ganesan@nhs.net

Abstract

The British Gynaecological Cancer Society and the British Association of Gynaecological Pathologists 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* germline and tumour testing in patients with ovarian cancer in routine clinical practice. In particular, the group explored models of consent, quality standards identified at pathology, laboratory and experience/data from pioneering cancer 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 in this manuscript.

Introduction

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

To manage this increased demand and ensure timely access to testing early on in the patient care pathway, models of delivery using surgeons, oncologists or clinical nurse specialists to "mainstream" germline testing have been developed in many 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 are referred to genetics services.

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

Until 2018, the evidence base for maintenance PARP inhibition strategies was restricted to women with relapsed ovarian cancer. However, following publication of the SOLO-1 trial, the evidence for benefit has been 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.[11]

There are currently two methods by which *BRCA* testing may be undertaken, each of which detects slightly different pathogenic variants due to the pathogenesis of the mutations and the limitations of the analytical techniques. *Germline testing* is undertaken on blood samples and will detect inherited pathogenic variants, including the large duplications/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. Approximately two-thirds of the mutations detected in tumour will be of *germline* (inherited) origin, however nearly 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.[11] Therefore, patients and clinicians need as much information as possible to guide treatment choices in the first-line setting.

Thus, there is an urgent clinical need to clearly identify women whose 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 approximately

50% more women whose families may benefit from predictive testing and subsequent screening and prevention in unaffected individuals.[12]

Implementing these tests into routine practice at first-line treatment of ovarian cancer requires careful consideration of issues around scheduling of 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. This guidance document evaluates the underlying evidence and sets out recommendations for implementation into clinical practice in the United Kingdom.

Detection of different DNA variants in germline testing

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

Scheduling of germline and tumour BRCA testing

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

Evidence from the SIGNPOST study

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

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).

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 and tumour tests are requested from the gynaecological oncology clinic.

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

Evidence from Public Health England

Data from Public Health England shows that as of end of February 2020, from a total of 17,384 pathogenic *BRCA* variants reported by all labs in England, 1,830 were large genomic rearrangements. (Personal communication from Fiona McRonald, Programme Manager, Molecular, Genomic and Research Data National Disease Registration, Public Health England). See Figure -1. However, it is widely accepted in England, that there are several 'hotspots' for large genomic rearrangements, which also coincide with less access to testing, thus, the true proportion of large genomic rearrangements in this population may be closer to 15-17% of pathogenic variants. This 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 large genomic rearrangements of *BRCA*. Conversely, germline testing alone will miss a proportion of patients with only somatic variants in *BRCA.* Ongoing studies in Scotland will provide information for local populations.

Each health system will need to establish baseline rates to determine whether sequential testing or parallel testing is optimal for their patient groups. 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.

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 should start 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 can be carried out by a trained gynaecological oncologist, the referring gynaecologist with expertise in gynaecological oncology (cancer unit

lead in the UK), oncologist or adequately trained clinicians (Clinical Nurse Specialist). Some patients may need to access the genetics service for pre-test counselling and this should be supported where possible.

Initial consultation

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

Consultation before primary cytoreductive surgery

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

Consultation after primary cytoreductive surgery

If the pathology of the surgery reveals non-mucinous high-grade epithelial ovarian cancer, the patient should be 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 and the nominated pathologist should be informed.

Consultation before biopsy in patients planned to receive neoadjuvant chemotherapy:

If the patient is not suitable for primary cytoreductive surgery (or in cases of diagnostic uncertainty) counselling about tumour *BRCA* testing should be performed before the imaging-guided biopsy or diagnostic laparoscopy. Informed consent should be obtained either in the form of a verbal discussion which is documented or through a formal consent form. 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 (electronic records, letter or email).

Special Considerations:

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. Experience from the BRITROC study suggests that image guided biopsy using an 18-gauge needle and two passes are feasible and acceptable to patients and results in adequate tissue sampling.[13] If the pre-chemotherapy biopsy does not yield 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.

Diagnostic laparoscopy

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

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

Ascitic fluid should be sent to the pathology laboratory to obtain a tumour cell-rich block. A summary of indications, timing, sequence of testing and consent process is summarised in Table 1.

Pathology - Tissue handling and pathways for tumour BRCA testing

The mutation testing relies on detecting a mutant allele in a background of wild type alleles. It is important that adequate numbers of malignant cells are available to provide DNA for the test. Therefore, maximising the tissue available in a diagnostic biopsy is of paramount importance. Any biopsy done with suspicion of tubo-ovarian cancer must be sampled in at least two blocks. One block (with the lesser volume of tumour) should have an H&E (hematoxylin and eosin) 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. In case of diagnostic uncertainty,

in order to preserve tissue, the case should be sent to a cancer centre for review before further tissue is used for immunohistochemistry. The second block should have an H&E stain to confirm presence of malignancy. This is the tissue that needs to be sent to the nominated pathologist/s. In resection specimens, 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 a designated pathologist. Cellblock from cytology received with suspicion of ovarian cancer should be sent to pathologist if confirmatory of tubal/ovarian high-grade serous carcinoma.

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

Genomic Laboratory Hub considerations

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

Genomic target test turnaround times for genomic laboratory hubs in England are set by National Health Service England. The key turnaround times appropriate for ovarian cancer are 21 calendar days for 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.

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 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. 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.

Crucially, with the new framework, consent is rightly seen as a process whereby an 'offer' is made, adequate information provided and discussions to enable informed choice by patients are provided. Until the 'patient choice' forms are readily available in the UK (as detailed in the Genomics education programme), 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 General Medical Council standards. (https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent)

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

316 *Recording of BRCA status and multidisciplinary team meeting outputs*

317 Consistency of terminology is important to avoid confusion. For instance, use of the term
318 "BRCA positive" should be avoided as it can be interpreted to mean the diametric opposites of
319 the positive presence of a mutation or the positive presence of protein. To avoid confusion the
320 following terms should therefore be used: germline variant – a variant detected in the blood
321 sample vs. tumour variant – a variant detected in the tumour. Importantly, without reference
322 to the blood sample, a tumour variant could be either germline or somatic. Somatic variant –
323 a pathogenic variant detected in the tumour sample which is not present in the blood sample.
324 To define a somatic variant therefore requires that both a blood and a tumour sample have
325 been analysed.

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

333 ## *Patient perspectives*

334 Conversations with gynaecological cancer charities have highlighted issues of concern and
335 importance for patients that need to be considered when implementing *BRCA* testing.
336 Critically, patients should feel reassured that the timing of *BRCA* testing is their decision as

patients may feel ready to undergo testing at different points in their journey. High quality, culturally appropriate information is vital to this. Table 3

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. Recommendations for testing are summarised in Table 4. 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. 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 chemoprevention to minimize their ovarian cancer and breast cancer risk.

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Conflicts of interest

Sudha Sundar has received honoraria from Astra Zeneca outside the submitted work. Christina Fotopoulou has received honoraria from Ethicon, Tesaro, MSD/Astra Zeneca, Clovis, Roche, GSK. Ranjit Manchanda reports grants from Barts Charity, grants from The Eve Appeal, personal fees from Astra Zeneca, MSD, outside the submitted work. Rebecca Bowen reports personal fees from GSK, personal fees from AstraZeneca, personal fees from Clovis, from Tesaro, outside the submitted work. Jonathan Frost has nothing to disclose. Ketan Gajjar has

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Table – 2. Classes of variants.

Table – 3. Patients perspectives on BRCA testing

Table -4. Recommendations for BRCA testing in ovarian cancer the UK

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