

# British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for germline and tumor testing for BRCA1/2 variants in ovarian cancer in the United Kingdom

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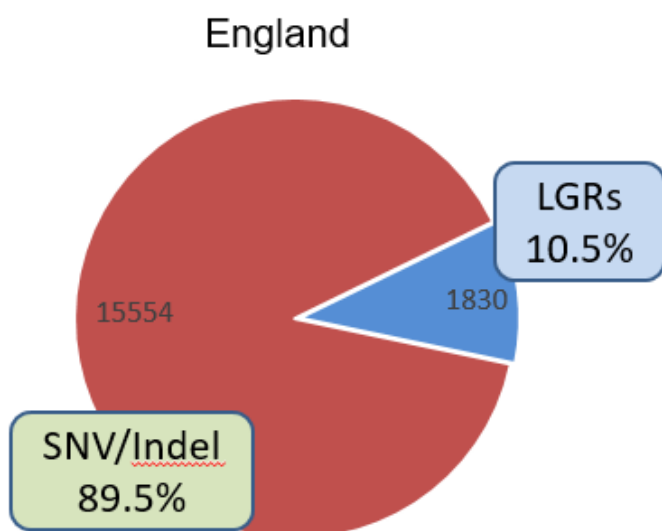
**British Gynaecological Cancer Society/British Association of  
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 the United Kingdom**

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## Figures and Tables from manuscript

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)



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

### **Tubo-ovarian cancer and BRCA**

The frequency of *BRCA1* and *BRCA2* germ-line pathogenic variations (mutations) in women with tubo-ovarian cancer is variably quoted. If all tubo-ovarian cancers are taken into consideration, the stated frequency is 10 – 15%. [Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, Friedlander M, Fox S, Bowtell D, Mitchell G. *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol*. 2012 Jul 20;30(21):2654-63. doi: 10.1200/JCO.2011.39.8545.]. When somatic mutations are included, this figure rises to 20% or greater. [Ledermann JA, Drew Y, Kristeleit RS. *Homologous recombination deficiency and ovarian cancer*. *Eur J Cancer*. 2016;60:49-58. doi:10.1016/j.ejca.2016.03.005].

### **Recombinant DNA Repair**

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

### **Recombinant DNA repair and BRCA pathogenic variants**

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

### **Germline mutations vs somatic mutations**

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

### **Testing for BRCA pathogenic variants (mutations)**

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

### **Reasons for tBRCA testing**

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

### **Role of the pathologist**

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

#### Understanding pre-analytic variables

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

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

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

#### Laboratory processes

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

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

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

### The request forms

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

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

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

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

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

### Choosing material for testing

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

#### ***Biopsy of suspected tuboovarian carcinoma:***

- Cores blocked separately (at least 2 blocks)
- H&E on both blocks to confirm cancer
- One block (preferably the one with less tissue/tumour) for confirmatory IHC
- IHC to confirm high grade serous carcinoma (PAX8+ve, WT1 +ve, ER +ve. p53 mutation/aberrant) (<https://www.thebagp.org/download/bagp-uknegas-project-p53-interpretation-guide-2016/>) *If there is diagnostic uncertainty, in order to preserve tissue for testing, further immunostains should not be done. The available material should be sent to Cancer Centre for review and diagnosis.*
- Tissue/blocks, H&E and immunostained slides should be sent to nominated pathologist.

#### ***Resection specimen from known high grade tuboovarian serous carcinoma:***

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

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

- H&E to confirm cancer
- Minimal IHC to confirm high grade serous carcinoma (PAX8+ve, WT1 +ve, ER +ve. p53 mutation/aberrant)
- Block, H&E and IHC slides sent to nominated pathologist.

### Sending material for testing

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

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

#### Recording the report

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

#### Audit

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



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## Receiving a BRCA1 and BRCA2 test result that identifies an alteration

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### Information sheet for patients with cancer

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

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

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

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

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

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

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

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



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

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### Information sheet for patients with cancer

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

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

#### What does this result mean for me?

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

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

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

#### What does this result mean for my relatives?

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

There is currently no known effective form of ovarian screening. If a woman has more than one relative with ovarian cancer, removal of the ovaries is sometimes considered.

All women are eligible to have mammograms from 47 years in the National Breast Screening Programme. Depending on the family history, some women may be eligible for mammograms from 40 years.

If this is the case in your family, please discuss this further with your cancer team.

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

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

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

### Cancer in the general population

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

### Why am I being offered a genetic test?

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

### What are genes?

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

### What are cancer-causing genetic variants called?

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

### How do changes in genes cause cancer?

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

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

### Which genes are associated with ovarian cancer?

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

### How do we test for genetic variants?

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

1. Tumour testing to look for **somatic** variants. Your oncologist will send a sample of your tumour onto a specialist laboratory to test it for variants in *BRCA1* and *BRCA2*. These results will take around 5 weeks to be reported.
2. A blood test to look for **germline** variants. Your treating team will take a blood sample from you and ask you to sign a consent form to have this sample stored. A member of the genetics team will contact you to explain more about testing your blood sample for variants in *BRCA1* and *BRCA2*. The results may take around 6-8 weeks to be reported.

### What are the outcomes of testing? (1)

#### 1. **Somatic** testing (from your tumour)

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

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

## What are the outcomes of testing? (2)

### 1. Germline testing (from your blood sample)

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

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

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

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

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

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

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

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

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

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

### Family history information

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



### Websites for further Information

Breast awareness (Macmillan):

<http://www.macmillan.org.uk/Cancerinformation/Testscreening/Breastscreening/Breastawareness.aspx>

Ovarian symptoms (Ovarian Cancer National Alliance):

<http://www.ovariancancer.org/about-ovarian-cancer/symptoms/>

### Details regarding your test

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

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

1 **British Gynaecological Cancer Society/British Association of**  
2 **Gynaecological Pathology consensus for germline and tumour testing for**  
3 ***BRCA1/2* variants in ovarian cancer in the United Kingdom**

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9

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40  
41

42 Abstract

43 The British Gynaecological Cancer Society and the British Association of  
44 Gynaecological Pathologists established a multidisciplinary consensus group  
45 comprising experts in surgical gynaecological oncology, medical oncology, genetics,  
46 laboratory science and clinical nurse specialists to identify the optimal pathways to  
47 *BRCA* germline and tumour testing in patients with ovarian cancer in routine clinical  
48 practice. In particular, the group explored models of consent, quality standards  
49 identified at pathology, laboratory and experience/data from pioneering cancer  
50 centres. The group liaised with representatives from ovarian cancer charities to also  
51 identify patient perspectives that would be important to implementation.

52 Recommendations from this consensus group deliberations are presented in this  
53 manuscript.

54

55

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56

57 **Introduction**

58 Pathogenic germline *BRCA1/2* variants play a key role in the etiology of epithelial  
59 ovarian cancer. Recent studies showing the prevalence of pathogenic *BRCA*  
60 germline mutations in patients with high-grade serous ovarian cancer of 13-15% as  
61 well as the recognition of the clinically significant role of therapeutic poly-ADP ribose  
62 polymerase (PARP) inhibition in *BRCA* deficient tumours has led to an expansion in  
63 demand for germline *BRCA* testing.<sup>1-6</sup> The Cancer Genome Atlas (TCGA) identified  
64 somatic and germline *BRCA* pathogenic variants in ~22% of high-grade serous  
65 ovarian cancers.<sup>7</sup>

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



72 Different models have developed across the UK with variable testing criteria,  
73 availability and access.<sup>4, 8, 9</sup> Some models restrict testing to defined histological  
74 criteria (high-grade serous or endometrioid), others restrict testing to age groups  
75 (under 70 years). However, there is considerable variability in implementation of  
76 mainstream germline *BRCA* testing worldwide with some centres still relying on  
77 individual clinicians referring patients to regional genetics centres and approximately  
78 30% of eligible patients not being offered testing.<sup>10</sup>

79

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

86

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

98 Crucially, PARP inhibition increases progression-free survival in patients with  
99 somatic *BRCA* mutation.<sup>11</sup> Therefore, patients and clinicians need as much  
100 information as possible to guide treatment choices in the first-line setting.

101 Thus, there is an urgent clinical need to clearly identify women whose tumours  
102 contain deleterious *BRCA* mutations early in their ovarian cancer treatment journey

103 to maximize the population of women afforded the opportunity of PARP inhibitor  
104 treatment upon completion of first-line chemotherapy. Additionally, unselected  
105 germline testing identifies approximately 50% more women whose families may  
106 benefit from predictive testing and subsequent screening and prevention in  
107 unaffected individuals.<sup>12</sup>

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

#### 114 *Detection of different DNA variants in germline testing*

115 Next generation sequencing based technologies are used for detection of *BRCA*  
116 'point mutations' (single nucleotide variants or small insertion/deletion variants  
117 typically <40 bp in size) in both blood (germline) and tumour samples. Although  
118 pathogenic large genomic rearrangements can be detected in germline samples

119 using next generation sequencing, the algorithms show reduced sensitivity for  
120 smaller, single exon large genomic rearrangements. Consequently, pathogenic large  
121 genomic rearrangements in *BRCA* are typically detected in clinical laboratories using  
122 multiplex ligation dependent probe amplification in blood samples. However,  
123 multiplex ligation dependent probe amplification has a high analytical failure rate in  
124 formalin fixed paraffin embedded derived tumour DNA due to poor DNA quality and  
125 genomic instability present in many ovarian tumours and is consequently not  
126 routinely employed.

#### 127 *Scheduling of germline and tumour BRCA testing*

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

#### 130 Evidence from the SIGNPOST study

131 A concomitant/parallel panel germline and tumour genetic testing pathway for all  
132 high-grade non-mucinous epithelial ovarian cancer was initially introduced at Barts  
133 Health (North East London Cancer Network) in 2016. This involved an initial period  
134 of training of clinical staff (surgeons, medical oncologists, clinical nurse specialists,

135 design of patient information materials and was undertaken within the SIGNPOST  
136 (Systematic Genetic Testing for Personalised Ovarian Cancer Therapy) study  
137 (ISRCTN 16988857). Germline testing included testing for *BRCA1*, *BRCA2*,  
138 *RAD51C*, *RAD51D*, *BRIP1*. Tumour testing was undertaken for *BRCA1* and *BRCA2*  
139 genes. Both germline and tumour testing were done in parallel. This was offered  
140 both prospectively and retrospectively to those with a pre-existing diagnosis.

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

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

149 At Imperial College Healthcare NHS Trust, parallel germline and tumour BRCA  
150 genetic testing is offered to all eligible ovarian cancer patients. The cancer team

151 discuss the pathways and possibility of genetic testing and its implications with the  
152 patient at initial presentation. If consent is obtained, germline and tumour tests are  
153 requested from the gynaecological oncology clinic.

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

163 Evidence from Public Health England

164 Data from Public Health England shows that as of end of February 2020, from a total  
165 of 17,384 pathogenic *BRCA* variants reported by all labs in England, 1,830 were  
166 large genomic rearrangements. (Personal communication from Fiona McDonald,

167 Programme Manager, Molecular, Genomic and Research Data National Disease  
168 Registration, Public Health England). See Figure -1. However, it is widely accepted  
169 in England, that there are several 'hotspots' for large genomic rearrangements,  
170 which also coincide with less access to testing, thus, the true proportion of large  
171 genomic rearrangements in this population may be closer to 15-17% of pathogenic  
172 variants. This would be consistent with data from the Manchester and Royal  
173 Marsden labs (unpublished).

174

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

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

### 187 *Timing of BRCA testing in relation to first-line treatment*

188 The consensus group reflected on two issues in this section; the first to preserve  
189 patient choice and autonomy in making an informed decision, the second the crucial  
190 utility of knowledge of *BRCA* status in decisions for  
191 neoadjuvant/adjuvant/maintenance treatments at first-line settings. The consensus  
192 group also had discussions with ovarian cancer charities representing patient  
193 perspectives. The consensus group agreed that preserving patient choice in timing  
194 of testing was key. However, discussions around *BRCA* testing should start at the  
195 earliest available opportunity in a patient's cancer diagnosis journey.

196 In the ideal scenario, earliest testing at the time of diagnosis of ovarian cancer is vital  
197 so that *BRCA* status is available when it is clinically most relevant to the patient and



198 should factor in the local turnaround time for testing and the potential need for  
199 genetic counselling. It is recognized that patients may feel ready to undergo testing  
200 at different points in their cancer journey. The counselling and consenting can be  
201 carried out by a trained gynaecological oncologist, the referring gynaecologist with  
202 expertise in gynaecological oncology (cancer unit lead in the UK), oncologist or  
203 adequately trained clinicians (Clinical Nurse Specialist). Some patients may need to  
204 access the genetics service for pre-test counselling and this should be supported  
205 where possible.

#### 206 Initial consultation

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

#### 212 Consultation before primary cytoreductive surgery

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

225 Consultation after primary cytoreductive surgery

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

229 was not obtained prior to surgery, this should be done and the nominated pathologist  
230 should be informed.

231 Consultation before biopsy in patients planned to receive neoadjuvant  
232 chemotherapy:

233 If the patient is not suitable for primary cytoreductive surgery (or in cases of  
234 diagnostic uncertainty) counselling about tumour *BRCA* testing should be performed  
235 before the imaging-guided biopsy or diagnostic laparoscopy. Informed consent  
236 should be obtained either in the form of a verbal discussion which is documented or  
237 through a formal consent form. The fact whether the patient has provided or declined  
238 consent for tumour testing should be recorded in the pathology request form after  
239 biopsy or conveyed to the pathologist by other means (electronic records, letter or  
240 email).

241 *Special Considerations:*

242 Imaging-guided biopsy

243 In order to obtain adequate amount of chemotherapy naïve tissue, extra cores of  
244 tumour tissue should be obtained for the purpose of successful tumour *BRCA*

245 mutation testing. This must be recorded in the histopathology request form.  
246 Experience from the BRITROC study suggests that image guided biopsy using an  
247 18-gauge needle and two passes are feasible and acceptable to patients and results  
248 in adequate tissue sampling.<sup>13</sup> If the pre-chemotherapy biopsy does not yield  
249 adequate tissue sample for *BRCA* testing, tumour testing should be reconsidered  
250 from the interval debulking surgery specimens in patients with negative germline  
251 testing. As the success rate of tumour sequencing from post chemotherapy  
252 specimens is lower (impaired DNA yield) compared to chemotherapy naïve tissue,  
253 maximum attempt should be made to obtain adequate amount of tissue during pre-  
254 treatment biopsy. If debulking surgery is not performed after neoadjuvant  
255 chemotherapy, repeat imaging-guided biopsy for tumour testing should be  
256 considered.

257 Diagnostic laparoscopy

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

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

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

264 *Pathology - Tissue handling and pathways for tumour BRCA testing*

265 The mutation testing relies on detecting a mutant allele in a background of wild type  
266 alleles. It is important that adequate numbers of malignant cells are available to  
267 provide DNA for the test. Therefore, maximising the tissue available in a diagnostic  
268 biopsy is of paramount importance. Any biopsy done with suspicion of tubo-ovarian  
269 cancer must be sampled in at least two blocks. One block (with the lesser volume of  
270 tumour) should have an H&E (hematoxylin and eosin) stain with a confirmatory panel  
271 of PAX8, WT1, ER and p53. In context of morphology, PAX8 +ve, WT1 +ve, ER +ve  
272 and p53 mutation/aberrant staining ([https://www.thebagp.org/download/bagp-ukneqas-](https://www.thebagp.org/download/bagp-ukneqas-project-p53-interpretation-guide-2016/)  
273 [project-p53-interpretation-guide-2016/](https://www.thebagp.org/download/bagp-ukneqas-project-p53-interpretation-guide-2016/)) is confirmatory for tubal/ovarian high-grade serous  
274 carcinoma. In case of diagnostic uncertainty, in order to preserve tissue, the case  
275 should be sent to a cancer centre for review before further tissue is used for

276 immunohistochemistry. The second block should have an H&E stain to confirm  
277 presence of malignancy. This is the tissue that needs to be sent to the nominated  
278 pathologist/s. In resection specimens, the reporting pathologist should send one  
279 block of primary or metastatic carcinoma containing maximum viable and well-fixed  
280 tumour with its H&E-stained slide to the a designated pathologist. Cellblock from  
281 cytology received with suspicion of ovarian cancer should be sent to pathologist if  
282 confirmatory of tubal/ovarian high-grade serous carcinoma.

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

292 *Genomic Laboratory Hub considerations*

293 The NHS Genomic Laboratory Hub network has limited capacity to undertake  
294 assessment of pathology samples for adequacy for somatic *BRCA* analysis from  
295 ovarian cancer patients. Their specialist expertise is the analysis of nucleic acids. It  
296 is the primary responsibility of the pathology laboratory holding the tissue sample to  
297 undertake an assessment of the adequacy of tissue samples for tumour *BRCA*  
298 analysis. This should include an assessment of the neoplastic cell content of the  
299 sample. It is recommended that the neoplastic cell content of samples should be at  
300 least twice the limit of detection of the assay used. For next generation sequencing  
301 based assays, the typical minimum neoplastic cell content for reliable detection of  
302 pathogenic variants is 20%. Formalin fixed paraffin embedded samples with less  
303 than 20% neoplastic cell content and regions of higher neoplastic cell content may  
304 be 'rescued' by macrodissection in the genomic laboratory. Macrodissection by the  
305 referring pathologist should, therefore, be considered for any samples where the  
306 neoplastic cell content is less than the minimum recommended by the genomics  
307 laboratory. A clearly marked H&E-stained guide slide with areas of neoplasia ringed

308 using an indelible marker should be sent along with unstained slide mounted  
309 sections. The H&E guide slide should be derived from a serial section next to the  
310 sections sent for genomic analysis. Tissue morphology can change as successive  
311 sections are cut from the block and a neighbouring section mitigates against  
312 macrodissecting an inappropriate region of the tissue section.

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

#### 318 *Consent issues*

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



324 To support this, the Genomics Education Programme has developed a competency  
325 framework that identifies eight areas of proficiency to facilitate and consent patients  
326 to genomic tests. ([https://www.genomicseducation.hee.nhs.uk/consent-a-competency-  
328 framework/](https://www.genomicseducation.hee.nhs.uk/consent-a-competency-<br/>327 framework/)). It is intended as a cross-professional guide for best practice and has  
329 been designed around four categories of healthcare professionals based on their  
330 training and experience with genomics. The competency framework can be used by  
331 individual healthcare professionals as a guide to help them identify their learning  
332 needs. For educators, the framework provides a mechanism to recognise the training  
333 needs of health professional groups, and to structure training so that consent  
334 conversations about genomic testing can be delivered consistently across different  
335 specialties. In addition, the competencies can be used to evaluate how consent is  
336 being facilitated in different practice areas to enhance the delivery of genomic  
337 medicine.

337 Crucially, with the new framework, consent is rightly seen as a process whereby an  
338 'offer' is made, adequate information provided and discussions to enable informed  
339 choice by patients are provided. Until the 'patient choice' forms are readily available

340 in the UK (as detailed in the Genomics education programme), the current consent  
341 forms can be used and adapted to indicate if a patient has provided consent for  
342 somatic/germline/or combination (parallel) testing. It must be recorded in the patient  
343 notes that the discussion about opting to have a BRCA test has taken place over  
344 different points in the diagnostic/treatment work up. The consenting process should  
345 comply with General Medical Council standards. ([https://www.gmc-uk.org/ethical-](https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent)  
346 [guidance/ethical-guidance-for-doctors/consent](https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent))

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

#### 350 *Recording of BRCA status and multidisciplinary team meeting outputs*

351 Consistency of terminology is important to avoid confusion. For instance, use of the  
352 term “BRCA positive” should be avoided as it can be interpreted to mean the  
353 diametric opposites of the positive presence of a mutation or the positive presence of  
354 protein. To avoid confusion the following terms should therefore be used: germline  
355 variant – a variant detected in the blood sample vs. tumour variant – a variant

356 detected in the tumour. Importantly, without reference to the blood sample, a tumour  
357 variant could be either germline or somatic. Somatic variant – a pathogenic variant  
358 detected in the tumour sample which is not present in the blood sample. To define a  
359 somatic variant therefore requires that both a blood and a tumour sample have been  
360 analysed.

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

### 369 *Patient perspectives*

370 Conversations with gynaecological cancer charities have highlighted issues of  
371 concern and importance for patients that need to be considered when implementing

372 *BRCA* testing. Critically, patients should feel reassured that the timing of *BRCA*  
373 testing is their decision as patients may feel ready to undergo testing at different  
374 points in their journey. High quality, culturally appropriate information is vital to this.

375 Table 3

## 376 Conclusions

377 Germline testing has significant implications for patients, in terms of therapy choices,  
378 but also for their families in terms of risk management and the development of  
379 additional tumours. Tumour *BRCA* testing identifies an additional subgroup of  
380 women who have benefit from PARP inhibitors. Recommendations for testing are  
381 summarised in Table 4. It remains of critical importance to stratify patients and  
382 identify those who do not have a *BRCA* (germline/somatic) pathogenic variant as this  
383 group of women are least likely to benefit from PARP inhibitors and should therefore  
384 be considered for studies of novel therapies/combinations going forward.  
385 Additionally, family members who have a pathogenic/likely pathogenic variant can  
386 opt for a range of interventions such as reproductive choices, prenatal genetic

387 diagnosis, planning a family, risk reduction surgery, screening or chemoprevention to  
388 minimize their ovarian cancer and breast cancer risk.

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408

409

410

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413 cancer patients that are large genomic re-arrangements.

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417 Table – 3. Patients perspectives on BRCA testing

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