FAQS FOR NON-GENETICS HEALTH CARE PROFESSIONALS ON

INFORMED CONSENT FOR INHERITED (GERMLINE) AND TUMOUR (SOMATIC) BRCA TESTING

1. **Which patients** should be considered for germline and tumour BRCA (refers to BRCA 1 & BRCA 2) testing in relation to the PARP inhibitor olaparib?

2. **When** should I discuss these tests with my patient?

3. What is the **likelihood** of finding a germline and/or tumour BRCA mutation (variant) in my patient?

4. What are the **implications for my patient** of identifying a germline BRCA mutation?

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9. What **patient information** materials are available for my patient?

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12. Can the test results be **inconclusive**? What are the implications of inconclusive results?

13. What are the implications of finding **no BRCA mutation** in my patient's blood or tissue sample?

14. Are there **other cancer predisposition genes** I should consider in my patient?

1. Which patients should be considered for germline and tissue BRCA testing in relation to the PARP inhibitor olaparib?

Germline and tumour BRCA testing should be considered in those who have a diagnosis of high grade serous epithelial ovarian cancer, primary peritoneal or fallopian tube cancer AND have previously responded to platinum-based therapy AND have relapsed and are commencing a second or subsequent line platinum-based treatment. They should have no contraindication to the use of olaparib as maintenance therapy.

If the patient has previously undergone germline BRCA testing, there is no need for that to be repeated and tumour testing only needs to be done.

If you have a query regarding the result of a BRCA test carried out in the past, e.g. if there is no record of the result or the test found a 'variant of uncertain significance' (VUS), you should contact the Cancer Genetics Service to discuss this.

Note in a patient who has previously undergone a bone marrow transplant, a blood sample cannot be used for germline testing. They should be referred to the genetics service to arrange appropriate testing.

2. When should I discuss these tests with my patient?

If indicated, olaparib should be commenced as maintenance treatment within eight weeks of completion of a second line course of platinum-based therapy. As the test results may take up to 12 weeks, BRCA testing should be offered to potentially eligible patients at the time of relapse following first line treatment.

A number of patients may subsequently not respond to their platinum-based therapy, in which case they will not proceed to olaparib maintenance therapy, regardless of their BRCA test result.

3. What is the **likelihood** of finding a germline and/or a tumour BRCA mutation (variant) in my patient?

The frequency of germline and tumour BRCA mutations is up to 38%[1] and 8.5-10%[2], respectively in patients with platinum-sensitive recurrent high-grade serous ovarian cancer.

[1] Dann RB, DeLoia JA, Timms KM, Zorn KK, Potter J, Flake DD, et al. BRCA1/2 mutations and expression: Response to platinum chemotherapy in patients with advanced stage epithelial ovarian cancer. Gynecologic Oncology 2012;125:677–82.

[2] Dougherty BA, Lai, Z, Hodgson, DR, Orr, MCM, Hawryluk, M, et al. Biological and clinical evidence for somatic mutations in BRCA1 and BRCA2 as predictive markers for olaparib response in high-grade serous ovarian cancers in the maintenance setting. Oncotarget, Vol. 8, (No. 27), pp. 43653-43661.

4. What are the **implications for my patient with ovarian cancer** of identifying a germline BRCA mutation?

The implications in relation to personal cancer risk are an increased risk of other cancers, particularly breast cancer. There can also be an increased risk of melanoma, pancreatic and other BRCA related cancers.

As it is an inherited cancer predisposition, there are implications for biological (blood) male and female relatives who may also carry the gene.

A woman with a BRCA1 gene mutation has a lifetime risk (to 80yrs) of breast cancer of up to 90% and a lifetime risk of ovarian cancer of up to 60%. A woman with a BRCA2 mutation has a lifetime risk of breast cancer of up to 85% and a lifetime risk of ovarian cancer of up to 30%. There are other cancers that may arise in individuals with variants (mutations) in these genes but the lifetime risk of developing these is much lower [3].

The measures that can be taken to reduce these risks include prophylactic surgery (bilateral mastectomy and/or bilateral salpingo-oophorectomy (surgery to remove fallopian tubes and ovaries). Breast surveillance with MRI +/- mammography is recommended for women with a BRCA mutation who have not had prophylactic surgery. There is currently no recommended ovarian surveillance.

With your patient's agreement referral to genetic services (enclosing a copy of the genetic result) is recommended, and the effect of a BRCA mutation on personal cancer risk and the approach to informing relatives would be addressed in more detail at the cancer genetics consultation.

5. What are the **implications for my patient's family** of finding a germline BRCA mutation and how is this managed?

If your patient is found to have a germline BRCA mutation, then it is likely that this has been inherited and that biological (blood) relatives – both males and females, could also carry the BRCA variant (mutation) and be at risk of BRCA associated cancers (including those referred to above and male breast and prostate cancer). Those currently unaffected by cancer could still harbour the BRCA variant (mutation).

During the consent process, sharing results with family members will have been discussed and recorded, (most patients are happy to do so). The patient should be reminded of this when results are communicated. The patient should firstly share the genetic BRCA test result with her first degree relatives (parents, siblings, children), given the implications this may have for both male and female

[3]. https://d1ijoxngr27nfi.cloudfront.net/research-divisions/protocol-3-brca-mutation-carrier-20150209-v4.pdf?sfvrsn=5e7f6f69_2

relatives who may wish to be tested. Typically, during her consultation with the clinical genetics service, disclosure to relatives will be discussed and the patient may be given a 'to whom it may concern' letter that she may use to disseminate the information to her first degree relatives if she prefers.

The patient's relatives should **not** be offered testing through the olaparib testing pathway and should be offered genetic counselling by the Cancer Genetics Service in advance of testing. This testing of unaffected relatives is known as predictive or cascade screening and must be preceded by genetic counselling by a qualified genetic counsellor or genetic consultant.

6. What are the **implications for my patient and their family** of identifying a tumour BRCA mutation?

A patient with a tumour BRCA mutation is more likely to respond to PARP inhibitor therapy and is eligible for maintenance treatment with olaparib.

Both a germline and tumour BRCA test are required to determine that the mutation is a tumour mutation only.

If the mutation is found solely in the patient's tumour, then it is unlikely to be inherited. As such, tumour mutations are unlikely to confer any additional cancer risk to either the individual or to their families. The additional risks are conferred with a germline mutation.

7. What are the **issues I should discuss** with my patient as part of the informed consent process?

In summary, the following issues should be discussed: the purpose of the tests in relation to their choice of treatment; the possibility that they may be found to have an inherited cancer predisposition and if so, that it could have been inherited by other family members also; the protections offered by Irish law in relation to use of genetic results; the possibility that a test may be inconclusive.

- The purpose of the tests is to check for a germline or tumour mutation in BRCA genes, which would predict likelihood of response to olaparib.
- Patients should be told the test may yield six possible results:

    1. A germline BRCA mutation is identified
    2. A tumour BRCA mutation is identified
    3. A germline and tumour BRCA mutation is identified
    4. A germline 'variant of uncertain (or unknown) significance' (VUS) identified
    5. A germline 'variant of uncertain significance' (VUS) plus tumour BRCA mutation identified
    6. No germline or tumour mutations are identified

Note: Tumour BRCA mutation is identified and germline status is not determined

- There may still be a genetic explanation for your patient's cancer as they could have a mutation in a gene not tested for or unknown at this time and there may be circumstances that would warrant referral to genetic services.
- Discuss the benefits, risks, implications and limitations of the test e.g test sensitivity and specificity and impact on blood relatives.
- Discuss consent that the genetic test may be used for the benefit of other family members and made available for use in genetic counselling of other family members attending genetic centres, if requested.
- Discuss consent to communicate the genetic result to the GP and/or other healthcare professionals involved in the patient's care.
- Discuss consent that DNA may be stored indefinitely at the testing laboratory and/or other testing centres.
- Discuss consent that the DNA may be used confidentially for quality assurance purposes.
- Under the provisions of Part 4 of the Disability Act 2005, an insurer cannot request, take into account or process the results of genetic tests.

8. Is **written consent** required?

Yes, written consent is a requirement for genetic testing. Evidence of written consent must accompany the blood and tissue samples and is therefore incorporated into the order request forms for germline and tumour BRCA testing. A copy of the test request-consent forms should also be held locally in the patient's medical record.

9. What **patient information** materials are available for my patient?

A patient information leaflet for BRCA testing via this pathway is available on the NCCP website www.hse.ie/nccpchemoregimens or direct link here. This should be provided to all patients offered the test.

10. Who will give my patient **the results**?

The result will be emailed to you, the ordering clinician, at the email address you provide on the test request form. You should explain the result to the patient, its implications for olaparib eligibility, and recommendation for referral to the Cancer Genetics Service if indicated.

Patients with an identified germline mutation, or a germline 'variant of uncertain significance', (VUS), should be referred with the patient's agreement to the cancer genetics service, where they will be prioritised for review. Those in whom no germline mutation is found should still be offered a referral to the genetics service if there is a separate indication e.g. a patient with multiple primary cancers, young age of cancer onset or a strong family history such as a number of first degree relatives with breast/ovarian or bowel cancer.

11. Who else will have access to the result?

The germline test result (including if no mutation has been found) can be used by genetics health care professionals dealing with their relatives, if the patient has consented to this. This is therefore included in the test request-consent form.

12. Can the test result be **inconclusive**? What are the implications of an inconclusive result?

Yes, it is possible that a germline 'variant of uncertain significance' (VUS) is identified, meaning the implication of the mutation in their BRCA gene is unclear. In this case the patient is not eligible for olaparib. The patient should be offered a referral to the Cancer Genetics Service to discuss their result.

It is also possible that the tumour BRCA mutation test fails, either owing to insufficient quantity/quality of tumour DNA, or failure to meet the test's quality control criteria. In this case, full germline BRCA mutation sequencing can be performed to assess for germline BRCA mutations only.

13. What are the implications of a finding of **no BRCA mutation** in my patient?

If no mutation has been identified either germline or tumour, the patient is not eligible for olaparib. Referral to the genetics service should only be made if there is a separate indication e.g. a patient with multiple primary cancers, young age of cancer onset or a strong family history such as a number of first degree relatives with breast/ovarian or bowel cancer.

14. Are there **other cancer predisposition genes** I should consider in my patient?

If a patient has multiple primary cancers, young age of cancer onset or a strong family history such as a number of first degree relatives with breast/ovarian or bowel cancer, they should be referred to the genetics service for a more detailed risk assessment and possible further genetic testing. These additional test results would not affect choice of systemic therapy for their ovarian cancer.

If you need to discuss a patient, please contact the Cancer Genetics Services, St. James's Hospital, Dublin 8, Tel:- 01-4103759