PROCEDURE FOR THE ORDERING OF INHERITED (GERMLINE) AND TUMOUR (SOMATIC) BRCA GENE MUTATION TESTING BY MEDICAL ONCOLOGISTS TO INFORM DECISION TO USE THE PARP INHIBITOR OLAPARIB IN SELECTED PATIENTS

Background

Olaparib is a PARP inhibitor which is approved for reimbursement for;

- maintenance therapy in patients with advanced (FIGO stages III and IV) BRCA1/2-mutated high grade epithelial ovarian, primary peritoneal or fallopian tube cancer who are in response (complete or partial) following completion of first-line platinum based chemotherapy
- maintenance therapy in patients with a diagnosis of serous epithelial ovarian, primary peritoneal or fallopian tube cancer, and a germline or somatic BRCA (refers to BRCA 1 & BRCA 2) mutation, provided they have responded to a platinum-based therapy post relapse.

Direct ordering of germline BRCA genetic tests was introduced in 2017 for Consultant Medical Oncologists for a specific group of patients, to determine their likelihood of responding to olaparib therapy. Tumour testing for BRCA mutations was introduced in October 2020.

Note: These pathways are confined to those patients meeting the current license and reimbursement criteria for olaparib therapy. They cannot be used for research purposes or to inform potential new treatment indications in the future e.g. in patients with breast cancer. All other patients where genetic testing is under consideration should be referred through existing pathways to the Cancer Genetics Service for assessment and counselling prior to testing.

Those eligible for testing under these pathways:

- Have a diagnosis of;
    - advanced (FIGO stages III and IV) high grade epithelial ovarian, primary peritoneal or fallopian tube cancer and are commencing first-line platinum based chemotherapy
    - high grade serous epithelial ovarian cancer (HGSC), 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
- Have no known contraindication to the use of olaparib as maintenance therapy
- Patients with a known BRCA (somatic or germline) mutation need not be referred for additional mutation testing
- Patients who have previously undergone full germline BRCA mutation screening* without detection of a pathogenic or likely pathogenic germline variant will not benefit from additional germline analysis and should be considered for tumour BRCA testing
- Patients who have previously undergone full germline BRCA mutation screening* and tumour analysis should not require additional testing

*Predictive BRCA testing is only used to exclude specific familial variants and is not equivalent to full BRCA mutation screening

Patients must be deemed eligible by their clinician and testing must follow the pathway as outlined in this document.

First Line Maintenance Treatment

If clinically indicated, olaparib should be commenced as maintenance treatment within eight weeks of completion of platinum-based therapy (See NCCP national chemotherapy regimens for ovarian cancer).

- Note; Where debulking surgery is required, the last dose of platinum chemotherapy should be within 12 weeks of starting olaparib maintenance

Given the test turnaround time of up to 6[1] weeks, germline BRCA1/2 testing should be offered to potentially eligible patients at the time of commencement of first line platinum treatment.

Platinum Sensitive Relapsed Maintenance treatment

If clinically indicated, olaparib should be commenced as maintenance treatment within eight weeks of completion of a second line course of platinum-based therapy (See NCCP national chemotherapy regimens for ovarian cancer). Given the test turnaround time of up to 6[1] weeks, germline BRCA1/2 testing should be offered to potentially eligible patients at the time of relapse following first line platinum treatment and treatment planning for the second or subsequent line of platinum treatment.

Patient information and consent

The indication for testing is to determine likely response to olaparib therapy. However, the identification of a germline BRCA mutation has significant other implications for the patient and their relatives, which should be discussed by the medical oncologist with the patient in advance of testing. Information materials to assist in this discussion are provided on the NCCP website.

Written consent is required for genetic testing and a copy must accompany the test requests. A combined test request/consent form is provided for both germline and tumour BRCA testing. A copy of

[1] 90% of test results within this turnaround time of 6 weeks

the consent should also be held in the patient's records locally. The result of a germline BRCA test is extremely useful in any future genetic counselling of family members. The consent form therefore includes the option to consent to future sharing of the test result for this purpose[2].

Note that it is standard practice for extracted DNA to be stored in the laboratory. This facilitates any future testing, which is only carried out with the consent of the patient or next of kin.

Test request

A genetic test request and consent form specific for this purpose is provided by the testing laboratory and should be completed using BLOCK CAPITALS. These have been pre-populated with information relevant to this indication. Please ensure that it is applicable to your patient and insert any additional relevant clinical details.

A valid hospital email address of a Consultant & CNS/Secretary must be provided for return of germline test results (ensure email address is from a healthmail connected agency[3] e.g. HSE email address). Please provide two such email addresses on the order form.

Samples must meet minimum sample identification requirements to be accepted for genetic testing. These identification requirements are: a) patient's forename & surname and date of birth or medical record number and b) these identifiers must be present on the sample tube and the genetic test request form and must match exactly.

Germline BRCA testing

The sample required is 3-5ml of venous blood in EDTA anticoagulant. This should be sent at room temperature by post (or courier) to Beaumont Hospital Molecular Pathology Laboratory, Beaumont Hospital, Dublin 9, D09 V2N0 or to Cancer Molecular Diagnostics Laboratory, St James's Hospital, James's Street, Dublin 8, D08 RX0X. Please refrigerate the sample if there will be more than a 24 hour delay before posting. Do not freeze the sample.

[2] Appropriately qualified Senior Health Care Professional to consent patient.

[3] All public and voluntary hospitals and some private hospital emails are connected securely to healthmail. To check if a particular institution is healthmail connected, please go to: https://www.ehealthireland.ie/A2I-HIDs-Programme/Healthmail. Note that personal email accounts or those related to academic postings are not connected to healthmail and should not be used for return of results.

Any queries regarding the sample, sample identification requirements or transport should be directed to biomarkers@beaumont.ie / 01-809 3726 or cmd@stjames.ie/ 01-4163575/3576.

Tumour BRCA testing

The samples required are ovarian cancer tissue block/slides from the patient's previous biopsy or surgery. These samples are stored in the hospital's pathology laboratory archive. The block must be well selected with an approximate neoplastic cell content of ideally >50% and representative H&E included. This should be sent at room temperature with a copy of the block(s) histopathology report within 5 working days of patient registration by courier to Beaumont Hospital Molecualr Pathology Laboratory, Beaumont Hospital, Dublin 9, D09 V2N0 or to Cancer Molecular Diagnostics (CMD), St James's Hospital, James's Street, Dublin 8, D08 RX0X.

Any queries regarding the sample, sample identification requirements or transport should be directed to biomarkers@beaumont.ie /01-8093726 or cmd@stjames.ie /01-416 3575/3576.

Results

An integrated report detailing the findings for both germline and tissue samples (where relevant) will be prepared by the testing laboratory and forwarded to the requesting clinician as indicated on the request form.

Treatment and follow up

Olaparib treatment is indicated only where there is a recognised pathogenic mutation identified in the BRCA genes. The treatment decision rests with the treating medical oncologist and will depend on other issues including response to platinum therapy[4].

If a germline 'variant of uncertain significance' (VUS) is identified, the patient is not eligible for olaparib. However, the patient should still be offered a referral to the Cancer Genetics Service to discuss their result.

[4] See www.hse.ie/nccpchemoregimens or direct link to olaparib regimens and BRCA testing materials here

If no mutation has been identified either germline or tumour, the patient is not eligible for olaparib. A referral to genetics services should be considered if you have concerns such as, a patient with young age of onset, a patient with multiple primary cancers or a strong family history of cancer, such as a number of first degree relatives with breast/ovarian or bowel cancer.

	Results	**Olaparib treatment**	**Offer genetics referral**
1.	Germline BRCA mutation identified only	Eligible	Yes
2.	Tumour BRCA mutation identified only	Eligible	No
3.	Both germline and tumour BRCA mutation identified	Eligible	Yes
4.	Germline 'variant of uncertain (or unknown) significance' (VUS) identified	Not eligible	Yes
5.	Germline 'variant of uncertain significance' (VUS) plus tumour BRCA mutation identified	Eligible	Yes
6.	No mutation identified	Not eligible	If a strong family history

With the patient's agreement, a referral should be made to the Cancer Genetics Service, to discuss the implications of the results for the patient and their family.
Patients with a tumour BRCA mutation who have declined germline testing should be offered a referral to Cancer Genetics Services as they may still have a hereditary cancer.

Resources

The following resource materials are available on the NCCP website at www.hse.ie/nccpchemoregimens or direct link here[5].

- Patient information leaflet
- Test request process document, full version & summary version
- Olaparib treatment chemotherapy regimens
- BRCA testing – Frequently asked questions for non-genetics healthcare professionals
- Link to BRCA genetic test request-consent form available from testing laboratories

If you have any difficulty accessing these materials, contact the NCCP at 01 8287100 or oncologydrugs@cancercontrol.ie

[5] http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/BRCA%20testing%20for%20olaparib.html

Referrals to clinical cancer genetics

Cancer genetics referrals can be sent to

- Cancer Genetics Service, St James's Hospital, Dublin 8, Tel 01 4103759 http://www.stjames.ie/Departments/DepartmentsA-Z/C/CancerGenetics/DepartmentOverview/

If you have any queries or feedback on this document, please email oncologydrugs@cancercontrol.ie