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

Background

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

- The treatment of adult patients with germline BRCA1/2- mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy

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. Direct ordering of germline BRCA testing has now been introduced for talazoparib in a specific cohort of breast cancer patients as per the above indication.

Note: These pathways are confined to those patients meeting the current license and reimbursement criteria for olaparib and talazoparib therapies only. They cannot be used for research purposes or to inform potential new treatment indications in the future e.g. in patients with prostate 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.

This document refers specifically to the direct ordering of germline BRCA tests to support prescribing of talazoparib. Resource materials to support the direct ordering BRCA testing pathway for talazoparib prescribing are available here[1]

[1] https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/brca%20testing%20for%20parp%20inhibitors.html

Those eligible for testing under this pathway:

- Have a diagnosis of;
    - HER2-negative locally advanced or metastatic breast cancer and should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless unsuitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy
- Have no known contraindication to the use of talazoparib therapy
- 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

*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.

Patient information and consent

The indication for testing is to determine likely response to talazoparib 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 germline BRCA testing. A copy of 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.

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

Test request

A genetic test request and consent form 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.

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.

Results

A report detailing the findings for the germline sample will be prepared by the testing laboratory and forwarded to the requesting clinician as indicated on the request form.

[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.

Treatment and follow up

Talazoparib treatment is indicated only where there is a germline mutation identified in the BRCA genes. The treatment decision rests with the treating medical oncologist. If no germline mutation has been identified, the patient is not eligible for talazoparib.

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

A referral to genetics services should be considered if you have concerns for inherited predisposition to cancer on the basis of the patient or family characteristics such as, a patient with young age of onset, a patient with multiple primary cancers or a strong family history of cancer, such as male breast cancer, or a number of first degree relatives with breast/ovarian and /or pancreatic cancer.

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.

	Results	**Talazoparib treatment**	**Offer genetics referral**
1.	Germline BRCA mutation identified	Eligible	Yes
2.	Germline 'variant of uncertain (or unknown) significance' (VUS) identified	Not eligible	Yes
3.	No germline BRCA mutation identified	Not eligible	If a strong family history

Resources

The following resource materials are available on the NCCP website at www.hse.ie/nccpchemoregimens or direct link here[4]

- Patient information leaflet
- Test request process document, full version & summary version
- Talazoparib treatment chemotherapy regimen
- 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

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

[4] https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/brca%20testing%20for%20parp%20inhibitors.html