# GUIDANCE FOR MEDICAL ONCOLOGISTS ON TESTING REQUIREMENTS BY DIRECT ORDERING TO INFORM PARPi TREATMENT OPTIONS

| VERSION | DATE PUBLISHED | AMENDMENT | APPROVED BY |
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| 1 | 04/09/2023 | | NCCP Molecular Diagnostics Advisory Group |
| 2 | 01/11/2023 | Updated to include Niraparib/Abiraterone (Akeega) indication in mCRPC | NCCP |
| 3 | 29/11/2023 | Inclusion of reference to PARPi indications not requiring testing | NCCP Molecular Diagnostics Advisory Group |

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## Note on HRD Terminology

The terminology Homologous Recombination Deficient (HR Deficient) and Homologous Recombinant Proficient (HR proficient) is used in this document.
Note : The terminology used in the drug indication licensed by the European Medicines Agency is homologous recombination deficiency (HRD) positive which is synonymous with Homologous Recombination Deficient (HR deficient ) in this document.
Homologous Recombinant Proficient (HR proficient) therefore indicates that the tumour is homologous recombination deficiency (HRD) negative.

## 1. Background

Direct order of germline BRCA testing was introduced by the NCCP in 2017 for Consultant Medical Oncologists for a specific group of patients to allow timely access to testing to help inform treatment decisions with PARP inhibitors (PARPi). Testing was expanded to include tumour BRCA and HRD testing in subsequent years. These direct ordering pathways may be reviewed once mainstreaming of cancer genetic testing as defined in the Hereditary Model of Care[1] has been implemented.

A number of PARPi are approved for reimbursement by the HSE which require testing to determine eligibility for treatment. These indications are detailed in Table 1 below. To note there are some PARPi indications approved for reimbursement by the HSE which do not require testing to determine eligibility for treatment and these are detailed in Table 2.

**Table 1: PARPi Indications approved for reimbursement by the HSE requiring testing (01/11/2023)**

| | Drug | Tumour | Indication | Reimbursement Date |
|---|---|---|---|---|
| 1 | Olaparib | Ovarian | As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy | 01/11/2017 |
| 2 | Olaparib | | As monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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 | 01/12/2020 |
| 3 | Olaparib | | In combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability | 01/09/2023 |
| 4 | Olaparib | Prostate | As monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA 1/2 mutations (germline and/or somatic) who have progressed following prior hormonal therapy that included a new hormonal agent | 01/03/2023 |

[1] NCCP Hereditary Cancer Model of Care available April 2023. Available here

| | | | | |
|---|---|---|---|---|
| 5 | Nirarparib plus Abiraterone Acetate (Akeega™) | Prostate | Niraparib in combination with abiraterone acetate and prednisone/prednisolone for the treatment of adults with metastatic castration resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated | 01/11 2023 |
| 6 | Talazoparib | Breast | As monotherapy 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. | 01/05/2021 |

- **Table 2: PARPi Indications approved for reimbursement by the HSE NOT requiring testing (01/11/2023)**

| | Drug | Tumour | Indication | Reimbursement Date |
|---|---|---|---|---|
| 1 | Niraparib | Ovarian | As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy | 01/03/2021 |
| 2 | Niraparib | | As monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) 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 | 01/04/2023 |

- Patients who have previously undergone germline BRCA variant screening without detection of a pathogenic or likely pathogenic germline variant will not benefit from repeat germline analysis and should be considered for tumour BRCA testing and HRD testing only as relevant to the indication being considered for treatment.
- Patients with ovarian cancer who have previously undergone germline BRCA variant screening and tumour analysis without detection of a pathogenic or likely pathogenic germline or tumour variant should only require HRD testing.
- All other patients where genetic testing for identification of cancer predisposition is under consideration should be referred through existing pathways to the Cancer Genetics Service.

## 2. Testing pathways to support prescribing of PARP inhibitors

Tables 3a -3c below detail the testing required in breast, ovarian and prostate cancer to determine eligibility for PARPi in line with HSE reimbursed indications.

**Table 3a: Breast Cancer PARPi Testing Requirements**

| Tumour | Indication | Considerations | Testing required | Available Testing Laboratories in Ireland |
|---|---|---|---|---|
| **Breast** | Talazoparib as monotherapy for 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 | • Intention to treat with talazoparib<br>• Meet eligibility criteria of NCCP National SACT regimen here<br>• Have not had a positive pathogenic BRCA 1/2 germline test result previously | **germline BRCA testing** | SJH/Beaumont |

**Table 3b : Ovarian Cancer PARPi Testing Requirements**

| Tumour | Indication | Considerations | Testing required | Available Testing Laboratories in Ireland |
|---|---|---|---|---|
| **Ovarian** | Olaparib as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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 | • Intention to treat with platinum chemotherapy<br>• Meet eligibility criteria of NCCP National SACT regimens here<br>• Have not had a positive pathogenic BRCA 1/2 (somatic or germline) or HR deficient HRD test result previously | **tumour BRCA and HRD testing**<br>Where a tBRCA test fails (due to sample) consideration can be given to direct ordering gBRCA testing by the medical oncologist in line with this guidance. | Interim out of country outsourcing<br>Expected SJH/Beaumont end q4 2023 TBC |
| | Olaparib in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability | | | |
| **Ovarian** | Olaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy | • Intention to treat with platinum chemotherapy<br>• Meet eligibility criteria of NCCP National SACT regimens here<br>• Have not had a positive pathogenic BRCA 1/2 (somatic or germline | **tumour BRCA testing**<br>Where a tBRCA test fails (due to sample) consideration can be given to direct ordering gBRCA testing by the medical oncologist in line with this guidance. | SJH/Beaumont |

**Table 3c : Prostate Cancer PARPi Testing requirements**

| Tumour | Indication | Considerations | Testing required | Available Testing Laboratories in Ireland |
|---|---|---|---|---|
| **Prostate** | Olaparib as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA 1/2 mutations (germline and/or somatic) who have progressed following prior hormonal therapy that included a new hormonal agent | • Intention to treat with olaparib or Niraparib in combination with abiraterone (Akeega)<br>• Meet eligibility criteria of NCCP National SACT regimen here<br>• Have not had a positive pathogenic BRCA 1/2 (somatic or germline) test result previously | **•tumour BRCA and MLPA testing**<br>**•Reflex germline BRCA testing of patients who test positive for tumour BRCA**<br>o Where a suitable tumour sample is not available for testing the patient can be offered gBRCA testing[1]<br>Or<br>o Where a tBRCA test fails (due to sample) reflex gBRCA testing[1] may be carried out and the case will be referred back to the prescribing Consultant Medical Oncologist to determine next steps | SJH/Beaumont |
| **Prostate** | Niraparib in combination with abiraterone acetate and prednisone/prednisolone for the treatment of adults with metastatic castration resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated | | | |

[1] In line with consent given

## 3. Patient information and consent

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

Topics for discussion with the patient with regard to the test request form may include

- The requirement for written consent. Written consent is required in the case of germline BRCA testing.
  - Some test request forms may be a combined test request/consent form where both germline and tumour BRCA testing is required.
- A copy of the written consent will be held in the patient's records locally and may also be sent with the test request depending on the laboratory doing the test.
- An option on the test request form to consent to future sharing of the test results. This is for the purpose of future genetic counselling of family members[2] .
- Information on the test request form with regard to the 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.

A Patient Information Leaflet on Testing to inform PARP inhibitor treatment in cancer is available here

## 4. Test request

### 4.1 Best Practice for Test Request Forms

In line with best practice;

- The test request form should be completed using BLOCK CAPITALS.
- A valid hospital email address of a Consultant & CNS/Secretary should be provided for return of germline test results (for security please ensure the email address is from a healthmail connected agency[3] e.g. HSE email address).
- It is recommended that two different contact email addresses are provided on the order form to ensure continuity of care in the event of leave etc.
- Samples must meet minimum sample identification requirements to be accepted for testing.
  - The minimum identification requirements are:

[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.

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.

**4.2 Germline BRCA testing Sample requirement**

Sample requirements parameters should be confirmed with the laboratory providing the testing service. Currently in country direct ordering germline testing for BRCA 1/2 is available from St James's Hospital and Beaumont Hospital. Their current requirements for such samples are:

- 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
- The sample should be refrigerated if there will be more than a 24 hour delay before posting
- Do not freeze the sample

**4.3 HRD and/or Tumour BRCA testing Sample requirement**

Sample requirements parameters should be confirmed with the laboratory providing the testing service for tBRCA and HRD testing which is expected to be out of country initially.
Once the testing is established in St James's Hospital and Beaumont Hospital a test request form specific for this purpose will be provided by the testing laboratory and their requirements for such samples are:

- Prostate or ovarian cancer tissue block/slides from the patient's previous biopsy or surgery.
    - These samples will be stored in the hospital's pathology laboratory
- For the test to be successful 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 Molecular 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 the testing laboratory biomarkers@beaumont.ie /01-8093726 or cmd@stjames.ie /01-416 3575/3576.

## 5. Results

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

Where HRD testing has been carried out the report will also provide details on the type of HRD assay used and cut-off points for determining HRD status.

## 6. Treatment and follow up

The treatment decision rests with the treating medical oncologist, in discussion with the patient, and will depend on the test results, the indication and other factors e.g. response to platinum therapy in patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. Tables 3a-c below detail the patients eligible for PARPi therapy for HSE reimbursed indications and incorporate recommendations on referral to cancer genetics services as outlined in Section 7 below.

## 7. Referral to Cancer Genetics Services

The tables 3a-3c below detail the possible test results from the testing required in breast, ovarian and prostate cancer and recommendations on referral to Cancer Genetics Services for follow up. In summary the following patients should be offered a referral to cancer genetics services.

1. Patients where a germline pathogenic BRCA variant or germline VUS is identified
2. Patients where a tumour BRCA pathogenic variant is identified and no germline BRCA testing results are available
3. Patients who are HR deficient
4. Patients with a strong family history who are HR proficient or no tumour BRCA or germline BRCA pathogenic variants have been identified

   i.e. 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 irrespective of the results of germline or tumour BRCA or HRD testing.

Cancer genetics referrals can be sent to

- Cancer Genetics Service, St James's Hospital, Dublin 8, Tel 01 4103759
  https://www.stjames.ie/services/hope/cancergeneticsservice/

**Note : All referrals to Cancer Genetics Services should include a copy of the BRCA testing and HRD testing (where available) results and a copy of the pathology report.**

**Table 4a: BREAST CANCER: Possible Germline BRCA testing results and Referral to Cancer Genetics Services**

| Tumour | Indication | Testing required | Results | Parp Inhibitor Treatment | Offer Genetics referral |
|---|---|---|---|---|---|
| **Breast** | 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 | **germline BRCA testing** | Germline BRCA pathogenic variant identified | Eligible | Yes |
| | | | Germline 'variant of uncertain (or unknown) significance '(VUS) identified | Not eligible | Yes |
| | | | No germline BRCA pathogenic variant identified | Not eligible | If a strong family history |

**Table 4b: OVARIAN Cancer: Possible tumour BRCA and HRD testing results and Referral to Cancer Genetics Services**

| Indication | Testing required | Results | Olaparib Treatment | Olaparib and Bevacizumab treatment | Offer Genetics referral |
|---|---|---|---|---|---|
| Olaparib as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) 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 | **tumour BRCA and HRD testing** Where a tBRCA test fails (due to sample) consideration can be given to direct ordering gBRCA testing by the medical oncologist in line with this guidance. | HR deficient and tumour BRCA pathogenic variant identified | Eligible | Eligible | Yes |
| Olaparib in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability | | HR deficient and tumour BRCA 'variant of uncertain (or unknown) significance' (VUS) identified | Not eligible | Eligible | Yes |
| | | HR deficient and no tumour BRCA pathogenic variant identified | Not eligible | Eligible | Yes |
| | | HR proficient and no tumour BRCA pathogenic variant identified | Not eligible | Not eligible | If a strong family history |
| Olaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy | **tumour BRCA testing** Where a tBRCA test fails (due to sample) consideration can be given to direct ordering gBRCA testing by the medical oncologist in line with this guidance. | tumour BRCA pathogenic variant identified | Eligible | n/a | Yes |
| | | Tumour BRCA 'variant of uncertain (or unknown) significance' (VUS) identified variant identified | Not eligible | n/a | No |
| | | No tumour BRCA pathogenic variant identified | Not eligible | n/a | If a strong family history |

**Table 4c: PROSTATE Cancer: Possible tumour BRCA and germline BRCA testing results and Referral to Cancer Genetics Services**

| Tumour | Indication | Testing pathway | Results | Parp Inhibitor Treatment | Offer Genetics referral |
|---|---|---|---|---|---|
| **Prostate** | Olaparib as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA 1/2 mutations (germline and/or somatic) who have progressed following prior hormonal therapy that included a new hormonal agent<br><br>Niraparib in combination with abiraterone acetate and prednisone/prednisolone for the treatment of adults with metastatic castration resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated | **•tumour BRCA and MLPA testing**<br>**•Reflex germline BRCA testing of patients who test positive for tumour BRCA**<br>o Where a suitable tumour sample is not available for testing the patient can be offered gBRCA testing[1]<br>Or<br>o Where a tBRCA test fails (due to sample) reflex gBRCA testing[1] may be carried out and the case will be referred back to the prescribing Consultant Medical Oncologist to determine next steps | Germline BRCA pathogenic variant identified only | Eligible | Yes |
| | | | Tumour BRCA pathogenic variant identified only | Eligible | No |
| | | | Both germline and tumour BRCA pathogenic variant identified | Eligible | Yes |
| | | | Germline 'variant of uncertain (or unknown) significance' (VUS) identified | Not eligible | Yes |
| | | | Tumour BRCA 'variant of uncertain (or unknown) significance' (VUS) identified | Not eligible | No |
| | | | No pathogenic variant identified | Not eligible | If a strong family history |

[1] In line with consent given

## 8. Resources

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

- Test request process document, full version
- Olaparib and Talazoparib Systemic anti-cancer therapy (SACT) regimens
- Patient Information Leaflet on Testing to inform PARP inhibitor treatment in cancer

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

***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/testing%20to%20inform%20parp%20inhibitor%20cancer%20treatment%20.html