GUIDANCE FOR MEDICAL ONCOLOGISTS ON TESTING REQUIREMENTS

BY DIRECT ORDERING TO INFORM PARPi TREATMENT OPTIONS

Version	Date	Amendment	Approved By
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
4	20/05/2024	Updated Prostate tissue BRCA testing sample requirement	NCCP Molecular Diagnostics Advisory Group
5	31/07/2024	Updated HRD testing locations	NCCP
6	11/04/2025	Updated to include Olaparib indication in eBC and pancreatic cancer. Updated testing pathway in prostate cancer All updates highlighted in yellow	NCCP Molecular Diagnostics Advisory Group

Table of Contents

List of Tables

1.0 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 (10/04/2025)

	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

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

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
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
7	Olaparib	Breast	Monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.	01/05/2025
8	Olaparib	Pancreas	As monotherapy for the maintenance treatment of adult patients with germline BRCA1 /2 mutations who have metastatic adenocarcinoma of the pancreast and have not progressed after a minimum of 16 weeks of platinum treatment within a first line chemotherapy regimen	01/05/2025

Table 2: PARPi Indications approved for reimbursement by the HSE NOT requiring testing (10/04/2025)

	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

2.0 Testing pathways to support prescribing of PARP inhibitors

Tables 3a -3d below detail the testing required in breast, ovarian, prostate and pancreatic 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	Monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.	• Intention to treat with olaparib • Meet eligibility criteria of NCCP National SACT regimen here • Have not had a positive pathogenic BRCA 1/2 germline test result previously	**germline BRCA testing**	SJH/Beaumont
	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 • Meet eligibility criteria of NCCP National SACT regimen here • 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
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 • Meet eligibility criteria of NCCP National SACT regimens here • Have not had a positive pathogenic BRCA 1/2 (somatic or germline) or HR deficient HRD test result previously	**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.	SJH/Beaumont
	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 • Meet eligibility criteria of NCCP National SACT regimens here • Have not had a positive pathogenic BRCA 1/2 (somatic or germline) test result previously	**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.	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	• Metastatic prostate cancer being considered for treatment • Have not had a positive pathogenic BRCA 1/2 (somatic or germline) test result previously	**•tumour BRCA and MLPA testing** **•Reflex germline BRCA testing of patients who test positive for tumour BRCA** o Where a suitable tumour sample is not available for testing the patient can be offered gBRCA testing[1] Or 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

Table 3d : Pancreatic Cancer PARPi Testing requirements

Tumour	Indication	Considerations	Testing required	Available Testing Laboratories in Ireland
Pancreas	Olaparib as monotherapy for the maintenance treatment of adult patients with germline BRCA1 /2 mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first line chemotherapy regimen	• Metastatic pancreatic cancer being considered for treatment with platinum chemotherapy • Meet eligibility criteria of NCCP National SACT regimen here • Have not had a positive pathogenic germline BRCA 1/2 test result previously	• **germline BRCA testing**	SJH/Beaumont

3.0 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

4.0 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).

[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/ehealth-functions/access-to-

- 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:

        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 or Ovarian Tumour BRCA testing Sample requirement

Sample requirements parameters should be confirmed with the laboratory providing the testing service for tBRCA and HRD testing.

Testing is established in St James's Hospital and Beaumont Hospital and a test request form specific for this purpose is provided by these laboratories and their requirements for such samples are:

- 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

information-a2i/healthmail1/ . 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.

4.4 Prostate Tumour BRCA testing Sample requirement

- Testing on archived diagnostic biopsy or resection sample is possible.
- Pathologists should select the optimal core from a prostate biopsy series for tissue BRCA testing in prostate cancer
    - Consideration should be given to the age of the block and the most recent tissue selected if possible.
    - Tissue with the most abundant tumour and highest tumour cellularity is preferred (ideally ≥50%). Samples with a lower neoplastic cell content (20-50%) can be analyzed but are more likely to generate unusable data.

- Where possible the tumour sample and a blood sample for germline testing should be sent together to the testing laboratory

- Where a tumour BRCA test fails a second core from the same biopsy or surgery **should not** be sent for analysis.
    - Engagement with the Consultant Medical Oncologist is recommended to consider next steps
    - Consideration may be given to re-biopsy of the patient depending on the individual patient circumstances which may be aided by imaging to determine area of high tumour content.
        - Where a patient has bone metastatic prostate cancer a weak decalcification method (preferably EDTA) should be used

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.

5.0 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.

6.0 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-d 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.

7.0 Referral to Cancer Genetics

The tables 3a-3d below detail the possible test results from the testing required in breast, ovarian prostate and pancreatic 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/cancer/yourtreatmentandcare/servicesandtreatments/cancergeneticsservice/ (cancergenetics@stjames.ie)

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 HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy .	**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 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** •**Reflex germline BRCA testing of patients who test positive for tumour BRCA** o Where a suitable tumour sample is not available for testing the patient can be offered gBRCA testing[1] Or 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

Table 4d: PANCREATIC Cancer: Possible tumour BRCA and germline BRCA testing results and Referral to Cancer Genetics Services

Tumour	Indication	Testing required	Results	Parp Inhibitor Treatment	Offer Genetics referral
Pancreas	As monotherapy for the maintenance treatment of adult patients with germline BRCA1 /2 mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first line chemotherapy regimen	**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

8.0 Resources

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

- Niraparib, 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 STP@cancercontrol.ie

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

[4] https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/testing-to-inform-parp-inhibitor-cancer-treatment.html