Germline BRCA1 and BRCA2 Testing in Patients with HER2-negative* locally advanced or metastatic breast cancer *Breast Cancer Eligible to Receive PARP Inhibitors

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1.Objective and Scope

The aim of this document is to provide clinical staff with guidance on the germline BRCA1 and BRCA2 (gBRCA1/gBRCA2) gene testing pathway for patients with HER2-negative, locally advanced or metastatic breast cancer who are potentially eligible for a PARP inhibitor.

2. NICE guidance

Two PARP inhibitors have been recommended by NICE as options for treating in adults HER2-negative, locally advanced or metastatic breast cancer with germline BRCA1 or BRCA2 mutations

Olaparib is an option for patients who have had

- an anthracycline **and** a taxane as neoadjuvant or adjuvant treatment, or for metastatic disease, unless these are not suitable, and
- endocrine therapy if they have hormone receptor (HR)-positive breast cancer, unless this is not suitable.

Talazoparib is an option for patients who have had:

- an anthracycline **or** a taxane, or both, unless these treatments are not suitable, and
- endocrine therapy if they have hormone receptor (HR)-positive breast cancer, unless this is not suitable.

Talazoparib is recommended for use after an anthracycline or a taxane, or both, which is a wider population than the licensed population for olaparib. It is envisaged that talazoparib is used

- for HR-positive, HER2-negative advanced breast cancer with BRCA mutations: second or third line, after first-line CDK4/6 inhibitors and second-line anthracycline **or** taxane-based therapy (if not previously used for early breast cancer)
- for triple negative advanced breast cancer with BRCA mutations: first or second line, after immunotherapy, anthracycline **or** taxane-based therapy (if not previously used for early breast cancer).

Olaparib has not been directly compared with talazoparib in a clinical trial. But an indirect comparison suggests that it is likely to work as well as talazoparib. A cost comparison suggests olaparib has lower costs than talazoparib

3.Eligibility for cancer predisposition gene testing for PARP inhibitor treatment in HER2-negative advanced breast cancer (R444 criteria)

Patients who are potentially eligible based on clinical criteria for a PARP inhibitor are eligible for germline BRCA testing. This is based on The National Genomic Test Directory R444 criteria.

BRCA1, BRCA2 and PALB2 will be tested.

The majority of constitutional pathogenic variants in PALB2 are associated with a high lifetime breast cancer risk as well as an increased risk of other cancers. Identification of a constitutional pathogenic variant in PALB2 is **not**, at the present time, relevant for determining eligibility for PARP inhibitor treatment. However, testing of PALB2 is associated with high clinical utility, given the high associated cancer risks and cost-effective risk-reducing interventions that could be enacted for presymptomatic carrier relatives.

Note: This is a change to the previous strategy in which patients being tested for Olaparib eligibility only, were tested for the R208 panel (BRCA1, BRCA2, PALB2, RAD51C, RAD51D, ATM and CHEK2).

4.Cancer predisposition gene testing based on personal and family history of breast cancer (R208 criteria)

Oncology/surgical oncology healthcare professionals with appropriate training and experience can directly request the germline gene R208 panel (BRCA1, BRCA2, PALB2, RAD51C, RAD51D, ATM and CHEK2) if one of the following criteria are met:

- Triple negative breast cancer diagnosed under 60
- Breast cancer diagnosed under 40
- Bilateral breast cancer diagnosed under 60
- Ashkenazi Jewish ancestry and breast cancer at any age
- Grandparent from Westray (Orkney) or Whalsay (Shetland) and breast cancer at any age
- Assigned male at birth with breast cancer

These criteria form part of the National genomic test directory criteria R208.

5.Patients who meet both R444 and R208 criteria

In patients who meet R444 and R208 criteria, then R208 testing should be performed, which includes all genes relevant to both indications.

Please tick all R444 and R208 criteria that apply on the Breast Oncology genomic request form, to allow AWMGS to perform the appropriate gene panel.

6.Referral to cancer genetics based on personal and family history of cancer

Patients with a personal history of breast cancer can be referred to the All Wales Medical Genomics Service (AWMGS) if one or more of the following criteria are met:

1. Individual with cancer:
    - Breast cancer age < 40 years; or
    - Male breast cancer (any age); or
    - Bilateral breast cancer (any age); or
    - Breast AND ovarian cancer (any age)

2. Individual with breast or ovarian at any age and 1 first degree relative (FDR)* (male or female) with:
    - Breast cancer (any age); or
    - Ovarian cancer (any age); or

*Second degree relative (SDR) - if the intervening relative is male

3. Individual with breast or ovarian at any age and 2 or more FDR or SDR relatives (same side of family) with:
    - Breast and/or ovarian cancer at any age

Referral to clinical genetics may sometimes be appropriate outside of these criteria. Please refer to AWMGS referral criteria or contact the on call genetics team (AWMGS Cancer Genetics Referral Guidelines).

7.Breast Oncology germline gene panel request process

Germline cancer predisposition gene testing is performed by the AWMGS.

All samples for R444 or R208 testing should be accompanied with a Breast Oncology genomic request form.

The request form can be downloaded from the AWMGS website (AWMGS)

Please tick all reasons for testing that apply.

Healthcare professionals are responsible for ensuring appropriate consent has been obtained prior to sample submission.

A recommended consent form to record written consent for germline testing is available from the AWMGS website.

A minimum of 5ml of blood is required to be collected in an EDTA tube.

The current turnaround time for testing is 6 weeks. There is an option to tick an 'expedite' box on the form. Please only tick this when required.

8.All Wales Medical Genomics Service contact details

All Wales Medical Genomics Service

Canolfan Iechyd Genomig Cymru (CIGC)

Cardiff Edge Business Park

Longwood Drive

Whitchurch

Cardiff

CF14 7YU

Telephone: +44(0)2921844023
Fax: +44(0)2921844043
Email: Lab.genetics.cav@wales.nhs.uk

9.Interpreting test results

All reports on germline gene R444/R208 panel will include statements about:

- Whether any germline pathogenic or likely pathogenic variants in cancer predisposition genes were found
- Whether the patient is potentially eligible for PARP inhibitors

Patients with a germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant will potentially be eligible for PARP inhibitors.

Patients with a germline pathogenic or likely pathogenic variant in a cancer predisposition gene will need referral to a clinical genetics service.

Patients without a pathogenic or likely pathogenic variant in a cancer predisposition gene will need referral to clinical genetics service if their personal or family history of cancer meets the AWMGS referral criteria.