Clinical Guidance for *BRCA* Gene Testing for Hormone-Relapsed Metastatic Prostate Cancer

Written by:	Samantha Cox (Consultant Oncologist, Velindre Cancer Centre) John Staffurth (Consultant Oncologist, Velindre Cancer Centre) Sheila Palmer-Smith (Principal Clinical Scientist, All Wales Genomics Service) Diana Matthews (Advanced Oncology Pharmacist, Velindre Cancer Centre)
Reviewed by:	Urology CSG, WCN All Wales Medical Genomics Service
Approved by:	All Wales Genomics Oncology Group (AWGOG)
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Contents

Objective and scope

The aim of this document is to provide clinical staff with guidance on the genetic testing pathway for treatment decision-making in patients with hormone-relapsed metastatic prostate cancer.

The guidance describes the recommended testing pathway to identify patients who may be suitable candidates for olaparib, based on the presence of a pathogenic or likely pathogenic somatic and/or germline *BRCA1* or *BRCA2* variant. Please note within this guideline, the term 'variant' refers to a pathogenic or likely pathogenic variant.

Please note this guideline refers to but does not cover germline *BRCA* gene testing for cases of suspected inherited prostate cancer (see R430 Inherited prostate cancer testing criteria, National Genomic Test Directory Testing Criteria for Rare and Inherited Disease).

This guideline also summarises the prescribing information and recommended baseline investigations and on-treatment monitoring requirements for olaparib.

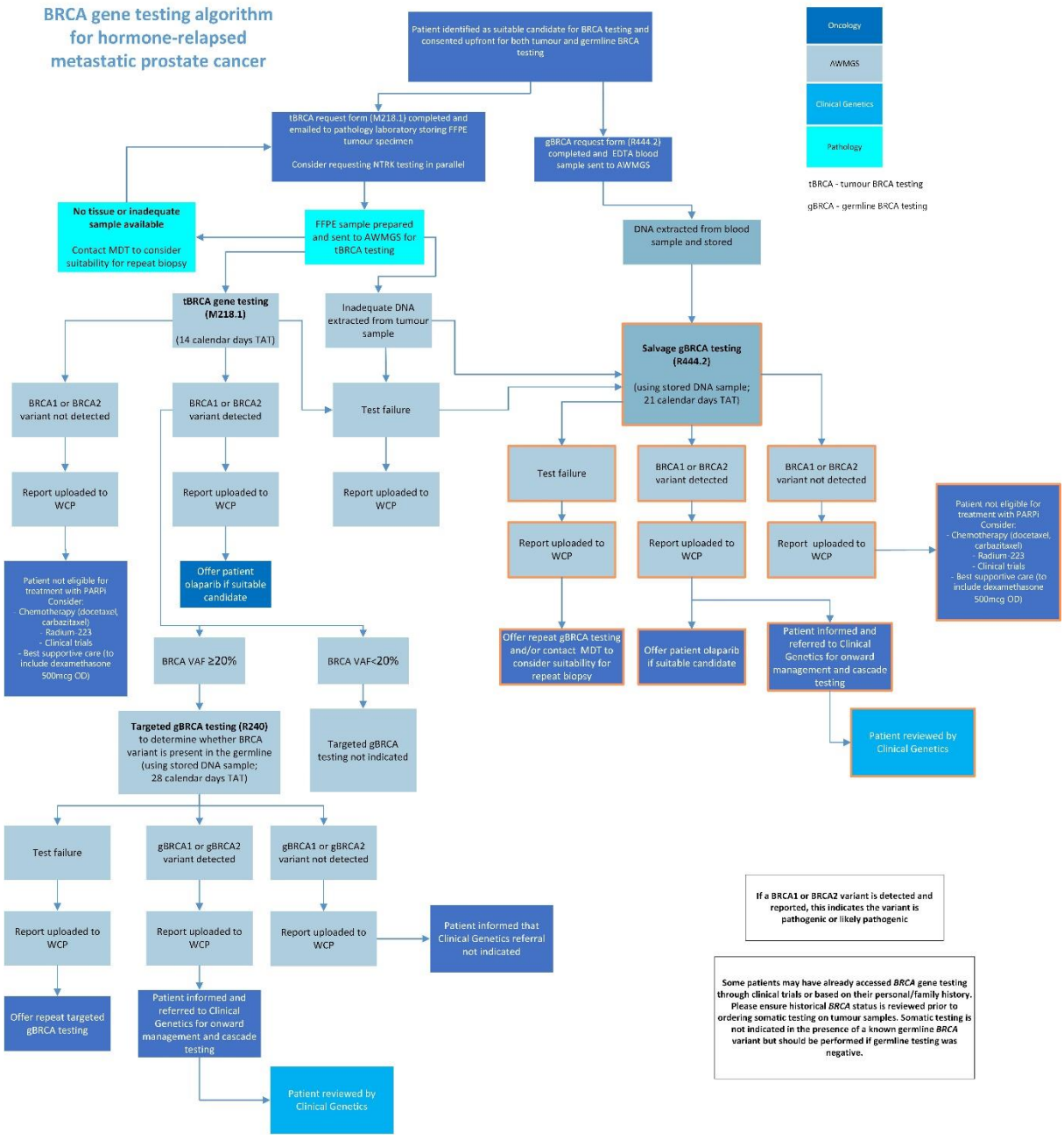
When requesting BRCA testing, the requesting clinician is responsible for ensuring test results are signed off and acted on, in line with the recommendations in this clinical guidance document and the test reports. It is recommended that all oncology centres have an agreed process in place for signing off both the somatic and any germline testing results to guide treatment decision-making and onward referral to Clinical Genetics where necessary.

Abbreviations

ADT	Androgen deprivation therapy
ARTT	Androgen receptor targeting treatment
AWGL	All Wales Genomics Laboratory
AWGOG	All Wales Genomics Oncology Group
AWMGS	All Wales Medical Genomics Service
BRCA	BReast CAncer gene
ct DNA	Circulating DNA (liquid biopsy)
CT TAP	Computed tomography thorax/abdomen/pelvis
DNA	Deoxyribonucleic acid
FFPE	Formalin-fixed paraffin-embedded
HRD	Homologous recombination deficient
HRR	Homologous recombination repair
LHRH	Luteinising hormone releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer
mHSPC	Metastatic hormone-sensitive prostate cancer
NGS	Next Generation Sequencing
nmCRPC	Non metastatic castration-resistant prostate cancer
NTRK	Neurotrophic tyrosine receptor kinase
PARP	Poly (adenosine diphosphate [ADP]-ribose) polymerase

PARPi	Poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor
PSA	Prostate specific antigen
QA	Quality assurance
RNA	Ribonucleic acid
rPFS	Radiological progression free-survival
SOC	Standard of care
TAT	Turnaround time
TRK	Tropomyosin receptor kinase
VAF	Variant allele frequency
WCP	Welsh Clinical Portal

BRCA testing overview flowchart



For clarity the pathway has been split into the 'Core', 'Follow-up' and 'Salvage' sections – see Appendix 3

Background

Prostate cancer is the commonest cancer in men in the UK, with approximately 50,000 men diagnosed annually (The Royal College of Surgeons on England, 2021). 13% of men present with metastatic disease at diagnosis and other men may develop metastatic disease after initial radical therapy. The current initial standard of care (SOC) for metastatic hormone sensitive prostate cancer (mHSPC) is permanent androgen deprivation therapy (ADT); multiple trials have shown an overall survival advantage with the addition of docetaxel chemotherapy and/or androgen receptor targeting treatments (ARTT) such as abiraterone acetate, enzalutamide, darolutamide or apalutamide (STAMPEDE, CHAARTED, LATITUDE, ENZAMET, ARASENS, PEACE-1 etc). Median failure-free survival for men with mHSPC in the abiraterone arm of STAMPEDE was approximately 4 yrs (James et al., 2017); this disease state is known as metastatic hormone relapsed or castrate-resistant prostate cancer (mCRPC). Second-line therapy for mCRPC depends on agents used in the first-line setting: men who have been treated with ADT and an ARTT second-line therapy is with docetaxel and vice versa.

It is recognised that genomic variants in multiple pathways exist in many prostate cancers. The genomic profile is similar at initial diagnosis and at progression on ADT (except for an increase in genomic variants in the androgen receptor pathway). Approximately 15-30% of prostate tumours have loss of function variants in genes involved in homologous recombination repair (HRR) of DNA. The tumour suppressor *BRCA* genes (*BRCA1* and *BRCA2)* and *ATM* are the most frequently mutated HRR genes.

Acquired genetic changes within the DNA of tumour cells are termed somatic variants and are not inheritable (i.e. cannot be passed on to subsequent generations) whereas germline variants are changes in DNA which have usually been inherited from parents and are present in all nucleated cells of the body. Evidence suggests that somatic *BRCA* variants are more frequent than germline *BRCA* variants with a meta-analysis reporting rates of 11.26% versus 5.26%, respectively, in patients with hormone-relapsed metastatic prostate cancer (Valsecchi et al., 2023).

Individuals with a germline *BRCA* variant have an increased risk of developing breast, ovarian, prostate and pancreatic cancer. A variety of risk management options are available for some of these cancers depending on tumour type, including screening, chemoprevention and risk-reducing surgery. Inheritance of germline *BRCA* variants is autosomal dominant so 'at-risk' relatives of an individual carrying such a variant can have predictive genetic testing to clarify their risk.

Variants in *BRCA1* or *BRCA2* can result in the accumulation of DNA damage and tumorigenesis. Germline *BRCA2* variants have been reported to be associated with an adverse prognosis, but it is not known if this applies to somatic variants. There are no current clinical parameters (e.g., age, Gleason score) that can identify patients with an underlying somatic variant from those without, although prostate cancer patients with *BRCA2* variants may present at a younger age, with higher Gleason scoring tumours and increased frequency of both lymph node and distant metastases resulting in an increased mortality rate (Cimadamore et al., 2020).

Damage to DNA can result in single-strand DNA breaks which under normal conditions, are repaired by a family of enzymes known as the poly (ADP-ribose) polymerases (PARPs). If these single-strand DNA breaks are not repaired at the time of DNA replication prior to cell division, double-strand DNA breaks occur. These are usually detected and repaired by the *BRCA1* or *BRCA2* proteins and cell division proceeds. If a patient with *BRCA1* or *BRCA2 v*ariant receives a PARP inhibitor (PARPi), both

mechanisms of DNA repair are blocked – the *BRCA* proteins are non-functional due to the *BRCA* genetic variant and the PARP-mediated repair pathway is blocked by the drug, a concept known as synthetic lethality. Cells must subsequently rely on more error-prone mechanisms for DNA repair, but the resulting build-up of double-strand breaks leads to irreparable DNA damage and cell death.

The efficacy of olaparib in prostate cancer was investigated in the phase III PROfound (NCT02987543) trial (de Bono et al., 2020). This was a 2:1 randomised controlled trial in men with mCRPC who had all been treated previously with enzalutamide or abiraterone; they were randomly allocated to receive 300 mg of olaparib twice daily versus 160 mg of enzalutamide daily or 1000 mg of abiraterone daily in 387 patients with variants in either *BRCA1*, *BRCA2* or *ATM* (Cohort A – 245 patients) or *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L* (Cohort B – 142 patients). In cohort A, the olaparib group had improved median radiological progression free-survival (rPFS of 7.4 vs. 3.6 months, $p < 0.001$) and median overall survival (18.5 vs. 15.1 months, HR 0.64; $p = 0.02$). The ATM group demonstrated limited activity (median rPFS 5.36 months vs. 4.70 months). For cohort B, interpreting results are limited by the relatively small sample size and this has led to a different license in the US (all 15 HRR genes) and Europe (only *BRCA1/2* and *ATM*). In the licensed population and the *BRCA*-mutation prior taxane subgroup, both median progression-free survival and overall survival was higher with olaparib (9.0 months and 17.5 months, respectively) compared with abiraterone or enzalutamide retreatment (1.9months and 11.9 months, respectively) (NICE, 2023).

NICE has approved the use of olaparib as a treatment option for *BRCA1* or *BRCA2* positive hormone-relapsed metastatic prostate cancer that has progressed after a newer hormonal treatment (abiraterone, enzalutamide, apalutamide or darolutamide) via the Cancer Drugs Fund; treatment is indicated in the presence of germline and/or somatic *BRCA* variants (NICE, 2023b).

This document describes the All Wales *BRCA* testing pathway for hormone-relapsed metastatic prostate cancer.

Eligibility criteria for *BRCA* gene testing

Patients who are suitable candidates for immediate treatment with olaparib will be eligible for *BRCA* testing.

To access *BRCA* gene testing, **all** 4 of the following criteria must be met:

1. Hormone-relapsed metastatic prostate cancer AND
2. Disease progression during or after previous treatment with an androgen receptor targeting treatment (ARTT) +/- docetaxel and for whom a change in systemic therapy is being considered AND
3. No previous treatment with a PARPi AND
4. Performance status 0-2 and general suitability for olaparib

ARTT is defined as treatment with enzalutamide, abiraterone, apalutamide or darolutamide (NHS England, 2023).

The purpose of *BRCA* gene testing is to identify patients who may benefit from treatment with PARPi. **It is the responsibility of the treating clinician to ensure the above criteria are met**. It is recommended that clinical groups within each of the cancer centres review and update their systemic anticancer treatment algorithms to clearly identify when treatment with PARPi is indicated within the standard treatment pathway.

Overview of *BRCA* testing pathway

Olaparib is positioned as a second or subsequent line treatment option for *BRCA1* or *BRCA2* variant positive hormone-relapsed metastatic prostate cancer having progressed following previous treatment with ARTT. As such, all patients will already be known to an oncologist, and it is anticipated that requests for testing will be made by the treating oncology team rather than via diagnostic MDTs.

The *BRCA* testing pathway is as follows:

1. The oncology team must discuss the need for *BRCA* testing with the patient and consent the patient for germline *BRCA* testing.
2. The oncology team must complete both tumour (M218) and germline (R444.2) All Wales Medical Genomics Service (AWMGS) test request forms.
3. The oncology team should send the tumour request form (M218) to the pathology laboratory as tumour testing will be conducted on archival formalin-fixed paraffin-embedded (FFPE) diagnostic tissue samples. If there is no archival tissue available (no sample taken, no remaining tissue or tissue fails quality assurance (QA)), then patients should be considered for repeat image-guided biopsy to obtain tissue. It should be noted that testing on tissue samples is preferred due to technical limitations in DNA extraction from bone specimens. The pathology laboratory should prepare the tumour sample (see Histopathological sample preparation requirements section) and send the slides with the request form to AWMGS.
4. In parallel, the oncology team should arrange for an EDTA (purple topped bottle, minimum 5ml) blood sample to be taken from the patient and sent with the germline test request form (R444.2) to AWMGS. DNA from the blood sample will be extracted and stored.
5. DNA will be extracted from the tumour sample and *BRCA* sequencing will be performed (turnaround time of 14 calendar days from receipt of sample).
6. If sequencing on the tumour sample fails or if there is insufficient DNA for sequencing to be carried out, AWMGS will initiate salvage germline *BRCA* testing using the extracted DNA from the blood sample (M444.2; turnaround time of 21 calendar days). If germline *BRCA* testing fails, repeat germline testing +/- repeat biopsy should be considered.
7. If a pathogenic or likely pathogenic *BRCA1* or *BRCA2* variant with a variant allele frequency (VAF) of 20% or greater is detected in the tumour sample, a targeted test to determine whether the identified variant is also present in the germline will be initiated automatically by AWMGS using the stored DNA from the blood sample (R240; turnaround time of 28 calendar days) (see Interpreting a tumour BRCA gene test result section). Treatment with olaparib can be initiated before this result is available as the purpose of this targeted test is

to inform the risk of future cancers in the patient and to facilitate cascade testing of family members

8. If a pathogenic or likely pathogenic *BRCA1* or *BRCA2* variant has a VAF of less 20%, targeted germline testing will not be initiated.
9. If targeted germline *BRCA* testing fails, repeat targeted germline testing should be performed.
10. Tumour and germline *BRCA* testing reports will be uploaded separately to Welsh Clinical Portal (WCP) by AWMGS and PDF copies will be emailed to the requesting clinician.
11. The oncology team must inform the patient of the *BRCA* gene testing results and use the results to guide treatment decision-making +/- onward referral to Clinical Genetics if indicated (using the accelerated referral form).

Please note circulating DNA (ctDNA) is currently not a commissioned testing strategy via AWMGS.

Some patients may have already accessed *BRCA* gene testing through clinical trials or based on their personal/family history. It is the responsibility of the treating clinician to ensure the results of any previous *BRCA* testing are reviewed prior to requesting tumour testing. Please note historical germline *BRCA* testing reports will not be visible on WCP; if the oncology team believe a patient has previously had a test via AWMGS, please indicate this on the request form(s).

Tumour testing is not indicated in the presence of an already known germline *BRCA* variant as olaparib can be prescribed if the indications for treatment are met (see Eligibility criteria for treatment with olaparib section).

If a patient has previously accessed germline testing but a *BRCA* variant was not identified, tumour *BRCA* gene testing on a tumour specimen should still be performed to identify those patients with an acquired *BRCA* variant.

Germline *BRCA* testing consent process

Current guidance recommends germline testing requires patient consent (Royal College of Physicians, 2019). It is the responsibility of the individual requesting the test to obtain this in line with AWMGS guidelines and it is assumed that this has been done if a sample is sent for testing. A standardised consent form and checklist of the recommended information to be discussed with patients is available from the AWMGS and a downloadable version is available on the WCN website; a copy is also available in Appendix 2 (see BRCA consent and checklist). The consent form should be kept in the patient record and/or uploaded to the electronic patient record where available. A consent form does not need to be completed for tumour *BRCA* gene testing.

Approximately 50% of those identified as having a somatic *BRCA* variant in their tumour will also have this variant present in their germline; this may have implications for both their male and female blood relatives.

Patients should be informed that a negative tumour *BRCA* gene test result does not exclude a germline *BRCA* variant or a germline variant in another gene associated with an increased risk of prostate

cancer. A family history should be taken and a referral to Clinical Genetics for germline testing should be arranged if the referral criteria are met, in line with the current AWMGS guidance.

Any patient with a significant personal and/or family history of prostate cancer that meets the R430 criteria for germline testing (NHS England, 2024) should be referred to the Clinical Genetics service for assessment of their family history and discussion about whether further genetic testing using the hereditary prostate cancer panel and appropriate cascade testing is indicated, regardless of the result of tumour or germline *BRCA* gene testing. These testing criteria include:

- Proband diagnosed with prostate cancer at <50 years
- Ashkenazi Jewish ancestry and prostate cancer at any age
- Proband diagnosed with metastatic prostate cancer <60 years
- Proband diagnosed with prostate cancer with a family history of prostate cancer where the likelihood of identifying a pathogenic variant in the relevant target gene is at least 10%.

NTRK gene fusion testing

Patients with prostate cancer may be eligible for treatment with a TRK-inhibitor (larotrectinib or entrectinib) as a last-line therapy if the tumour is found to express a *NTRK* (Neurotrophic tropomyosin-receptor kinase) gene fusion, in line with the All Wales *NTRK* gene fusion testing clinical guidance document.

To optimise tissue preservation and handling, the clinical team should consider requesting RNA Next Generation Sequencing (NGS) to detect *NTRK* gene fusions in parallel with (i.e. at the same time as) *BRCA* gene testing. Please note both *BRCA* and *NTRK* testing can be requested using the same AWMGS request form.

Tumour *BRCA* gene testing request process

There are likely to be local considerations across the various regions of Wales in terms of the test requesting pathway. However, all requests should be made using the appropriate AWMGS request forms which are available at: http://www.medicalgenomicswales.co.uk.

The oncology team should complete the patient demographic information and enter their responsible clinician's name and email address in the appropriate sections. The form should then emailed to the local pathology laboratory storing the diagnostic specimen which is to be tested (see table 1).

University Health Board	**Generic email address(es)**
Aneurin Bevan	ABB.HistReferralRGW@wales.nhs.uk
Betsi Cadwaladr	BCU.CellPathMolecular@wales.nhs.uk
Cwm Taf Morgannwg	CTM.CellularPathologyMolecularRequests@wales.nhs.uk
Cardiff and Vale	Mg.Cellpath@wales.nhs.uk
Hywel Dda	WWGH.Histology@wales.nhs.uk

	HDD.Secretaries@wales.nhs.uk
Swansea Bay	SBUResearch.Histology@wales.nhs.uk

Table 1: Generic email address details for health boards

Tumour *BRCA* gene testing is performed on the initial diagnostic tumour sample. The sample requires preparation (slide cutting and tumour assessment) by the local pathology laboratory storing the sample prior to them sending it to the All Wales Genomics Laboratory (AWGL) at the AWMGS in Cardiff for analysis. **Requests should therefore not be made directly to the AWGL as this will introduce delays to the pathway as samples are not stored here and histopathology services are unavailable in this laboratory.**

If there is no archival tissue available (no sample taken, no remaining tissue or tissue fails quality assurance QA), then patients should be considered for repeat image-guided biopsy to obtain tissue. It should be noted that testing on tissue samples is preferred due to technical limitations in DNA extraction from bone specimens. **AWGL must be informed if the oncologist or pathology laboratory subsequently identify that tissue is not available for tumour BRCA gene testing to avoid delays in testing pathway. If AWGL do not receive a tissue sample within two weeks of receiving a blood sample, the requesting clinician will be contacted by AWGL to ascertain if tissue testing will be required.**

The pathology laboratory should prepare the sample in line with the AWMGS recommendations (see Histopathological sample preparation requirements section). The pathology laboratory should complete the remaining sections of the request form and send a paper copy of the form with the prepared slides directly to the AWGL within a 5 working day turnaround time. It should be noted that historical specimens may be stored off-site and, in such circumstances, the turnaround time for this stage may be longer.

Upon receipt of the sample at AWGL, the tumour BRCA testing report will be available within 14 calendar days, salvage BRCA germline testing within 21 calendar days and targeted BRCA germline testing within 28 calendar days. A PDF copy of the report will be emailed to the requesting clinician(s) (as listed on the request form) and uploaded to the WCP system.

The contact details for the AWGL are as follows:

All Wales Genetics Laboratory
Institute of Medical Genetics
University Hospital of Wales
Heath Park
Cardiff CF14 4XW
Telephone: 02921845347
Email address: Admin.Genetics.cav@wales.nhs.uk
Website: http://www.medicalgenomicswales.co.uk
Opening hours: Monday – Friday 8.30am – 5:00pm

Histopathological sample preparation requirements

The local pathology laboratory storing the diagnostic specimen should prepare the sample as follows before sending the slides with the completed histopathological section of the request form to AWGL:

Multi-target DNA NGS panel (*BRCA1* & *BRCA2* gene variants)	10 x 5-micron air dried sections mounted on slides
	1 x 5-micron H&E-stained slide with tumour area highlighted
Multi-target RNA NGS panel (structural variants/gene fusions in *NTRK1-3 genes*) (to be requested in parallel with BRCA testing) *Note: slides for RNA NGS to ideally be prepared in an RNase-free environment*	10 x 5-micron air dried sections mounted on slides
	1 x 5 micron H&E stained slide with tumour area highlighted

Table 2: Tissue requirements for *BRCA/NTRK* testing

Please note that AWGL will be returning all unused slides to the referring pathology laboratory to file as part of the archive.

Interpreting a tumour *BRCA* gene test result for treatment-decision making

All reports will include statements about:

- Whether any pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* were detected in the tumour sample
- Whether the patient may be a suitable candidate for PARPi if the current eligibility criteria for treatment are met
- Whether targeted germline *BRCA* testing will be initiated by AWMGS to determine if the identified *BRC*A variant is also present in the germline

Information on the type of *BRCA* variant detected will be included. A sequence variant is a small scale change in DNA, typically a substitution of one base (DNA letter) with another or a deletion or insertion event involving a few bases; these are detected by comparing the sequence of the patient's DNA to the reference sequence. A copy number variant is a larger scale change in DNA, typically a deletion or duplication of 100s or 1000s of bases of DNA; these are detected by assessing whether the number of DNA reads at various positions throughout the gene are significantly higher (duplication) or lower (deletion) than expected. The method used to analyse blood DNA usually

detects both sequence and copy number changes; the method currently used to analyse DNA from FFPE tumour samples detects only sequence changes.

If a pathogenic or likely pathogenic variant in *BRCA1* or *BRCA2* is detected in the tumour sample, it may be necessary for AWMGS to initiated germline testing to determine whether the identified *BRCA* variant is also present in the germline. This need will be determined by the variant allele frequency (VAF). The VAF is the proportion of reads containing the variant. VAF is an indicator of whether the variant is likely to be present in just the tumour (low % VAF) or present in the germline as well as the tumour (higher % VAF).

- If the VAF is 20% or greater, AWMGS will automatically initiate germline testing using the stored DNA from the blood sample. Treatment with olaparib can be initiated before this result is available as the purpose of this targeted test is to inform the risk of future cancers in the patient and to facilitate cascade testing of family members.
- If the VAF is below 20%, germline testing is not indicated.

It is the clinical responsibility of the oncology team to inform the patient of the *BRCA* gene testing results. If a germline *BRCA* variant is subsequently identified, the team must also refer the patient to Clinical Genetics for onward management and cascade testing (using the accelerated referral form) (see Interpreting a germline BRCA gene test result to determine constitutional BRCA status section).

Interpreting a salvage germline *BRCA* gene test result (when tumour *BRCA* testing fails)

If sequencing on the tumour sample fails or if there is insufficient DNA for sequencing to be carried out, AWMGS will initiate salvage germline *BRCA* testing using the extracted DNA from the blood sample.

All reports will include statements about:

- Whether any pathogenic or likely pathogenic germline variants in *BRCA1* or *BRCA2* were detected in the blood sample and if this confirms a diagnosis of a *BRCA1* or *BRCA2*-related cancer susceptibility
- Whether the patient may be a suitable candidate for PARPi if the current eligibility criteria for treatment are met

Patients who are diagnosed with *BRCA1* or *BRCA2*-related cancer susceptibility are at increased risk of developing further *BRCA1 or BRCA2*-related cancers, respectively. At-risk relatives are up to 50% risk of inheriting the pathogenic variant and may be offered pre-symptomatic genetic testing to determine their germline status for this variant.

It is the clinical responsibility of the oncology team to inform the patient of the *BRCA* gene testing results. If a germline *BRCA* variant is identified, the team must also refer the patient to Clinical Genetics for onward management and cascade testing (using the accelerated referral form).

Interpreting a targeted germline *BRCA* gene test result to determine constitutional *BRCA* status

If a pathogenic or likely pathogenic *BRCA1* or *BRCA2* variant with a variant allele frequency (VAF) of 20% or greater is detected in the tumour sample, a targeted test to determine whether the identified variant is also present in the germline (constitutional *BRCA* status) will be initiated automatically by AWMGS using the stored DNA from the blood sample.

All reports will include statements about:

- Whether the pathogenic or likely pathogenic germline variant in *BRCA1* or *BRCA2* identified in the tumour sample was also detected in the blood sample and if this confirms a diagnosis of a *BRCA1* or *BRCA2*-related cancer susceptibility
- Whether the family (to include the patient and any at-risk relative) should be referred to Clinical Genetics.

Patients who are diagnosed with *BRCA1* or *BRCA2*-related cancer susceptibility are at increased risk of developing further *BRCA1 or BRCA2*-related cancers, respectively. At-risk relatives are at 50% risk of inheriting the pathogenic or likely pathogenic variant and may be offered pre-symptomatic genetic testing to determine their germline status for this variant.

It is the clinical responsibility of the oncology team to inform the patient of the *BRCA* gene testing results. If a germline *BRCA* variant is subsequently identified, the team must also refer the patient to Clinical Genetics for onward management and cascade testing (using the accelerated referral form).

Eligibility criteria for treatment with olaparib

To receive olaparib, the following criteria must be met for **all** patients:

1. Confirmed somatic and/or germline *BRCA1* or *BRCA2* variant
2. Hormone-relapsed metastatic prostate cancer with disease progression during or after previous treatment with an androgen receptor targeting treatment (ARTT) +/- docetaxel and for whom a change in systemic therapy is being considered
3. Recent baseline imaging performed within last 8 weeks (including CT TAP and bone scan)
4. No previous treatment with a PARPi
5. Performance status 0-2
6. Laboratory investigations remain acceptable for treatment with a PARPi

Olaparib should continue until disease progression, unacceptable toxicity or patient choice to stop treatment.

Baseline investigations and on-treatment monitoring for olaparib

Repeat PSA at each 4-week cycle; repeat scans are to be considered if there is clinical suspicion of progression based on symptoms, PSA or performance status.

Table 3 summarises the required baseline investigations and on-treatment monitoring for patients receiving PARPi.

Investigation		Baseline	On-treatment
Blood tests	FBC	✓	✓
	RLB	✓	✓
	PSA	✓	✓
Imaging (CT TAP and bone scan)		✓	As clinically indicated

Table 3: Baseline and on-treatment monitoring requirements for olaparib

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Appendix 1 Prescribing information for olaparib

Drugs/Dosage	Starting Dose: 300mg orally TWICE a day Dose reduction 1: 250mg orally TWICE a day Dose reduction 2: 200mg orally TWICE a day Olaparib is available as 100mg and 150mg tablets Do NOT use capsules as they are not equivalent Continuous administration until progression of the underlying disease or unacceptable toxicity	
Administration	Oral tablets twice a day Olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib may be taken with or without food, but roughly at the same time each day. If a patient misses a dose of olaparib, they should take their next normal dose at its scheduled time.	
Anti-emetics	Olaparib can be mildly emetogenic. Provide metoclopramide 10mg TDS PRN for first cycle and then on an ad hoc basis.	
Regular investigations	FBC, RLB & PSA	Initially monthly; if patient stable on treatment, increase to every 2 months (at clinician discretion)
Special considerations	Olaparib has a moderate influence on the ability to drive and use machines. Patients may experience fatigue, asthenia or dizziness. Patients who experience these symptoms should observe caution when driving or using machines. Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.	
Treatment review	Initially monthly; if patient stable on treatment, increase to every 2 months (at clinician discretion)	

Common side effects (>10% patients)	Fatigue, anaemia, neutropenia, thrombocytopenia, leucopenia, decreased appetite, dizziness, headache, dysgeusia, cough, dyspnoea, nausea, vomiting, diarrhoea, and dyspepsia, upper abdominal pain.	
Occasional side effects (1-10%)	Infections, stomatitis, upper abdominal pain, rash, rise in creatinine and venous thromboembolism.	
Rarer toxicities	Pneumonitis, myelodysplastic syndrome, acute myeloid leukaemia	
Toxicity Management		
Fatigue	Omit for up to 14 days until it resolves to grade 1 or less then:	
	Grade 2	Restart at same dose if first occurrence, or apply a dose reduction for the second occurrence.
	Grade 3 or 4	Restart with a dose reduction.
Nausea	Nausea was generally reported very early, with first onset within the first month of treatment. Vomiting was reported early, with first onset within the first two months of treatment. Both nausea and vomiting were reported to be intermittent and can be managed by dose interruption, dose reduction and/or antiemetic therapy.	
Pneumonitis	New or worsening pulmonary symptoms e.g. dyspnoea - treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately.	
Haematological toxicity	For prolonged haematological toxicities, interrupt olaparib and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a haematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics.	
Anaemia	**Hb<90g/l**	Dose interrupt for a maximum of 14 days until ≥90g/l. If first occurrence, continue on same dose. If repeated or if with concomitant, neutropenia or thrombocytopenia then dose reduce.
	Hb<80g/l	dose interrupt for a maximum of 14 days until ≥90g/l the restart at a dose reduction
Neutropenia	**<1.0 x 10^9/L**	Dose interrupt until neutrophils ≥1.0 and restart at same dose if first occurrence, or reduced dose if repeated occurrence
Thrombocytopenia	Platelet count **75-100** x 10^9/L	Clinician discretion as to whether to interrupt for up to 14 days

	Platelet count **<75** x 10^9/L	Omit until ≥75 then restart at the same dose. If repeated occurrence dose reduce.
Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)	Occurred in <1.5% of patients exposed to olaparib monotherapy and the majority of events had a fatal outcome but these were mainly ovarian cancer patients previously treated with at least 2 line of platinum chemotherapy. Monitor patients for haematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed	
Venous thromboembolic (VTE)	VTE including pulmonary embolism occurred in 8% of patients with mCRPC. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.	
Renal Impairment	Creatinine clearance 51 to 80 ml/min (Mild renal impairment)	No dose adjustment required
	Creatinine Clearance 31 to 50ml/min (Moderate renal impairment)	200 mg (two 100 mg tablets) twice daily
	Creatinine Clearance <30 ml/min (Severe renal impairment)	Not been studied in this population. If used, the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events.
Hepatic Impairment	Mild or moderate hepatic impairment (Child-Pugh classification A or B)	Olaparib can be administered with no dose adjustment.
	Severe hepatic impairment (Child-Pugh classification C),	Olaparib is not recommended as safety and pharmacokinetics have not been studied.
Contraception	It is not known whether olaparib or its metabolites are found in seminal fluid. Male patients must use a condom during therapy and for 3 months after receiving the last dose when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients must also use highly effective contraception if they are of childbearing potential. Male patients should not donate sperm during therapy and for 3 months after receiving the last dose.	
Drug Interactions	Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative agents should be considered.	

	If a strong CYP3A inhibitor must be co-administered, the recommended olaparib dose reduction is to 100 mg (one 100 mg tablet) taken twice daily (equivalent to a total daily dose of 200 mg). If a moderate CYP3A inhibitor must be co-administered, the recommended dose reduction is to 150 mg (one 150 mg tablet) taken twice daily (equivalent to a total daily dose of 300 mg).

Appendix 2 BRCA consent form and checklist

Clinical teams are advised to use the most up-to-date versions of these forms which are available at the WCN website

AWMGS
All Wales Medical Genomics Service

Prostate Cancer Genomic Testing (M218.1/R444.2)
Patient Information sheet

Prostate cancer occurs in around 1 in 8 men in the UK population. Cancer occurs by chance in most people. Around 10% of men with prostate cancer carry a variant in a cancer gene (also sometimes called a gene change or gene alteration) that gives an increased chance of developing of prostate cancer.

Why am I being offered this test?
Your specialist has offered to arrange testing for you because you have been diagnosed with prostate cancer. This test will look for variants in the *BRCA1* and *BRCA2* genes, that are associated with an increased chance of developing prostate, breast and ovarian cancer. Identifying whether you have an alteration in one of these genes in your tumour cells only or an inherited alteration in one of these genes may mean that there are different treatment options available to you. The result of this test may also give information about your chance of developing another cancer in the future.

If you have previously had genetic testing and been confirmed to carry a *BRCA* gene alteration, you do not require this test. Please inform your specialist if you think you have had testing in the past.

How is testing being arranged?
Your specialist will discuss the testing with you, including the possible outcomes, which are outlined below. Testing will either be performed on your prostate tumour tissue or blood sample, but occasionally both will be tested.

What are the possible results from testing?

- **A BRCA variant is identified in your tumour tissue**
  Your oncologist will discuss what treatment options may be available to you because of this result.

  Testing on your blood sample may be initiated to determine whether the *BRCA* variant is only present in your tumour or whether the variant is a germline (inherited) variant. This testing is not necessary when the variant is only present at a low level in the tumour, as this suggests the variant is acquired and not inherited. If the variant is only present in your tumour tissue, your chance of developing other *BRCA* related tumours in the future is not increased and your relatives are not at risk of carrying the same *BRCA* variant.

  If the BRCA variant is found to only be present in your tumour tissue you do not require a referral to the Clinical Genetics Service unless you have a significant personal and/or family history of breast, ovarian, pancreatic, or prostate cancer. If you have a family history of cancer you should discuss with your specialist whether a referral to Clinical Genetics is indicated.

- **A BRCA variant is identified in your blood (germline)**
  This testing will be performed if a *BRCA* variant is identified in your tumour tissue or if testing on your tumour tissue was unsuccessful. If a germline *BRCA* variant is identified this confirms that you have a genetic predisposition and potentially have an increased chance of developing further associated tumours. If testing shows that you have a germline gene variant, your specialist will refer you to the Clinical Genetics service. You will be offered an appointment within a few weeks to discuss what this result means regarding your future risk and the options that you may want to consider to manage this risk. At an appointment you will be asked for details of your family history, and the options for your family members will be discussed.

- **No BRCA variants detected**
  If your test does not identify any variants in the *BRCA* genes, this does not mean that you do not carry an inherited gene variant that could be associated with an increased risk of cancer. If you do not have a family history of prostate, breast or ovarian cancer, there is not usually an increased risk for close relatives and a referral to Clinical Genetics is not needed. However, if you were diagnosed with prostate cancer under the age of 60 or have Ashkenazi Jewish ancestry or a family history of breast, ovarian or prostate cancer you may be eligible for further genetic testing and your specialist can refer you to the Clinical Genetics service.

Does the testing have implications for my family?
If you are found to carry a germline *BRCA* gene variant it is possible that some of your relatives may carry the same gene variant and they will have the option of being tested. Relatives who carry the same gene variant will be offered personalised information about what risk management options, such as screening or risk-reducing surgery, are available to them.

Where can I find more information?
If you have questions regarding genetic testing, you can discuss them with your specialist or you can contact the All Wales Medical Genomics Service.

South East Wales (Cardiff) – 02921 834000
South West Wales (Swansea) – 01792 285972
North Wales (Wrexham) - 03000 858 477

For more information please visit our website:

https://medicalgenomicswales.co.uk/

Consent form: M218.2/R444.2 *BRCA* gene testing - hormone-relapsed metastatic prostate cancer

Patient details (*affix patient's addressograph label or print*)
Patient name:
Date of birth:
NHS No:

Section 1: To be completed by the health professional

	Initials
The patient meets the eligibility criteria for *BRCA* gene testing as outlined in the BRCA testing mCRPC Clinical Guidance Document	

	Initials
I have obtained consent from the above-named patient for *BRCA* genetic testing	
I have given the patient a copy of the "Prostate Cancer Genomic testing" information sheet	

I confirm I have discussed the following points:	Initials
The purpose of the test and the possible implications.	
What the following outcomes of testing may mean for the patient and their relatives: a. A pathogenic/likely pathogenic variant identified. b. No variants identified.	
Depending on the result, a referral to Clinical Genetics may be appropriate.	
Results may be delayed if there is a problem with the sample or the test	

_____ _____ __/__/____
Signature Print name Date (dd/mm/yyyy)

Section 2: To be completed by the patient

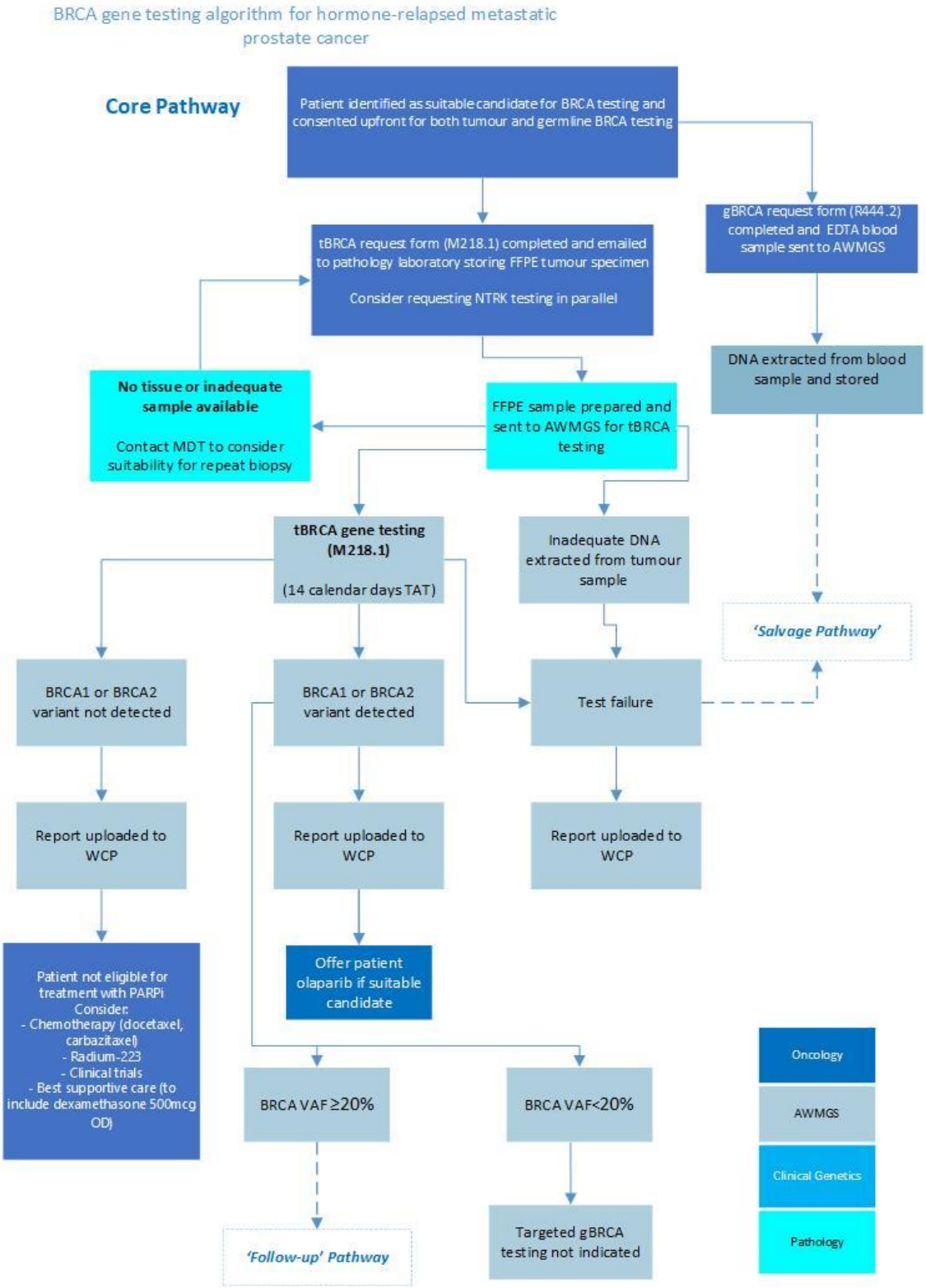
	Initials
I consent for my sample to be tested for *BRCA* gene changes and understand that the result will form part of my NHS medical record.	
I have received a copy of the "Prostate Cancer Genomic Testing" information sheet and have had the opportunity to ask questions.	
I understand the implications of the test for me and the rest of my family.	
I understand: a. I can change my mind at any stage and choose not to receive the results. b. The possible outcomes of this testing. c. Depending on the results I may be referred to my local genetics service. d. My result may be used for the benefit of my family members. e. My result may be used to provide advice and / or testing for my relatives. f. My sample will be stored in a DNA bank but no guarantee can be given that it will be available indefinitely or that it will be of sufficient quality for future testing. g. My results may be delayed if there is a problem with my sample or the test. h. My sample may be used anonymously for the development of new tests	

_____ _____ __/__/____
Signature Print name Date (dd/mm/yyyy)

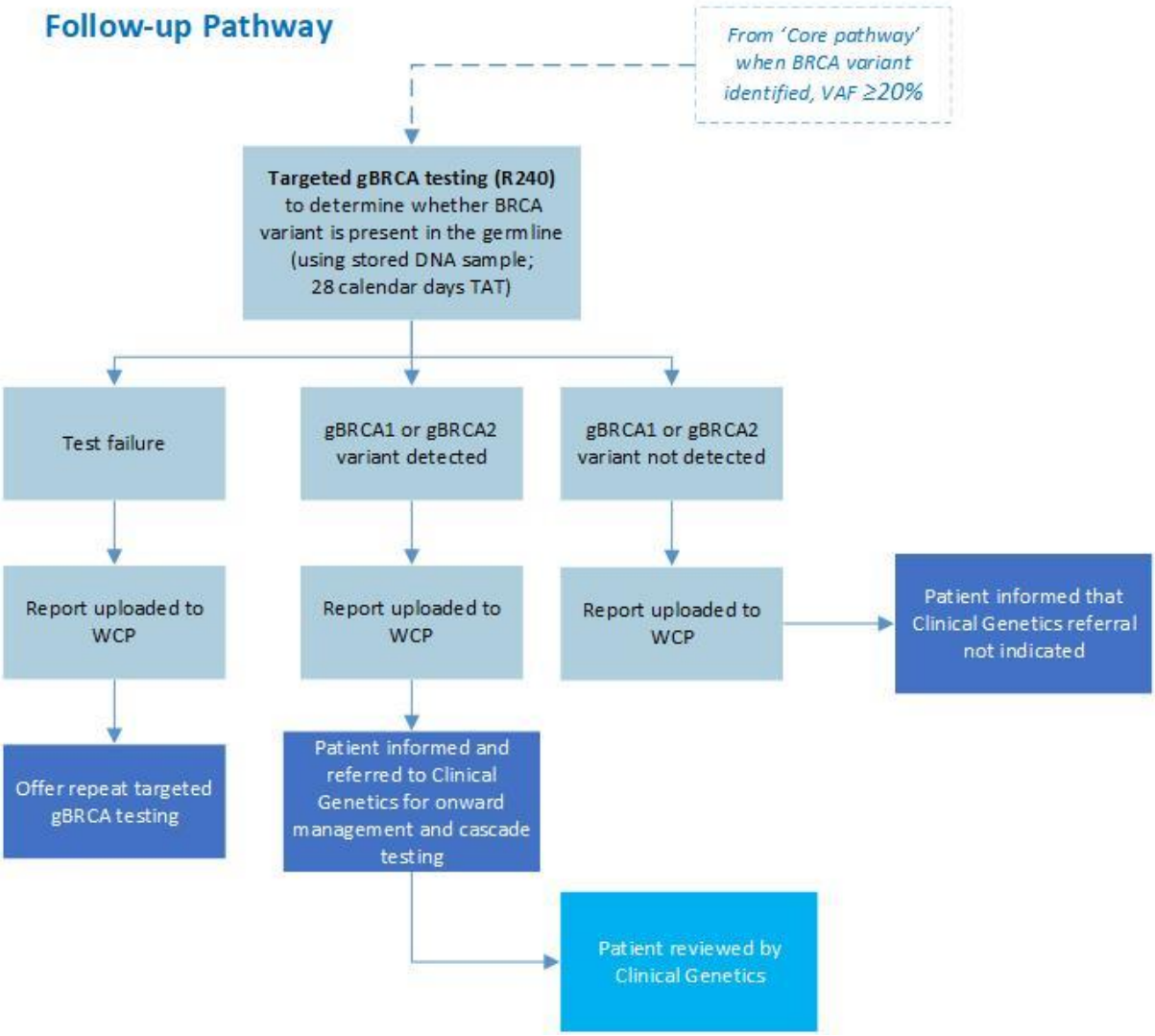
Further information about NHS Wales data use can be accessed at: https://dhcw.nhs.wales/ig/information-governance/your-privacy-your-rights/

Cardiff and Vale University Health Board	Revision: 1.0	Filename: M218.1-R444.2 consent form
Institute of Medical Genetics	Author: S Nisbet	Authorised by: Dr A Murray
Clinical Medical Genetics	Date of issue: Dec 2023	Page: 1 of 1

Appendix 3 Breakdown of the pathway



BRCA gene testing algorithm for hormone-relapsed metastatic prostate cancer



BRCA gene testing algorithm for hormone-relapsed metastatic prostate cancer

Salvage Pathway