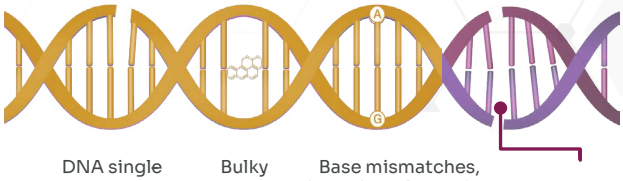
Genomic testing for *BRCA* alterations in prostate cancer

An introduction and overview of BRCA alterations and their detection in metastatic castration resistant prostate cancer (mCRPC) for healthcare professionals involved in the testing and treatment pathways.

What are *BRCA* alterations?

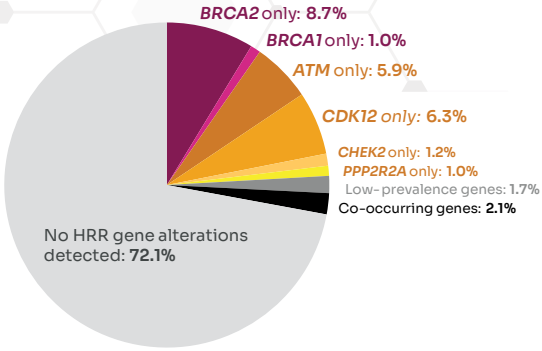
BRCA1 and *BRCA2* are genes involved in the homologous recombination repair (HRR) pathway, a critical mechanism for the repair of DNA double-strand breaks[1,2]. Alterations in HRR genes lead to a reliance on more error-prone repair pathways, resulting in the accumulation of genetic instability and promoting tumour growth[3,4].

Figure 1. DNA Damage Repair Pathways[5]



Adapted from Lord CJ and Ashworth . 2012.

Figure 2. Frequency of HRR alterations in mCRPC[6]



Why test for *BRCA* alterations in mCRPC?

Prognosis and familial risk. *BRCA* alterations are associated with more aggressive disease in mCRPC, and inherited variants are linked with an increased risk of developing prostate, ovarian, breast, and other cancers[7-10].

Treatment decision-making. Identification of pathogenic variants can inform treatment decisions, as BRCA-deficient tumours demonstrate increased sensitivity to certain targeted agents[7-10].

Tumour tissue testing can detect both **germline** (inherited) and **somatic** (acquired) alterations, but cannot distinguish between the two. Blood-based testing identifies only **germline** variants, which represent approximately half of all *BRCA* variants[11-14]. Written informed consent is generally required prior to germline testing[10,12].

Where to test?

- Central and South GLH
- East GLH
- North East and Yorkshire GLH
- North Thames GLH
- North West GLH
- South East GLH
- South West GLH
- Scotland
- Wales
- Northern Ireland

Image adapted from NHS England Genomic Laboratory Hubs.[15]

Please note: In some areas there may be local testing hubs. Check locally for test request forms.

Referrals for testing will be triaged by the local genomics services to ensure the most appropriate test is performed. For your local genomics services, please consult the regional map and QR codes.

Below links direct to external websites. AstraZeneca / MSD are not responsible for the content or the privacy policy of any third-party websites.

Central and South GLH

East GLH

North East and Yorkshire GLH

North Thames GLH

North West GLH

South East GLH

South West GLH

Scotland

Wales

Northern Ireland

Reach out to us at AZDiagnostics@astrazeneca.com if you would like to discuss BRCA testing, pre-analytics, mainstreaming, or ctDNA in more detail.

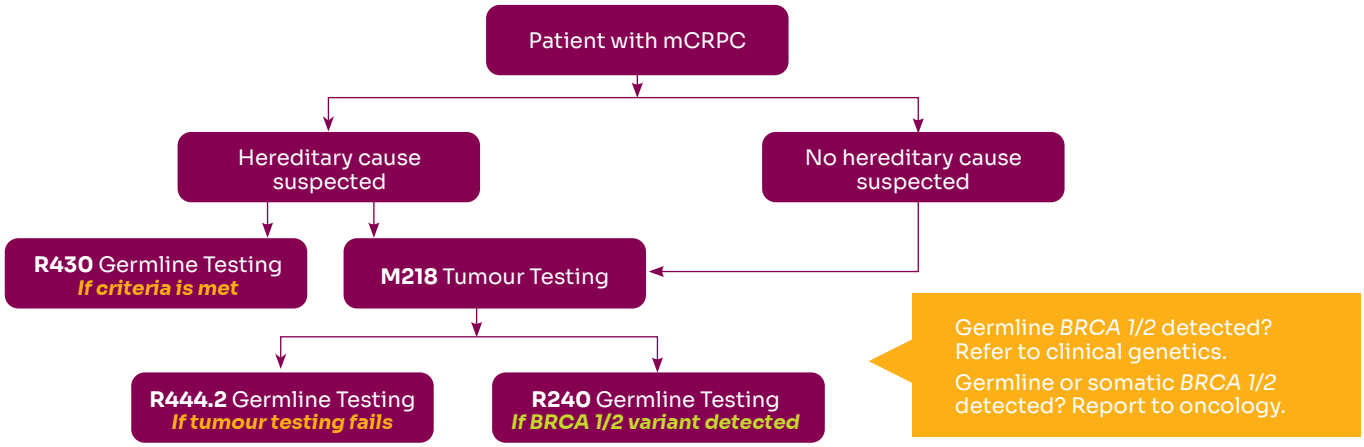
Who to test?

The information in this section, including Figure 3, refer to testing in England as set out by the national genomic test directory. For test availability, pathways, and eligibility criteria outside of England, refer to local guidance.

England Test Directory

TEST CODE	TEST NAME	TARGET GENE(S)	ELIGIBILITY CRITERIA
M218.1	Multi-target NGS panel - small variant for somatic/tissue testing	*BRCA1, BRCA2*	Patient is eligible for NICE recommended PARP inhibitor and has a diagnosis of metastatic castration-resistant prostate cancer. Somatic analysis should be performed first, germline analysis (R444.2) should only be performed should there be insufficient tissue, or the somatic analysis has failed.
R430	Inherited prostate cancer	Small panel	Eligible if patient has any of the following: ▪ Diagnosed with prostate cancer at < 50 years ▪ Diagnosed with metastatic prostate cancer at < 60 years ▪ Ashkenazi Jewish ancestry and diagnosed with prostate cancer |at any age ▪ ≥1 grandparent from Whalsay (Shetland) and diagnosed with prostate cancer at any age ▪ Diagnosed with prostate cancer and a CanRisk score of >10% where they do not meet criteria for R208, R207 or R210 Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present
R444.2	NICE recommended PARP inhibitor treatment	Small panel	Metastatic, castration-resistant prostate cancer where somatic tumour testing (M218.1) has failed.
R240	Diagnostic testing for known variant(s)	Specific Target	Patient clinically affected with specific disorder where a variant has been identified in the patient during somatic testing that is likely to be germline origin and causative

Figure 3. Abbreviated NHS pathway for testing in England[16]. Process varies in devolved nations; refer to local guidance. For more detailed pathway, contact AstraZeneca Diagnostics.



Maximising test success

As per data from clinical trials, insufficient tumour or DNA content can lead to test failures in ~30% of tissue samples from mCRPC patients. Factors influencing test success include tissue collection method, tissue preservation approach, and the age of block tested. Although bone biopsy may not be recommended, if samples are available use ethylenediaminetetraacetic acid (EDTA) for decalcification where appropriate[17]. Contact AstraZeneca Diagnostics (see end of page 2) for more information on maximising test success rates.

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