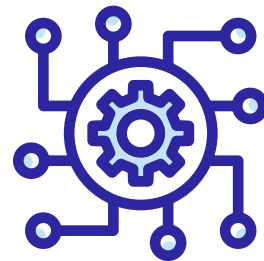
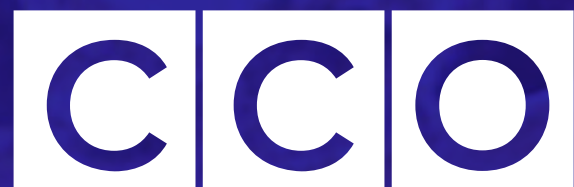
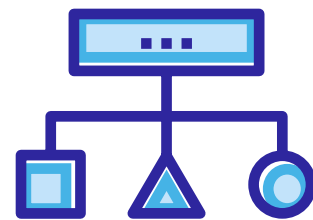


Biomarker Testing in Prostate Cancer

An Essential Component in Transforming Care



Clinical algorithm for genetic and genomic testing



Flow of sample during genomic testing



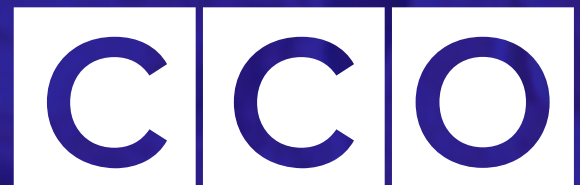
Approved therapies for M1 metastatic castration resistance prostate cancer with HRR or MMR alterations



Reporting

Biomarker Testing in Prostate Cancer

**An Essential Component
in Transforming Care**

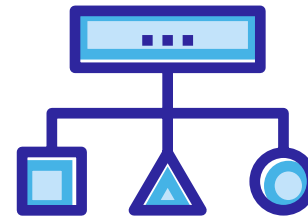




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- The flowchart illustrates the management of patients with a breast biopsy, showing the path from biopsy to various testing options based on NCCN risk categories and clinical history.
- BIOPSY**
- Central Box (NCCN Risk Categories):**
- NCCN Very Low or Low Risk + Family History**
 - NCCN Intermediate + Family History or + Intraductal/Cribriform
 - NCCN High Risk
 - NCCN Very High Risk
- Testing Options:**
- Tissue or cfDNA based testing** (if NCCN Very Low or Low Risk + Family History** or NCCN Intermediate + Family History or + Intraductal/Cribriform)
 - Genetic testing** (if NCCN Intermediate + Family History or + Intraductal/Cribriform)
 - Tissue or cfDNA based testing** (if NCCN High Risk or NCCN Very High Risk)
- Conditions for Testing:**
- Any M1 by imaging
 - Any post XRT[†] recurrence
 - Any N1
 - Any M1
 - Post RP[‡] recurrence
- Legend:**
-→ If not done previously

[†]XRT = Radiation Therapy; [‡]RP = Radical Prostatectomy

Flow of sample during genomic testing



- For somatic genomic testing, tissue representative of metastatic disease is preferred vs. blood based cfDNA testing. This may require rebiopsy in patients who do not present with de novo metastatic disease, those with long intervals between diagnosis and advanced disease, and those where there is uncertainty if the primary tissue represents the metastatic disease.
- Factors that impact the success of tissue-based testing include amount of tumor tissue present (more tumor > less tumor), age of the FFPE block (newer > older), and fixation (bone biopsies should be either non-decalcified or briefly decalcified in EDTA).
- The major factor impacting the success of blood-based cfDNA testing is the total metastatic disease burden. Patients with lower disease burden are at increased risk of false negative/inconclusive test results for HRR mutations and homozygous copy loss. The presence of HRR gene mutations that are only present in circulating white blood cells (WBC) and not tumor cells (clonal hematopoiesis of indeterminate potential [CHIP]) must be considered in cfDNA based testing in the absence of concurrent WBC testing.

Approved therapies for M1 metastatic castration resistance prostate cancer with HRR or MMR alterations

Note: FDA approved indications and/or professional guideline recommended regimens vary based on prior receipt of (and eligibility for) chemotherapy and/or novel hormonal therapy.

Deleterious mutations or homozygous copy loss in *BRCA1/2* and other HRR genes

- PARP inhibitors +/- novel hormonal therapy: olaparib, talazoparib + enzalutamide

Deleterious mutations or homozygous copy loss in *BRCA1/2*

- PARP inhibitors +/- novel hormonal therapy: rucaparib, niraparib + abiraterone, olaparib + abiraterone

MSI-high (MSI-H), mismatch repair deficiency (dMMR) or tumor mutation burden high (TMB-H)

- Checkpoint inhibitors: pembrolizumab or dostarlimab (MSI-H/dMMR only)



Reporting

Genetic testing reports with variants in HRR and/or MMR genes should precisely indicate the identified variant (at the nucleotide and encoded protein level) and describe the level of pathogenicity according to standardized approaches.

Somatic genomic tissue- and cfDNA-based testing has the potential to identify variants conferring sensitivity to PARP inhibitors/checkpoint inhibitors, as well as “passenger” variants that do not confer the same level of sensitivity. Differences in responses to PARP inhibitors across *BRCA1/2* and other HRR genes have also been reported (*BRCA2* alterations best supported). In MSI-H/dMMR prostate cancer that also have HRR mutations, checkpoint inhibitor therapy is better supported than PARP inhibitor therapy.

For HRR genes, testing should assess both deleterious (“pathogenic”) mutations and loss of both gene copies (“homozygous loss, two-copy loss, or deep deletion”). In most contexts, functional loss of both copies of HRR genes (“biallelic loss”) is required to confer sensitivity to PARP inhibitors. Hence, in addition to the report clearly identifying any deleterious HRR gene alterations, it should also include a statement describing biallelic loss status for any HRR gene variant, or at a minimum, the observed tumor content and mutation allele frequency (VAF).

Approved therapies and profession guidelines change frequently; hence, review of currently approved therapies and guidelines are recommended for testing and treatment decision making.