Homologous Recombination Repair Testing Patterns and Barriers in Metastatic Hormone-Sensitive and Metastatic Castration-Resistant Prostate Cancer Across Europe: A Real-World Survey

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Background

- Prostate cancer (PC) is the second most common cancer worldwide in men[1] and once PC becomes castration-resistant, alternatives to hormonal treatments are required.
- Cells with homologous recombination repair mutations (HRRm) have been shown to be more vulnerable to poly-ADP ribose polymerase (PARP) inhibitors, limiting DNA repair mechanisms and ultimately causing cell death.[2]
  - HRRm are associated with an increased risk of and indicate a more aggressive disease.[3-4]
- In clinical trials PARP inhibitors demonstrated longer overall survival than current treatments in the metastatic castration-resistant PC (mCRPC) setting, for patients with HRR mutations.[5]
- Current accessibility of PARP inhibitors as monotherapy in Europe is mostly limited to patients who have undergone genetic testing for HRR genes, especially *BRCA1* and/or *BRCA2*. [6]
- The European Society for Medical Oncology guidelines recommend germline testing for *BRCA2* and other HRR genes in all patients with metastatic PC (mPC).[7]
- As indications for novel treatments in the mCRPC treatment setting continue to require HRR mutations, there is a need to understand patient HRRm testing patterns in the real-world.

Objective

- To describe real-world HRRm testing patterns in patients with mCRPC and metastatic hormone-sensitive prostate cancer (mHSPC), as well as physician-cited barriers to testing.

Methods

Study design

- Data were drawn from the Adelphi Real World PC Disease Specific Programme™ (DSP™).
- HRR genes of interest were: *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.*
- Descriptive statistics were used, and statistical comparisons were not conducted.

Data source

- The Adelphi Real World DSP is a cross-sectional survey, with elements of retrospective data collection, of physicians and their adult patients with mPC in France, Germany, Italy, Spain, and the United Kingdom (UK) from November 2022 – May 2023.
- Data sources used for analysis included electronic patient record forms (PRFs), and the physician attitudinal survey.
- The methodology has been previously described,[8-9] validated,[10] and demonstrated to be representative and consistent over time.[11]

Eligibility

- Physicians were eligible for inclusion if they met the following criteria:
  - Specialty in medical oncology or urology; saw a minimum of four mPC patients per month; and personally responsible for prescribing decisions for patients with mPC.
- Physicians reported data on the next four consecutively consulting patients with mHSPC and the next eight consecutively consulting patients with mCRPC who met the eligibility criteria:
  - Aged ≥18 years at diagnosis; physician-confirmed diagnosis of mHSPC/mCRPC; receiving active drug treatment for mHSPC/mCRPC; not participating, or ever participated, in a clinical trial at time of data collection.
- For inclusion in this study, patients with PC as their only malignancy were included in the analysis.

Study variables

- Study variables included patient demographics/clinical characteristics, genomic testing patterns and barriers to testing. Descriptive statistics were used to describe demographics/ clinical characteristics, testing patterns and barriers.

Results

- Overall, 221 physicians (84% medical oncologists [med onc], 16% urologists [uro]) reported data for 2612 patients (mHSPC n=875, mCRPC n=1737).
  - Of all patients, 86% were managed by med oncs, and 14% were managed by uros (mHSPC: 85% med onc/15% uro, mCRPC: 86% med onc/14% uro).

Patient demographics and clinical characteristics

- For patients with mHSPC and mCRPC, median (interquartile range; IQR) age was 71.0 (66.0–77.0) and 73.0 (68.0–78.0) years, and 81% and 77% had an ECOG score of 0–1, respectively (Table 1).

Table 1. Patient Demographics and Clinical Characteristics

	All patients with mHSPC (n=875)	France (n=200)	Germany (n=194)	Italy (n=166)	Spain (n=172)	UK (n=143)
Patient demographics						
Age in years, median (IQR)	71.0 (66.0–77.0)	74.0 (68.0–79.0)	69.5 (66.8–73.0)	72.0 (65.0–79.0)	71.0 (67.0–77.0)	72.0 (66.0–77.0)
Days since mHSPC diagnosis (IQR)	187.0 (93.0–354.2)	247.0 (118.0–426.0)	152.5 (72.2–331.5)	196.0 (84.8–349.8)	199.5 (107.8–341.0)	147.0 (82.0–334.0)
ECOG score at data collection, n (%)						
0–1	710 (81)	158 (79)	133 (69)	138 (83)	154 (90)	127 (89)
2–4	165 (19)	42 (21)	61 (31)	28 (17)	18 (10)	16 (11)
Patient family history of cancer, n (%)						
Family history	83 (9)	24 (12)	15 (8)	20 (12)	19 (11)	5 (3)
No family history	737 (84)	163 (82)	158 (81)	142 (86)	149 (87)	125 (87)
Unknown	55 (6)	13 (6)	21 (11)	4 (2)	4 (2)	13 (9)
	All patients with mCRPC (n=1737)	**France (n=388)**	**Germany (n=394)**	**Italy (n=335)**	**Spain (n=348)**	**UK (n=272)**
Patient demographics						
Age in years, median (IQR)	73.0 (68.0–78.0)	75.0 (69.2–79.0)	70.0 (68.0–73.2)	74.0 (70.0–80.0)	73.0 (68.0–78.0)	73.0 (68.0–77.8)
Days since mCRPC diagnosis (IQR)	159.5 (79.0–359.2)	156.5 (79.0–356.8)	153.0 (95.0–252.0)	148.0 (50.0–426.0)	182.0 (81.5–374.5)	167.0 (82.5–387.0)
ECOG score at data collection, n (%)						
0 – 1	1337 (77)	278 (72)	245 (62)	278 (83)	302 (87)	234 (86)
2 – 4	397 (23)	109 (28)	147 (37)	57 (17)	46 (13)	38 (14)
Unknown	3 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
Patient family history of cancer, n (%)						
Family history	205 (12)	44 (11)	35 (9)	56 (17)	54 (16)	16 (6)
No family history	1413 (81)	325 (84)	316 (80)	263 (79)	277 (80)	232 (85)
Unknown	119 (7)	19 (5)	43 (11)	16 (5)	17 (5)	24 (9)

ECOG – Eastern Cooperative Oncology Group; IQR – interquartile range; UK – United Kingdom

Testing patterns in the mHSPC setting

- Of all mHSPC patients (n=875), 25% (n=223) received a HRRm test.
  - Of patients tested for HRRm, 35% were positive (germline mutation 15%; somatic mutation 17%; unknown mutation type 4%).
  - Overall, 90% of patients who received a HRRm test were managed by med oncs, and 10% by uros.
  - In Germany, a total of 37% of patients received a HRRm test, whereas in the UK 8% received a HRRm test.
- Of tested patients (n=223), 98% (n=219) were tested for *BRCA1/2*.
  - Of those tested for *BRCA1/2*, a total of 90% (n=197) of patients were being treated by a med onc and 10% (n=22) of patients were being treated by a uro at time of data collection.
  - Among patients tested for *BRCA1/2*, 77% of patients received this as their only HRRm test.
- Of patients tested for *BRCA1/2* (n=219), 32% were positive (germline mutation 15%; somatic mutation 15%; unknown mutation type 4%; Figure 1a).
- For patients who received a HRRm test (n=223), 75% were conducted at mPC diagnosis and 22% had a family history of cancer (Figure 2a).
  - Of HRRm-tested patients in Spain (n=42), 95% were tested at mPC diagnosis, whilst of HRRm-tested patients in Germany (n=71) this was 61%.
- Forty-three percent of tests were conducted as a single gene test, whilst 27% were conducted as multiple single gene tests, and 30% were conducted using a multigene panel.
- The most reported samples used for HRRm testing were tissue and blood (58% and 47%, respectively).

Testing patterns in the mCRPC setting

- Of all mCRPC patients, 37% (n=640) received a HRRm test.
  - Of patients tested for HRRm (n=640), 32% were positive (germline mutation 13%; somatic mutation 17%; unknown mutation type 5%).
  - In Germany (n=394), a total of 49% of patients received a HRRm test, whereas in the UK (n=272), 12% received a HRRm test.
- Of tested patients (n=640), 99% (n=639) were tested for BRCA1/2.
  - Of those tested for *BRCA1/2*, a total of 92% (n=591) of patients were being treated by a med onc and 8% (n=48) of patients were being treated by a uro at time of data collection.
  - For patients who were tested for *BRCA1/2* (n=639), 73% were tested for only *BRCA1/2*.
- Of patients tested for BRCA1/2 (n=639), 31% were positive (germline mutation 12%; somatic mutation 16%; unknown mutation type 4%; Figure 1b).
- For patients who received a HRRm test (n=640), 43% were conducted at castration-resistance/progression following mHSPC treatment (Figure 2b), and 19% had family history of cancer.
  - Of HRRm-tested patients in Spain (n=126), 56% were tested at castration-resistance/progression following mHSPC treatment, whereas in HRRm-tested patients in Germany (n=193) 33% were tested at the same timepoint.
- Thirty-four percent of tests were conducted as a single gene test and 34% were conducted using a multigene panel, whilst 31% were conducted using multiple single gene tests.
  - Of HRRm-tested patients in France (n=155), 58% received their genetic test by use of a multigene panel, whereas of HRRm-tested patients in Spain (n=126), 9% were tested using a multigene panel, with 62% receiving a test from multiple single gene tests.
- The most reported samples used for the HRRm test were tissue and blood (60% and 52%, respectively).
  - Of those HRRm tested patients with mCRPC in Italy (n=132), 70% of patients had a blood sample taken, and 65% had a tissue sample taken. While in France (n=155), 39% had a blood sample tested, and 70% had a tissue sample tested.

Figure 1a. BRCA1/2 results in patients with mHSPC (all patients n=219)

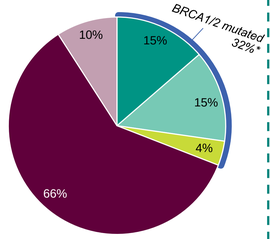
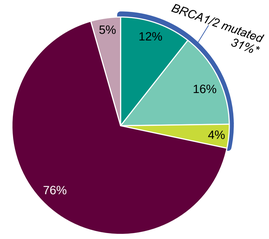


Figure 1b. BRCA1/2 results in patients with mCRPC (all patients n=639)



BRCA1/2 – breast cancer gene 1/2; mHSPC – metastatic hormone-sensitive prostate cancer; mCRPC – metastatic castration-resistant prostate cancer
**Numbers may add up to more than overall sum as the options for BRCA1 and BRCA2 are not mutually exclusive. For example, a patient with a BRCA1 germline mutation may also have a BRCA2 somatic mutation, thus is counted in each category*

Figure 2a: Timepoint of HRRm test in patients with mHSPC

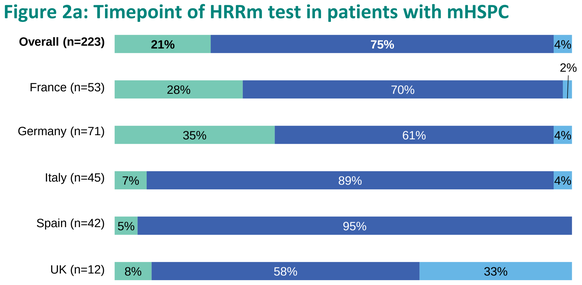
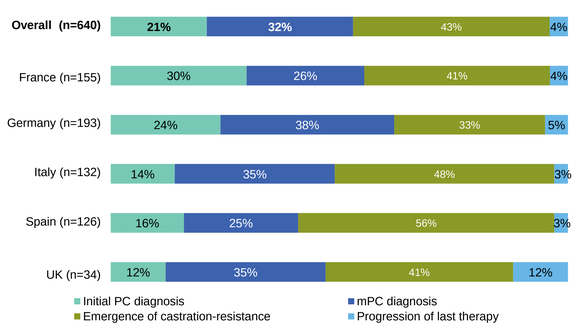


Figure 2b: Timepoint of HRRm test in patients with mCRPC



HRRm – homologous recombination repair mutation; mCRPC – metastatic castration-resistance prostate cancer; mPC, metastatic prostate cancer, PC – prostate cancer; UK – United Kingdom.

Physician-stated barriers

- Physician-stated barriers to genomic testing included high cost (37%) and lack of reimbursement (32%; Figure 3a).
  - Physicians in Italy and Spain frequently reported difficulty accessing the latest genetic tests (45% and 45%), compared to 26% in Germany, 21% in France and 21% in the UK (Figure 3a).
- Of physicians who conducted HRR testing (n=214), 77% stated the reason for conducting HRR testing was to inform treatment decisions (Figure 3b).
  - In Spain, determining genetic risk of PC development in family members was reported as a reason for HRR testing by 72% of physicians.

Figure 3a: Top five physician-stated barriers to genetic testing)

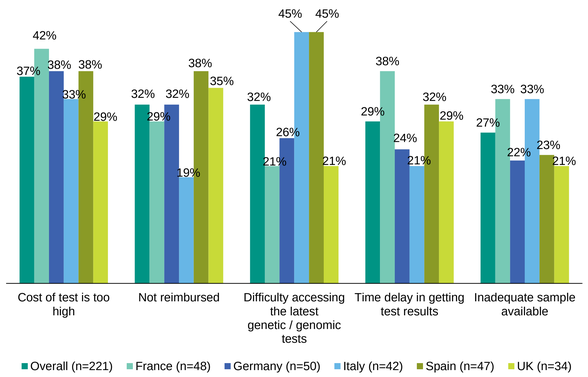
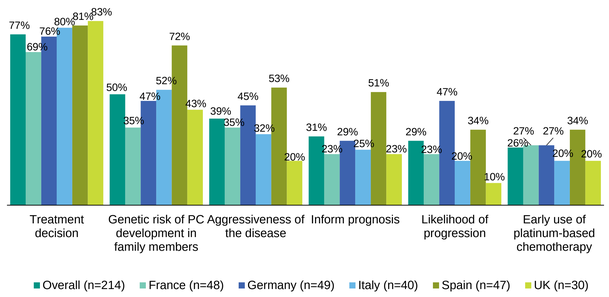


Figure 3b: Top six physician stated reasons for HRR testing



HRR – Homologous recombination repair; PC – prostate cancer; UK – United Kingdom

Conclusions

- HRRm testing remains limited in patients with either mHSPC or mCRPC.
  - Approximately, one in four patients with mHSPC received a HRRm test while one in three patients with mCRPC received a HRRm test.
- Underuse of testing further restricts patient access to multiple life-prolonging therapies in the mCRPC setting. Addressing reimbursement and cost overall may encourage broader and potentially earlier testing, allowing for timely identification of patients who might benefit from personalised treatments.

Limitations

- Participating patients may not reflect the general metastatic PC population since the DSP only includes patients who are consulting with their physician. This means that patients who consult more frequently have a higher likelihood of being included. Recall bias, a common limitation of surveys, might also have affected responses of both physicians and patients. However, physicians did have the ability to refer to the patients' records while completing the PRF, thus minimizing the possibility of recall bias..

Disclosures

- Data collection was undertaken by Adelphi Real World as part of an independent survey, entitled the Adelphi Real World Prostate Cancer V DSP. Merck & Co., Inc., Rahway, NJ, USA. did not influence the original survey through either contribution to the design of questionnaires or data collection. The analysis described here used data from the Adelphi Real World Prostate Cancer V DSP. The DSP is a wholly owned Adelphi Real World product. Merck & Co., Inc., Rahway, NJ, USA. is one of multiple subscribers to the DSP. Publication of survey results was not contingent on the subscriber's approval or censorship of the publication.
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