pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Olaparib (Lynparza)

Submitted Reimbursement Request:
Olaparib as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and deleterious or suspected deleterious germline and/or somatic mutations in the homologous recombination repair genes *BRCA* or *ATM* who have progressed following prior treatment with a new hormonal agent

Submitted By: AstraZeneca Canada Inc.	**Manufactured By:** AstraZeneca Canada Inc.
NOC Date: August 21, 2020	**Submission Date:** September 22, 2020
Initial Recommendation: April 1, 2021	**Final Recommendation:** April 21, 2021

Approximate per Patient Drug Costs, per Month (28 Days)	Olaparib costs $65.89 per 100 mg or 150 mg tablet. At the recommended dose of 600 mg (taken as two 150 mg tablets orally twice daily), olaparib costs $7,380 per 28-day cycle.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of olaparib as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and deleterious or suspected deleterious germline and/or somatic mutations in the homologous recombination repair (HRR) genes *BRCA* or *ATM* who have progressed following prior treatment with a new hormonal agent/ androgen receptor-axis-targeted therapy (ARAT) if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Eligible patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of olaparib compared with investigators' choice of an ARAT based on statistically significant and clinically meaningful improvements in radiographic progression-free survival (rPFS) and overall survival (OS), a manageable toxicity profile, and no detrimental impact on quality of life (QoL). However, given the lack of robust direct or indirect comparative data, pERC was unable to conclude on the relative efficacy and safety of olaparib compared with other relevant treatment options, such as taxane-based chemotherapy (i.e., docetaxel, cabazitaxel) or radium-223.

pERC also concluded that olaparib aligns with the following patient values: delays disease progression, the onset of symptoms, pain progression, and skeletal-related events; has manageable side effects

	with no negative impact in QoL; fulfills an unmet need; and offers an additional treatment option with a convenient oral route of administration. pERC concluded that olaparib was not cost-effective at the submitted price versus available comparators in Canada and that a reduction in drug price would be required to improve its cost-effectiveness to an acceptable level. pERC also noted that the CADTH base case estimates are informed by the sponsor-submitted indirect treatment comparison, which is highly uncertain. pERC noted that the budget impact of introducing olaparib may potentially be underestimated due to the uncertainty associated with the availability of HRR mutation testing and detection rates.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of olaparib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of olaparib. pERC noted that a reduction in the price of olaparib would be required in order to improve the cost-effectiveness to an acceptable level and to decrease the predicted budget impact. **Homologous Recombination Repair Companion Test** pERC considered that the determination of the presence of deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes *BRCA* or *ATM* is required prior to the initiation of treatment with olaparib monotherapy. The Committee noted that it would be ideal for jurisdictions to have HRR testing results by the time of initiating an ARAT to manage both the patient population and the budget impact of a reimbursement recommendation. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers). The number of new prostate cancer cases in 2020 has been estimated at approximately 23,300, with 4,200 expected deaths. One in 4 patients with prostate cancer will die of the disease. The 5-year survival rate of mCRPC is approximately 30%. Both germline and somatic alterations in DNA repair genes occur in 20% to 30% of patients with mCRPC. Metastatic castration-resistant prostate cancer mutations in the *BRCA* (*BRCA1* and/or *BRCA2*) gene are the most common HRR gene mutations (*BRCA2* is more prevalent than *BRCA1*), with ATM being the second most frequently mutated HRR gene. It has been suggested that patients with mCRPC who carry an HRR gene mutation have a poorer prognosis compared with noncarrier mCRPC patients. There are currently no standard funded biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations. Available treatment options in Canada for patients with mCRPC who have progressed following prior treatment with an ARAT (i.e., enzalutamide or abiraterone) include taxane-based chemotherapy (docetaxel, cabazitaxel [approved only after docetaxel]), radium-223 (for patients with bone predominant disease), and alternate ARAT (abiraterone or enzalutamide). The most commonly offered treatment is taxane-based chemotherapy; however, many patients are not eligible to receive taxane-based chemotherapy because of their older age and comorbidities. Sequencing of alternate ARATs is rarely done and funded only in a few provinces. pERC agreed with the pCODR Clinical Guidance Panel (CGP), the registered clinicians providing input, and the patient advocacy group that there is an unmet need for effective new therapies with manageable toxicity profile in the mCRPC setting. pERC highlighted the unmet need for treatments with new mechanism of actions with biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated on the results of 1 randomized, multinational, open-label, phase III trial (PROfound) that evaluated the efficacy and safety of olaparib compared with the investigators' choice of an ARAT (i.e., enzalutamide, abiraterone) in patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes *BRCA* or *ATM* who have progressed following prior treatment with an ARAT. pERC noted that the PROfound trial had 2 cohorts; however, only cohort A (patient with *BRCA1*, *BRCA2*, and *ATM* mutations) was deliberated on. Cohort B included patients with a mutation in 12 additional genes involved in HRR (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L*) and was not included in the CADTH requested reimbursement criteria. pERC considered that rPFS, the primary outcome of the trial, was statistically significant and clinically meaningful in favour of olaparib. Key secondary outcomes — objective response rate (ORR), time-to-pain progression, and OS — were also statistically significant in favour of olaparib. pERC noted that an advantage in OS for patients receiving olaparib was observed despite a high rate of crossover from the control to the olaparib group. pERC agreed with the CGP and the registered clinicians providing input for this submission that the improvements in rPFS and OS of the magnitude observed in the PROfound trial (i.e., approximately 4 months' delay to disease progression or death and prolonged OS of approximately 4 months) are within the range of improvements seen with other approved agents in this incurable disease setting and are of clinical importance in a heavily pre-treated patient population with currently no biomarker-directed standard therapy options.

pERC deliberated on the safety of olaparib and noted that most patients in the trial experienced at least 1 any-grade treatment-emergent adverse event (TEAE); those occurring most frequently in both groups included anemia, nausea, fatigue or asthenia, and decreased appetite. More grade 3 or higher AEs and serious adverse events (SAEs) occurred in the olaparib group, most of which were attributable to anemia. It was noted that AEs appeared to be manageable with treatment interruptions and dose modifications. Overall, pERC agreed with the CGP as well as with the registered clinicians providing input, that olaparib's overall toxicity profile was acceptable and manageable.

pERC members discussed the available patient-reported outcomes data from the PROfound trial and noted that results suggested that olaparib showed less deterioration in health-related QoL functioning over time

compared with the control group. As well, patients appeared to benefit from a prolonged time-to-pain progression compared with the control group. However, the Committee noted that given the open-label design of the trial, the exploratory nature of the analysis, the relatively low compliance rates, and the gradually declining number of patients providing assessments over time, there was uncertainty in the results. The Committee concluded that, overall, there appeared to be no detriment to QoL from the treatment with olaparib compared with the investigators' choice of an ARAT.

Furthermore, pERC discussed olaparib in the context of other currently available treatment options in the requested patient population. pERC agreed with the CGP and the registered clinicians that commonly used standard of care options for patients with mCRPC include taxane-based chemotherapy (docetaxel, cabazitaxel [approved only after docetaxel]) and radium-223 (for patients with bone predominant disease) and rarely an alternate ARAT (abiraterone or enzalutamide). pERC noted that taxane-based chemotherapy is the most commonly offered treatment; however, many patients are not eligible to receive taxane-based chemotherapy because of their older age and comorbidities. Sequencing of alternate ARATs is rarely done and not funded in most provinces. pERC noted that there is currently insufficient evidence to guide the sequencing of treatments after progression on an ARAT, as well as a paucity of treatment options. pERC agreed with the CGP that the current treatment selection in this setting depends on patient preferences, comorbidities, individual toxicity profiles, types of prior treatment received, and treatment availability. pERC highlighted the benefit of having more than 1 option for treatment from a patient tolerance perspective. As well, pERC noted the unmet need for treatments with new mechanism of actions with biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations.

In the absence of a direct comparison of olaparib with other relevant treatment options, pERC considered sponsor-provided indirect treatment comparisons (ITCs) comparing the efficacy of olaparib with docetaxel, cabazitaxel, radium-223, and an ARAT. pERC noted that the results of the ITCs favoured olaparib for PFS in the comparison with docetaxel, cabazitaxel, and an ARAT. [redacted] The results for OS favoured olaparib in the comparison with an ARAT, with [redacted]. However, pERC acknowledged the limitations noted by the CADTH Methods Team and agreed with concerns regarding the lack of data to assess the comparative effect of cabazitaxel, docetaxel, and and radium among *BRCA1*, *BRCA2*, and *ATM* carriers and heterogeneity across the study designs and populations. Therefore, pERC agreed with the CGP's and CADTH Methods Team's conclusion that there is uncertainty with respect to the comparative effectiveness of olaparib versus docetaxel, cabazitaxel, and radium-223.

In summary, pERC concluded that, compared with the investigators' choice of an ARAT, there is a net clinical benefit of olaparib based on statistically significant and clinically meaningful improvements in rPFS and OS, a manageable toxicity profile, and no detrimental impact on QoL. However, given the lack of robust direct or indirect comparative data, pERC was unable to conclude on the relative efficacy and safety of olaparib compared with other relevant treatment options, such as taxane-based chemotherapy (i.e., docetaxel, cabazitaxel) or radium-223.

pERC deliberated on the patient advocacy group input from 1 patient group and noted that, according to patients, key symptoms of concern with prostate cancer included fatigue and a general loss of physical condition, difficulty in getting an erection, and problems with urination. Issues with loss of bladder and bowel control and living with uncertainty and mental health issues such as anxiety, panic attacks, and depression were also highlighted. The majority of patients reported that the most important symptoms to manage were fatigue and general loss of physical condition. None of the patient respondents had direct experience with using olaparib for prostate cancer. pERC considered that patient respondents valued maintenance of QoL, delay in the onset of symptoms, reduced side effects, and an increased ease of use. Additionally, pERC commented on the delay in pain progression and skeletal-related events observed with olaparib, the unmet need for biomarker-directed therapies, and the ease of taking olaparib orally versus having to go to the hospital for IV infusions. pERC concluded that olaparib aligned with the following patient values: delays disease progression, the onset of symptoms, pain progression, and skeletal-related events; has manageable side effects with no negative impact on QoL; fulfills an unmet need; and offers an additional treatment option, with a convenient oral route of administration. However, pERC noted that in some jurisdictions, oral medications are not funded by the same mechanism as intravenous cancer medications.

pERC deliberated on the cost-effectiveness of olaparib compared with currently recommended treatment alternatives. pERC noted that the comparative efficacy of olaparib versus docetaxel and cabazitaxel was highly uncertain. Even compared to the investigators' choice of an ARAT, pERC noted that the relative benefit of olaparib was highly uncertain due to the methodology used to account for treatment switching. pERC concluded that olaparib would not be considered cost-effective at a willingness to pay threshold of $50,000 per QALY and substantial price reductions would be required as it was unclear if olaparib offered a clinical benefit over docetaxel or cabazitaxel.

pERC also discussed the budget impact analysis. pERC considered the estimated budget impact to be considerable and noted that, moving forward, the budget impact would be contingent on the testing availability, clinical use and detection rates.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated on:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the sponsor's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from 1 patient advocacy group Canadian Cancer Survivor Network (CCSN)
- Input from 4 registered clinicians: one each from British Columbia, Alberta, Ontario, and Nova Scotia
- Input from CADTH's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One registered clinician from Ontario
- The PAG
- The sponsor, AstraZeneca Canada Inc.

The pERC Initial Recommendation was to recommend reimbursement of olaparib as monotherapy for the treatment of adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes *BRCA* or *ATM* who have progressed following prior treatment with a new hormonal agent/ ARAT if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the registered clinician from Ontario, the PAG, and the sponsor agreed with the Initial Recommendation. No feedback on the pERC Initial Recommendation was received from a patient advocacy group.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of olaparib as a monotherapy for the treatment of adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in HRR genes *BRCA* or *ATM* who have progressed following prior treatment with an ARAT.

Studies included: One multinational, open-label, randomized phase III trial (PROfound trial)

The CADTH systematic review included 1 randomized controlled trial (RCT) (PROfound) that assessed the efficacy and safety of olaparib as a monotherapy compared with the investigators' choice of an ARAT (i.e., enzalutamide or abiraterone) in patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes *BRCA* or *ATM* who have progressed following prior treatment with an ARAT.

A total of 387 patients were randomized (Cohort A included 245 patients and Cohort B included 142 patients). Patients were included in Cohort A if they had a *BRCA1*, *BRCA2*, or *ATM* mutation, whereas those in Cohort B had a mutation in 12 other genes involved in HRR (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*). Patients in both Cohort A and Cohort B were randomized in a 2:1 ratio to receive either olaparib (300 mg twice daily) or the investigators' choice of an ARAT (enzalutamide [160 mg daily] or abiraterone acetate [1,000 mg daily with 5 mg of prednisone twice daily]). Cohort A was the primary analysis population and analyses of Cohort A were included in the multiple testing hierarchy whereas results for Cohort B were non-inferential. Data from Cohort B were

beyond the scope of the review, as it did not include *BRCA1*, *BRCA2*, or *ATM* carriers, and therefore did not align with the population in the requested reimbursement criteria.

At the time of the final analysis — March 20, 2020 — the duration of treatment was 7.6 (range = 0.03 to 28.9) months in the olaparib group and 3.6 (range = 0.6 to 29.1) months in the control group. Among the 83 patients in the control group who crossed over to receive olaparib, the median duration was 4.8 (range = 0.2 to 28.9) months.

Patients were included in the trial if they met the following criteria: males aged 18 years and older with a histologically confirmed diagnosis of prostate cancer; progressed on prior ARAT (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or CRPC; radiographic progression while on androgen deprivation therapy (ADT) (or after bilateral orchiectomy); qualifying HRR mutation in tumor tissue by the Foundation Medicine Clinical Trial Improvement Amendments HRR (LYNPARZA HRR) clinical trial assay; normal organ and bone marrow function; and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2. Patients were permitted to be enrolled in the trial if they had previous taxane-based chemotherapy.

Patients in the control group who had radiographic progression by blinded independent central review (BICR) were eligible to crossover and receive olaparib. However, patients who had radiographic progression as assessed by the investigator were not permitted to crossover until after the primary analysis. Patients who crossed over to receive olaparib were able to continue treatment until the investigator's opinion was made, as long as they did not meet any other discontinuation criteria.

Patient populations: Median age 68, majority with *BRCA2* alterations, most received previous taxane-based chemotherapy

Among patients in Cohort A, the median age in the olaparib group was 68 (range: 47 to 86) years and 67 (range: 49 to 86) years in the control group, more than half of all patients had measurable disease at baseline (59% in olaparib and 55% in control), and the majority of patients received previous taxane-based chemotherapy (65% in olaparib and 63% in control). In Cohort A, the median time from mCRPC to randomization was 23.3 (range = -6 to 121) months in the olaparib group and 22.5 (range = 1 to 105) months in the control group. The percentage of patients with visceral metastases was 28% in the olaparib and 39% in the control group, the median baseline prostate-specific antigen (PSA) concentration was 62.2 (interquartile range [IQR], 21.9 to 280.4) in olaparib and 112.9 (IQR, 34.3 to 317.1) in the control group. There were 37% of patients with an ATM alteration in the olaparib group and 29% of patients in control group, 49% of patients with a *BRCA2* alteration in the olaparib group and 57% in the control group, and 5% of patients with a *BRCA1* alteration in the olaparib and 6% in the control group.

Key efficacy results: Statistically significant improvements in rPFS and OS in favour of olaparib

The primary end point was rPFS by BICR using Response Evaluation Criteria in Solid Tumors (RECIST 1.1 regarding soft tissue) and Prostate Cancer Clinical Trials Working Group 3 (PCWG3 bone) criteria in Cohort A. Secondary outcomes were confirmed ORR by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A, rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A+B, pain progression based on the Brief Pain Inventory Short Form (BPI-SF) item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) in Cohort A and OS in Cohort A.

The first data cut-off date was on June 4, 2019, which represents the date of the primary analysis and a median follow-up of 12.57 (range = 1.87 to 23.89) months in the olaparib group and 13.19 (range = 0.95 to 23.23) months in the control group for Cohort A. The second data cut-off date was on March 20, 2020, which represents the date of the final analysis and a median follow-up of 21.91 (range = 1.87 to 33.41) months in the olaparib group and 21.04 (range = 0.95 to 32.76) months in the control group for Cohort A.

At the primary analysis, 65.4% (n = 106) of patients in the olaparib group had progressed or died as compared to 81.9% (n = 68) of patients in the control group. The median rPFS, as assessed by BICR in the olaparib group, was 7.39 (95% confidence interval [CI], 6.24 to 9.33) months and it was 3.55 (95% CI, 1.91 to 3.71) months in the control group. Treatment with olaparib was associated with a statistically significant prolonged rPFS, as assessed by BICR compared to the control group (hazard ratio [HR] = 0.34; 95% CI, 0.25 to 0.47; P < 0.001). A pre-specified sensitivity analysis of rPFS, as assessed by the investigator, showed similar results (HR = 0.24; 95% CI, 0.17 to 0.34).

The effect of olaparib on rPFS, as assessed by BIRC was compared to the control group and stratified by genotype carrier status in Cohorts A + B. For *BRCA1* and/or *BRCA2* carriers, olaparib was associated with a longer rPFS, as assessed by BICR and as compared to the control group (HR = 0.22; 95% CI, 0.15 to 0.32), while there was no treatment difference on rPFS, as assessed by BICR, for ATM carriers. However, these results should be interpreted with caution because they are considered exploratory and not adjusted for multiplicity.

Thirty-three percent of patients in the olaparib group had confirmed ORR as compared to 2% in the control group. A statistically significant difference in ORR was demonstrated with an odds ratio of 20.86 (95% CI, 4.18 to 379.18; P < 0.001).

Treatment with olaparib was associated with a statistically significant prolonged time-to-pain progression as compared to the control group (HR = 0.44; 95% CI, 0.22 to 0.91; P = 0.02).

The interim analysis for OS occurred at the primary analysis (June 4, 2019) and 33.3% of patients (n = 54) had died in the olaparib group as compared to 47.0% (n = 39) in the control group. At that time, 51 of 83 (61%) patients in Cohort A and 24 of 48 (50%) patients in Cohort B switched over to receive olaparib. The median OS was 18.5 (95% CI, 17.22 to not reached) months in the olaparib group and 15.11 (95% CI, 11.33 to 19.09) months in the control group. Treatment with olaparib was associated with prolonged survival time as compared to the control group (HR = 0.62; 95% CI, 0.41 to 0.95; P = 0.02). At the final analysis (March 20, 2020), 67% of patients in the control group of Cohort A had crossed over and received olaparib (n = 56). In the olaparib group, 56.2% of patients (n = 91) had died as compared to 68.7% (n = 57) of patients in the control group. The median OS was 19.1 (95% CI, 17.4 to 23.4) months in the olaparib group and 14.7 (95% CI, 11.9 to 18.8) months in the control group. Treatment with olaparib was associated with a statistically significant prolonged survival time as compared to the control group (HR = 0.69; 95% CI, 0.50 to 0.97; P = 0.02). Results may be confounded because of patient crossover to olaparib in the control group. Pre-specified sensitivity analysis adjusting for patient crossover showed a similar treatment effect (HR = 0.42, 95% CI, 0.19 to 0.91).

Patient-reported outcomes: Overall there appears to be no detriment to QoL from the treatment with olaparib compared with the investigators' choice of ARAT

The Functional Assessment of Cancer Therapy—Prostate Cancer (FACT-P) and the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) were used to assess health-related quality of life (HRQoL) in Cohort A. The questionnaires were administered at baseline, week 8, week 16, and week 24, and then were continued to be administered to all patients (who had not withdrawn consent) every 8 weeks until 24 weeks after progression. Patients who discontinued treatment prior to having radiographic progression as assessed by BICR or as assessed by the investigator (post primary analysis) were given the assessments for 24 weeks post progression. The HRQoL analyses were not included in the testing hierarchy and therefore no adjustments were made for type I error.

In Cohort A, the baseline patient adherence rates for the FACT-P were 68% for patients receiving olaparib and 70% for patients receiving control, whereas the overall adherence rate was 60% for those who received olaparib (n = 162) and 53% for those who received control (n = 83).

At baseline, the mean (standard deviation) FACT-P total scores were similar between the olaparib and the control group in Cohort A. Results suggested that olaparib showed less deterioration in health-related QoL functioning over time compared with the control group.

There was a clinically meaningful difference between the study groups in Cohort A for the adjusted mean change from baseline to week 32 in FACT-P total score, trial outcome index, and PCS. Results for FWB, PWB, and FAPSI-6 were not clinically meaningful. A higher proportion of patients in the olaparib group reported clinically meaningful improvements in HRQoL.

The baseline patient adherence rates for the EQ-5D-5L were [redacted] for patients receiving olaparib and [redacted] for patients in the control group, [redacted] for those who received olaparib ([redacted]) and [redacted] for those in the control group ([redacted]). There were [redacted]. The EQ-5D-5L data [redacted].

Due to the open-label design of the trial, the exploratory nature of the analyses, the relatively low compliance rates, and the gradually declining number of patients providing assessments over time, there was uncertainty in the results.

Safety: Manageable Toxicities

Most patients in the trial experienced at least 1 any-grade TEAE. In the final analysis, 96% and 88% of patients experienced an any-grade TEAE in the olaparib and control groups, respectively. The most frequently occurring TEAEs in both groups included: anemia (olaparib: 50%, control: 15%, crossover: 52%), nausea (olaparib: 43%, control: 21%, crossover: 29%), fatigue or asthenia (olaparib: 42%, control: 33%, crossover: 25%), and decreased appetite (olaparib: 31%, control: 18%, crossover: 18%). More patients in the olaparib group reported an AE of grade 3 or higher as compared to those in the control group (olaparib: 52%, control: 40%, crossover: 59%). Most of the grade 3 or higher AEs were attributable to anemia in both study groups: anemia (olaparib: 23%, control: 5%, crossover: 29%).

More patients in the olaparib group had an SAE as compared to the control group and crossover (37% versus 30% versus 33%). More patients in the olaparib group had serious anemia relative to the control group (9% versus 0%).

Twenty percent of patients in the olaparib group discontinued their assigned therapies due to an AE, as compared to 8% in the control group. More patients in the olaparib group than the control group had an AE leading to treatment interruption or a dose reduction (46% versus 19% and 23% versus 5%, respectively).

Overall, there were 19 AEs leading to death in the trial (olaparib = 4% [n = 10] versus control = 5% [n = 6] and crossover = 4% [n = 3]). Two deaths in the trial were considered to be related to the study drug: 1 death in the olaparib group from pneumonia and neutropenia and 1 death from pleural effusion in the control group.

Limitations: No direct comparative data to taxane-based chemotherapy (docetaxel, cabazitaxel)

The CADTH Methods Team summarized and critically appraised sponsor-provided ITCs comparing the efficacy of olaparib with docetaxel, cabazitaxel, radium-223, and an ARAT. The results suggested that, for PFS, olaparib was favoured in the comparison with docetaxel, cabazitaxel, and an ARAT. [redacted]. The results for OS favoured olaparib in the comparison with an ARAT, with [redacted].

The CADTH Methods Team concluded that, because of a high heterogeneity between the trials (lack of data to assess the effect of cabazitaxel, docetaxel, and radium-223 among *BRCA1*, *BRCA2*, and *ATM* carriers; differences in prior anti-cancer therapies; presence of visceral metastases; and the administration of prophylactic granulocyte colony-stimulating factor), the comparative effectiveness estimates from the ITCs are likely biased and the magnitude or direction of the bias cannot be established. Although the investigators conducted a matched adjusted indirect comparison (MAIC) to account for the heterogeneity, the impact of the heterogeneity was still unclear because the results of the MAIC may be biased due to the exclusion of many important effect modifiers.

Need and burden of illness: Unmet need for targeted treatment for patients with mCRPC who harbour HRR mutations

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers). The number of new prostate cancer cases in 2020 has been estimated at approximately 23,300, with 4,200 expected deaths. One in 4 patients with prostate cancer will die of the disease. The 5-year survival rate of mCRPC is approximately 30%. Both germline and somatic alterations in DNA repair genes occur in 20% to 30% of patients with mCRPC. Metastatic castration-resistant prostate cancer mutations in the *BRCA* (*BRCA1* and/or *BRCA2*) gene are the most common HRR gene mutations (*BRCA2* is more prevalent than *BRCA1*), with ATM being the second most frequently mutated HRR gene. It has been suggested that patients with mCRPC and an HRR gene mutation have a poorer prognosis compared with unselected mCRPC patients. There are currently no standard funded biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations. Available treatment options in Canada for patients with mCRPC who have progressed following prior treatment with an ARAT (i.e., enzalutamide or abiraterone) include taxane-based chemotherapy (docetaxel, cabazitaxel [approved only after

docetaxel]), radium-223 (for patients with bone predominant disease), and alternate ARAT (abiraterone or enzalutamide). The most commonly offered treatment is taxane-based chemotherapy; however, many patients are not eligible to receive taxane-based chemotherapy because of their older age and comorbidities. Sequencing of alternate ARATs is rarely done and funded only in a few provinces. There is an unmet need for effective new therapies with manageable toxicity profile for patients with mCRPC who harbour HRR mutations (*BRCA1*, *BRCA2*, and *ATM* mutations) and who may not be eligible for standard of care therapies.

Registered clinician input: Olaparib fulfills unmet need, better tolerated than docetaxel
Clinician input was provided by 4 individual clinicians: 1 each from British Columbia, Alberta, Ontario and Nova Scotia. There are currently no standard, funded, biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations; therefore, according to clinician input, olaparib would be meeting a significant unmet need. Clinicians stated that they would prescribe this drug to patients with HRR gene-mutated mCRPC who have progressed after an ARAT and either before or after taxane-based chemotherapy, depending on a patient's fitness and preferences. These patients do not have alternative effective therapies and this drug is significantly different from other available therapies. Additionally, there are no subpopulations who should be restricted from receiving this therapy if eligible HRR mutations have been identified. It was stated that the drug under review is comparable in efficacy to taxane-based chemotherapy (though limited by cross-trial comparisons of very different patient populations) but demonstrates a significantly improved tolerability. The advantage of olaparib is that it would be more tolerable in patients who are not eligible for taxane-based or platinum-based chemotherapy. Clinicians indicated that the drug under review would not replace an available treatment but would be preferred to other therapies for patients with HRR gene mutations after an ARAT because of the ease of administration, tolerability, and efficacy. HRR alteration testing should be implemented, as patients would need access to testing in order to be eligible for the treatment under review.

PATIENT-BASED VALUES

Values of patients with prostate cancer: Maintaining QoL, delay in the onset of symptoms, reduction in side effects, increase in ease of use due to oral administration.
One patient group, CCSN, provided input on olaparib for mCRPC. The most common symptoms of prostate cancer reported by patients were fatigue and general loss of physical condition, difficulty in getting an erection, and problems with urination. Issues with a loss of bladder and bowel control, living with uncertainty, and mental health issues such as anxiety, panic attacks, and depression were also highlighted. The majority of patient respondents indicated that the most important symptoms to manage were fatigue and general loss of physical condition; others highlighted that urination problems were essential to manage.

The majority of respondents indicated that their needs are being met by their current treatments and that they have not had issues accessing their current therapy. However, it was noted that since many advanced cancer cases become castration-resistant, there is a need for more therapies. The most commonly reported expectation for a new drug was being able to maintain QoL. Respondents also indicated that they valued a delay in the onset of symptoms, a reduction in the side effects they experience from their current medications or treatment, and an increased ease of use due to oral administration. Most patients valued a new drug with no or fewer side effects than with current treatment.

Patient values on treatment: None of the patient respondents had experience with olaparib
None of the participants in the survey had experience with the drug under review.

ECONOMIC EVALUATION

Olaparib is available as a 100 mg or 150 mg tablet. The recommended total daily dose of olaparib is 600 mg, taken as two 150 mg tablets twice daily, with a 100 mg tablet available for dose reduction. It is recommended that olaparib treatment be continued until progression of the underlying disease or unacceptable toxicity. At a submitted price of $65.89 per 150 mg tablet, the total drug acquisition cost of olaparib per patient, per 28 days was $7,380, and $96,269 annually.

The sponsor submitted a cost-utility analysis based on a partition-survival model that compared olaparib to investigators' choice of an ARAT (abiraterone acetate, or enzalutamide), cabazitaxel, or docetaxel, for adult patients with mCRPC and deleterious germline and/or somatic mutations in HRR. The model consisted of 3 primary health states (progression-free survival [PFS], progressed disease, and death). Progression was defined according to objective rPFS criteria. Costs and clinical outcomes (i.e., QALYs and life-years [LYs]) were modelled over a 10-year time horizon from the perspective of the public health care payer. Clinical efficacy was based on OS and rPFS curves from the PROfound trial for olaparib and investigators' choice of an ARAT, which were extrapolated using parametric survival analysis to determine the proportion of patients in each health state over the model time horizon. Hazard ratios for cabazitaxel were obtained from a sponsor-submitted indirect treatment comparison and applied to the investigators' choice of an ARAT rPFS and OS curves. The comparative efficacy of docetaxel was assumed to be equal to cabazitaxel. Health state utility values applied in the economic model were calculated from a regression model based on the PROfound trial population.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- The OS for investigators' choice of an ARAT is uncertain because of methods used to account for treatment switching that occurred in the PROfound trial. Specifically, the assumption that switchers would achieve the full treatment effect as those who were initially assigned to olaparib may not be clinically appropriate. Due to the lack of clinical data available to inform the OS of non-switchers, the true OS benefit for patients receiving only investigators' choice of an ARAT remains unknown.
- The CADTH clinical review concluded that the comparative efficacy estimates of olaparib versus cabazitaxel and docetaxel are highly uncertain due to clinical heterogeneity between the trials (e.g., HRR genotype status, proportion of patients with visceral metastases, etc.) and the exclusion of effect modifiers.
- There was uncertainty regarding the long-term parametric extrapolations of OS and rPFS beyond the observed trial period for olaparib and investigators' choice of an ARAT. The sponsor's chosen extrapolated curves do not align with clinical expectations of the anticipated treatment effects of olaparib beyond the trial period. The extrapolation of OS beyond the trial period following radiographic progression was highly uncertain.
- There was uncertainty with the utility values used in the model. Health state utilities were adjusted to incorporate additional time-to-death disutilities in the final year prior to death, which may have double-counted the disutility associated with post-progression survival.
- Total drug acquisition costs of olaparib and investigators' choice of an ARAT were likely underestimated because of the sponsor's use of rPFS data to model treatment discontinuation.
- The cost of docetaxel was overestimated since there is a generic formulation available

Given issues with the sponsor's probabilistic sampling, CADTH undertook deterministic reanalyses of the economic model to address several limitations, including a more clinically plausible extrapolation for OS, rPFS, and time to treatment discontinuation (TTD); and the use of trial-based utility estimates according to progression only.

Based on CADTH reanalyses, the incremental cost-effectiveness ratio (ICER) for olaparib versus docetaxel was $459,527 per QALY gained; a 71% price reduction for olaparib is required to achieve an ICER of less than $50,000 per QALY. The CADTH base case is reliant on estimates from the sponsor's indirect treatment comparison regarding the comparative efficacy versus docetaxel and cabazitaxel. As noted by CADTH clinical experts, there is no robust evidence to ascertain which of the agents (i.e., olaparib, docetaxel, cabazitaxel, or radium-223) has superior efficacy. Given the high degree of clinical uncertainty, to ensure cost effectiveness at any willingness-to-pay threshold, a further price reduction may be required so that olaparib costs no more than the lowest cost comparator.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact

CADTH revised the market shares for olaparib and comparator treatments and reduced the cost of docetaxel as part of the base case, which resulted in an estimated budget increase of $29,030,654 over 3

years. Uncertainty remains with the potential market uptake of olaparib in light of the uncertainty around HRR testing availability and detection rates in mCRPC.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Maureen Trudeau, who did not vote due to her role as Committee Chair.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of olaparib for mCRPC, through their declarations, no members had a real, potential, or perceived conflict and based on the application of the *pCODR Conflict of Interest Guidelines*, none of the members were excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the CADTH website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *pCODR Disclosure of Information Guidelines*.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
Eligible patient population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with olaparib:	
• patients with ECOG PS > 2	• The PROfound trial included patients with ECOG PS of 2 or less. Most patients in the trial had ECOG PS of 0 or 1. The CGP noted that approximately 15% of patients seen in clinical practice have worse performance status than patients included in the PROfound trial (ECOG > 2). pERC agreed with the CGP that it would be reasonable to offer olaparib to patients with ECOG PS of > 2, especially in patients whose poor ECOG PS may be directly related to the underlying prostate cancer or tumour-related symptoms.
• patients who have had previous treatment with DNA-damaging cytotoxic chemotherapy (e.g., platinum or mitoxantrone)	• The PROfound trial excluded patients with previous treatment with DNA-damaging cytotoxic chemotherapy. In amendment 3 (June 4, 2018), it was clarified that patients could have received prior treatment with DNA-damaging cytotoxic chemotherapy for non-prostate cancer. pERC agreed with the CGP that it would be reasonable to generalize the PROfound trial results to patients who have had previous treatment with DNA-damaging cytotoxic chemotherapy (e.g., platinum or mitoxantrone) because olaparib has a completely different mechanism of action and no overlapping toxicities.
• patients with brain metastases	The PROfound trial excluded patients with known brain metastases. The CGP noted that brain metastases are rare in patients with mCRPC. pERC agreed with the CGP and recommended discretion of the treating physician for use of olaparib in patients with stable brain metastases.
• patients who were unable to tolerate either enzalutamide or abiraterone	• pERC agreed with the CGP that there is currently no evidence on switching patients who are intolerant to enzalutamide to abiraterone or vice versa. However, pERC and the CGP agreed that it would be reasonable to offer olaparib to patients who are unable to tolerate an ARAT.
• patients who have not experienced an ARAT.	• The PROfound trial included patients who must have progressed on prior ARAT (i.e., enzalutamide and/or abiraterone) for the treatment of metastatic prostate cancer and/or CPRC. Only very few patients in the overall study population received an ARAT before the development of mCRPC. The CGP noted that patients who were ARAT-naive were excluded from the PROfound study. pERC agreed with the CGP that there is currently insufficient evidence to generalize the results of the PROfound trial to these patients.
If recommended for reimbursement, PAG noted that patients currently treated with a taxane-based regimen would need to be addressed on a time-limited basis. Hence, PAG is seeking advice on whether such patients could be switched to olaparib if their	pERC agreed with the CGP that patients with mCRPC and *BRCA1*, *BRCA2*, or *ATM* mutations, who have received prior ARAT therapy, are currently receiving a taxane-based regimen, and have not progressed would need to be addressed on a time-limited basis.

mutation tests results are found to be positive.	
Implementation factors	
PAG noted that patients with specific alterations in any of the 15 HRR genes were included in the trial and seeks confirmation that the overall effect is generalizable to every tested mutation.	pERC noted that the CGP felt that the trial results can be generalized to patients in Cohort B with additional 12 gene mutation (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, and *RAD54L*), as these patients were included in the PROfound trial and have aggressive disease with very few therapeutic options. However, Cohort B is beyond the Health Canada–approved indication and the reimbursement request, which are limited to Cohort A (*BRCA1, BRCA2*, and *ATM*); therefore, pERC was unable to recommend olaparib for patients in Cohort B.
PAG noted that, in the trial, disease progression was evaluated according to imaging-based findings. However, in actual practice, clinicians often use a combination of radiographic, biochemical, and clinical factors, and usually determine progression and discontinuation of therapy upon worsening of 2 of these 3 criteria. Hence, PAG seeks a clear definition of disease progression (e.g., through a combination of radiographic, biochemical, and clinical results) and advice on criteria for treatment discontinuation.	Commonly, clinicians will seek confirmation of progression in all possible areas, i.e., PSA progression, clinical progression (i.e., well-being of patient), and radiographic progression. At least 2 out of these 3 criteria should be confirmed to discontinue treatment. PSA and radiographic progression tend to align with each other. However, if a patient has PSA progression alone (no radiographic progression or development of symptoms attributable to cancer progression), then a patient may continue treatment. If radiographic progression occurs without PSA progression or loss of clinical benefit, treatment may continue beyond radiographic progression. According to the PROfound trial protocol, the investigational product could be discontinued based on objective radiographic progression by BICR alone (criteria for bone progression required a confirmation scan ≥ 6 weeks later). pERC agreed with the CGP that the trial parameters in the PROfound trial set for treatment discontinuation are generalizable to the Canadian clinical practice, as radiographic and PSA progression tend to align with each other. pERC and the CGP agreed that the trial parameters, as well as the Health Canada Product Monograph treatment discontinuation criteria, are reasonable.
• PAG is seeking guidance on potentially stopping olaparib to manage toxicity and then restarting the therapy.	pERC agreed with the CGP that the recommendations regarding dose reduction, as set out in the Health Canada Product Monograph, are reasonable. "Treatment may be interrupted to manage adverse events and dose reduction can be considered. The recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 500 mg. If a further dose reduction is required, the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 400 mg." (Product Monograph LYNPARZA) In the PROfound trial, treatment with olaparib could be interrupted or dose-reduced due to any observed toxicities. Repeated dose interruptions were allowed for a maximum of 4 weeks; the study investigators were to be informed if the interruption lasted longer than this period. pERC and the CGP felt that the parameters set out in the trial, which allowed a 4-week dose interruption before restarting olaparib, seemed reasonable.
Sequencing and priority of treatment	
Circumstances where olaparib would be preferable to standard docetaxel chemotherapy.	pERC agreed with the CGP that olaparib would be preferable in patients who harbour *BRCA1, BRCA2*, or *ATM* mutations following progression on ARAT therapy. These tumours are biologically

	more aggressive and it makes the most sense to use a more targeted therapy as early as possible in the disease course. Many patients are ineligible for docetaxel chemotherapy or refuse this treatment based on side effects. Therefore, olaparib would be an option for these patients. Additionally, the drug under review is taken orally; therefore, it is easier for both patients and the healthcare system to administer, especially during the COVID-19 pandemic.
Options after failure of olaparib including potential ARAT re-treatment.	pERC was unable to make an informed recommendation on the optimal sequencing of available treatments following disease progression on treatment with olaparib. pERC noted that it did not review evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon the implementation of reimbursement of olaparib and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.
Sequences of drugs leading to olaparib including reserving the latter for patients who have progressed on all ARATs and taxane-based options.	As previously mentioned, pERC and the CGP noted that olaparib would be preferable in patients who harbour *BRCA1, BRCA2*, or *ATM* mutations following progression on ARAT therapy. These tumours are biologically more aggressive and it makes the most sense to use a more targeted therapy as early as possible in the disease course. Olaparib should not be reserved for patients who have progressed on all ARATs and taxane-based options. As many studies have demonstrated, sequencing ARATs is not effective and many patients are not eligible for taxane-based chemotherapy. The option to use olaparib after an ARAT as per the study inclusion criteria should be an option. There is insufficient evidence to determine whether olaparib should preferentially be used in patients who have already received docetaxel prior to progressing on an ARAT or not. The exploratory subgroup analysis from the PROfound trial suggested a benefit in patients irrespective of prior taxane-based chemotherapy use. The use of taxane-based chemotherapy in mCRPC greatly depends on patient preference, as many patients are either unfit or unwilling to receive chemotherapy. pERC agreed with the CGP that prior taxane-based chemotherapy use should not be an exclusion for the reimbursement of olaparib. pERC agreed with the CGP that, as olaparib is a genomically driven treatment, the most important indication is in applicable HRR mutations regardless of prior docetaxel use in the mCRPC setting.
For patients who received docetaxel in the metastatic castrate-sensitive space, is there evidence and interest for using olaparib in the castrate-resistant space?	pERC agreed with the CGP that the number of patients who receive docetaxel in the mCSPC space has significantly declined over the last several years. pERC and the CGP felt that it would be reasonable to use olaparib in the mCRPC space for patients who received docetaxel in the mCSPC space. Because olaparib is a genomically driven treatment, pERC agreed with the CGP that the most important indication is in applicable HRR mutations regardless of prior docetaxel use in the mCSPC setting.
Sequencing and priority of treatment	
PAG noted that the HRR assay used in the trial was the LYNPARZA HRR assay and would like to know if other assays or homegrown	pERC noted that the BRCA and ATM mutation status should be determined using a validated testing method.

methodologies could be used instead.	
PAG reflected on the relative clinical value of the HRR companion test. It is unclear if the test results from the HRR assay would significantly alter patient management; for instance, by predicting disease course or response to treatments. PAG seeks additional guidance on the broader use of HRR and *BRCA* test results in prostate cancer. This guidance would help inform the optimal time (e.g., at diagnosis, during treatment with an ARAT, upon progression) for when BRCA and/or HRR testing should be performed.	pERC agreed with the CGP that it would prefer to have testing done early in the treatment trajectory. Preferred timing would be either: • at diagnosis, to be able to inform family members and plan out treatment approaches; or • during treatment with an ARAT, to be able to treat patients with olaparib upon progression. If testing was to be initiated at the time of progression, time may run out before test results come back and patients will have to be started on an alternative treatment.

ARAT = androgen receptor-axis-targeted therapy; BICR = blinded independent central review; BRCA = breast cancer gene; CGP = Clinical Guidance Panel, CRPC = castration-resistant prostate cancer; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRR = homologous recombination repair; mCSPC = metastatic castration-sensitive prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; PAG = Provincial Advisory Group; pCODR = pan-Canadian Oncology Drug Review; pERC = pCODR Expert Review Committee; PSA = prostate serum antigen.