Summary

Drugs Under Review

ICER's report reviewed the clinical effectiveness and value of **olaparib (Lynparza®, AstraZeneca), rucaparib (Rubraca®, Clovis Oncology),** and **niraparib (Zejula™, Tesaro),**as maintenance therapy in women with platinum-sensitive disease, or as treatment of recurrent disease with a BRCA mutation. The report was subject to public deliberation during a meeting of the Midwest Comparative Effectiveness Public Advisory Council.

ICER Evidence Ratings

- In recurrent, BRCA mutated ovarian cancer, evidence is promising but inconclusive for both olaparib and rucaparib compared to standard chemotherapy. Evidence is insufficient on niraparib in this indication.
- For each of the three drugs used as maintenance therapy in platinum-sensitive disease, the evidence provides moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit when compared to surveillance.

Other Benefits

ICER's report also considered benefits beyond the data captured in clinical trials, including:

- A novel mechanism of action, providing an additional option in a disease space where treatments have not changed materially in 20 years.
- Added convenience of an oral medication

Value-Based Price Benchmarks

With the exception of olaparib for recurrent disease, all drugs would need to be discounted significantly to align with the potential benefit they provide to patients.

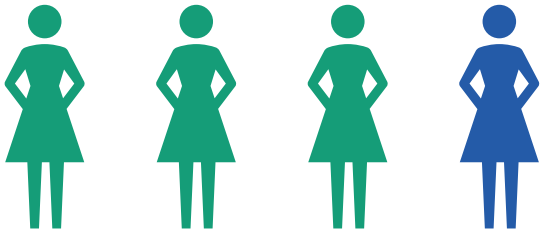
Depending on the drug, discounts needed range from 50-78%.

Key Policy Recommendations

- Current pricing of PARP inhibitors has the potential to align with clinical benefit in recurrent disease, but alignment will be more challenging in maintenance therapy. To facilitate affordability and patient access, prices must be lowered.
- Single-arm studies and surrogate endpoints do not provide the type of information that clinicians and patients need to make treatment decisions. Critical evidence gaps must be addressed in the design and execution of clinical research by researchers, manufacturers, and patient groups alike.
- Payers and manufacturers must work together to establish innovative payment mechanisms to seek affordability for patients, including outcomes based contracting and/or package discounting.

Do these new drugs meet an important need?

What is ovarian cancer?



Almost 75% of women with ovarian cancer are diagnosed with advanced disease.

Ovarian cancer is the fifth-leading cause of cancer death in women. Due to an absence of early symptoms and lack of an accurate screening strategy, nearly 75% of women with ovarian cancer are diagnosed with advanced disease. At this stage, recurrence is common, and those who continue through three or more lines of therapy are likely to die or experience recurrence within six months.

Treating ovarian cancer

There are several options for patients when they experience recurrence, including several chemotherapy regimens or a drug called bevacizumab (Avastin®, Genentech).

Recently, ongoing trials have indicated promising results for a newer class of targeted oral agents, poly ADP-ribose polymerase (PARP) inhibitors.

ICER's report looks at three FDA-approved PARP inhibitors:

Drug name
Olaparib (Lynparza®, AstraZeneca)
Rucaparib (Rubraca®, Clovis Oncology)
Niraparib (Zejula™, Tesaro)

The report reviews evidence on the three drugs for two populations:

- Treatment of recurrent ovarian cancer in women with a breast cancer (BRCA) gene mutation, and
- Maintenance therapy for recurrent disease in women who have previously responded to platinum-based chemotherapy ("platinum-sensitive" disease).

How strong is the evidence that **PARP inhibitors** improve patient outcomes?

Key Outcomes

ICER's report reviews evidence on key outcomes studied in clinical trials, including:

- **Overall survival (OS):** The length of time from the start of treatment for ovarian cancer, or from diagnosis, until death.
- **Progression-free survival (PFS):** Time from a pre-defined date to tumor progression or death.
- **Quality of life (QoL):** Patient-reported quality of life measured by multiple assessments.
- **Objective Response Rate (ORR):** The proportion of patients showing a confirmed complete or partial response to treatment, based on tumor measurement and other criteria.

Olaparib

For Recurrent, BRCA-Mutated Disease	**For Maintenance Therapy in Platinum-Sensitive Disease**
Only one study provided data in this population, and it did not include a comparator. **Overall survival:** Approximately 17 months. **Progression-free survival:** Approximately 7 months. Patients with platinum sensitivity had a longer PFS and higher response rate than platinum-resistant patients. While not a direct comparison, analyses of standard relapse therapies suggest median overall survival of 6-9 months and PFS of 4-6 months in similar patients. Data on patient-reported outcomes such as health-related quality of life were not reported.	**Overall survival:** Available data are still immature but show no OS benefit with olaparib. **Progression-free Survival:** In patients with an inherited BRCA mutation, PFS was approximately 19 months, as compared to 6 months in patients receiving placebo. For those without a BRCA mutation, PFS was approximately 7 months compared to 4 months for placebo. **Quality of Life:** Patient-reported outcomes show no significant differences with olaparib compared to placebo.

How strong is the evidence that **PARP inhibitors** improve patient outcomes?

Rucaparib

For Recurrent, BRCA-Mutated Disease	For Maintenance Therapy in Platinum-Sensitive Disease
Only one study provided data in this population, and it did not include a comparator. **Overall survival:** Data not reported **Progression-free survival:** Approximately 10 months. While not a direct comparison, analyses of standard ovarian cancer treatments suggest PFS of approximately 6 months in similar patients. Platinum-sensitive patients whose immediate prior treatment was a platinum therapy experienced a longer PFS. **Overall objective response rate:** About 54% of patients responded, with approximately a nine month median duration of response. Data on patient-reported outcomes are not available.	**Overall Survival:** Data not available **Progression-free survival:** In patients with a BRCA mutation, PFS was approximately 17 months, as compared to 5 months in patients receiving placebo. Across all patients, PFS was approximately 11 months compared to 5 months for placebo. **Quality of life:** Patient-reported outcomes showed no significant differences in QoL. Mature overall survival data are not yet available.

Niraparib

For Recurrent, BRCA-Mutated Disease	For Maintenance Therapy in Platinum-Sensitive Disease
ICER found no published studies of niraparib in this population, but a relevant study is ongoing.	**Overall survival:** Mature data not yet available. **Progression-free survival:** In patients with inherited BRCA mutations, PFS was approximately 21 months, as compared to 6 months in patients receiving placebo. For those without an inherited BRCA mutation, PFS was approximately 9 months with niraparib, compared to 4 months for placebo. **Quality of life:** Patient-reported outcomes showed no significant differences in QoL with niraparib compared to placebo.

How strong is the evidence that **PARP inhibitors** improve patient outcomes?

Harms

The most common side effects of PARP inhibitors are nausea, vomiting, anemia, thrombocytopenia (too few platelets in the blood), and neutropenia (low white blood cell count). The most serious complications are myelodysplastic syndrome and acute myeloid leukemia, which have been reported in a small minority of patients (≤2%). While uncommon, these complications have been associated with death.

Dose reductions due to toxicity were common for all three agents.

Sources of uncertainty

Data availability: Final overall survival data demonstrating statistically-significant improvement over historical treatment options are not available. Many patients receive multiple post-progression therapies, so it is harder to detect a survival benefit attributable to any individual treatment.

Progression-free survival endpoint: There is ongoing debate about the use of PFS to evaluate clinical benefit. Some clinical experts feel it is a reasonable endpoint in maintenance therapy, while others note that the lack of a clear survival or quality of life benefit may not justify the additional toxicity.

Trial limitations: Evidence for patients with BRCA-mutated recurrent disease is limited to one single-arm trial for olaparib and rucaparib, and findings on niraparib in this population are not yet available. Comparator data are also unavailable, so gains in overall survival, progression-free survival, or quality of life compared to other therapies are unknown.

Comparative data: There is a lack of head-to-head comparative data between the PARP inhibitors, and differences in trial design, study populations, and outcome measurement prevented even indirect comparisons.

Generalizability: Evidence from the key trials may have limited validity for the broader patient population in the U.S., as patient populations included in most trials represent only a minority of those with ovarian cancer.

How strong is the evidence that **PARP inhibitors** improve patient outcomes?

ICER evidence ratings

Drug name	Recurrent, BRCA-mutated disease	Maintenance therapy in platinum-sensitive disease
Olaparib	Evidence promising but inconclusive	**Comparable or Better** Evidence gives moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit.
Rucaparib	Evidence promising but inconclusive	
Niraparib	Insufficient evidence	

Other benefits

While substantial uncertainty remains about the impact of PARP inhibitors on overall survival and quality of life, these agents may offer other benefits not captured in clinical trials. Other benefits noted in the report include:

- **Convenience:** Because the PARP inhibitors are taken orally, they may provide more convenience for those otherwise needing to travel long distances to receive chemotherapy treatments.
- **Novel mechanism of action:** Although there is uncertainty around the long-term benefit and safety of PARP inhibition, these agents offer a novel mechanism of action and add an additional tool to the treatment armamentarium. Few effective treatment options exist in this space, and treatment paradigms have not changed materially in the last 20 years.

What are the economic impacts?

Long-term cost-effectiveness at net price

With the possible exception of olaparib for recurrent, BRCA-mutated disease, **each of the drugs exceeded commonly accepted long-term cost-effectiveness thresholds** of $50,000-$150,000 per quality adjusted life-year (QALY).

For recurrent, BRCA-mutated disease
Compared to standard chemotherapy (pegylated liposomal doxorubicin + carboplatin)

Olaparib: **$146,200/QALY**
Rucaparib: **$294,600/QALY**

For maintenance therapy in platinum-sensitive disease
Compared to placebo (observation)

For disease with BRCA mutation
Olaparib: **$324,100/QALY**
Niraparib: **$291,500/QALY**
Rucaparib: **$369,175/QALY**

For disease without inherited BRCA mutation
Niraparib: **$1.9 million/QALY**

Analyses used net drug prices that incorporated an assumed 10% discount from wholesale acquisition costs (WAC), based on manufacturer input on expected rebates and discounts. Results should be interpreted with caution, given the lack of available estimates of overall survival for most of these populations.

ICER's value-based price benchmarks

To fall within ICER's threshold value range of $100,000 to $150,000 per QALY, **these PARP inhibitors would require discounts** that are greater than the expected discounts from WAC, **except for olaparib for recurrent BRCA-mutated disease.**

For Recurrent BRCA-Mutated Disease

Drug Name	WAC per Month*	Price to Achieve $100,000-$150,000/QALY	Discount from WAC to Reach Thresholds	Net Price within Benchmark Range?
Olaparib	$13,679	$8,930-$12,587	8% to 35%	✓
Rucaparib	$13,940	$5,091-$7,007	50% to 63%	✗

For Maintenance Therapy in Platinum-Sensitive Disease with BRCA mutation

Drug Name	WAC per Month*	Price to Achieve $100,000-$150,000/QALY	Discount from WAC to Reach Thresholds	Net Price within Benchmark Range?
Olaparib	$13,679	$3,682-$5,607	59% to 73%	✗
Niraparib†	$14,965	$3,952- $6,437	57% to 74%	✗
Rucaparib	$13,940	$3,053-$4,817	65% to 78%	✗

**WAC as of August 23, 2017 † For niraparib in maintenance therapy without inherited BRCA mutation, no price would meet $100,000 or $150,000 per QALY, due to high cost relative to the small observed clinical benefit*

Potential short-term budget impact

For each of the drugs and populations of interest, the estimated annual potential budgetary impact of treating the entire eligible populations did not exceed the $915 million threshold. Therefore, **the drugs are unlikely to generate access or affordability alerts.**

Public Deliberation and Evidence Votes

Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) Votes

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) deliberated on key questions raised by ICER's report at a public meeting on September 14, 2017. The results of the votes are presented below. More detail on the voting results is provided in the full report.

1. In patients with recurrent BRCA-mutated disease, is the evidence adequate to demonstrate that the net health benefit of treatment with olaparib is greater than that of treatment with standard chemotherapy?

Yes: 4 votes	No: 5 votes

2. In patients with platinum-sensitive disease who are eligible for maintenance therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with olaparib is greater than that of surveillance alone?

Yes: 7 votes	No: 2 votes

3. In patients with recurrent platinum-sensitive, germline BRCA-mutated disease who are eligible for maintenance therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with niraparib is greater than that of surveillance alone?

Yes: 8 votes	No: 1 vote

4. In patients with recurrent platinum-sensitive disease who are eligible for maintenance therapy and do not have germline BRCA mutations, is the evidence adequate to demonstrate that the net health benefit of treatment with niraparib is greater than that of surveillance alone?

Yes: 6 votes	No: 3 votes

5. In patients with recurrent BRCA-mutated disease, is the evidence adequate to demonstrate that the net health benefit of treatment with rucaparib is greater than that of treatment with standard chemotherapy?

Yes: 5 votes	No: 4 votes

Council members also voted on key "Other Benefits" and "Contextual Considerations" of olaparib for recurrent BRCA-mutated disease*.

Other Benefits: Council members cited reduced complexity of the treatment regime, reduced caregiver burden, and a novel mechanism of action as key benefits.

Contextual Considerations: Council members noted that PARP inhibitors' intended use in a condition of high severity, in terms of impact on length of life and/or quality of life, and in a disease with a high lifetime burden of illness were key contextual considerations.

6. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, in patients with recurrent BRCA-mutated disease, what is the long-term value for money of olaparib compared with PLD+C?

Low: 5 votes	Intermediate: 4 votes	High: 0 votes

**Other benefit, contextual consideration, and value votes were not taken for other agents. Olaparib used in recurrent, BRCA-mutated disease was the only agent meeting commonly accepted cost-effectiveness thresholds.*

Key Policy Recommendations

The Midwest CEPAC engaged in a moderated discussion with a policy roundtable of subject-matter experts about how best to apply evidence on PARP inhibitors in policy and practice. The roundtable included patients, clinical experts, and a pharmacy benefit manager representative. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. Below are the top-line policy implications; for more information please see the full report.

Payers and Manufacturers

- Current pricing of PARP inhibitors has the potential to align with clinical benefit in recurrent disease, but alignment will be more challenging in maintenance therapy. To facilitate affordability and patient access, prices must be lowered.
- Payers and manufacturers must work together to establish innovative payment mechanisms to seek the best affordability for patients, including outcomes based contracting and/or package discounting.

Manufacturers

- Broaden eligibility criteria for patient assistance programs to counter the impact of financial toxicity.
- Price PARP inhibitors differentially by dosage strength, so that patients are not financially penalized when doses must be reduced to manage side effects.

Patient Advocacy Organizations

- Press researchers and manufacturers for an increased role in study design, so that comparisons and outcomes of most interest will be included.

Researchers, Manufacturers, and Patient Groups

- Single-arm studies and surrogate endpoints do not provide the type of information that clinicians and patients need to make treatment decisions. Critical evidence gaps like these must be addressed in the design and execution of clinical research.
- Manufacturers and researchers should standardize research protocols and outcome measurement and perform post-marketing head-to-head assessments to facilitate comparison of the individual agents. Patient groups should demand such standardization.
- Further research should be conducted to identify the patients who might benefit most from a maintenance regimen and those for whom surveillance remains a viable option.

Payers and Providers

- Eliminate methods of provider reimbursement that provide significant financial incentives favoring intravenous drugs over oral treatments.
- Health plans should work closely with clinicians to provide guideline-concordant testing for genetic mutations and consider adjustments to coverage policies based on the testing results.

Key Policy Recommendations (continued)

Recommendations from Policy Roundtable Participants on Methods for Prioritizing Innovation

ICER solicited feedback on areas of lower-value or wasteful care for ovarian cancer that could be reduced or eliminated to make additional headroom in health-system budgets for higher-value services. Policy Roundtable participants at the public meeting suggested the following:

- Limit screening in asymptomatic women.
- Centralize care at centers of excellence.
- Use integrative therapies to manage side effects of treatment.
- Educate nurses and nurse practitioners on efficient care management.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).

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