A Comparator Choice Set Framework for Value-Based Drug Pricing under the Inflation Reduction Act: Evidence from Enzalutamide (Xtandi®)

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BACKGROUND AND OBJECTIVE

- Under the Inflation Reduction Act (IRA), the Centers for Medicare & Medicaid Services (CMS) is required to consider therapeutic alternatives when negotiating prices for selected drugs, incorporating information on alternatives' prices and comparative clinical effectiveness. Cost-effectiveness analysis (CEA) has therefore been proposed as a tool to inform IRA price negotiations.
- However, **a central challenge remains unresolved: how to define appropriate therapeutic alternatives for value assessment.**
- Existing approaches typically rely on clinical practice guidelines, prevailing standards of care, trial comparators, and expert judgment to select one or more individual comparators, followed by **pairwise CEA comparisons** with the target drug. While pragmatic, this approach may not reflect how patients and clinicians actually choose treatments.
- **A patient-centered perspective instead asks: in the absence of the target drug, what combination of clinically appropriate options would patients receive?**
- These alternatives may include multiple treatments—or no treatment at all—weighted by real-world practice patterns and patient preferences.
- **This study proposes a comparator choice set framework to address this gap in IRA value assessment.**

STRUCTURE

Overview:

Stage 1: Apply the Comparator Choice Set Framework to IRA-Selected Drugs and Explain Its Rationale.

- We extend prior work on choice set–based value assessment by comparing two clinically relevant treatment choice sets:

(1) a restricted choice set excluding the target drug, and

(2) an expanded choice set including the target drug alongside all clinically appropriate alternatives.

- Rather than relying on pairwise comparisons between individual therapies, the framework evaluates the incremental value of adding the target drug to the feasible treatment choices available to patients and clinicians.
- This approach captures substitution across multiple alternatives, reflects real-world treatment patterns and patient preferences, and provides a more patient-centered perspective for IRA value assessment.

Stage 2: Illustrate the Framework Using Xtandi® (Enzalutamide plus ADT), a Drug Selected in the Second Round of IRA Negotiations.

METHODS

What is comparator choice set?[1]

Comparator Choice Set (CCS)

In the real world, before a new drug is available, patients and clinicians choose from multiple clinically appropriate options. Each option is chosen with a certain probability based on real-world practice patterns and patient preferences.

CCS evaluates the value of adding the new drug to this existing choice set.

Example: Before the new drug is available

Real-world choice set (without the new drug)

Treatment A	Treatment B	Treatment C	Treatment D	No treatment / Best supportive care
Survival gain 6 months, Monthly cost $3,000	Survival gain 10 months, Monthly cost $6,000	Survival gain 4 months, Monthly cost $1,500	Survival gain 7 months, Monthly cost $2,500	Survival gain 2 months, Monthly cost $500
25%	30%	20%	15%	10%

Market shares reflect real-world practice patterns and patient preferences (Sum = 100%)

After the new drug becomes available

Same existing options + Treatment E (new drug): Survival gain 12 months, Monthly cost $7,500

Not all patients switch to the new drug. Some switch from existing options, while others continue with their current choice.

CCS captures substitution across multiple alternatives and evaluates the incremental value of adding the new drug from a patient-centered, real-world perspective.

- Reflects real-world decision making among multiple alternatives
- Weights alternatives by real-world practice patterns and preferences
- Captures substitution and partial uptake of the new drug
- Provides a patient-centered estimate of the incremental value of adding the new drug to the feasible choice set

Traditional Pairwise CEA

Each analysis compares only two options at a time (the new drug vs. one comparator). It implicitly assumes that all patients would switch to the new drug if it is cost-effective, ignoring other available alternatives.

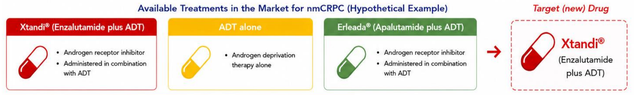
Example: Pairwise comparisons with existing options

Treatment E (new drug): Survival gain 12 months, Monthly cost $7,500	VS	Treatment A: Survival gain 6 months, Monthly cost $3,000	→ Choose one
Treatment E (new drug): Survival gain 12 months, Monthly cost $7,500	VS	Treatment B: Survival gain 10 months, Monthly cost $6,000	→ Choose one
Treatment E (new drug): Survival gain 12 months, Monthly cost $7,500	VS	Treatment C: Survival gain 4 months, Monthly cost $1,500	→ Choose one
Treatment E (new drug): Survival gain 12 months, Monthly cost $7,500	VS	Treatment D: Survival gain 7 months, Monthly cost $2,500	→ Choose one
Treatment E (new drug): Survival gain 12 months, Monthly cost $7,500	VS	No treatment / Best supportive care: Survival gain 2 months, Monthly cost $500	Many pairwise comparisons are needed

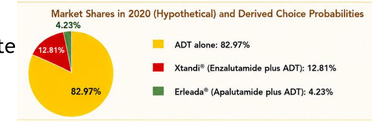
- Considers only two options at a time, ignoring other available alternatives
- Assumes all patients would switch to the new drug if it is cost-effective
- Requires many pairwise comparisons, increasing respondent burden and complexity
- May not reflect real-world treatment selection and substitution across multiple options

COMPARATOR CHOICE SET IN IRA VALUE ASSESSMENT: APPLICATION TO XTANDI® (ENZALUTAMIDE PLUS ADT)

- We assumed there were three treatment options for non-metastatic castration-resistant (nmCRPC) in the market.



- Market shares for three treatment options were derived from published literature.[2] These market shares were used to generate choice probabilities in the comparator choice set framework.



Choice probabilities:

P(choose Xtandi® over ADT alone) = 13.37%

P(choose Xtandi® over Erleada®) = 75.18%

- We developed a payer-perspective, monthly-cycle, three-state Markov model for nmCRPC using the 2018 ICER evidence report as the primary input source.[3] Transition probabilities were derived from the PROSPER and SPARTAN trial MFS and OS data for Xtandi® and Erleada®. Costs and utilities were based on the ICER 2018 estimates and inflated to 2026 U.S. dollars, with all future costs and outcomes discounted to 2026.
- Market The value-based price of Xtandi® was estimated under the Comparator Choice Set framework by identifying the price at which the incremental cost-effectiveness ratio reached the willingness-to-pay threshold of $100,000 per QALY gained.

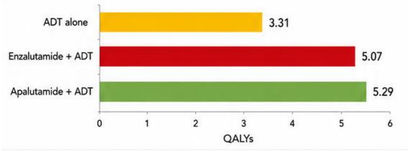
REFERENCES

1. Jiao, Boshen, et al. "Evaluating Policies of Expanding Versus Restricting First-Line Treatment Choices: A Cost-Effectiveness Analysis Framework." Value in Health 27, no. 4 (2024): 433–440.
2. ASCO GU 2025. "Real-World Use and Outcomes of Darolutamide, Enzalutamide, and Apalutamide for Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC): Race Subgroup Analysis." UroToday (2025). Accessed May 7, 2026.
3. Institute for Clinical and Economic Review (ICER). Prostate Cancer. Boston, MA: ICER, 2018. Accessed May 7, 2026.

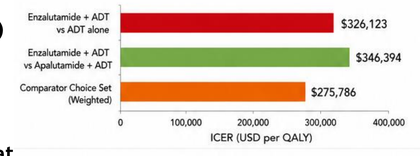
RESULTS AND KEY INSIGHTS

1. Total Costs (USD)

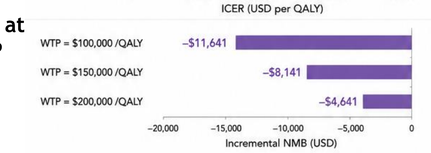
2. QALYs



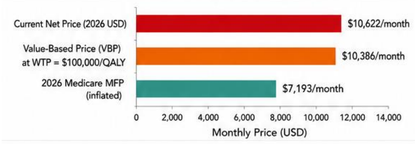
3. ICERs (USD per QALY)



4. INMB (USD) at Different WTP Thresholds (CCS)



5. Value-based Price (VBP) of Xtandi® (CCS)



6. Pairwise CEA: Range of VBPs

Key insights:

- The comparator choice set framework evaluates the marginal value of adding a drug to the set of clinically appropriate alternatives.
- By moving beyond traditional pairwise comparisons, the framework avoids value estimates driven by arbitrary comparator selection.
- The approach incorporates real-world treatment substitution and patient treatment choice probabilities.
- The framework provides a more transparent and policy-relevant basis for CMS drug price negotiations under the IRA.

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