Patient-Level Modeling Approach Using Discrete-Event Simulation: A Cost-Effectiveness Study of Current Treatment Guidelines for Women with Postmenopausal Osteoporosis

Quang A. Le, PharmD, PhD

SUMMARY

Decision tree and Markov models have been the most commonly used modeling methods in health economic evaluations. Both methods are known for their limitations. Discrete-event simulation (DES), an event-driven model in continuous time at the patient level, is a relatively new method in health economic evaluations that addresses some limitations of the common modeling techniques. Specifically, with the advent of personalized medicine, conventional methods for value assessment that are based on population-level measures might not be appropriate. The best treatment would depend on patient characteristics and clinical profiles.

Value assessment of health interventions can vary substantially and may lead to different health decision making due to patient heterogeneity. As such, modeling at the patient level is an appropriate approach for value assessment of health interventions. The DES model has several advantages, such as flexibility, ability to reflect patient heterogeneity, increased precision, and better characterization of modeling uncertainty, that may be preferred to decision tree and Markov models. In addition, with increasing health care spending and drug prices, it is important to quantify value of available treatment options for women with postmenopausal osteoporosis (PMO).

The purpose of this Viewpoints article was to describe and demonstrate an application of a DES model to evaluate the cost-effectiveness of the current treatment guidelines for women with PMO. In particular, the DES model indicated that the optimal treatment at the common willingness-to-pay thresholds between \$100,000 per quality-adjusted life-year (QALY) and \$150,000 per QALY was denosumab. Analysis of patient heterogeneity in terms of low, medium, high, and very high risk of fractures resulted in a similar conclusion.

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Modeling techniques are normally used to assess the values of new health interventions and inform health policy makers to make funding decision under scarce resources. Currently, decision tree and Markov models are the most common modeling methods in health economic evaluations.¹ Both methods are known for their limitations. The decision tree model, a rather simple modeling approach, estimates the likelihood of potential outcomes without explicitly accounting for the effect of time.² The Markov model (MM) is a health-state transition model in discrete time where patients moving through health states in predetermined time cycles.² Alternatively, discrete-event simulation (DES) is an event-driven model in continuous time where a series of clinically related events are sampled for individual patients.³⁻⁵ A DES

model can address a variety of issues in health economic evaluation, as modeling time to clinical events is more flexible and natural than modeling health-state transition in discrete time as in an MM.

For example, health states in an MM are mutually exclusive (i.e., a patient can only stay in 1 health state at a time). More commonly, patients tend to have multiple health conditions and/or experience several clinical events, so event-based modeling with a DES is a flexible and natural approach to address this major limitation of the MM.^{3,4} Furthermore, in DES modeling, clinical events can naturally occur at any time rather than constantly being checked at the end of cycles, as with Markov modeling. Therefore, time-to-event modeling in DES is more efficient than periodically checking time, since in most cycles, no clinical event would occur in many patients.^{3,4} DES modeling can also account for the effect of individual patient history on future events and in clinical events in which rates depend on time of occurrence.^{3,4} This is another major limitation in the MM, commonly known as a “memory-less” model.⁶ Moreover, a DES model can resolve the competing-risk problem, where multiple clinical events compete to occur at the end of each cycle in an MM by naturally translating these risks into times until each clinical event occurs.^{3,4}

Value assessment of health interventions can vary substantially and may lead to different health decision making due to patient heterogeneity.⁷ A new treatment may not be considered cost-effective if it is given to a patient with an average risk, but it may become a cost-effective treatment option when given to a high-risk population. On the contrary, a different health intervention may be cost-effective for an average-risk population, while it may not be cost-effective in a low-risk patient. A recent systematic review indicated that most published national pharmacoeconomic guidelines recommend analysis of patient heterogeneity in economic evaluation, but a majority of published health economic evaluation studies did not report patient heterogeneity analyses, and those that did report it simply stratified by age groups.^{8,9}

With the advent of personalized medicine, the best treatment would depend on patient characteristics and clinical profile. Thus, modeling at the patient level is an appropriate approach for value assessment of health interventions. Flexibility, especially in complex models; the ability to reflect patient

heterogeneity; increased precision; and better characterization of modeling uncertainty are advantages that DES modeling may have over Markov modeling. Here, we describe and apply the DES model to evaluate the cost-effectiveness of current treatment guidelines for women with postmenopausal osteoporosis (PMO).

Methods

Discrete-Event Simulation Approach in Health Economic Evaluation

DES is modeled at the individual level. Each individual has unique attributes (e.g., patient demographic and clinical characteristics) and undergoes a series of possible clinical events (e.g., death, hip fracture, stroke, being diagnosed with severe obesity, and adverse events) over time. Such clinical events may, in turn, affect the individual attributes (e.g., having stroke increases the risk of second stroke and death, or having an osteoporotic fracture increases the risk of having another fracture).^{3,4} Commonly, a series of clinical events (or event list) is constructed by randomly sampling time-to-event distribution for each event (typically using time-to-event distributions such as Weibull, exponential, and Gompertz). They are then placed in the order of occurrence and attached to each individual.²

Each individual carries an event list describing the type of events and the timing when the events may occur to the individual over time (e.g., a series of clinical events in osteoporosis may include time to hip fracture, time to vertebral fracture, time to wrist fracture, and time to death). The event list may be updated after each event to reflect the effect of previous events on current or future events.^{3,4} Outcomes such as quality-adjusted life-years (QALYs) and related costs (e.g., treatment costs, potential costs of adverse events, and inpatient and outpatient costs) for each patient are updated and recorded at each clinical event and for all clinical events accordingly.

The DES Model for Osteoporosis Treatment

Six major clinical events were included in the model: hip fracture, vertebral fracture, nonhip nonvertebral (NHNV) fracture, death due to hip fracture, entering a nursing home after hip fracture, and death due to causes other than hip fracture. In the DES model, a patient can experience multiple hip, vertebral, and NHNV fractures. In addition, for patients who experience hip fracture, there is a possibility that they would die from hip fracture or enter a nursing home.

Risk factors for fractures, including age, previous fracture after age 50, biological mother experienced a hip fracture after age 50, weight over 120 pounds, current smoker, and total hip T-score, were sampled to estimate annual rates for hip, vertebral, and NHNV fractures.¹⁰ On entry into the model, a set of time-to-events (TTEs) for hip, vertebral, and NHNV fractures and all-causes death were generated for each patient based on the specific patient risk factors generated previously. To generate further fractures after an initial hip, vertebral, or NHNV

fracture, the DES model updates the patient's age and other clinical characteristics and generates another set of TTEs for hip, vertebral, and NHNV fractures and all-cause death.

Once all 18 TTEs were sampled, the model determined the sequence of these clinical events that occurred first (based on its TTE) to the model 10-year time horizon or patient death. For each clinical event, relevant costs and QALYs were recorded and added. The simulation process continued until the individual patient died or the model reached the end of the time horizon, and all the costs and QALYs were recorded for this patient. The next patient then entered the model and the simulation ended when the last patient died or the model reached the end of the time horizon. TTEs, related costs, and QALYs for all patients were recorded.

TTEs for all the fractures were generated using exponential distribution as follows, where U is a uniformly distributed random number between 0 and 1²:

$$TTE \text{ for fracture event} = (1 \div \text{annual fracture rate}) \times (-\ln(U) \div \text{fracture hazard ratio})$$

Treatment Effects and Real-World Adherence Rates

Comparative effectiveness of 7 osteoporosis treatment strategies based on treatment guidelines included (1) alendronate (weekly oral bisphosphonate), (2) risendronate (monthly oral bisphosphonate), (3) zoledronic acid (yearly intravenous bisphosphonate), (4) denosumab (6 monthly subcutaneous injections), (5) teriparatide (daily subcutaneous injections), (6) abaloparatide (daily subcutaneous injections), and (7) placebo (severed as natural process of osteoporotic fractures).^{11,12}

Treatment effects in terms of fracture risk reduction of alendronate, risendronate, zoledronic acid, denosumab, and teriparatide compared with the placebo group were based on 2 meta-analyses of randomized controlled trials for PMO therapies and the clinical trial for abaloparatide (Table 1).¹³⁻¹⁵

Real-world adherence rates for alendronate, risendronate, zoledronic acid, denosumab, teriparatide, and abaloparatide were assumed to be 35.1%, 28.9%, 61.0%, 68.3%, 59.1%, and 59.1%, respectively.¹⁶ The model also assumed that a linear, gradual offset of fracture reduction benefits would last over the subsequent 3-5 years after active treatment.¹⁸⁻²²

Costs and Health Utilities

Drug costs were based on the 2017 wholesale acquisition cost (WAC) price from RED BOOK.²³ Estimated annual costs after a hip, vertebral, and NHNV fracture were derived from literature (Table 1).^{24,25} All costs were adjusted to 2017 U.S. dollars based on the Consumer Price Index.

The initial health utility of 0.806 was based on the average age of women with PMO from Black et al. (2001).¹⁰ In addition, Table 1 reported the specific health-disutility decrements (multipliers) during the first and subsequent years for each fracture site.^{27,28}

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TABLE 1 DES Model Input Parameters for Natural History and Treatment Effects: Base-Case, Lower, and Upper Values and Distributions for Probabilistic Sensitivity Analysis

DES Model Input Parameter	Base-Case Value	Lower Value	Upper Value	Distribution	References
Natural history^a					
Age (years)	73.3	66.0	80.6	Normal	Black 2001 ¹⁰
Weight (kg)	75.6	65.6	85.6	Normal	National Vital Statistic Reports 2014 ³⁰
Current smoking (%)	7.8	N/A	N/A	Binomial	Black 2001 ¹⁰
Previous fracture after age 50 (%)	39.2	N/A	N/A	Binomial	Black 2001 ¹⁰
Maternal hip fracture (%)	10.4	N/A	N/A	Binomial	Black 2001 ¹⁰
Using arms to stand from a chair (%)	4.4	N/A	N/A	Binomial	Black 2001 ¹⁰
Total hip T-score	-2.5	-2.0	-3.0	Normal	Assumed for PMO
Annual probability of nursing home after hip fracture (%)	12.2	N/A	N/A	No change	Pham 2011, ²¹ Schousboe 2005, ³¹ Leibson 2002 ³²
Annual probability of death due to hip fracture (%)	21.9	N/A	N/A	No change	Brauer 2009 ³³
Treatment effects (relative to placebo)^b					
Fracture hazard ratios of abaloparatide					
Hip fracture	0.57	0.32	1.00	Log-normal	ACTIVE Trial ¹⁵
Vertebral fracture	0.14	0.05	0.39	Log-normal	ACTIVE Trial ¹⁵
NHNV fracture	0.57	0.32	1.00	Log-normal	ACTIVE Trial ¹⁵
Fracture hazard ratios of teriparatide					
Hip fracture	0.50	0.09	2.75	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Vertebral fracture	0.31	0.19	0.52	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
NHNV fracture	0.62	0.40	0.97	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Fracture hazard ratios of denosumab					
Hip fracture	0.60	0.37	0.98	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Vertebral fracture	0.31	0.24	0.40	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
NHNV Fracture	0.80	0.67	0.96	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Fracture hazard ratios of zoledronic acid					
Hip fracture	0.59	0.35	0.83	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Vertebral fracture	0.28	0.22	0.35	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
NHNV fracture	0.74	0.63	0.86	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Fracture hazard ratios of risedronate					
Hip fracture	0.74	0.58	0.94	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Vertebral fracture	0.59	0.47	0.75	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
NHNV fracture	0.79	0.67	0.89	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Fracture hazard ratios of alendronate					
Hip fracture	0.62	0.40	0.96	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Vertebral fracture	0.51	0.40	0.63	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
NHNV fracture	0.80	0.68	0.95	Log-normal	Stevenson 2005, ¹³ Hopkins 2011 ¹⁴
Costs^c					
Monthly cost of abaloparatide	1,625	1,300	1,950	Log-normal	Redbook 2017 ²³
Monthly cost of teriparatide	3,248	2,598	3,897	Log-normal	Redbook 2017 ²³
Monthly cost of alendronate (oral bisphosphonate)	10	8	12	Log-normal	Redbook 2017 ²³
Monthly cost of denosumab	1,128	903	1,354	Log-normal	Redbook 2017 ²³
Monthly cost of zoledronic acid	400	320	480	Log-normal	Redbook 2017 ²³
Monthly cost of risedronate	60	48	72	Log-normal	Redbook 2017 ²³
Average cost per hypercalcemia event	208	166	249	Log-normal	Liu 2006 ¹⁷
Average cost per nausea event	100	80	120	Log-normal	Assumed
Average cost per gastrointestinal event	129	103	155	Log-normal	Assumed
Average annual cost of hip fracture	32,687	26,150	39,224	Log-normal	O'Hanlon 2017 ²⁴
Average annual cost of vertebral fracture	14,717	11,774	17,660	Log-normal	O'Hanlon 2017, ²⁴ Tosteson 2008 ²⁵
Average annual cost of NHNV fracture	13,463	10,770	16,156	Log-normal	O'Hanlon 2017 ²⁴
Incremental cost of subsequent hip fracture	18,820	15,056	22,584	Log-normal	Weaver 2017 ²⁶
Annual cost of nursing home care	87,252	69,801	104,702	Log-normal	Genworth 2017 ³⁴

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TABLE 1 DES Model Input Parameters for Natural History and Treatment Effects: Base-Case, Lower, and Upper Values and Distributions for Probabilistic Sensitivity Analysis (*continued*)

DES Model Input Parameter	Base-Case Value	Lower Value	Upper Value	Distribution	References
Health utilities^d					
Initial HU	0.806	0.725	0.887	Beta	Brazier 2002 ²⁷
Post-hip fracture: first year (HU decrement)	0.797	0.717	0.877	Beta	Brazier 2002, ²⁷ Kanis 2004 ²⁸
Post-hip fracture: subsequent years (HU decrement)	0.900	0.810	0.990	Beta	Brazier 2002, ²⁷ Kanis 2004 ²⁸
Post-hip fracture: nursing home stay	0.400	0.360	0.440	Beta	Brazier 2002, ²⁷ Kanis 2004 ²⁸
Post-vertebral fracture: first year (HU decrement)	0.820	0.738	0.902	Beta	Brazier 2002, ²⁷ Kanis 2004 ²⁸
Post-vertebral fracture: subsequent years (HU decrement)	0.931	0.838	1.00	Beta	Brazier 2002, ²⁷ Kanis 2004 ²⁸
Post-NHNV fracture: first year (HU decrement)	0.753	0.678	0.828	Beta	Brazier 2002, ²⁷ Kanis 2004 ²⁸
Post-NHNV fracture: subsequent years (HU decrement)	0.813	0.732	0.894	Beta	Brazier 2002, ²⁷ Kanis 2004 ²⁸

Notes: All drug costs were based on the 2017 wholesale acquisition cost from RED BOOK Online.²³ All other costs were adjusted to 2017 U.S. dollars based on the Consumer Price Index.

^aThese demographic and clinical characteristics were used to estimate the annual rates for hip, vertebral, and NHNV fractures based on Black et al. (2001).¹⁰

^bLower and upper values were based on the 95% confidence interval reported from meta-analysis studies and relevant clinical trials.

^cLower and upper costs were assumed to be 20% of the mean (base-case) values.

^dLower and upper health utilities were assumed to be 10% of the mean (base-case) values.

DES = discrete-event simulation; HU = health utility; N/A = not applicable; NHNV = nonhip, nonvertebral; PMO = postmenopausal osteoporosis.

Base-Case Analysis

The baseline patient in the model was a 73.3-year-old woman with PMO with an average total hip T-score of -2.5 based on the average patient in Black et al.¹⁰ Risks for hip, vertebral, and NHNV fractures in women with PMO (natural history for fractures) were derived from Black et al. based on patient risk factors.¹⁰ The model applied a discount rate of 3% for both costs and QALYs and was analyzed from the perspective of a health care payer. The DES model simulated 100,000 individual patients for each treatment strategy to estimate the average total per-patient costs and QALYs in a 10-year time horizon.

Sensitivity Analysis and Patient Heterogeneity

Probabilistic sensitivity analysis was performed by generating 10,000 samples of model probabilistic parameters and, within each sample, 10,000 patients were generated (Table 1). With multiple treatment strategies, cost-effectiveness frontier analysis was performed to identify the optimal strategy at different willingness-to-pay (WTP) thresholds.²⁹

In addition, several scenarios of patient heterogeneity were examined including (1) women at low risk of fracture (aged 50-65 years without a previous fracture), (2) women at medium risk of fracture (aged 75 years), (3) women at high risk of further fracture (aged 75 years with a previous fracture), (4) women at very high risk of further fracture (aged 75 years with a previous fracture and total hip T-score ≤ -2.5), and (5) in women who experienced hip fractures.

Results

Base-Case Cost-Effectiveness Analysis Results

Over a 10-year time horizon, the DES model yielded average total discounted per-patient costs of \$15,961, \$14,129, \$16,221, \$20,112, \$15,973, \$45,573, and \$28,216 and QALYs of 6.504, 6.549, 6.537, 6.601, 6.599, 6.619, and 6.629 for placebo, alendronate, risedronate, zoledronic acid, denosumab, teriparatide, and abaloparatide, respectively (Table 2). Cost-effectiveness frontier analysis showed that when the WTP threshold was $\leq \$36,745$ per QALY, alendronate was the optimal treatment; for WTP thresholds between \$36,745 per QALY and \$409,017 per QALY, denosumab was the optimal treatment; and abaloparatide was favored if the WTP threshold was above \$409,017 per QALY.

Sensitivity Analysis and Patient Heterogeneity Results

Table 2 also reports results of patient heterogeneity analyses of different subgroups of patients. For women at low risk of fracture, frontier-curve analysis indicated that the optimal treatments at WTP thresholds of $\leq \$103,642$ per QALY, between \$103,642 per QALY and \$480,322 per QALY, and $\geq \$480,322$ per QALY were alendronate, denosumab, and abaloparatide, respectively. In the subgroup of women at medium risk of fracture, the optimal treatments at WTP thresholds of $\leq \$18,168$ per QALY, between \$18,168 per QALY and \$389,120 per QALY, and $\geq \$389,120$ per QALY were also alendronate, denosumab, and abaloparatide, respectively.

Relatively similar to women at medium risk of fracture, the optimal treatments for the subgroup of women at high risk of fracture were also alendronate, denosumab, and abaloparatide

TABLE 2 Cost-Effectiveness Results for Base-Case and Patient Heterogeneity Analysis in Subgroups of Women at Low, Medium, High, and Very High Risk of Fracture and Women with Hip Fractures over a 10-Year Time Horizon

	Placebo	Abaloparatide	Teriparatide	Denosumab	Zoledronic Acid	Risedronate	Alendronate
Base-case analysis							
Total cost	15,961	28,216	45,573	15,973	20,112	16,221	14,129
Total QALY	6.504	6.629	6.619	6.599	6.601	6.537	6.549
Low risk of fracture^a							
Total cost	7,695	21,755	39,084	9,495	13,421	9,098	6,817
Total QALY	6.715	6.791	6.783	6.766	6.769	6.735	6.740
Medium risk of fracture^b							
Total cost	20,062	30,968	48,421	18,710	22,945	18,978	17,638
Total QALY	6.360	6.502	6.489	6.470	6.471	6.397	6.411
High risk of fracture^c							
Total cost	21,499	31,835	49,397	19,558	23,907	20,391	18,890
Total QALY	6.283	6.447	6.432	6.413	6.413	6.325	6.342
Very high risk of fracture^d							
Total cost	24,076	33,028	50,649	20,872	25,294	22,586	20,855
Total QALY	6.174	6.384	6.362	6.340	6.340	6.228	6.249
Experienced hip fracture^e							
Total cost	93,544	83,462	99,526	71,075	76,543	86,893	80,545
Total QALY	5.347	5.773	5.783	5.736	5.721	5.468	5.537

^aWomen aged between 50 and 65 years without a previous fracture.

^bWomen aged 75 years or older.

^cWomen with PMO aged 75 years or older with a previous fracture.

^dWomen with PMO aged 75 years or older with a previous fracture and total hip T-score ≤ -2.5 .

^eWomen who experienced hip fracture during the 10-year period.

PMO = postmenopausal osteoporosis; QALY = quality-adjusted life-year

at WTP thresholds of $\leq \$9,445$ per QALY, between $\$9,445$ per QALY and $\$358,834$ per QALY, and $\geq \$358,834$ per QALY, respectively. In the subgroup of women at very high risk of fracture, however, the optimal and preferred treatments were denosumab and abaloparatide at WTP thresholds $\leq \$277,297$ per QALY and $\geq \$277,297$ per QALY, respectively.

Furthermore, in the subgroup of women who experienced hip fractures during the 10-year period, the optimal treatments at WTP thresholds of $\leq \$342,536$ per QALY, between $\$342,536$ per QALY and $\$1,522,943$ per QALY, and $\geq \$1,522,943$ per QALY were also denosumab, abaloparatide, and teriparatide, respectively.

Discussion

For modeling clinical events in continuous time rather than health-state transition in discrete time, the DES model is therefore a more flexible and natural approach than the commonly used MM. In addition, at patient-level simulation, a DES model can reflect patient heterogeneity, increase precision, and better characterize modeling uncertainties that are suitable for value assessment at different levels of decision making and that are aligned with personalized/precision medicine.

The cost-effectiveness analysis study of the current treatment guidelines for women with PMO using DES modeling demonstrated that denosumab was the preferred treatment strategy in most commonly accepted WTP thresholds between $\$100,000$ per QALY and $\$150,000$ per QALY in the United States. Because the DES is an event-driven model, simulates at patient-level data, and runs in continuous and uninterrupted time, it is more flexible than other commonly used modeling approaches and can address a wide variety of issues in health economic evaluation.^{3,4} Importantly, its ability to easily reflect patient heterogeneity has been demonstrated in this study. There are many meaningful ways to characterize patient heterogeneity based on patient characteristics and clinical profile. We examined several assumed scenarios of patient heterogeneity where patients would be considered as low, medium, high, and very high risk of fracture and in a subgroup of women who experienced hip fractures during the 10-year period. In patient heterogeneity analysis, our results indicated that alendronate, a cheap generic oral bisphosphonate, appeared to be a preferred treatment in the subgroup of women at low risk fracture. However, in subgroups of women who were at high risk or very high risk of fracture or those who experienced hip fractures, denosumab was the preferred treatment option.

Limitations

There are couple of limitations with the current DES model that need to be discussed. First, fracture risks in terms of patient characteristics and clinical profile were sampled independently in the model. However, these fracture risks tend to be correlated, so the simulation process might produce some unrealistic patient profiles. This limitation can be addressed if there is a previously known correlation matrix of the risk factors, so they can be sampled accordingly.

Second, TTE was sampled by the use of random numbers, so random chance could allow unlikely outcomes, and important outcomes may not be sampled frequently enough. Third, the DES model assumed time to fracture events followed an exponential distribution (i.e., constant fracture hazard rates over time). As a result, the model might have underestimated the actual fracture rates, as they have been shown to increase with age over time; as such, the fracture risk reduction of treatment strategies might also have been underestimated.

Finally, the DES model can be computationally expensive, especially when performing probabilistic sensitivity analyses. However, the current DES model for women with PMO was able to perform 100 million simulations (10,000 samples, each containing 10,000 individual patients) for each treatment strategy in approximately 7.5 hours.

Conclusions

This study demonstrated that DES is an alternative modeling approach that can incorporate individual characteristics and clinical profiles into value assessments to compare treatment strategies at the patient level. When applied to evaluate the cost-effectiveness of current treatment options for women with PMO, the DES model indicated that alendronate might be the preferred treatment option in women at low risk of fracture. Denosumab, on the other hand, appeared to be the optimal treatment strategy in most commonly accepted WTP thresholds in the United States, regardless of the fracture risk level.

Authors

QUANG A. LE, PharmD, PhD, College of Pharmacy, Western University of Health Sciences, Pomona, California.

AUTHOR CORRESPONDENCE: Quang A. Le, PharmD, PhD, College of Pharmacy, Western University of Health Sciences, 309 E. Second St., Pomona, CA 91766. Tel.: 909.706.3821; E-mail: qle@westernu.edu.

DISCLOSURES

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