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## ONCOLOGY: RESEARCH ARTICLE

# Premedication prior to PEG-asparaginase is cost-effective in pediatric patients with acute lymphoblastic leukemia

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## Abstract

**Background:** PEG-asparaginase is critical in pediatric acute lymphoblastic leukemia (ALL) therapy but is highly immunogenic. Severe allergic reactions lead to substitution of further PEG-asparaginase with *Erwinia*. *Erwinia* is associated with more frequent dosing, increased expense, and limited availability. Premedication may reduce rates of allergic reactions.

**Procedures:** This Markov model evaluated the cost-effectiveness of three strategies: premedication plus therapeutic drug monitoring (TDM), TDM alone, and no premedication or TDM. We modeled two scenarios: a standard-risk (SR) B-ALL patient receiving two asparaginase doses and a high-risk (HR) patient receiving seven asparaginase doses. The model incorporated costs of asparaginase, premedication, TDM and clinic visits, and lost parental wages associated with each additional *Erwinia* dose. We incorporated a five-year time horizon with a societal perspective. Outcomes were *Erwinia* substitutions avoided and differences in quality-adjusted life years (QALYs). Probabilistic and one-way sensitivity analyses evaluated model uncertainty.

**Results:** In both scenarios, premedication was the least costly strategy. In SR and HR scenarios, premedication with monitoring resulted in 8% and 7% fewer changes to Erwinia compared with monitoring alone and 3% and 2% fewer changes compared with no premedication/monitoring, respectively. Premedication resulted in the most QALYs gained in the SR patients. Individual variation of model inputs did not change premedication/monitoring favorability for either scenario. In probabilistic sensitivity analyses, premedication/monitoring was favored in >87% of iterations in both scenarios.

**Conclusion:** Compared with other strategies, premedication use and asparaginase level monitoring in children with B-ALL is potentially cost-saving.

**KEYWORDS**
acute lymphoblastic leukemia, allergic reaction, cost-effective, Erwinia asparaginase, PEG-asparaginase, premedication

## 1 | INTRODUCTION

Asparaginase is a key component of therapy in childhood acute lymphoblastic leukemia (ALL). Asparaginase achieves its antileukemic effect through depletion of plasma L-asparagine, an amino acid that
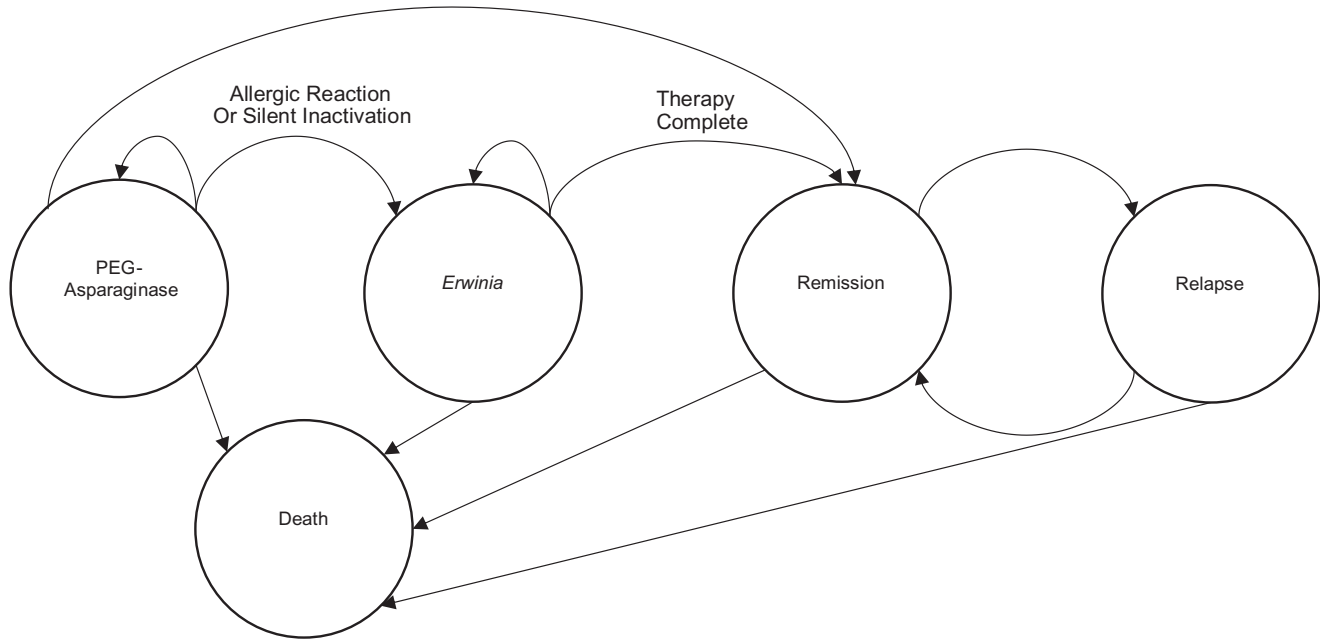
**FIGURE 1** Schematic of model health states. Circles represent Markov health states. All patients begin with an initial dose of PEG-asparaginase. Arrows indicate transition from one health state to another, with transition occurring in the direction of the arrowhead. Arrows returning to the same Markov health state indicate individuals remaining in that state for the next model cycle. For example, individuals in the "PEG-asparaginase" health state may experience an allergic reaction or silent inactivation, in which case they will receive *Erwinia* during the next model cycle. If there is no allergic reaction or silent inactivation, they will either receive another dose of PEG-asparaginase in the next model cycle, or if they have completed all doses of asparaginase therapy they will transition to the remission health state. At any time point, there is a possibility of death

leukemia cells are unable to synthesize independently.[1] The most commonly utilized form of asparaginase is PEG-asparaginase. Drug reactions following PEG-asparaginase are seen in up to 20% of patients and can range in severity from mild cutaneous reactions to life-threatening systemic reactions, such asanaphylaxis.[2–5] Severe reactions necessitate a change from PEG-asparaginase to *Erwinia chrysanthemi* asparaginase, which is less immunogenic.[2] Milder hypersensitivity reactions may also warrant a change in medication formulation when accompanied by the development of anti-asparaginase antibodies.[2] These antibodies result in decreased asparaginase activity and reduced efficacy contributing to poor outcomes due to subtherapeutic asparaginase activity.[6] In some cases, anti-asparaginase antibodies may develop without any associated clinical symptoms, a phenomenon termed silent inactivation. Although successful substitution of PEG-asparaginase with *Erwinia* maintains excellent disease-free survival in the event of clinical hypersensitivity or silent inactivation, the decreased half-life of *Erwinia* requires more frequent administration.[7,8] In addition, global shortages limit *Erwinia* availability and can lead to omission of critical asparaginase therapy.

Strategies to identify and reduce complications associated with PEG-asparaginase therapy include therapeutic drug monitoring of serum asparaginase activity levels to identify silent inactivation and premedication to prevent clinical hypersensitivity reactions. Premedication prior to PEG-asparaginase is effective in reducing the incidence of hypersensitivity reactions leading to PEG-asparaginase discontinuation, though it has not yet been adopted as standard practice.[5,9,10]

Premedication regimens vary widely and include acetaminophen, diphenhydramine, antihistamines, and/or corticosteroids. Advantages to premedication include low expense, wide availability, and general tolerability. In this study, we conducted a cost-effectiveness analysis to evaluate three strategies in pediatric patients with B-ALL: premedication with therapeutic drug monitoring, therapeutic drug monitoring alone, and no premedication or drug monitoring. We compared strategies in terms of the number of medication changes to *Erwinia* prevented and associated quality-adjusted life years (QALYs). Our aim was to determine in which circumstances premedication is cost-effective from a societal perspective and in the context of overall leukemia-directed therapy.

## 2 | METHODS

### 2.1 | Decision analysis model

We created a Markov model using TreeAge Pro Healthcare 2020 (TreeAge Software, Williamstown, Massachusetts, USA) to evaluate three strategies in pediatric patients with B-ALL: (1) premedication plus therapeutic drug monitoring (TDM), (2) TDM alone, and (3) no premedication or TDM. Model schematic pictured in Figure 1. We modeled these strategies in two patient scenarios: a standard-risk patient with B-ALL receiving two asparaginase doses and a high-risk patient with B-ALL receiving seven asparaginase doses. The

modeled number of asparaginase doses incorporated is consistent with doses received by most children enrolled on current active Children's Oncology Group (COG) trials for standard- and high-risk B-ALL (AALL1731 and AALL1732, respectively). All patients received an initial dose of PEG-asparaginase. If a hypersensitivity reaction or silent inactivation occurred, PEG-asparaginase was assumed ineffective and patients received an additional dose of *Erwinia* asparaginase. Subsequent asparaginase doses were replaced by *Erwinia*; premedication and TDM were not used with *Erwinia* doses. We assumed silent inactivation was not recognized in patients not receiving premedication or TDM and resulted in a decreased event-free survival (EFS) due to ineffective asparaginase therapy. Following administration of all asparaginase doses, patients transitioned to the remission state. Models for each clinical scenario cycled monthly over a five-year time horizon, with model health states depicted schematically in Figure 1. Our analysis took the societal perspective, accounting for direct medical costs and costs due to lost parental productivity. Content experts in pediatric oncology reviewed model development.

## 2.2 | Model parameters

Probabilities, costs, utilities, and corresponding ranges are listed in Supporting Information Table S1. We drew on the results of published clinical trials, observational studies, and our institutional experience to determine the probability of hypersensitivity reaction following asparaginase with and without premedication.[3–5,9–15] Based on expert recommendations, we utilized the probability of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or greater allergic reaction to indicate changes in asparaginase formulation.[2] Though reported hypersensitivity reaction risks may differ with intravenous or intramuscular administration, we used overall risk of reaction regardless of administration route. The hypersensitivity reaction risk varied with each asparaginase dose to reflect increased risk with earlier asparaginase doses.[4,11–14,16,17] We estimated the hospitalization risk following hypersensitivity reaction as the proportion of patients who had CTCAE grade 3 or greater reactions.[11–15,17,18] According to the CTCAEv4.0, grade 3 hypersensitivity reactions are prolonged reactions, recurrent reactions following initial improvement or reactions in which hospitalization is indicated.[19] The silent inactivation risk was obtained from the literature, where the risk varied with each asparaginase dose using the same distribution seen with hypersensitivity reactions.[5,6,9–11,14,15,20–25]

Therapy-related mortality risk was obtained from COG trials evaluating standard-risk and high-risk patients with B-ALL.[26,27] Mortality risk in disease remission was determined using annual National Center for Health Statistics mortality rates adjusted by the standardized mortality ratio associated with pediatric ALL survivors.[28,29] Disease relapse risk was based on the EFS published in previous B-ALL leukemia trials AALL0331 and AALL0232.[26,27] We assumed a reduced EFS in patients with unrecognized silent inactivation.[6] The probabilities of second or greater disease remission following relapse, recurrent relapse, and relapse therapy-associated mortality were based on clinical trials and review articles.[30,31]

Medication costs were obtained from the Federal Supply Schedule (FSS).[32] Medication doses for the representative standard-risk patient were calculated using growth parameters for a three-year-old boy in the 50% for height and weight, as this is the peak age in which childhood B-ALL presents.[33,34] Medication doses for the representative high-risk patient were calculated based on growth parameters for a 15-year-old boy in the 50% for height and weight.[34] We selected an adolescent patient to evaluate the effect of greater body weight, and therefore medication doses, on model outcomes. All adolescent patients are considered high risk by National Cancer Institute criteria. Costs for asparaginase were estimated based on the number of vials required to complete each dose, assuming vials could not be split to create multiple doses. As premedication policies varied, we assumed all patients received acetaminophen, diphenhydramine, hydrocortisone, and famotidine. We then determined the range of costs associated with this premedication policy; the base-case cost was the median value of this range. The costs associated with hypersensitivity reactions, therapy for relapsed disease, and palliative therapy were obtained from the literature.[35–37] We assumed each replacement of PEG-asparaginase with *Erwinia* was associated with five additional clinic visits and five days of caretaker lost productivity. The cost of each additional clinic visit was obtained from the literature and adjusted for 2020 prices by the consumer price index inflation calculation.[38] The cost associated with lost productivity was determined using the employment statistics national table and assuming loss of an 8-hour workday.[39]

We used published literature to determine the healthcare quality-of-life utility experienced by pediatric patients with ALL receiving therapy, in remission, and with relapsed disease.[36,40–42] We estimated that hospitalization for hypersensitivity reactions decreased utility by 20%. The disutility associated with death was calculated based on life expectancy and with remaining life years discounted by 3% per year to determine discounted life expectancy lost due to death.

## 2.3 | Sensitivity analysis

One-way and probabilistic sensitivity analyses were completed to account for model uncertainty. When multiple sources were used to obtain base-case values, the range of values obtained from the literature was used. If ranges were not available then costs were adjusted by ±15%, and probabilities or utilities were adjusted by an absolute ±10%. All model parameters were varied over their ranges individually in one-way sensitivity analyses to evaluate the effect of each parameter on model results. Probabilistic sensitivity analysis then varied all model parameters simultaneously over distributions fitted to ranges listed in Table 1 through 1000 Monte Carlo iterations. Gamma distribution functions were applied to cost parameters and beta distribution functions were applied to probabilities and utilities.

**TABLE 1** Cost, percentage of patients requiring change to *Erwinia* and QALYs associated with each strategy in standard-risk and high-risk models

| Strategy | Cost | Patients requiring *Erwinia*, % | QALYs |
| --- | --- | --- | --- |
| Standard-risk model | | | |
| Premedication/monitoring | $40 545 | 11.6% | 2.92 |
| No premedication/monitoring | $42 538 | 14.4% | 2.84 |
| Monitoring only | $45 131 | 19.3% | 2.91 |
| High-risk model | | | |
| Premedication/monitoring | $197 935 | 12.0% | 1.13 |
| No premedication/monitoring | $209 190 | 14.3% | 1.06 |
| Monitoring only | $227 692 | 19.1% | 1.14 |

## 3 | Results

### 3.1 | Base-case analysis

In both standard-risk and high-risk simulations, premedication and monitoring was the least costly strategy (Table 1). In the standard-risk model, premedication with monitoring cost $4586 less than monitoring alone, resulting in 7.7% fewer changes to *Erwinia* and 0.01 additional QALYs. This strategy cost $1993 less than no premedication or monitoring, resulting in 2.8% fewer changes to *Erwinia* and 0.08 additional QALYs. Thus, in the standard-risk model, premedication with monitoring was the least costly strategy and resulted in the greatest total QALY; in cost-effectiveness terms, premedication was a dominant strategy, with other strategies being more expensive and less effective. In the high-risk scenario, premedication cost $29 757 less than monitoring alone resulted in 7.1% fewer medication changes and 0.01 fewer QALYS; consequently, monitoring alone was expensive, costing >$2 million/QALY gained compared with premedication and monitoring. Premedication cost $11 255 less than no premedication/monitoring resulted in 2.3% fewer changes to *Erwinia* and 0.07 additional QALYs.

### 3.2 | One-way sensitivity analyses

Individual variation of all model inputs in one-way sensitivity analyses did not change the favorability of premedication and monitoring in either scenario. In the standard-risk scenario, premedication with monitoring was the dominant strategy when compared with monitoring alone with variation of all parameters. When premedication with monitoring was compared with no premedication or monitoring, variation in the probability of allergy without premedication to the minimum end of this range resulted in no premedication/monitoring being the less costly strategy. In this scenario, no premedication/monitoring cost $427 less than premedication and monitoring and resulted in 0.08 fewer QALYs. Therefore, premedication/monitoring cost $5686/QALY gained. This is considered cost-effective using a conservative willingness-to-pay threshold of $50 000 per QALY gained.

In the high-risk model, premedication with monitoring was the dominant strategy with individual variation of all parameters when compared with no premedication or monitoring. Monitoring alone resulted in more QALYs compared with premedication with monitoring. However, the incremental cost-effectiveness ratio (ICER) remained >$1 500 000/QALY gained with variation in all model parameters.

### 3.3 | Probabilistic sensitivity analysis

In probabilistic sensitivity analyses, varying all parameters simultaneously over distributions 1000 times, premedication, and monitoring was favored in >87% of model iterations in both standard-risk and high-risk scenarios at any willingness-to-pay threshold selected (Figure 2A and 2B).

## 4 | DISCUSSION

In this study, we demonstrate that premedication use prior to PEG-asparaginase is cost-saving, results in fewer changes to *Erwinia*, and in most scenarios, the greatest number of QALYs. Continued PEG-asparaginase therapy is advantageous for several reasons. Although both PEG-asparaginase and *Erwinia* are equally effective in terms of long-term disease control, *Erwinia* is associated with increased cost.[7,32] *Erwinia* has a significantly shorter half-life, requiring six doses to achieve the therapeutic effect of a single dose of PEG-asparaginase.[1,8] Moreover, global shortages have resulted in limited supplies of *Erwinia*, which can lead to delay or omission of this medication. Although there has been documented success with reexposure to PEG-asparaginase following hypersensitivity reactions with premedication use and intensive care monitoring, this approach remains unsuccessful in a subset of patients.[43] In contrast, a primary preventive approach with premedication is inexpensive, utilizes readily available medications, and is associated with limited adverse effects.

Though premedication is not yet considered standard of care, several groups have published on their successful experiences with premedication prior to PEG-asparaginase.[5,9,10] Based upon their results, Cooper et al. recommended the universal use of premedication prior to PEG-asparaginase.[9] In contrast, Losasso et al. concluded that premedication was only indicated in patients receiving more than two

**FIGURE 2** Probabilistic sensitivity analysis. Effect of varying all parameters simultaneously on the percent of iterations in which premedication and monitoring is favored for standard-risk (A) and high-risk (B) models
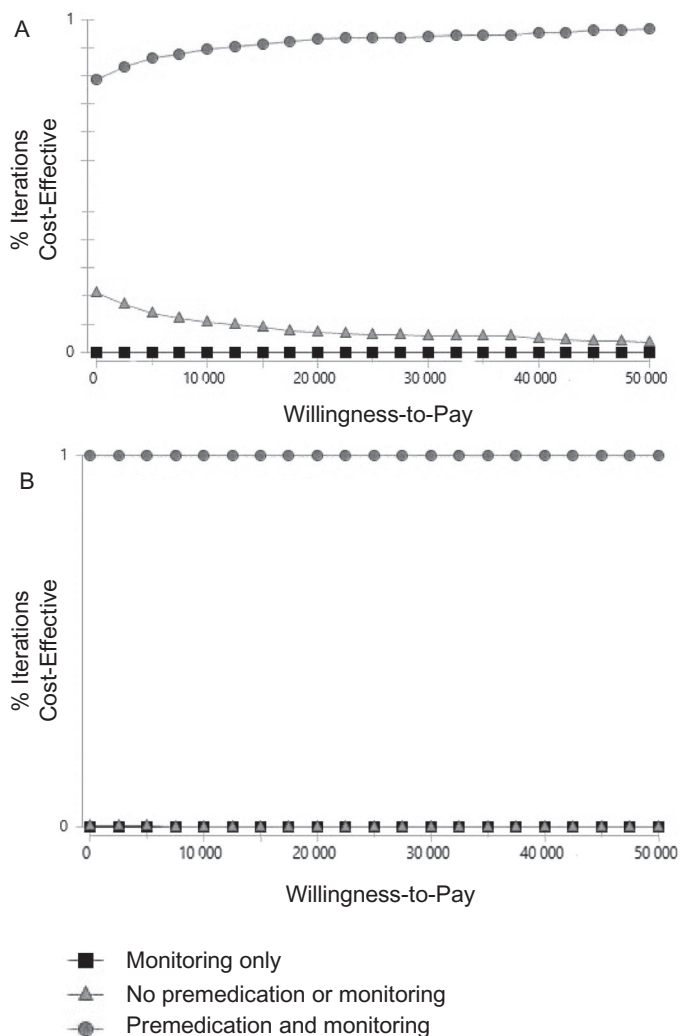


doses of PEG-asparaginase due to the infrequent development of hypersensitivity reactions with the initial dose.[10] We believe that premedication prior to all PEG-asparaginase doses is reasonable and has demonstrated the cost-effectiveness of premedication in a model limited to only two doses of PEG-asparaginase. In the literature, approximately one-third of hypersensitivity reactions occur following the second dose of PEG-asparaginase.[4,11–14,16,17] In our model, we assumed patients given premedication received acetaminophen, diphenhydramine, hydrocortisone, and famotidine. Many published premedication protocols use some combination of these medications. By assuming patients received all of the medications used in published protocols, our model incorporated the most expensive potential premedication strategy. Despite this approach, our model output found premedication was the least costly strategy overall. Considering other less expensive medication combinations would only increase the cost savings of the premedication strategy.

Routine premedication does carry some disadvantage. Antihistamines and corticosteroids may mask the clinical symptoms, which can indicate asparaginase neutralization. Therefore, when premedication is utilized, consensus guidelines recommend the use of serum asparaginase level monitoring to identify silent inactivation, which is not prevented by premedication.[2] However, testing is now commercially available and relatively inexpensive and therefore presents only a minor hindrance. Additionally, though generally well tolerated, antihistamines may be associated with fatigue or with a paradoxical stimulant effect, which can be distressing to children and their parents. Premedication use also marginally increases the time required for asparaginase administration, as premedications are typically administered 30-60 minutes prior to asparaginase in order to achieve ideal effect.

In our study, we modeled the use of either two or seven doses of PEG-asparaginase, which reflects the recommended therapy for most children with B-cell ALL treated on clinical trials currently offered by the COG. Over 90% of children and adolescents in the United States with a diagnosis of malignancy are treated within a COG member institution.[44] However, alternate medication schedules are utilized by other large consortium groups within the United States. Children with newly diagnosed ALL enrolled on Dana-Farber Cancer Institute ALL Consortium Protocol 16-001 were administered 16 doses of PEG-asparaginase, without use of routine premedication.[45] The St Jude Total Therapy Study 16 administered a similar number of doses of PEG-asparaginase to patients with standard-risk or high-risk ALL, though the frequency of premedication use was not described in the

study results.[46] As most hypersensitivity reactions occur with the first several doses of asparaginase, premedication has the potential to be even more cost-effective in scenarios where patients receive more doses.[4,11–14,16,17] A recent survey of pediatric hematology-oncology providers administering therapy using COG, Dana-Farber or St Jude ALL protocols found that 65% of providers utilized premedication for the first and/or subsequent doses of PEG-asparaginase.[47] Uptake of premedication is likely to increase as more data become available.

Several model assumptions impact the results presented. We assumed that development of a CTCAE grade 2 or greater allergic reaction resulted in discontinuation of PEG-asparaginase and change to *Erwinia*, on the basis of published consensus guidelines.[2] However, with limitations in *Erwinia* availability, some providers may choose to reexpose patients to PEG-asparaginase following CTCAE grade 2 reactions, especially if the timing of the reaction was questionable or symptoms could be attributed to a different exposure. If a greater threshold was utilized to indicate a need to change medication formulation, there would be fewer opportunities for premedication to prevent this undesirable effect. In our sensitivity analysis, we observed that when the probability of an allergic reaction in the setting of no premedication was varied to the minimum end of its range, premedication was no longer the least costly strategy, though premedication remained cost-effective despite this when considering the additional QALYs gained. In addition, we based the probability of EFS on the results of studies published in the literature. As the long-term results of more recent clinical trials become available, EFS is projected to further increase. This would be expected to have a favorable consequence on the cost-effectiveness of premedication as data in the literature support a decreased EFS in children who are unable to receive all doses of asparaginase therapy.[7] Lastly, we incorporated the overall risk of hypersensitivity reaction following PEG-asparaginase into our model regardless of formulation. Larger studies reported conflicting information on whether the risk of hypersensitivity reactions is greater with intravenous versus intramuscular formulations; some reviews found no significant difference in the risk of high-grade hypersensitivity reactions between formulations.[16,48,49] Our results could differ if this is the case.

In summary, premedication is inexpensive, widely available, and results in fewer switches from PEG-asparaginase. Consideration should be given to the routine use of premedication prior to all doses of PEG-asparaginase in view of the importance of this medication in ALL therapy.

## AUTHOR CONTRIBUTIONS

Meghan McCormick conceptualized the manuscript, developed the cost-effectiveness model, analyzed and interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript for important intellectual content. Jillian Lapinski conceptualized the manuscript, analyzed and interpreted the data, and reviewed and revised the manuscript for important intellectual content. Erika Friehling conceptualized and designed the study and reviewed and revised the manuscript for important intellectual content. Kenneth Smith made substantial contributions to the development of the cost-

effectiveness model, interpreted the data and reviewed and revised the manuscript for important intellectual content. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## CONFLICTS OF INTEREST

The authors have no financial relationships or conflicts of interest relevant to this article to disclose.

## DATA SHARING STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.