Cost-Effectiveness of Nusinersen and Universal Newborn Screening for Spinal Muscular Atrophy

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Objective To evaluate the cost-effectiveness of nusinersen with and without universal newborn screening for infantile-onset spinal muscular atrophy (SMA).

Study design A Markov model using data from clinical trials with US epidemiologic and cost data was developed. The primary interventions studied were nusinersen treatment in a screening setting, nusinersen treatment in a nonscreening setting, and standard care. Analysis was conducted from a societal perspective.

Results Compared with no screening and no treatment, the incremental cost-effectiveness ratio (ICER) for nusinersen with screening was $330 558 per event-free life year (LY) saved, whereas the ICER for nusinersen treatment without screening was $508 481 per event-free LY saved. For nusinersen with screening to be cost-effective at a willingness-to-pay (WTP) threshold of $50 000 per event-free LY saved, the price would need to be $23 361 per dose, less than one-fifth its current price of $125 000. Preliminary data from the NURTURE trial indicated an 85.7% improvement in expected LYs saved compared with our base results. In probabilistic sensitivity analysis, nusinersen and screening was a preferred strategy 93% of the time at a $500 000 WTP threshold.

Conclusion Universal newborn screening for SMA provides improved economic value for payers and patients when nusinersen is available. *(J Pediatr 2020;227:274-80)*.

Spinal muscular atrophy (SMA) is a neuromuscular disorder with an estimated incidence of 1 in 11 000 live births and is the second-most common fatal autosomal recessive disorder after cystic fibrosis.[1-3] SMA leads to progressive muscle atrophy and weakness and is one of the leading genetic contributors to infant mortality.[4-6] Type 1 SMA is the most common and most severe form of the disease, with onset in the first 6 months of life. Infants with type 1 SMA have rapid progression of weakness leading to complete loss of voluntary movement, severe dysphagia, and life-threatening respiratory insufficiency. Children with this condition typically do not survive the second year.[7]

Introduction of new treatments has led to the inclusion of SMA in the Recommended Uniform Screening Panel's list of disorders to be screened at birth. Several US states have already approved or are currently considering legislation to mandate newborn screening for SMA.[8] Recent approval of onasemnogene abeparvovec-xioi, a gene replacement therapy for SMA, provides a therapeutic option for infants with SMA.[9] Another option includes the drug nusinersen, which has been shown to improve motor function and reduce the risk of mortality in infants with type 1 SMA.[10,11] Data reported to date suggest that earlier treatment with nusinersen leads to greater improvement in outcomes.[10] Recent results from a trial in presymptomatic patients suggest that earlier treatment is significantly more efficacious.[12] Universal screening for SMA at birth leads to earlier identification of disease and thus may lead to improved outcomes through earlier treatment.

Although initial efficacy studies of nusinersen demonstrated meaningfully improved health outcomes for patients with SMA, the high cost of the drug—$750 000 in the first year and $375 000 annually thereafter—can be a barrier to access for some patients.[13] The recent debate about the ethics of high-cost therapies for rare diseases has led to a growing concern that payers may decline to cover nusinersen or discontinue coverage if patients do not respond to therapy within arbitrary endpoints.[14-16] The high cost of nusinersen necessitates an economic evaluation of its use, along with an analysis of universal screening at birth.

CPT	Current Procedural Terminology
ICER	Incremental cost-effectiveness ratio
LY	Life year
PVA	Permanent ventilator assistance
QALY	Quality-adjusted life year
SMA	Spinal muscular atrophy
WTP	Willingness to pay

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A review of nusinersen by the Canadian Agency for Drugs and Technology in Health and the National Institute of Health and Care Excellence in the United Kingdom concluded that the list price was too high to be considered cost-effective, even at high willingness-to-pay (WTP) thresholds—a maximum price that healthcare consumers and private or public insurers will pay for a healthcare good or service.[17,18] However, treatment in the setting of universal screening has not been examined. In this study, we examine the cost-effectiveness of nusinersen treatment for infantile-onset SMA in a universal newborn screening setting.

Methods

A decision analytic Markov model was developed to evaluate universal screening and treatment of infantile-onset SMA with periodic injections of nusinersen. Markov decision models follow a hypothetical cohort of patients through distinct health states using estimated probability parameters to evaluate a policy or compare different sets of treatment options in terms of their effectiveness and cost. We set our model with parameters based on results of the ENDEAR trial, a 13-month randomized, multicenter, sham-controlled, phase 3 clinical trial.[10] We developed a secondary model using preliminary results (at the time of our analysis) of the phase 2 NURTURE trial (NCT02386553), which as of October 2018 showed that all patients with SMA were alive and demonstrated a motor milestone response of 92% within the first 13 months, to supplement our main results.[12] The strategies considered in our model included (1) nusinersen treatment with universal screening, (2) nusinersen treatment without universal screening, (3) universal screening and no treatment, and (4) no screening and no treatment.

Costs and outcomes were evaluated at 1-month intervals and then extrapolated for the lifetime of the cohort. We first simulated a cohort of hypothetical patients until death or reaching age 30 months, whichever occurred first. We limited our model's month-to-month time horizon to 30 months, because there do not exist data on the long-term survival rates of patients with type 1 SMA treated with nusinersen. Several assumptions on survival past 30 months were made owing to the lack of evidence of long-term benefits of nusinersen. Because respiratory insufficiency is the primary cause of morbidity for infants with SMA, patients who responded to treatment and survived to 30 months without permanent ventilator assistance (PVA) were assigned a life expectancy equivalent to that of patients suffering from severe asthma.[19] For patients with SMA who saw improvements in motor milestone response, we assigned a life expectancy halfway between that of a patient with asthma and that of the average patient from the general population from the 2015 National Vital Statistics Reports. The life expectancy of surviving infants with SMA requiring PVA was based on cohort studies of patients with Duchenne muscular dystrophy requiring nocturnal ventilation, because such persons are at risk of life-threatening respiratory disorders, exhibit muscle wasting and loss of motor skills, and have a short life expectancy (25 years).[20] The set of health states in the model varied depending on the treatment arm but consisted of the following: SMA-free, untreated SMA, treated SMA, motor milestone response, PVA, and death.

Our analysis was conducted from a societal perspective by including both direct medical costs and indirect work-related income loss of a caregiver.[21] The primary outcomes of the study were the expected discounted event-free life years (LYs) saved and expected discounted costs per infant. We defined event-free as patient history without the need for PVA or death. Costs and outcomes were discounted at the recommended 3% discount rate, with costs and outcomes multiplied by a discount factor, $1/(1+.03)^{year}$, applied to each year in the future; this reflects the economic principle that current health status is valued over future health status. The incremental cost-effectiveness ratio (ICER)—the ratio between the difference in cost and the difference in effectiveness between 2 strategies—was calculated for each strategy following similar methodologies examining the cost-effectiveness of newborn screening for congenital heart disease.[22,23] We also estimated the ICER per quality-adjusted LYs (QALYs) saved.

All infants in the nusinersen and screening arm were screened for SMA and then confirmed for type 1 in the first month after birth. In positive infants, 4 loading doses of nusinersen were administered. The drug is administered via lumbar puncture, and thus the associated costs in our model included both the nusinersen dose and the professional and facility payments of the procedure. These patients continued to receive periodic nusinersen injections every 4 months for the entirety of the model until death or failure to respond to treatment. Nonresponse was defined as patient transition to the PVA health state.

In the treatment with no screening strategy, we assumed that patients with SMA type 1 would not be diagnosed until age 6 months.[24] Similar to patients who had been diagnosed through screening, patients in this arm also received 4 loading doses of nusinersen and continued receiving doses until death or transition to PVA.

In the remaining nontreatment strategies, we modeled the natural progression of SMA based on calculations derived from the experience of the sham control group of the ENDEAR trial. The model's Markov state transition probabilities were then revised based on the preliminary results of the NURTURE trial and reported alongside our base model.

Model Inputs: Probabilities

The primary probability values of health-related events were based on calculations from the results of the ENDEAR trial and derived from other published literature (**Table I** and **Table II**; available at www.jpeds.com). The monthly probabilities of death and transition to PVA in patients receiving nusinersen treatment and untreated patients are reported in **Table I**. The prevalence of SMA was set as the median range of rates of SMA prevalence—9.4 per 100 000.[25] Our model studied only infantile-onset type 1 SMA,

which comprises 60% of all SMA diagnoses and is the most severe type.[26]

SMA-free patients in our model faced the risk of death but no other adverse health events. Monthly death probabilities were a function of age and calculated from US neonatal and postneonatal mortality rates from the Centers for Disease Control and Prevention's 2015 linked birth/infant death records. Child mortality rates were based on the 2015 National Vital Statistics Report. We assumed that patients with SMA who showed improvements in motor milestones as a result of treatment faced mortality rates at age 30 months equivalent to the normal population.

Model Inputs: Costs

Cost inputs were derived from the literature or based on Current Procedural Terminology (CPT) codes. We included both health system and indirect medical costs. The cost of SMA screening per infant was based on the Utah Legislature's 2018 increase in the total price of the newborn screening kit from $112.16 to $115.07. This legislative increase was explicitly mentioned to accommodate the inclusion of SMA as part of the Utah newborn screening kit. We did not account for other costs of screening (eg, instrumentation, staff time), because utilization of these resources is likely invariant to the inclusion of SMA. The cost of a single nusinersen administration was set at $125 000 based on current pricing information.

Direct medical costs of PVA were based on estimates from Sevick et al and adjusted to 2018 dollars using personal consumption expenditures chained to the price index for health care services.[27,28] Indirect medical costs of PVA consisted of the average reported wage loss of caregivers adjusted to 2018 dollars using the Bureau of Labor Statistics' Employment Cost Index for wages and salaries.

Facility costs associated with the administration of nusinersen were based on the private payer adjustments of Medicare's average payment for injection of substance into the lower or sacral spine (CPT 62311) and moderate sedation services of patient aged <5 years (CPT 99150).[29,30] Professional costs of therapeutic injection with image guidance (CPT 62323) and moderate sedation services for children aged <5 years (CPT 99151) were also included and adjusted to reflect the private payer's perspective.[31] Expected lifetime costs were then included as final costs in the model.[32,33] Cost inputs are summarized in Table II.

Model Inputs: Outcomes

QALY, a commonly used effectiveness outcome in economic evaluations, assesses the quality of life by applying utility weights for an illness. However, because there are no published utility valuations of pediatric patients with SMA, we used utility weights based on asthma as a proxy for patients with SMA surviving into adulthood without PVA.[34,35] Utility weights for patients with SMA are applied only after age 18 years for surviving patients for whom reliable data are available.[19] The QALY results supplement our primary evaluation based on LYs.

Previous economic evaluations examining treatments for pediatric populations have used discounted LYs saved as an effectiveness outcome.[23] Our study used event-free LYs saved, in which the event is defined as the need for PVA as an effectiveness outcome. We discuss the relative benefits of this effectiveness outcome in the discussion.

Sensitivity Analyses

Results from the ENDEAR trial demonstrate the benefits of early treatment with nusinersen on improved event-free survival compared with later treatment. We ran our model in a secondary scenario to account for the differences in survival and the likelihood of requiring ventilator assistance between early treatment and late treatment groups. Therefore, we present both base case results (ie, average patient response) and adjust our model to account for treatment time differentials in the ENDEAR trial. These adjustment factors were calculated based on results from Finkel et al[10] and are reported in Table I. In addition, model parameters were adjusted using preliminary results of NURTURE at the time of our analysis for additional estimates. Because the outcomes of NURTURE were dependent on patients receiving treatment while asymptomatic, results from the time-adjusted treatment outcomes of ENDEAR were used in the nusinersen treatment without universal screening strategy.

The list price of nusinersen is by far the most important component of costs and has been cited as the main factor in determining the cost-effectiveness of nusinersen therapy.[36] We conducted a threshold analysis by varying the price of nusinersen from $5000 to its current price of $125 000 to identify the price at which treatment would be cost-effective at various WTP thresholds. Finally, we performed probabilistic sensitivity analysis (PSA) to examine the impact of uncertainty in all the parameters simultaneously. The ranges for long-term life expectancy and costs were defined with wide upper and lower bounds owing to the lack of data on long-term healthcare utilization and benefits of nusinersen treatment (Table II).

Results

Compared with no screening and no treatment, the ICER for nusinersen treatment without screening was $508 481 per event-free LY saved and $522 118 per event-free QALY saved. Compared with no screening and nusinersen, the ICERs for screening newborns along with treatment were $193 867 per event-free LY saved and $199 510 per event-free QALY saved. Nusinersen without screening strategy was then eliminated by extended dominance of the combined strategies of no screening and no nusinersen and screening with nusinersen. Therefore, compared with no screening and no treatment, the ICER for screening and treatment was $330 558 per event-free LY saved, which is less than a WTP of $500 000 proposed by the Institute for Clinical and Economic Review for evaluating ultra-rare diseases.[37] Adjusting for early and late treatment effects produced higher outcomes but at

higher costs, owing to a higher proportion of patients avoiding PVA or death and receiving nusinersen treatment throughout life, as well as a higher proportion of infants surviving but remaining in PVA and incurring extra costs without additional event-free LYs saved. Table III reports the complete results, and Figure 1 summarizes the main results graphically.

Sensitivity Analysis

Figure 2 depicts the results of our PSA as a cost-effectiveness acceptability curve, showing that nusinersen with screening was a cost-effective strategy 93% of the time with a WTP of $500 000 per event-free LY saved. Figure 3 illustrates the results from our threshold analysis of the price of nusinersen. We found that at a per dose price of $23 361, universal screening and nusinersen therapy was a cost-effective strategy given a WTP of $50 000. For higher WTP levels of $100 000 and $150 000, cost-effectiveness was achieved with per dose prices of $41 813 and $60 266, respectively.

When using inputs derived from the preliminary results of presymptomatically treated patients in the NURTURE trial, we found a substantial increase (85.7%) in expected LYs saved with the nusinersen treatment with newborn screening strategy. As expected, the ICERs in the revised analysis using NURTURE data were greater than the base case analysis, owing to a higher proportion of patients surviving and incurring costs of annual nusinersen treatment over their lifetime. The ICERs were $254 881 per LY saved and $261 801 per QALY saved in the base case model for treatment in a screening setting compared with treatment alone.

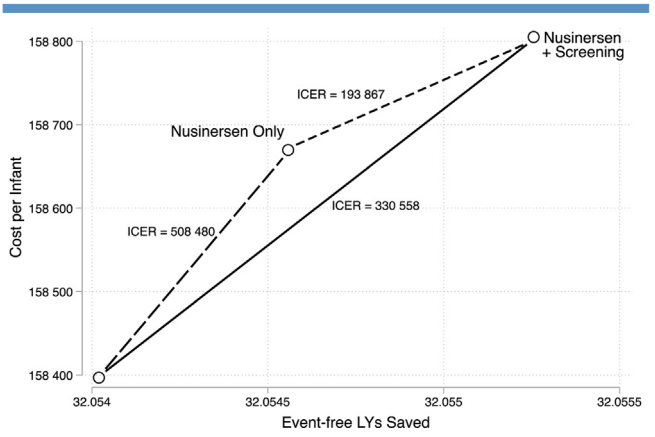

Figure 1. ICER per discounted event-free LY saved. The graph reports results from the base case ENDEAR trial model parameters. Effectiveness and cost outcomes are estimated per US live birth.

Discussion

Our analysis shows that nusinersen treatment in the setting of universal screening is a preferred strategy over treatment alone but is cost-effective only at high WTP thresholds (eg, >$300 000 per event-free LY). The clinical efficacy of medical interventions often conflicts with the prospective assessment of their economic value. For rare genetic diseases such as SMA, the high price of treatment coupled with the relative rarity of the condition inevitably makes it difficult to assess treatment as cost-effective using current standards of WTP thresholds.[38] However, patients with such rare diseases have been underserved through the lack of development of viable and economically feasible treatment.[39] This historical disparity may be attributable to the low return on investment for rare diseases and thus reduced incentives for commercial developers. Inevitably, important ethical considerations for such patients have been raised with respect to the economic evaluation of costly treatment for rare diseases.[40]

Table III. Results of cost-effectiveness analysis

Strategy	Costs per infant, $	Incremental costs, $	Event-free LYs	Event-free QALYs	Incremental LYs	Incremental QALYs	ICER-LY, $	ICER-QALY, $
Base case								
No treatment/no screening	158 397	—	32.0540	31.1517	—	—	—	—
Screening/no treatment	158 400	2.9	32.0540	31.1517	0	0	Dominated	Dominated
Nusinersen/no screening	158 670	272.8	32.0546	31.1522	0.0005	0.0005	508 481	522 118
Nusinersen + screening	158 805	135.4	32.0553	31.1529	0.0007	0.0007	193 867	199 510
NURTURE (preliminary)								
Nusinersen + screening	159 005	335.5	32.0559	31.1535	0.0013	0.0013	254 881	261 803
Adjustment for early and late treatment								
No treatment/no screening	158 396.9		32.0540	31.1517	—	—	—	—
Screening/no treatment	158 399.8	2.9	32.0540	31.1517	0	0	Dominated	Dominated
Nusinersen/no screening	158 630.2	233.4	32.0544	31.1521	0.0004	0.0004	561 873	575 144
Nusinersen + screening	158 886.3	256.0	32.0555	31.1532	0.0011	0.0010	239 885	247 492
NURTURE (preliminary)								
Nusinersen + screening	159 005.1	374.9	32.0559	31.1355	0.0014	0.0014	260 833	268 152

Adjustment probability parameters are reported in Table I. ICERs are reported using precision to 6 significant digits.

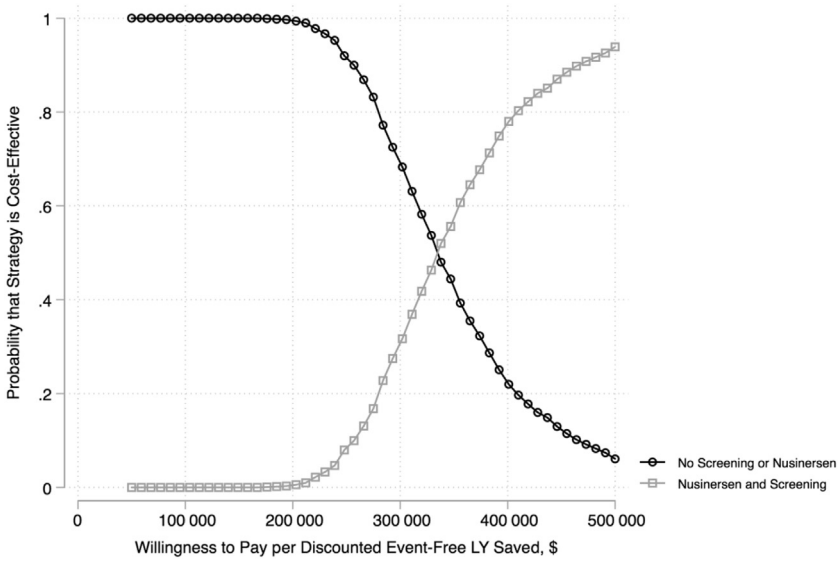

Figure 2. Probability of cost-effectiveness based on the base case model and a list dosage price of nusinersen at $125 000.

Although our base case results are in line with previous economic evaluations of nusinersen, the addition of universal newborn screening improves the economic viability of nusinersen. In our base case analysis, compared with no screening or treatment, the combination of universal screening and treatment with nusinersen yielded an ICER below the WTP of $500 000 per LY saved, a WTP threshold that has been previously recommended for rare diseases (although later updated to $200 000 irrespective of therapeutic area) by the Institute for Clinical and Economic Review.[37]

Our methodology relied on LYs saved as our main effectiveness measure. Although QALYs were reported, determining utility weights for children is difficult, as discussed earlier.[34] Nevertheless, the Canadian Agency for Drugs and Technology in Health rejected the cost-effectiveness of nusinersen therapy using this threshold.[17] A recent analysis in Sweden reached a similar conclusion, yet reimbursement for nusinersen has been approved in that country.[36] Coverage in the US is likely to expand as further results of clinical trials are published. Major private payer reimbursements for

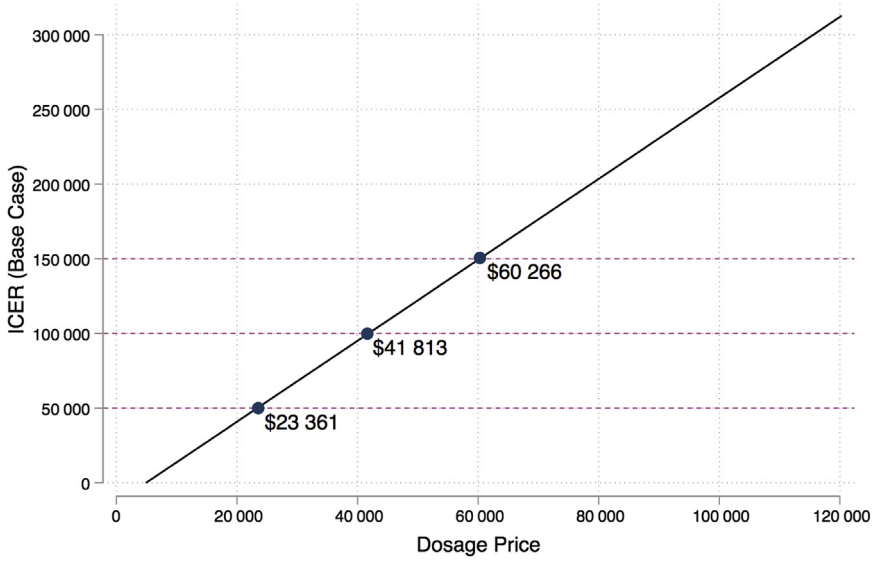

Figure 3. ICER per discounted event-free LY saved. Sensitivity analysis performed on the base case model. *Dashed horizontal lines* are set at 3 willingness-to-pay thresholds—$50 000, $100 000, and $150 000—with the corresponding nusinersen dosage price.

nusinersen require a confirmed diagnosis of SMA and observation of clinical response. In this scenario, early initiation and continued treatment of infantile-onset SMA is more likely with a policy of universal screening rather than treatment alone. Our present findings support the expansion of universal newborn screening.

The improvement in response to nusinersen treatment seen in presymptomatic patients is promising, but the long-term efficacy is uncertain. Economic evaluations of this treatment should be updated in the future as follow-up studies are conducted to gauge patient outcomes over time. In addition, similar Markov models can be used to evaluate alternative treatments, such as single-dose gene replacement therapy. Although preliminary studies suggest that this treatment is equally promising and with the added advantage over nusinersen of not requiring ongoing administration, gene therapy has been introduced at $2.1 million.[9,41] With such high costs, universal newborn screening likely will also play a pivotal role in improving both health outcomes and the economic value of gene replacement therapy.

Our study is subject to a number of limitations. First, our focus on event-free LYs saved as our primary health outcome ignores potential emotional and psychosocial stress considerations in the patients' family members.[42,43] We included indirect costs of caregiving for patients with SMA in the PVA health state, but adequate data on family members of a child with SMA were not available in the literature. However, this new effectiveness outcome is a conservative measure, because patients progressing to the PVA health state continue to accrue costs but do not contribute to the effectiveness of nusinersen. A utility approach with the inclusion of family spillovers will still value patients in the PVA health state, albeit at low utility values. Second, given the rarity of SMA, little is known about the long-term costs attributable to the disease, and further research is needed to improve our understanding of expected costs of surviving patients with SMA past the median survival time. In particular, the focus on respiratory symptoms, influencing our assumptions regarding costs based on life expectancy estimates of patients with severe asthma and Duchenne muscular dystrophy with ventilator support, should be reconsidered in future research when new data are available. We accounted for this limitation by setting a wide range of values on life expectancy and age-specific cost variables in probability sensitivity analysis. In addition, the sensitivity of our results by changing the long-term benefits and cost assumptions will also depend on the discount factor applied to outcome variables.

The ENDEAR trial along with preliminary results of NURTURE have demonstrated that nusinersen is an important innovation in SMA treatment; however, many have wondered whether the drug provides sufficient value to justify the high cost.[14-16] Our study examined the cost-effectiveness of nusinersen in the setting of universal newborn screening with a goal of treating presymptomatic infants. We demonstrated that universal newborn screening will reduce estimated ICERs compared with nusinersen alone. Our study provides additional support to the Recommended Uniform Screening Panel recommendations to expand universal newborn screening in all states to include SMA. Moreover, our study also provides alternative pricing recommendations based on sensitivity analysis. Using data from the ENDEAR trial, our analysis suggests that meeting a WTP threshold of $50 000 per LY saved would require a dosage price of nusinersen that is 19% of the current price.

Studies of rare diseases, like SMA, face common constraints owing to the lack of high-quality cost and outcomes data.[44] A study examining the cost-effectiveness of prenatal screening for SMA faced similar challenges.[45] Our model parameters represent an improvement on previous work, but more work is needed to fill this important gap in the literature. Continued follow-up of patients treated with nusinersen is needed to validate further economic evaluations. ■

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Table I. Probability inputs

Probability	Value	Distribution	Range	Reference
SMA prevalence	9.4 per 100 000	Beta	3.58-8.27 per 100 000	[25]
SMA type 1, %	60			[26]
Death, nusinersen, %	1.36	Beta	0.56-2.77	Monthly; calculations based on[9]
Death, no treatment, %	3.73	Beta	1.43-7.47	Monthly; calculations based on[9]
Death, NURTURE, %	0			[11]
Neonatal mortality rate	3.94 per 1000			2015 CDC NCHS linked birth/infant death records
Postneonatal mortality rate	1.96 per 1000			2015 CDC NCHS linked birth/infant death records
Child (1-4 y) mortality rate	2.49 per 1000			2015 National Vital Statistics Report Volume 66, No 6
Death, PVA, %	3.19	Beta	1.37-6.18	Bartlett et al 2000[46]
Ventilator support, nusinersen, %	1.94	Beta	0.76-4.14	Monthly; calculations based on[9]
Ventilator support, no treatment, %	2.89	Beta	0.84-5.94	Monthly - Calculations based on[9]
Ventilator support, NURTURE, %	0			[11]
MM response, nusinersen, %	5.29	Beta	1.55-9.27	Monthly, calculations based on[9]
MM response, no treatment, %	0.00			Monthly, calculations based on[9]
Adjustment for early treatment	0.516			Adjustment factor based on[9]
Adjustment for late treatment	1.484			Adjustment factor based on[9]
MM response, NURTURE, %	17.66			≤13 mo[11]
MM response, NURTURE, %	100			>13 mo

Table II. Cost and outcome inputs

Item	Value	Distribution	Range	Code	Notes
Single dose injection of nusinersen, $	125 000		5000-125 000	J2326	Current reported pricing
Marginal cost of SMA newborn screening, $	2.91	Gamma	1.94-4.45		2018 Utah legislative increase of Newborn Screening Kit
Lumbar puncture with image guidance, professional fee, $	102.60	Gamma	101-232	62323	CMS
Moderate sedation service of patient <5 y, professional fee, $	25.20			99151	CMS
Medicare to private payer rate, professional fee, %	23				[31]
Injection of substance into lower or sacral spine, facility fee, $	120.06	Gamma	141-315	62311	Average Medicare payment amount (2016)
Moderate sedation service of patient <5 y, facility fee, $	15.22			99150	Average Medicare payment amount (2016)
Medicare to private payer rate, facility fee %	66				[29,30]
Direct monthly costs, PVA, $	13 564		8898-19 351		[28]; PCE Health Services
Indirect monthly costs, PVA, $	1034	Gamma	678-1435		[28]; Bureau of Labor Statistics
Age-specific annual costs, 0-18 y, $	4552	Gamma	2936-6812		[32,33]
Age-specific annual costs, 19 y, $	4988	Gamma	Range varied for estimating final costs by health state		[32,33]
Age-specific annual costs, 20-39 y, $	3507				[32,33]
Age-specific annual costs, 40-44 y, $	4367				[32,33]
Age-specific annual costs, 45-64 y, $	6533				[32,33]
Age-specific annual costs, >65 y, $	16 346				[32,33]
LY, normal population	79.5 (29.91 discounted)	Gamma	17.6-44.1		[19]
LY, SMA without PVA (with presymptomatic treatment)	75 (29.48 discounted)	Gamma	19.8-44.6		[19]; asthma used as proxy
LY, SMA with PVA	25.3 (16.4 discounted)	Gamma	10.6-22.9		[20]; Duchenne muscular dystrophy with nocturnal ventilation used as proxy
QALY, normal population	71.4				[19]
QALY, SMA without PVA	64.4				[19]; asthma used as proxy