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Economic Evaluation

Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in The Netherlands

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ABSTRACT

Objectives: Spinal muscular atrophy (SMA) is a rare genetic disorder that causes progressive muscle weakness and paralysis. In its most common and severe form, the majority of untreated infants die before 2 years of age. Early detection and treatment, ideally before symptom onset, maximize survival and achievement of age-appropriate motor milestones, with potentially substantial impact on health-related quality of life. Therefore, SMA is an ideal candidate for inclusion in newborn screening (NBS) programs. We evaluated the cost-effectiveness of including SMA in the NBS program in The Netherlands.

Methods: We developed a cost-utility model to estimate lifetime health effects and costs of NBS for SMA and subsequent treatment versus a treatment pathway without NBS (ie, diagnosis and treatment after presentation with overt symptoms). Model inputs were based on literature, local data, and expert opinion. Sensitivity and scenario analyses were conducted to assess model robustness and validity of results.

Results: After detection of SMA by NBS in 17 patients, the number of quality-adjusted life-years gained per annual birth cohort was estimated at 320 with NBS followed by treatment compared with treatment after clinical SMA diagnosis. Total healthcare costs, including screening, diagnostics, treatment, and other healthcare resource use, were estimated to be €12 014 949 lower for patients identified by NBS.

Conclusions: NBS for early identification and treatment of SMA versus later symptomatic treatment after clinical diagnosis improves health outcomes and is less costly and, therefore, is a cost-effective use of resources. Results were robust in sensitivity and scenario analyses.

Keywords: cost-effectiveness analysis, economic evaluation, newborn screening, spinal muscular atrophy.

VALUE HEALTH. 2022; ■(■):■–■

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by functional loss of the *SMN1* gene. It leads to progressive, irreversible loss of motor neurons with a range of severe symptoms. In the first 6 months of life, untreated SMA type 1 patients have overt, rapidly progressing muscle weakness, leading to respiratory failure and death.[1,2] Chronic childhood-onset SMA variants are characterized by stalled gross motor development, causing inability to walk independently (SMA type 2) and ambulation loss later in life (SMA type 3). Rare adult-onset SMA type 4 primarily causes proximal weakness of arms and legs.[3] The reported incidence of SMA in the literature varies from 1:7000 to 1:11 000 births,[4-6] and the estimated prevalence is approximately 1 to 2 per 100 000 population.[7]

Three SMA treatments have been approved by the European Medicines Agency and the US Food and Drug Administration: nusinersen (Spinraza®), onasemnogene abeparvovec (Zolgensma®), and risdiplam (Evrysdi®). With different modes of action, these therapies aim to increase the availability of functional SMN protein. Clinical trial results demonstrate these treatments are effective against motor neuron loss and further disease progression. Earlier intervention has demonstrated better preservation of motor neurons and improved or preserved motor function.[8-11] Reports from presymptomatic treatments demonstrated greater potential for gain in motor performance and achievement of enhanced motor milestones.[8,12-14] Diagnosis and treatment of SMA as early as possible, before onset of symptomatic disease, are crucial to prevent irreversible motor neuron loss and reduced motor function,[15] thus achieving the best possible outcomes.[16,17] Therefore, SMA is a good candidate for inclusion in newborn screening (NBS).

Notably, several countries have already started NBS pilot and national programs for SMA, including Belgium, Germany, the United States, Australia, Italy, Spain, and Taiwan.[16,18-23] In July 2019, the National Health Council in The Netherlands positively

advised inclusion of SMA screening in the NBS program,[24] and the National Institute for Public Health and the Environment recently published an implementation plan for SMA inclusion within the Dutch NBS program in 2022.[25]

Cost-effectiveness evaluations can support the decision to implement an NBS program for SMA in The Netherlands. In particular, the cost, budgetary impact, and health gains compared with current practice need to be assessed in the context of generally limited healthcare budgets. The goal of this study was to assess the cost-effectiveness of NBS for SMA versus with SMA treatment after clinical diagnosis in The Netherlands.

Methods

Model Structure

Our cost-utility model was developed to evaluate the lifetime costs and health effects of 2 alternatives: treatment of SMA after identification by NBS versus treatment after clinical SMA diagnosis. The model framework is a combination of a decision tree and a Markov state-transition model (Fig. 1). A short-term decision tree was designed to capture the initial NBS outcomes and treatment options. Subsequently, a Markov model was linked to simulate the health outcomes and costs. In line with published health-economic models on SMA treatment, the Markov model includes the following health states: being within a broad range of normal development (BRND), walking, sitting, not sitting, and requiring permanent assisted ventilation (PAV).[26-29] These health states align with major developmental milestones of healthy infants and clinical outcomes assessed in SMA clinical studies. Motor milestones were described based on tests listed in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010.

The cost-effectiveness analysis was conducted in accordance with Dutch pharmacoeconomic guidelines, following both the payer and societal perspectives.[30] Notably, a lifetime time horizon (100 years) and annual discount rates of 4% for costs and 1.5% for health outcomes were applied. Costs were expressed at 2019 price levels.[31]

Population Cohort

The modeled cohort size was based on 169 680 newborns in The Netherlands in 2019. A cycle length of 6 months was applied for the first 3 years, followed by 12 months for the remainder of the model, to adequately reflect the rapid rate of motor development change in the first 3 years of a child's life while also allowing treatment cycles to be appropriately costed. After the first 3 years of life, by which time healthy children would have achieved the milestone of walking, a longer cycle length was applied, reflecting the reduced likelihood of developmental change.

Model Inputs

Model inputs consisted of screening parameters, epidemiologic parameters, clinical aspects, costs, and utilities (Table 1[4,6,25,32-39] Appendix Methods in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010 and Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010).[4,6,25,32-38,40] These were derived from published literature, health technology assessment agencies' reports, databases, and Dutch clinical expert opinion (see Acknowledgments section; hereafter referred to as expert opinion). In cases of disagreement regarding model inputs, consensus was reached by discussion with the authors and experts.

Screening parameters

In the model, the heel-prick test (as routinely used in Dutch NBS), in which a drop of blood is taken from the baby, is assumed to be used to identify the SMA genotype.[25] A real-time polymerase chain reaction genotyping assay for *SMN1* is then performed on a dried blood spot to detect homozygous *SMN1* deletion.[22] If the result is positive, SMA status can be confirmed and *SMN2* copy number, as a marker of the severity, can be determined by either droplet digital polymerase chain reaction or multiplex ligation-dependent probe amplification.[22,25] Coverage with heel-prick screening is >99% in The Netherlands.[41]

Epidemiological inputs

Our model base included the incidence of SMA patients detected by NBS. Nevertheless, because NBS does not identify *SMN1* point mutations, this patient group is assumed to be diagnosed clinically when symptoms occur. According to a feasibility study[25] and Dutch expert opinion, a maximum of 1% of patients with SMA have an *SMN1* point mutation, might therefore not be identified with NBS, and may be labeled as false-negatives. No false-positive results should be expected because all NBS tests are validated with a subsequent genetic test.[18,39] In addition, according to clinical results from an NBS study for SMA in Germany, no false-positives or false-negatives occurred during a 2-year period.[42]

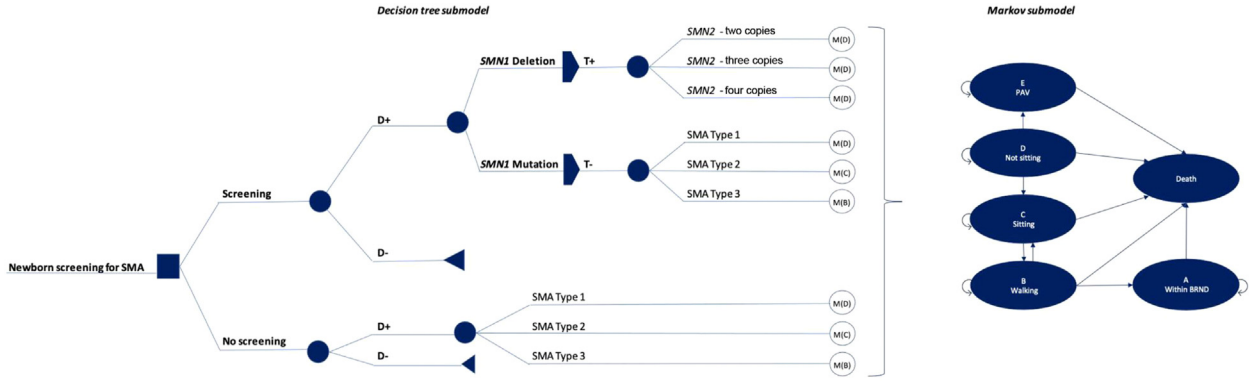
Because motor development and survival vary widely by SMA phenotype, which is largely influenced by *SMN2* gene copy number, our model included symptomatic patients with SMA types 1, 2, and 3, and presymptomatic newborns with specific *SMN2* gene copy numbers. It was estimated that 45%, 33%, and 22% of newborn patients had SMA with 2, 3, or 4 *SMN2* copies, respectively.[4,32] The percentage of symptomatic patients diagnosed of SMA types 1, 2, or 3 was estimated as 58%, 29%, and 13%, respectively.[6]

Clinical inputs

The Markov model is driven by short-term data on motor milestone achievement and long-term extrapolated survival estimates. In the model, both presymptomatic and symptomatic patients were assumed to be treated within the first 6 months, corresponding with the end of the first model cycle. Subsequently, patients achieving a motor milestone during a model cycle are transitioned into the next model cycle. Distinctive data sources were used to differentiate between health outcomes for presymptomatic and symptomatic patients. A targeted literature review was conducted to identify relevant clinical trials for approved SMA treatments used in both presymptomatic and symptomatic patients. Of the 6 single-arm trials and 2 trial extensions identified, some were considered to provide adequate input to represent the outcomes of presymptomatic treatment. In particular, the SHINE and ENDEAR studies were considered suitable for our model structure.[9,43] For further details on the trial selection, see the Appendix Methods in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010 and Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010.

Incorporating NBS for SMA will result in earlier diagnosis for patients by potentially 6 months for type 1, 1.7 years for type 2, and 4.2 years for type 3, based on the age of confirmed SMA genetic diagnosis.[39] After a diagnosis after NBS, a treatment decision should be made immediately to minimize the impact of loss of motor neurons and related symptoms.[9] In our model, early diagnosis and treatment initiation drives improvements in health-related quality of life through 2 mechanisms: (1) the absence of

Figure 1. Model structure. Note: After NBS, patients with negative results leave the decision tree and patients with positive results undergo genetic testing to confirm the SMA type and identify the severity of disease by estimating the *SMN2* copy numbers. Patients with *SMN1* gene mutation and positive patients in the without NBS scenario will be identified symptomatically based on the SMA type. Once an SMA type is identified, patients transition into a Markov model and are treated and modeled until they transition to the death health state (lifetime horizon). Patients enter the Markov model 6 months after SMA diagnosis. The exact health state in which a patient enters the model depends on the SMA type, with corresponding severity of disease progression as derived from the clinical trials. The transition through the health states is reflected by the arrows. The square, circle, triangle, and pentagon represent a decision, chance, terminal, and obligatory node, respectively.



BRND indicates broad range of normal development; D+, patients with SMA; D−, patients without SMA; M(…), transition to a Markov model; NBS, newborn screening; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy; T+, positive heel-prick test; T−, negative heel-prick test.

symptoms and (2) relevant delays in the occurrence of symptoms.[39,44]

Treatment after early detection was modeled with data from the NURTURE trial. NURTURE enrolled presymptomatic newborns only, and the mean age at therapy initiation was 20.6 days.[13] Other studies were used to reflect the clinical diagnosis and efficacy of symptomatic treatment. All patients with SMA type 1 and patients identified by NBS entered the model in health state D (not sitting) and were assigned to a subsequent health state or remained in health state D based on transition probabilities or survival data. Symptomatic patients with SMA types 2 and 3 entered the model in health state C (sitting) and health state B (walking), respectively.

The short-term data on milestone achievement were also based on clinical trials. Transition probabilities for presymptomatic children treated with either nusinersen or onasemnogene abeparvovec were based on the NURTURE clinical trial,[13] which enrolled only presymptomatic infants who were identified through affected sibling(s).[13] For symptomatic patients with SMA type 1, transition probabilities were calculated with data from START and STR1VE for those treated with onasemnogene abeparvovec and with data from ENDEAR and SHINE (an extension of ENDEAR) for patients treated with nusinersen.[9,12,14,41,43,45,46] Transition probabilities for symptomatic treated patients with SMA types 2 and 3 were based on the CS2/CS12 clinical trial.[47] Earlier diagnosis and treatment age in the model were based on assumptions and reflected symptom onset, diagnosis, and timely access to available treatments in clinical practice.[9,39,48] Compared with patients in ENDEAR/SHINE, patients in the START trial were younger at start of treatment, and fewer patients required ventilatory support.[9,43,49] Detailed information on the clinical trials is presented in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010.

In the model, it was assumed that the motor milestones achieved at the end of follow-up in the clinical trials (after 24 months for nusinersen and after 36 months for onasemnogene abeparvovec) were sustained until death.[50-52] No evidence exists that SMN protein expression stops or wanes over time, and data from the START trial and extension study demonstrated that patients treated with onasemnogene abeparvovec maintained achieved milestones up to 6 years and, in some cases, achieved additional milestones.[50-52]

Survival for each health state was extrapolated over time using the method reported by Guyot et al[53] (more detail is provided in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010). Extrapolations of the PAV, not-sitting, and sitting health states were based on published studies, such as Gregoretti et al[54] for PAV. The NeuroNEXT study was used to estimate long-term survival in the not-sitting state (death as well as transition to health state PAV).[55] Survival for SMA type 1 patients in the sitting state was modeled from a 52-year targeted prospective, as well as a retrospective, study.[56] For the walking and BRND health states, Dutch normal life expectancy was used.[57] Survival curves obtained from the literature were aligned with the age of the modeled population. Ages at the start of cycle 1 were 6, 18, and 48 months for patients with SMA types 1, 2, and 3, respectively.

In the base-case analysis, 94% of patients were treated with onasemnogene abeparvovec and 6% were treated with nusinersen. Percentages were based on expert opinion on ineligibility for onasemnogene abeparvovec. Risdiplam was not included in the model because clinical trial results were not available when the model was developed.

Cost inputs

The cost of NBS for SMA is based on various NBS components: the cost of the heel-prick test, the cost of performing the heel-prick test, and the cost of the laboratory analysis. The cost of performing the heel-prick test would not change with the addition of SMA screening because blood samples are already gathered for present screening purposes.[25] Laboratory analysis costs in NBS for SMA were the same as those for NBS for severe combined immunodeficiency at €4.95.[25] Infants who tested positive for SMA through NBS were recommended to receive genetic screening at a cost of €1600.[25,33] In the absence of NBS for SMA, the cost of

Table 1. Model parameters and values for the base-case analysis and sensitivity analyses.

Estimate	Value	Lower to upper bound	Distribution	Source
Epidemiologic inputs				
Incidence of SMA	0.0001*		Dirichlet	6
Incidence of SMA deletion				
Homozygous deletion	0.99		Dirichlet	25
Heterozygote deletion	0.01		Dirichlet	25
SMA types (detected without NBS)				
Type 1	58%		Dirichlet	6
Type 2	29%		Dirichlet	6
Type 3	13%		Dirichlet	6
SMN2 *copy numbers (detected with NBS)*				
SMN2—2 copies	45%		Dirichlet	4,32
SMN2—3 copies	33%		Dirichlet	4,32
SMN2—4 copies	22%		Dirichlet	4,32
Cost parameters†				
Screening costs				
Costs of the screening test (within NBS program)	€4.95	€3.96-€ 5.94	Gamma	25
Tariff for diagnostics for referred children	€1600	€1280-€ 1920	Gamma	33
Treatment costs per dose				
Onasemnogene abeparvovec	€1 945 000		Gamma	34
Nusinersen	€83 300		Gamma	25
Administration costs				
Onasemnogene abeparvovec	€3278	€2622-€3933	Gamma	35,36
Nusinersen	€3278	€2622-€3933	Gamma	36
Utility values‡				
Sitting health state	0.60	0.50-0.71	Beta	37
Not-sitting health state	0.19	0.16-0.22	Beta	38
PAV health state	0.00	0.00-0.00	Beta	39

NBS indicates newborn screening; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.
*1 in 10 000 population.
†Based on 2019 pricing.
‡Parameters of general population utilities are presented in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010.

diagnostics consists of the present genetic screening costs (Table 1[4,6,25,32-39]).

The model includes the annual costs per health state. A literature search on resource use by patients with SMA was performed and discussed with the aforementioned Dutch SMA expert(s). We determined that UK healthcare resource use study data were the best source to estimate healthcare costs by applying Dutch cost estimates. This approach was also used for the Dutch reimbursement dossier for onasemnogene abeparvovec and was accepted and published by Dutch authorities.[40] Data were obtained from a UK healthcare resource use study, National Health Service Prescription Cost Analysis, Dutch cost guidelines, and the Dutch Health Authority.[35,36,58,59] Costs per health state were specified for drug costs, medical tests, medical visits, hospitalizations, general practitioner and emergency visits, health material, ventilation, and social services. In the model, it was assumed that patients in the BRND health state generally do not require any additional resources with associated costs.

Treatment costs for nusinersen consisted of the cost of 4 loading doses administered within approximately 63 days of the initial dose and a maintenance dose administered once every 4 months thereafter (list price €83 300 per dose).[40] Administration costs were based on either inpatient or outpatient lumbar puncture at a cost of €3278 or €2473 per administration, respectively, and also dependent on the age of the patient.[40] Treatment costs for onasemnogene abeparvovec were based on the Dutch list price of the one-time treatment (€1 945 000),[34] and administration costs for the intravenous infusion were conservatively estimated at €3278 per administration.[36]

Societal perspective costs included the income lost per patient per health state, caregiver costs, and transportation costs (all based on Dutch cost guidelines).[37] Productivity losses from absences from paid work were included using the friction cost method for patients aged 18 to 65 years.[60] In the model, patients with SMA in the walking and BRND health states did not have additional absenteeism, except for those treated with nusinersen who must travel to receive treatment. It was assumed that 20% of patients with SMA in the sitting health state had paid employment. Patients with SMA who entered the not-sitting or PAV health states were assumed to never participate in the labor market. Unrelated medical costs, based on the Practical

Table 2. Disaggregated costs per 169 680 newborns in a scenario with and without NBS for SMA (€2019, discounted).

Estimate	Costs with NBS	Costs without NBS
Costs of screening and diagnostics		
Costs of heel-prick testing	€839 916	€0
Costs of genetic testing	€27 149	€27 149
Costs of healthcare		
Costs of SMA treatment, including administration	€37 682 058	€34 951 898
Medical costs	€7 832 167	€23 417 192
Total healthcare costs	€46 381 290	€58 396 239

NBS indicates newborn screening; SMA, spinal muscular atrophy.

Application to Include future Disease costs method, were tested in scenario analysis.[61]

Utility inputs

Quality-adjusted life-years (QALYs) for patients with SMA were modeled as dependent on the specified health states. Health state utility values were sourced from the literature. Based on the Institute for Clinical and Economic Review analysis of nusinersen and onasemnogene abeparvovec and the National Institute for Health and Care Excellence single technology appraisal of nusinersen,[27,46] the following health state utilities were identified: 0.00 was used for PAV as agreed to by the aforementioned Dutch clinical experts; 0.19 for not-sitting[38]; and 0.60 was used for the sitting health state.[37] For more detail on utilities, please see the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010.

The general population utility inputs for the walking and BRND health states were derived per cycle[62] and validated with Dutch utility values.[63] The approach used for utility estimation was reported and accepted in the Dutch reimbursement advice for onasemnogene abeparvovec.[40]

Sensitivity Analyses

A deterministic (univariate) sensitivity analysis (DSA) was conducted to evaluate the impact of parameter uncertainty by varying parameter values.

Probabilistic sensitivity analysis (PSA) captured parametric uncertainty and assessed the robustness of the model.[64] When unavailable, a standard error of 15% was applied. For independent probabilities and utilities, the beta distribution was applied. For costs, the gamma distribution was used. For correlated probabilities and distribution parameters, the Dirichlet distribution and Cholesky decomposition were applied. The Cholesky decomposition algorithm was used to account for correlation between parameters in survival distributions.

Scenario Analysis

The scenario analysis tested key model assumptions and robustness of the base-case incremental cost-effectiveness ratio (ICER) of key parameter variations in the model. The model discount rate, time horizon, analysis perspective, incidence, treatment percentage, costs for NBS, and percentage *SMN1* deletion were assessed in the scenario and combination analyses.

Model Programming and Validation

The model was programmed using Microsoft Excel (Microsoft Corporation, Richmond, VA). As validation, the model code was stress tested to generate results using a range of extreme parameter values.

Results

Base-Case Results

Tables 2 and 3 summarize the discounted cost outcomes and deterministic results, respectively, for the simulated cohort of 169 680 newborns in The Netherlands.

Overall, the expected number of newborns with SMA is 16.97 among 169 680 newborns. With NBS for SMA, all patients with SMA and homozygous *SMN1* deletion were detected. Patients with heterozygous *SMN1* deletion were detected after symptom development. In the scenario without SMA screening in NBS, all patients with SMA were clinically diagnosed at a later stage: younger than 6 months for SMA type 1, age 1.5 years for SMA type 2, and age 4 years for SMA type 3.

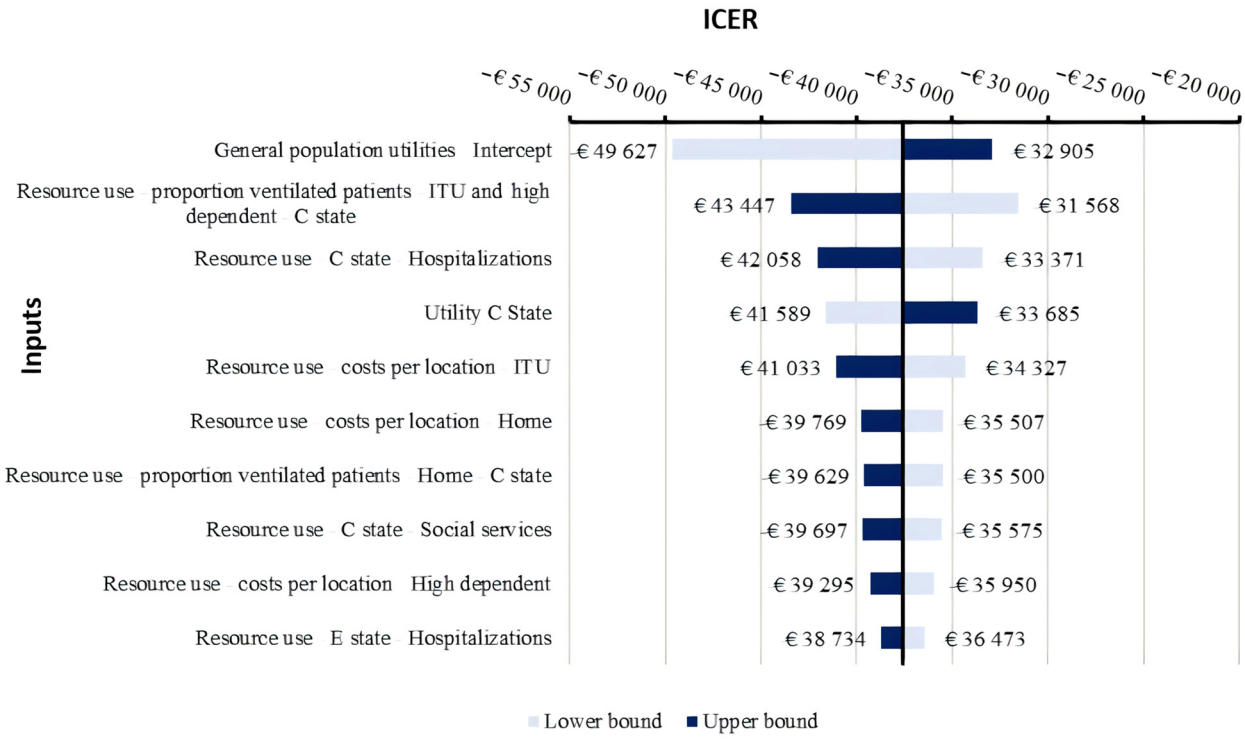
In the base-case analysis, the total cost of active screening was estimated at €839 916 per 169 680 newborns versus €0 without

Table 3. Deterministic results totals and per patient.

Strategy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER $\left(\frac{\Delta Costs}{\Delta QALYs}\right)$
Results for the total cohort							
With NBS	€46 381 290	771	660	−€12 014 949	283	320	−**€37 564**
Without NBS	€58 396 239	488	340				
Results per patient with SMA							
With NBS	€2 733 456	45.5	39	−€708 095	17	19	−**€37 564**
Without NBS	€3 441 551	29	20				

Note. All costs, LYs, and QALYs presented are discounted.
ICER indicates incremental cost-effectiveness ratio; LY, life-year; NBS, newborn screening; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy.

Figure 2. Tornado diagram with univariate sensitivity analysis results.



ICER indicates incremental cost-effectiveness ratio; ITU, intensive treatment unit.

screening. The treatment costs (treatment acquisition and administration) for patients with SMA were €37 682 058 with NBS and €34 951 898 without NBS. Total healthcare costs, including costs of screening, diagnostics, treatment, and resource use, were €46 381 290 with NBS versus €58 396 239 without NBS. After NBS and treatment of presymptomatic infants with SMA, discounted life-years gained and QALYs gained were estimated at 771 and 660, respectively. In the scenario without NBS for SMA, discounted life-years gained and QALYs gained were estimated at 488 and 340, respectively.

Compared with a no-NBS scenario, NBS saves €12 014 949 while increasing the patients' health by 320 QALYs, resulting in NBS being dominant over a scenario without NBS.

Sensitivity Analyses

The DSA resulted in a range of ICERs, and all indicated dominance. The parameters with the largest impact on ICERs were general population utilities, percentage of patients dependent on ventilated intensive treatment in the sitting health state, hospitalization costs in the sitting health state, utility in the sitting health state, and costs per ventilation in the intensive treatment unit (Fig. 2).

The PSA demonstrates that, compared with no NBS, NBS has a 100% probability of being cost-saving. The analysis demonstrated that the conclusion was robust at a willingness-to-pay threshold of €20 000/QALY (Fig. 3).

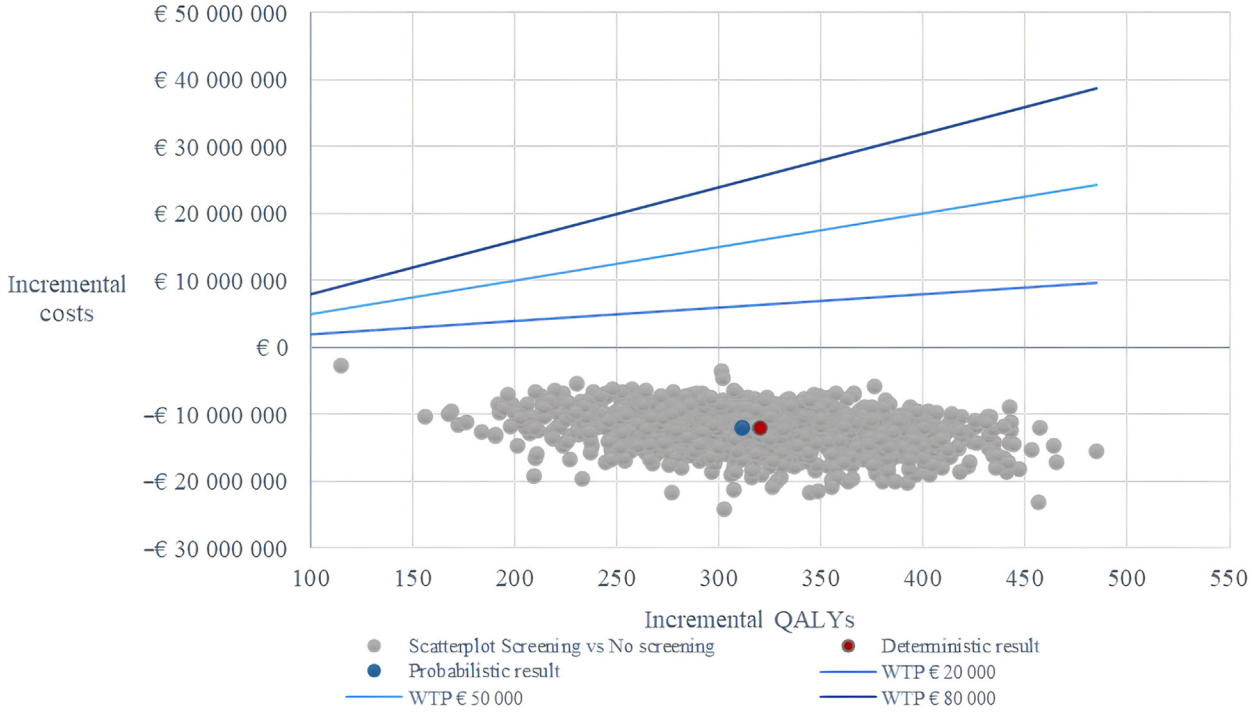
Scenario Analyses

Several additional scenario analyses were performed on the discount rate, time horizon, perspective, incidence, treatment percentage, and cost of NBS and are summarized in Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010. Most scenarios analyzed demonstrated dominance, and all scenarios and respective incremental costs and QALYs are presented in Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.010. Non-dominance resulted if shares of nusinersen treatment were increased to 50% and 75%, resulting in ICERs of €19 426 and €46 105 per QALY gained, respectively. Results from the combined scenarios demonstrate that NBS is cost-effective, with an ICER of €20 727 and €15 792 per QALY gained.

Discussion

In the base-case analysis, adding NBS for SMA was associated with a gain of 320 QALYs and savings of €12 014 949 per annual cohort of newborns over a lifetime time horizon compared with no NBS in The Netherlands, resulting in a cost-saving ICER (−€37 564 per QALY). These results suggest that, in the base-case scenario, NBS for SMA is cost-saving compared with no NBS for patients with SMA at a willingness-to-pay threshold of €20 000/QALY. Although screening and treatment are associated with an investment, these additional costs were offset by savings that occur with the timely (presymptomatic) identification and treatment of patients with SMA. As these patients achieve additional and higher motor milestones, their lifetime health outcomes are improved and healthcare costs are reduced, indicating that NBS for SMA is not only cost-effective but cost-saving. The results were based on inputs from local Dutch data, the literature, and expert opinion.[4,6,25,32-38,40] The QALY gains achieved through the screening strategy were driven by improved prognoses resulting from reduced disease progression (ie, patients achieved higher functioning motor milestones) and improved survival outcomes. Early diagnosis increased the relative discounted QALY gains by

Figure 3. Incremental cost-effectiveness plane, including WTP thresholds.



QALY indicates quality-adjusted life-year; WTP, willingness-to-pay.

>94% (340 QALYs without NBS and 640 QALYs with NBS). The QALY gain represents the result of treatment after clinical diagnosis (without NBS) and the start of presymptomatic treatment (with NBS). Our model is applicable for other or updated screening/no-screening inputs. The one-way DSA and PSA demonstrated the robustness of the model and the cost-effectiveness outcomes, demonstrating that NBS for SMA is cost-saving in a variety of sensitivity analyses. Therefore, our findings support the inclusion of screening for SMA in the NBS program in The Netherlands. The scenario analyses substantiate this conclusion because most of the scenarios resulted in cost-savings. Of all the parameters included, varying the treatment percentage assumption demonstrated the greatest impact on the cost-effectiveness outcome. The scenario analysis of including variations of multiple parameters at once was cost-effective, which was demonstrated for most of the scenarios. Results from the sensitivity and scenario analyses support the robustness of the economic model.

To the best of our knowledge, this is the first economic evaluation of NBS versus no NBS for SMA that accounts for the range in severity of SMA types 1, 2, and 3, the variable number of *SMN2* gene copies, and 2 available treatments (onasemnogene abeparvovec and nusinersen). An Australian cost-effectiveness study considered 2 available treatments only in the NBS arm (onasemnogene abeparvovec and nusinersen) whereas only one treatment in the no NBS arm (nusinersen).[64] Our analysis also differs from Shih et al[64] who used different scenarios, including treatment patterns, and did not demonstrate cost-effectiveness of NBS compared with no-NBS scenarios. Therefore, direct comparison with our results should be interpreted with caution. Other studies considered either nusinersen and patients with SMA type 1 or onasemnogene abeparvovec alone.[65,66] Furthermore, parameters in this model were adapted to values applicable to the Dutch population. We expect that our model would demonstrate similar results for other countries that share comparable characteristics with The Netherlands.

Ongoing follow-up studies demonstrated the long-term safety profile and sustained therapeutic effect of onasemnogene abeparvovec and support our assumption of lifelong durability of effect.[51,52] Lifelong transgene persistence and treatment effect were further supported by studies of adeno-associated virus vector-mediated gene delivery.[67-69] To date, no clinical trial of a disease-modifying treatment for SMA has reported relapse. The uncertainty around this assumption is investigated in scenario analyses by limiting the lifetime time horizon to shorter periods.

Because of limitations in published data (including a lack of head-to-head studies for onasemnogene abeparvovec and nusinersen), our model necessarily incorporated various assumptions, including that nusinersen and onasemnogene abeparvovec are equally effective, both over a lifetime time horizon. Obviously, current data can only support efficacy over a limited number of years; however, various data suggest sustained effect.[50-52] Data on costs for patients in the walking and sitting health states were also scarce. We accounted for this limitation by examining a wide range of cost values in the sensitivity analysis.

Another limitation of our study is related to the clinical trials we identified that were only single-arm studies. As a result, real-world observations may differ from our partly trial-based model outcomes. Exact costs of adding the SMA test to an NBS panel will strongly depend on the outcome of a tender and negotiations with providers, generally resulting in lower costs and thus enhancing our favorable outcomes. Both the sensitivity and specificity of the NBS test for SMA were assumed to be 100% based on reported analyses. Even if false-positives occurred, diagnosis is confirmed by clinical follow-up, so physical complications or treatment for patients with false-positive results would not occur.

Conclusions

We found that NBS for SMA results in additional health benefits and cost-savings for The Netherlands. The outputs from sensitivity and scenario analyses indicate the robustness of these results.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.06.010.

Article and Author Information

Accepted for Publication: June 3, 2022

Published Online: xxxx

doi: https://doi.org/10.1016/j.jval.2022.06.010

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Other (clinical assumptions, methods, model developments, parameter assumptions): Velikanova, van der Schans, Bischof, van Olden, Postma, Boersma

Conflict of Interest Disclosures: As employees, Matthias Bischof and Rudolf Walther van Olden reported owning Novartis stock or other equities. Cornelis Boersma and Maarten Postma reported receiving grants from Novartis Gene Therapies. No other disclosures were reported.

Funding/Support: The project was financially supported by Novartis Gene Therapies, Inc. Editorial support, including copyediting and formatting of the manuscript and appendix, was provided by Laura Sitler, ELS, Kay Square Scientific, Newtown Square, Pennsylvania.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study or collection, management, analysis, and interpretation of the data.

Acknowledgment: The authors acknowledge contributions to the development of this manuscript from Fay-Lynn Asselman, MSc (University Medical Center Utrecht), and Ludo van der Pol, MD, PhD (University Medical Center Utrecht), comprising, among other contributions, the validation of model assumptions, parameter inputs, and the results. The authors also thank Seren Phillips (Novartis Gene Therapies, Rotkreuz, Switzerland) for her critical review of the manuscript.

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