Cost-Effectiveness Analysis of Newborn Screening for Spinal Muscular Atrophy in Italy

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Introduction

- SMA, the leading genetic cause of death in early infancy, is an autosomal recessive disorder characterized by degeneration of lower motor neurons in the spinal cord and brainstem, leading to weakness and muscle atrophy, loss of independent breathing and swallowing, and early death[1-3]
- Severity of SMA is associated with the number of *SMN2* gene copies present, and SMA symptoms range from early infant death in children with SMA type 1 to less severe, but still clinically significant symptoms, in SMA types 2 and 3 to mild weakness in adults with SMA type 4[1]
- SMA is associated with substantial costs,[4] including inpatient, outpatient, and emergency care; medications; medical devices and mobility aids; respiratory and ventilatory assistance; and transportation[5–7]
- Three DMTs are currently available in the United States, European Union, and many other countries: nusinersen, an intrathecally administered ASO; risdiplam, an oral small-molecule drug, and onasemnogene abeparvovec, a one-time gene replacement therapy[8]
- These DMTs are the first treatments to substantially modify the clinical course of SMA and have greatly improved the prognosis for patients.[9–18] Treatment with DMTs can also reduce costs related to SMA.[19]
- Early detection of SMA through NBS allows for presymptomatic diagnosis and early intervention, which is associated with better health outcomes for patients[13–15]
  - NBS, or blood spot screening (first-tier test), involves a heel prick and collection of the blood onto a filter card/newborn screening card. Positive results are followed up with genetic testing (second-tier test).
  - NBS is widely implemented in the United States, with approximately 98% of newborns screened.[20] Several other countries have also launched pilot and national NBS programs for SMA, including Belgium, Germany, Australia, Italy, Spain, and Taiwan, but uptake is variable.[21,22]
  - Financial, technical, organizational, and ethical constraints have been cited as barriers to widespread implementation or delay of NBS for SMA[21]
  - With effective treatments available and reimbursed by the National Health Service (SSN), several regions in Italy that have completed pilot studies are continuing state-sponsored SMA NBS, while active pilot programs are ongoing in several other regions.[23] SMA NBS is not yet nationally approved in Italy.[23]

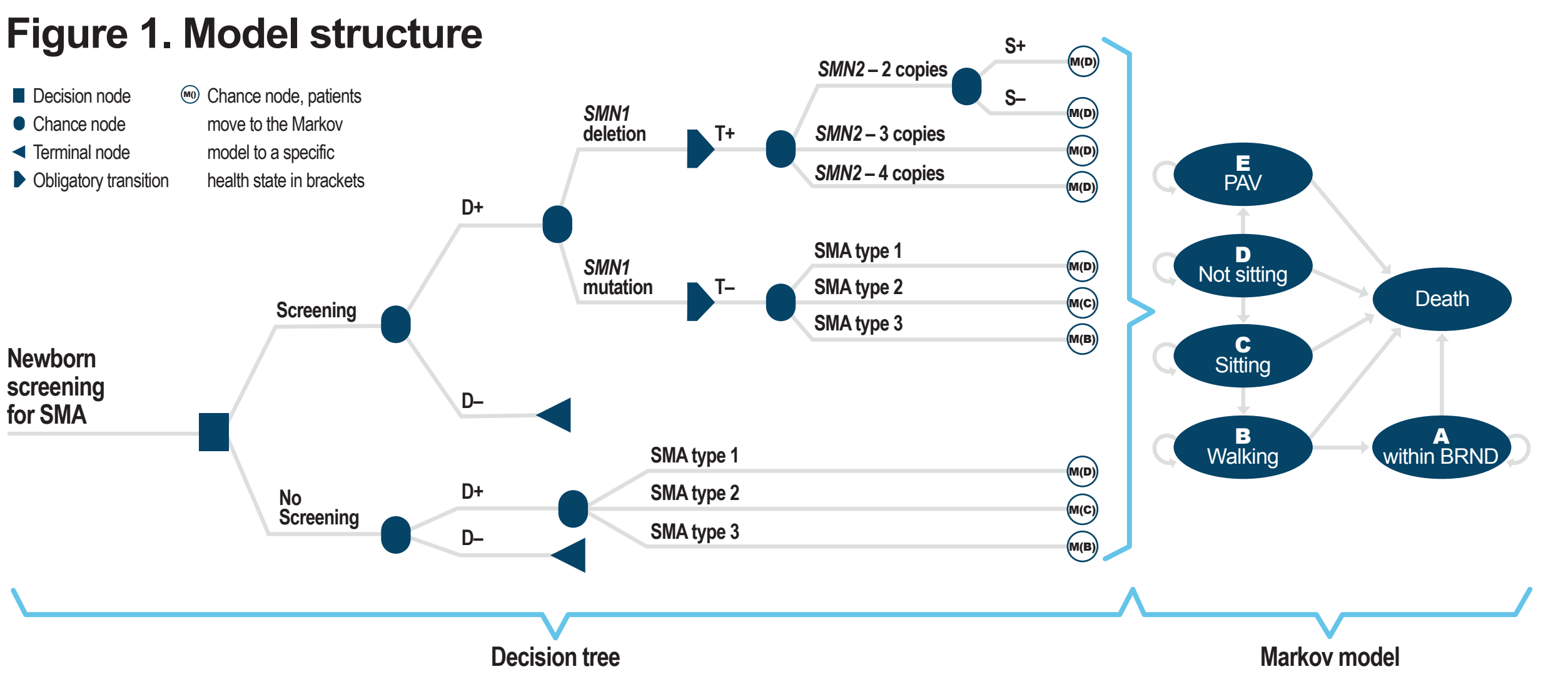
Objective

- We evaluated the cost effectiveness of universal NBS for SMA in Italy by comparing treatment of presymptomatically detected SMA occurring immediately after diagnosis with no NBS for SMA with treatment occurring after symptom detection and diagnosis

Methods

- We conducted a cost-utility analysis using a combination of decision tree and Markov model structures to estimate the lifetime health effects and economic costs of implementing universal NBS for SMA compared with no NBS in Italy
  - A cohort assumed to undergo NBS with presymptomatic or symptomatic treatment of SMA was compared with a non-NBS cohort with symptomatic treatment of SMA
  - The analysis was conducted from the perspective of the National Health Service in Italy (SSN)[24]
  - A lifetime time horizon was applied, and an annual discount rate of 3% was assumed for costs, life-years, and QALYs. A half-cycle correction was applied in the model.
- The decision tree captured NBS outcomes and costs, and the Markov modeling projected long-term health outcomes and costs following diagnosis (**Figure 1**). Patients in the model entered a specific Markov model health state (within a broad range of normal development [A], walking [B], sitting [C], not sitting [D], or permanent assisted ventilation [E]) after the decision tree depending on SMA type or *SMN2* copy number.
  - After NBS testing, SMA patients who were positively identified continued the decision tree and underwent genetic testing to confirm the SMA diagnosis and severity of disease by estimating the *SMN2* copy numbers
  - In the NBS scenario, patients with *SMN1* gene mutation were identified symptomatically based on the SMA type
  - Once *SMN2* copy number or an SMA type was identified, patients transitioned into a Markov model and were treated and modeled until they transitioned to the death health state (lifetime time horizon)
- NBS detects SMA caused by *SMN1* deletion only. Therefore, SMA caused by *SMN1* point mutations was not captured.
- Higher functioning health states were assumed to be associated with increased survival, higher utility values, and lower costs
- Regression from a higher functioning health state to a worse functioning health state was not considered in the model

Figure 1. Model structure



Note: D+, patients with SMA; D-, patients without SMA; T+, positive test; T-, negative test; S+, patients with symptoms at treatment initiation; S-, patients without symptoms at treatment initiation; M(…), transition to a Markov model health state. The transition through the health states is reflected by the arrows.
BRND, broad range of normal development; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy; *SMN1*, *survival motor neuron 1* gene; *SMN2*, *survival motor neuron 2* gene.

- Model inputs were based on existing literature,[10–18, 25–29] local data, and expert opinion
  - The inputs included a total cohort of 400,000 newborns, based on the expected average number of live births per year in Italy from 2021 through 2025
  - The SMA incidence was assumed to be one in 9,400[1]
  - SMA was caused by either homozygous gene deletion (96.2%) or point mutation (3.8%)[27]
  - The following assumptions were made:
    - Of cases detected presymptomatically, 45% of patients had two *SMN2* copies, 33% had three copies, and 22% had four copies
    - Of cases detected after symptom onset, 58% of patients had SMA type 1, 29% had type 2, and 13% had type 3[29]
    - In line with Italian SMA clinical expert opinion, 40% of patients with two *SMN2* copies identified via NBS become symptomatic before treatment initiation
  - Distinctive data sources were used to differentiate between health outcomes for presymptomatic and symptomatic patients:
    - Short-term data on milestone achievement and transition probabilities for patients treated presymptomatically were based on the clinical trials NURTURE,[14] RAINBOWFISH,[30] and SPR1NT[12,13]
    - Short-term data on milestone achievement and transition probabilities for symptomatic patients were based on clinical trial results from START,[9,31] STR1VE-US,[10] STR1VE-EU,[11] SHINE,[32] CS2/CS12,[17] and FIREFISH[15]
  - Survival for each health state was extrapolated over time using published studies[22,34,35]
  - For the walking and BRND health states, Italian general population life expectancy was used[33]
  - For DMTs, ex-factory prices net of mandatory discounts were considered (**Table 1**)
  - Treatment distributions were based on expert opinion
  - For patients with a symptomatic diagnosis of SMA type 1, and those with two or three copies of *SMN2*, 85% were assumed to receive onasemnogene abeparvovec
    - The remaining 15% of patients with SMA type 1 treated symptomatically were assumed to receive nusinersen (9%) or risdiplam (6%)
    - The remaining 15% of patients with two or three copies of *SMN2* treated presymptomatically or with two copies of *SMN2* identified via screening but treated symptomatically were assumed to have received nusinersen (**Table 2**)
    - Onasemnogene abeparvovec was considered also for presymptomatic patients with three *SMN2* copies, in line with its EMA approved indication. At present, it is not reimbursed for these patients in Italy.
    - Treatment for all patients with SMA type 2 or type 3 and all patients with four copies of *SMN2* are summarized in **Table 2**
- The cost of each heel prick test was assumed to be €6, and the cost of each second-tier test, which was used for confirmation after a positive heel prick test result, was assumed to be €600 (clinical expert opinion)
- Deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analyses were conducted to assess the robustness of the model and the validity of the results

Table 1. Drug cost

Treatment	Form	Units	Unit cost
Nusinersen	Vial	1	€63,175
Onasemnogene abeparvovec	Vial	1	€1,945,000
Risdiplam	Oral solution	60 mg (80 mL)	€7,477

Nusinersin dose regimen: initiate with four loading doses on Days 0, 14, 28, and 63. A maintenance dose should be administered once every 4 months thereafter. Each dose is 12 mg/5 mL (one vial). Risdiplam dose regimen: 2 months–2 years: 0.20 mg/kg daily; >2 years, <20 kg: 0.25 mg/kg daily; >2 years, ≥20 kg: 5 mg daily. Onasemnogene abeparvovec dose regimen: one-time dose of 1.1 × 10^{14} vector genomes per kilogram (vg/kg) of body weight.

Table 2. Model inputs: percentage of patients receiving treatment for SMA

	Onasemnogene abeparvovec	Nusinersen	Risdiplam	Best supportive care
Patients detected presymptomatically				
Two *SMN2* copies	85%	15%	0	0
Three *SMN2* copies	85%	15%	0	0
Four *SMN2* copies	0	55%	45%	0
Patients detected symptomatically				
SMA type 1	85%	9%	6%	0
SMA type 2	0	60%	40%	0
SMA type 3	0	60%	40%	0
Patients identified via newborn screening but treated symptomatically				
Two *SMN2* copies	85%	15%	0	0

SMA, spinal muscular atrophy; *SMN2*, *survival motor neuron 2* gene.

Results

- A total of 400,000 NBS (first-tier) tests were performed, and 38 patients received a second-tier genetic test (**Table 3**)
  - 38 cases of SMA were identified with NBS
  - All cases except one were diagnosed presymptomatically

Table 3. NBS Outcomes

Outcome	NBS	Non-NBS
Number of tests performed	**400,038**	**37.6**
NBS only (first tier)	400,000	0
Genetic test (second tier)	37.6	37.6
Number of cases identified and treated	**37.6**	**37.6**
Presymptomatic	36.2	0.0
Symptomatic	1.4	37.6

NBS, newborn screening.

- Base-case results demonstrated that NBS is dominant (less costly and more effective) compared with non-NBS
- NBS demonstrated incremental costs of –€143,267 on a population level and a gain of 386 QALYs over the lifetime of identified newborns (**Table 4**)

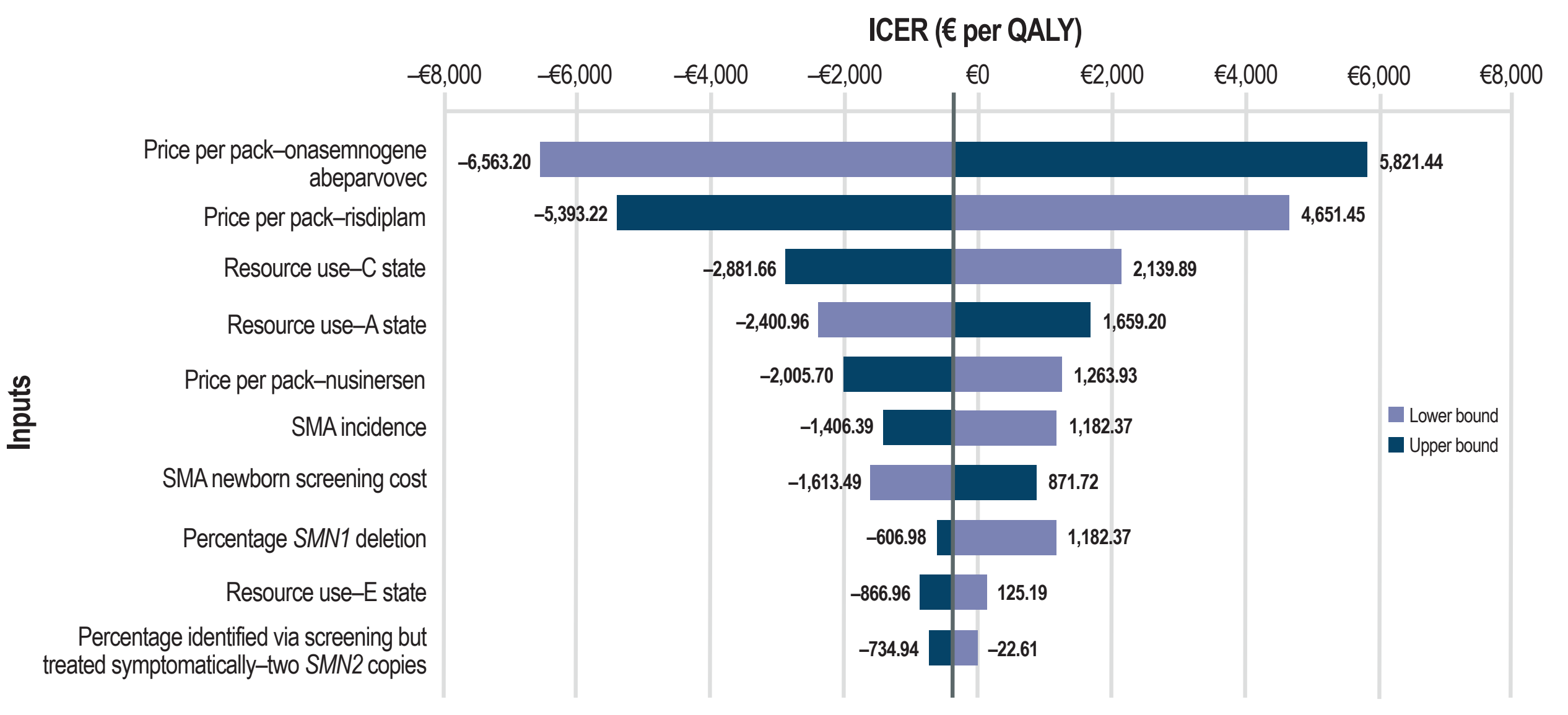
Table 4. Deterministic analysis results, base case

Strategy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER	INMB[a]
NBS	€129,166,831	979	851	–€143,267	318	386	Dominant	€7,868,972
Non-NBS	€129,310,097	660	465					

ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LY, life-year; NBS, newborn screening; QALY, quality-adjusted life-year.
[a] INMB results are calculated with €20,000/QALY willingness-to-pay thresholds.

- Deterministic (**Figure 2**), probabilistic sensitivity (**Table 5** and **Figure 3**), and scenario analyses (**Table 6**) demonstrated the robustness of the base-case results

Figure 2. Deterministic sensitivity analysis



ICER, incremental cost-effectiveness ratio; SMA, spinal muscular atrophy; *SMN2*, *survival motor neuron 2* gene.

Table 5. Probabilistic sensitivity analysis results

Strategy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
NBS	€128,387,680	828	–€132,965	371	–€358
Non-NBS	€128,520,646	457			

ICER, incremental cost-effectiveness ratio; NBS, newborn screening; QALY, quality-adjusted life-year.

Figure 3. Probabilistic sensitivity analysis: incremental cost-effectiveness plane

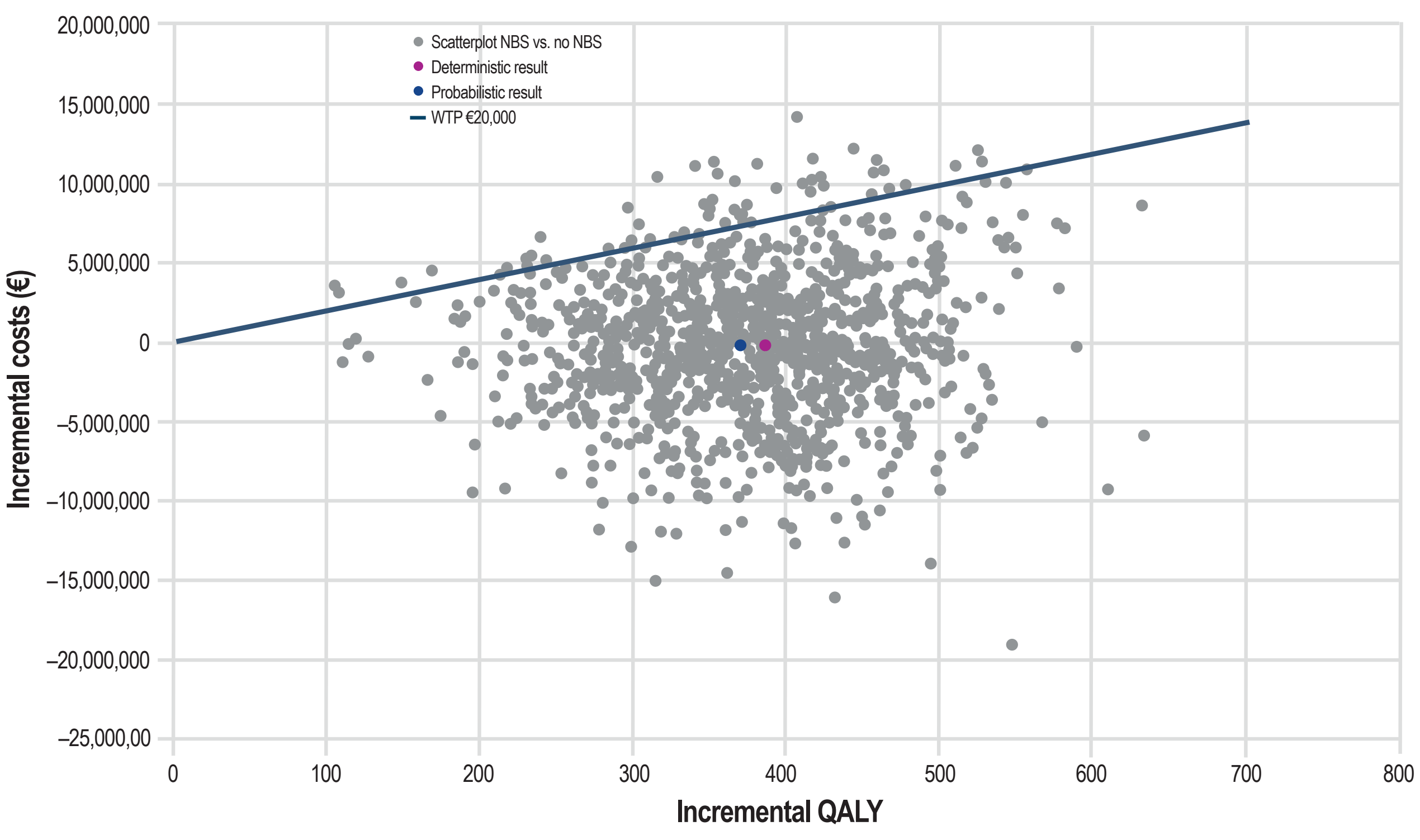


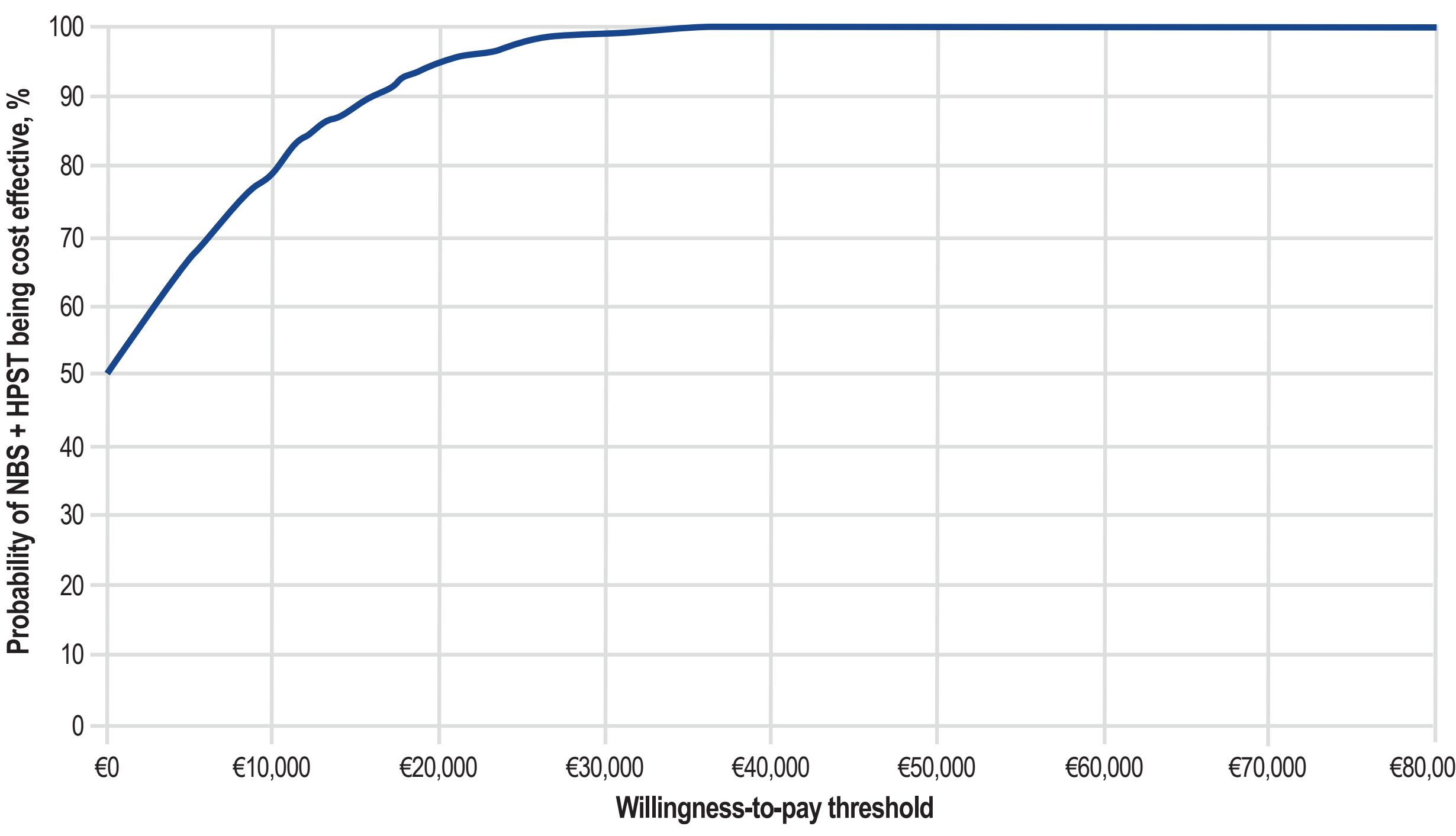
Table 6. Scenario analysis results

Strategy	Total costs	Total QALYs	Incremental total costs	Incremental QALYs	ICER
Time horizon – 15 years					
NBS	€84,362,027	342	€4,181,772	128	€32,766
Non-NBS	€80,180,255	214			
Time horizon – 50 years					
NBS	€118,691,918	738	–€2,812,691	311	–€9,048
Non-NBS	€121,504,609	427			

ICER, incremental cost-effectiveness ratio; NBS, newborn screening; QALY, quality-adjusted life-year.

- The NBS strategy has a 100% probability of being cost effective compared with non-NBS assuming a willingness-to-pay threshold of >€40,000 (**Figure 4**)

Figure 4. Cost-effectiveness acceptability curve



NBS, newborn screening; HPST, heel prick screening test.

Limitations

- To date, there are no data available from a randomized head-to-head clinical trial comparing efficacy of onasemnogene abeparvovec vs. nusinersen and vs. risdiplam for patients with SMA
- Because of the rarity of disease and the clinical trials' small sample sizes, the analysis has not made any adjustment for differences in patient characteristics between studies. A naive comparison was conducted.
- The generalizability of the results in the real world may be limited, as patients enrolled in clinical trials may differ from patients with SMA in the real world
- The model relies on extrapolations of survival and sustained benefits of motor milestones acquired for all treatments considered

Conclusions

- Routine NBS for SMA in Italy followed by presymptomatic SMA treatment results in improved health outcomes for patients with SMA
- This approach is a cost-effective use of resources from the perspective of the Italian National Health Service
- The evidence from this study underscores the utility, including cost effectiveness and value for money from the Italian National Health Service perspective, of NBS followed by presymptomatic SMA treatment
- In particular, this study should enable decision makers to understand the added value of NBS and advocate for its use for all patients. In doing so, it will be possible to improve public health in an economically sustainable way.

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Abbreviations

ASO, antisense oligonucleotide; BRND, broad range of normal development; DMT, disease-modifying treatment; NBS, newborn screening; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; *SMN1*, *survival motor neuron 1* gene; *SMN2*, *survival motor neuron 2* gene.

Acknowledgments and Disclosures

This study was funded by Novartis Gene Therapies, Inc.

Editorial support was provided by Angela Cimmino, PharmD, of Kay Square Scientific, Newtown Square, PA. This support was funded by Novartis Gene Therapies, Inc.

Disclosures: GG is an employee of AdRes HE&OR, which has received project funding by Novartis Gene Therapies for this work. **FSM** and **AM** have no conflicts to report. **MB** and **GMP** are employees of Novartis Gene Therapies. **MP** received support from Novartis for this work.

Presented at ISPOR Europe 2022, November 6–9, 2022, Vienna, Austria.