



Cost-Effectiveness Analysis of Newborn Screening for Spinal Muscular Atrophy (SMA) in the United States

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BACKGROUND

- Spinal muscular atrophy (SMA) is a rare neuromuscular disorder caused by mutations in the survival motor neuron 1 (*SMN1*) gene. Disease severity is correlated with both SMA type (e.g. I, II, III) and number of *SMN2* gene copies^{1,2}
- Breakthrough gene-targeted SMA treatments include one-time onasemnogene ABEPRAVOC
 - Onasemnogene ABEPRAVOC is approved by the United States (US) Food and Drug Administration in children under two years old with SMA with bi-allelic *SMN1* mutations via intravenous infusion³
 - The treatment is under evaluation in symptomatic SMA Types II and III, and pre-symptomatic treatment for all SMA types (NCT04042025, NCT03955679, NCT03505099)^{4,5}, and through a global managed access program

- Early detection of SMA through newborn screening (NBS) allows for pre-symptomatic diagnosis and intervention with gene-targeted therapy
- SMA was recently added to NBS guidelines, the US Recommended Uniform Screening Panel for newborns⁶. It is therefore important for US payers to understand the economic impact of NBS and pre-symptomatic gene therapy for SMA

OBJECTIVE

To understand the economic consequences of implementing NBS for SMA and pre-symptomatic treatment with onasemnogene ABEPRAVOC gene therapy among newborns in the US

METHODS

Model Overview

- A decision tree model was constructed using Microsoft® Excel 2016 (Figure 1)
 - Target population: a hypothetical cohort of 10,000 newborns
 - Perspective: US third-party payer
 - Time horizon: Lifetime
 - The model included three separate arms, each allowing for a different treatment strategy as summarized in Table 1

Figure 1. Decision model structure

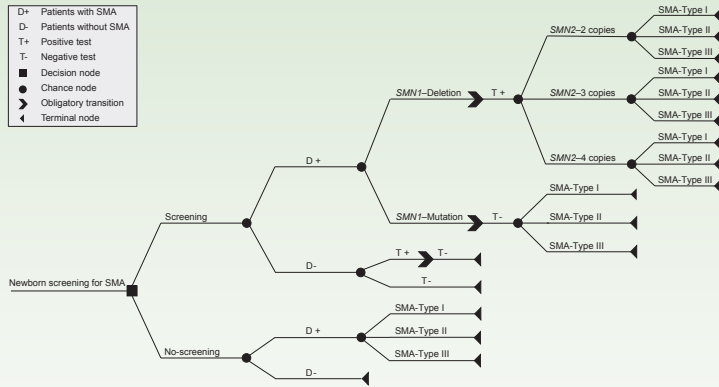


Table 1. Model arms

Description	SMA Screening	Treatment	
		Pre-symptomatic SMA*	Symptomatic SMA
Arm 1: No SMA screening + symptomatic treatment for SMA	-	NA	
Arm 2: SMA NBS + pre-symptomatic treatment for SMA	+	All SMA: onasemnogene ABEPRAVOC	SMA Type I: onasemnogene ABEPRAVOC
Arm 3: SMA NBS + pre-symptomatic treatment for SMA with ≤3 SMN2 gene copies	+	SMA ≤3 SMN2 copies: onasemnogene ABEPRAVOC SMA >3 SMN2 copies: BSC	SMA Types II/III: BSC

Key Model Assumptions

- The model considered SMA Types (I/II/III) and *SMN2* copy number (2/3/4, for SMA caused by gene deletion only)
 - Other SMA types (e.g. 0, IV), SMA subtypes, and *SMN2* copy number ≥4 were not considered
- All newborns underwent general NBS. For the strategies with SMA screening, all newborns underwent general NBS and SMA screening. Only the incremental cost of SMA screening was considered
- NBS detected SMA caused by *SMN1* deletion only. SMA caused by *SMN1* point mutations was assumed undetectable due to test limitations; all patients with this condition failed screening and could later develop symptomatic SMA
- Initial screening tests were assumed to have 100% sensitivity and 99.99% specificity; reflex tests confirmed positive screening tests with an assumed 100% sensitivity and 100% specificity
- Treatment was pre-symptomatic or symptomatic. Pre-symptomatic treatment occurred immediately after positive reflex test; symptomatic treatment occurred after symptoms and diagnosis
- Best supportive care (BSC) was assumed to incur no treatment costs
- Health outcomes for those without SMA were assumed equal to those with SMA Type III

RESULTS

- For 10,000 newborns, no SMA screening + symptomatic treatment for SMA Type I (Arm 1) generated 269,988 QALYs for a total treatment cost of \$2,628,116 over a lifetime horizon
- SMA NBS and pre-symptomatic treatment with onasemnogene ABEPRAVOC for positive tests (Arm 2) incurred a total cost of \$3,150,087 and produced 269,997 QALYs. The majority of the costs were attributable to treatment. The incremental cost per QALY gained was \$57,969/QALY when compared to no SMA screening
- If only pre-symptomatic patients with ≤3 *SMN2* copies were treated (Arm 3), the SMA NBS strategy cost \$2,485,813 and produced 269,996 QALYs. It was dominant when compared to no SMA screening, producing more QALYs at a lower cost
- Results were sensitive to treatment strategies (i.e. treatment depending on *SMN2* copy number) and distribution of SMA types. Prevalence of SMA and screening costs had a relatively small impact.
- Detailed results are presented in Table 4

LIMITATIONS

- Efficacy data for pre-symptomatic treatment with onasemnogene ABEPRAVOC were not available at the time of the analysis, hence the inputs relied on the conducted simulations. Optimization was required to estimate these outcomes because a single solution was not available
- The study cannot be generalized beyond the modeled population
 - The limited patient population did not include all SMA types and subtypes
 - The possibility of having ≥ 4 copies of *SMN2* was not modeled
 - Other treatment options available beyond onasemnogene ABEPRAVOC were not taken into consideration

Model Inputs

- Model inputs for epidemiology, test characteristics, and screening and treatment costs were based on publicly available literature (Table 2)
- The NBS approach for pre-symptomatic SMA diagnosis was based on methodology and results reported by Chien 2017⁸
- SMA screening costs included screening and reflex tests. Treatment costs comprised onasemnogene ABEPRAVOC drug and drug administration
- Inputs for lifetime costs and health outcomes (quality-adjusted life years [QALYs]) for each SMA type, onasemnogene ABEPRAVOC and treatment strategy were extracted or estimated
 - For symptomatic treatment and BSC, outputs from the Institute for Clinical and Economic Review (ICER) SMA report were used directly⁹
 - For pre-symptomatic treatment, estimates of lifetime costs and health outcomes by SMA type were not available, and thus were required to be estimated
 - To estimate these outcomes, data from the ICER SMA report were used to produce Markov traces that projected the lifetime costs and QALYs for each health state described in the ICER model (permanent ventilation, no sitting, sitting, walking)⁹
 - An optimization algorithm used the Markov trace output to estimate the proportion of the patients in each health state across SMA types, constrained by values in the ICER report, and to estimate the lifetime costs and QALYs for pre-symptomatic treatment of each SMA type (Table 3)

Table 2. Model inputs

Input*	Value	Source
SMA birth prevalence	9.4/100,000	Lally et al., 2017 ¹⁰
<i>SMN1</i> deletion / <i>SMN1</i> point mutation	95.00% / 5.00%	Kraszewski et al., 2018 ¹¹ ; Chien et al., 2017 ⁸
SMN2 copies and conditional SMA type distribution		
SMN2 - 2 copies (SMA Type I / II / III)	45.00% (78.88% / 16.48% / 4.64%)	Vill et al., 2019 ¹² ; Calucho et al., 2018 ¹³
SMN2 - 3 copies (SMA Type I / II / III)	19.00% (14.74% / 54.27% / 30.99%)	Vill et al., 2019 ¹² ; Calucho et al., 2018 ¹³
SMN2 - 4 copies (SMA Type I / II / III)	36.00% (0.58% / 11.41% / 88.01%)	Vill et al., 2019 ¹² ; Calucho et al., 2018 ¹³
SMA type distribution - undetected SMA or <i>SMN1</i> point mutation		
Type I / II / III	58.00% / 29.00% / 13.00%	Lally et al., 2017 ¹⁰
SMA NBS cost per newborn	\$10	Assumption
Reflex screening (per newborn with SMA-positive results from initial screening)	\$20	Assumption
Onasemnogene ABEPRAVOC drug cost	\$2,125,000	Red book 2019 ¹⁴
Onasemnogene ABEPRAVOC symptomatic administration ^b	\$141	CMS physician fee schedule 2018 ¹⁵ ; Red book 2018 ¹⁶
Onasemnogene ABEPRAVOC pre-symptomatic administration ^b	\$125	CMS physician fee schedule 2018 ¹⁵ ; Red book 2018 ¹⁶

Abbreviations: AAV2, Adeno-associated virus serotype 9; CMS, Centers for Medicare & Medicaid Services; NBS, Newborn Screening; SMA, Spinal Muscular Atrophy; SMN, Survival Motor Neuron; USD, United States Dollar

Notes: [a] Costs are reported in 2019 USD [b] Administration costs include intravenous infusion, anti-AAV9 diagnosis test (symptomatic treatment only), laboratory monitoring and prednisolone

Table 3. Expected SMA outcomes (per SMA patient)

Treatment by SMA type	Costs (2019 USD)	QALYs
Pre-symptomatic treatment with onasemnogene ABEPRAVOC^a		
SMA Type I	\$3,490,433	21.20
SMA Type II	\$3,248,000	22.26
SMA Type III	\$3,063,942	27.58
Symptomatic treatment with onasemnogene ABEPRAVOC		
SMA Type I	\$3,859,065	12.23
Symptomatic treatment with BSC		
SMA Type I	\$825,628	0.46
SMA Type II	\$1,501,353	11.30
SMA Type III	\$940,139	27.00

Abbreviations: BSC, Best Supportive Care; QALYs, Quality-Adjusted Life Years; SMA, Spinal Muscular Atrophy; USD, United States Dollar

Notes: [a] Values obtained from optimization based on ICER report

Model Outputs

- Total costs and QALYs were calculated for each modeled arm
- Incremental cost effectiveness ratios (ICER) were calculated for the following comparisons to determine the cost-effectiveness of adding SMA screening to NBS and pre-symptomatic gene therapy:
 - SMA NBS + pre-symptomatic treatment for SMA versus no SMA screening + symptomatic treatment for SMA (Arm 2 vs. Arm 1)
 - SMA NBS + pre-symptomatic treatment for SMA with ≤3 *SMN2* gene copies versus no SMA screening + symptomatic treatment for SMA (Arm 3 vs. Arm 1)

Table 4. Base-case results (per 10,000 newborns)

	Arm 1: No SMA screening + Symptomatic treatment for SMA	Arm 2: SMA NBS + Pre-symptomatic treatment for SMA	Arm 3: SMA NBS + Pre-symptomatic treatment for SMA with ≤3 SMN2 gene copies
Costs (2019 USD)			
Screening costs	NA	\$100,000	\$100,000
Reflex test costs	NA	\$31	\$31
Treatment costs	\$2,628,116	\$3,050,056	\$2,385,782
Total costs	\$2,628,116	\$3,150,087	\$2,485,813
Effectiveness			
QALYs	269,987.67	269,996.67	269,996.09
Incremental results			
Incremental costs	-	\$521,971	-\$142,303
Incremental QALYs	-	9.00	8.42
Incremental costs per QALY gained	-	\$57,969	Dominant

Abbreviations: NA, Not Applicable; NBS, Newborn Screening; QALYs, Quality-Adjusted Life Years; SMA, Spinal Muscular Atrophy; SMN, Survival Motor Neuron; USD, United States Dollar

CONCLUSION

- At a willingness-to-pay threshold of \$150,000 per QALY, adoption of NBS with SMA screening and allowing patients to receive effective pre-symptomatic gene therapy represents a cost-effective option for US payers
- Further research should expand on this analysis once more clinical inputs associated with pre-symptomatic treatment are available, such as results from the ongoing SPR1NT study (NCT03505099)⁵