



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

Ramesh Arjunji¹, Omar Dabbous¹, Anish Patel¹, Eric Wu², Jenny Zhou³, Michael Harvey³, Marie Louise Edwards⁴

¹AveXis, Inc., Bannockburn, IL, United States; ²Analysis Group, Boston, MA, United States; ³Analysis Group, London, United Kingdom; ⁴Analysis Group, New York, NY, United States

BACKGROUND

- SMA is a rare neuromuscular disorder caused by mutations in *SMN1*. Disease severity is correlated with both SMA type (e.g. 1, 2, 3) and number of *SMN2* copies^{1,2}
- Breakthrough gene-targeted SMA treatments include one-time onasemnogene abeparvovec
 - Onasemnogene abeparvovec is approved by the US Food and Drug Administration in children under 2 years old with SMA with bi-allelic *SMN1* mutations via intravenous infusion³
 - The treatment is under evaluation in symptomatic SMA types 2 and 3, and pre-symptomatic treatment for all SMA types (NCT04042025, NCT03955679, NCT03505099)⁴⁻⁶, 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 newborns.⁷ 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 abeparvovec 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 3 separate arms, each allowing for a different treatment strategy as summarized in **Table 1**

Figure 1. Decision Model Structure

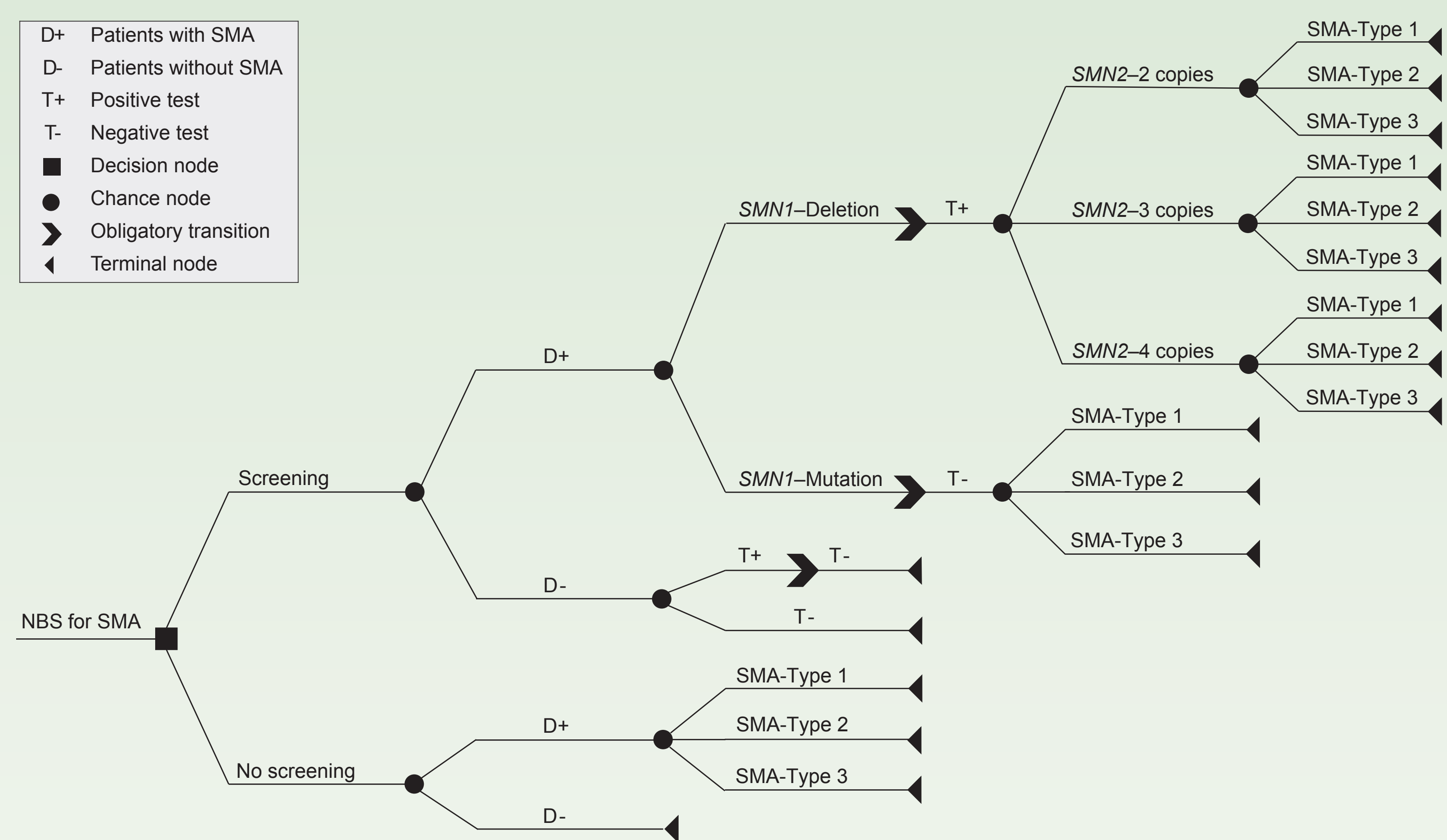


Table 1. Model Arms
Key Model Assumptions

Description	SMA Screening	Treatment	
		Pre-symptomatic SMA ^a	Symptomatic SMA
Arm 1: No SMA screening + symptomatic treatment for SMA	-	NA	
Arm 2: SMA NBS + pre-symptomatic treatment for SMA	+	All SMA: onasemnogene abeparvovec	SMA type 1: onasemnogene abeparvovec
Arm 3: SMA NBS + pre-symptomatic treatment for SMA with ≤3 <i>SMN2</i> copies	+	SMA ≤3 <i>SMN2</i> copies: onasemnogene abeparvovec	SMA types 2/3: BSC
		SMA >3 <i>SMN2</i> copies: BSC	

^aTreatment decisions were based on screening result, not SMA type. Patients were treated pre-symptomatically with onasemnogene abeparvovec prior to type determination.

- The model considered SMA types (1/2/3) and *SMN2* copy number (2/3/4, for SMA caused by gene deletion only)
 - Other SMA types (e.g. 0, 4), 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
- BSC was assumed to incur no treatment costs
- Health outcomes for those without SMA were assumed equal to those with SMA type 3

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 et al⁸
 - SMA screening costs included screening and reflex tests. Treatment costs comprised onasemnogene abeparvovec drug and drug administration

- Inputs for lifetime costs and health outcomes (QALYs) for each SMA type, onasemnogene abeparvovec and treatment strategy were extracted or estimated
 - For symptomatic treatment and BSC, outputs from the 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 ^a	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
<i>SMN2</i> copies and conditional SMA type distribution		
<i>SMN2</i> - 2 copies (SMA type 1/2/3)	45.00% (78.88% / 16.48% / 4.64%)	Vill et al., 2019 ¹² ; Calucho et al., 2018 ¹³
<i>SMN2</i> - 3 copies (SMA type 1/2/3)	19.00% (14.74% / 54.27% / 30.99%)	Vill et al., 2019 ¹² ; Calucho et al., 2018 ¹³
<i>SMN2</i> - 4 copies (SMA type 1/2/3)	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		
SMA type 1/2/3	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 abeparvovec drug cost	\$2,125,000	Red Book 2019 ¹⁴
Onasemnogene abeparvovec symptomatic administration ^b	\$141	CMS physician fee schedule 2018 ¹⁵ ; Red Book 2018 ¹⁶
Onasemnogene abeparvovec pre-symptomatic administration ^b	\$125	CMS physician fee schedule 2018 ¹⁵ ; Red Book 2018 ¹⁶

^aCosts are reported in 2019 USD. ^bAdministration 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 abeparvovec^a		
SMA type 1	\$3,490,433	21.20
SMA type 2	\$3,248,000	22.26
SMA type 3	\$3,063,942	27.58
Symptomatic treatment with onasemnogene abeparvovec		
SMA type 1	\$3,859,065	12.23
Symptomatic treatment with BSC		
SMA type 1	\$825,628	0.46
SMA type 2	\$1,501,353	11.30
SMA type 3	\$940,139	27.00

^aValues obtained from optimization based on ICER report.⁹

Model Outputs

- Total costs and QALYs were calculated for each modeled arm
- 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* copies versus no SMA screening + symptomatic treatment for SMA (Arm 3 vs. Arm 1)

RESULTS

- For 10,000 newborns, no SMA screening + symptomatic treatment for SMA type 1 (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 abeparvovec 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 abeparvovec 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 abeparvovec were not taken into consideration

ABBREVIATIONS: AAV9, adeno-associated virus serotype 9; BSC, best supportive care; CMS, Centers for Medicare and Medicaid Services; ICER, Institute for Clinical and Economic Review; NA, not applicable; NBS, newborn screening; QALYs, quality-adjusted life years; SMA, spinal muscular atrophy; *SMN*, survival motor neuron gene; USD, United States dollar.

REFERENCES: 1. Mercuri E, et al. *Lancet Neurol.* 2012;11(5):443-452. 2. Kolb SJ, Kissel JT. *Neurol Clin.* 2015;33(4):831-846. 3. AveXis Inc., [package insert]. 2019. 4. Clinicaltrials.gov. <https://clinicaltrials.gov/ct2/show/NCT04042025>, 2020. 5. Clinicaltrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03955679>, 2020. 6. Clinicaltrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03505099>, 2020. 7. Recommended Uniform Screening Panel, 2020. 8. Chien YH, et al. *J Pediatr.* 2017;190:124-129.e1. 9. Institute for Clinical and Economic Review, 2019. 10. Lally C, et al. *Orphanet J Rare Dis.* 2017;12(1):175. 11. Kraszewski JN, et al. *Genet Med.* 2018;20(6):608-613. 12. Vill K, et al. *J Neuromuscul Dis.* 2019;6(4):503-515. 13. Calucho M, et al. *Neuromuscul Disord.* 2018;28(3):208-215. 14. RED BOOK, www.ibm.com/products/micromedex-red-book, 2019. 15. Centers for Medicare & Medicaid Services physician fee schedule, 2018. 16. RED BOOK, www.ibm.com/products/micromedex-red-book, 2018.

DISCLOSURES: RA, OD, and AP are employees of AveXis, Inc., a Novartis company, and may own Novartis stock or other equities. EW, JZ, MH, and MLE are employee of Analysis Group, Inc. which has received consultancy fees from AveXis, Inc. for the conduct of this study.

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)⁶

Scan QR code or use the link below to access the poster



<http://novartis.medicalcongressposters.com/Default.aspx?doc=c90e9>