Economic Evidence for Decision Making in Pediatric Populations

by

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Dedication

This dissertation is dedicated to Mom and Dad. Thank you for your love and support.

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Abstract

When a child is affected by serious or chronic illness, the illness and associated treatment process not only has significant impact on the child, but also on the child's caregiver and other family members. Therefore, it is important to recognize and consider the effect of the illness and the corresponding support needed for the child as well as the child's family. This dissertation provides economic evidence for three issues in the decision-making process of interventions and policies that would potentially support both the pediatric population and their families.

The first chapter evaluated the long-term cost-effectiveness of newborn screening (NBS) and high costs treatment of spinal muscular atrophy (SMA) in the U.S. Recently available treatments for SMA, such as nusinersen (drug) and onasemnogene abeparvovec-xioi (gene therapy), carry high costs which raises the question of whether screening for SMA will be a policy that is considered economically favorable. A state-transition model was developed to compare strategies: (1) NBS and gene therapy, and (2) NBS and drug treatment, and (3) clinical identification and drug treatment. When incorporating the costs and health outcomes from both individuals with SMA and their caregiver, the results showed that when compared with clinical identification strategies, NBS with gene therapy, onasemnogene abeparvovec-xioi, had an incremental cost-effectiveness ratio of $103,669/quality-adjusted life-years (QALY), which is considered favorable under conventional willingness-to-pay thresholds, while NBS with drug treatment, nusinersen, did not.

The second chapter estimated the budget impact of NBS and treatment for SMA from the perspective of the Medicaid/Children's Health Insurance Program (CHIP) program, as they are

most likely to support the high-cost treatments of SMA. Using Michigan as an example, a budget impact analysis was carried out using a developed state-transition model and a spreadsheet model. Compared with clinical identification and drug treatment (nusinersen), the budget impact on the Medicaid/CHIP program for the strategy of NBS with gene therapy (onasemnogene abeparvovec-xioi), started at an estimated of $12 million in the first year and decreased to $7 million in the fifth year. Over a five-year period, the budget impact is projected to be $48 million, with a potential range between $21 million to nearly $100 million using alternative assumptions.

The third chapter explored what are the most important items when measuring family spillover effects for children with complex chronic conditions (CCC) from an economic perspective, with the goal of developing a core outcome set for measuring family spillover effects for children with complex chronic illness. This study followed the methodology developed by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative, and conducted a literature review, best-worst scaling survey, and stakeholder meetings. The best-worst scaling pilot survey of 30 respondents showed that, overall, items related to quality of life and informal caregiving time were chosen most frequently as having relatively higher impact on families of children with CCC, while items related to costs were chosen less frequently. The items that were chosen most frequently as most impact include: “Quit jobs or did not pursue a job in order to care for the child”, followed by “Caregivers’ quality of life” and “Family member’s quality of life”.

Chapter 1 Introduction

When a child is affected by illness, the illness and associated treatments not only have impact on the child physically and mentally, but also have impact on the child's family. This impact is known as family spillover effect and typically includes the direct effects on caregiver activities such as healthcare utilization, employment, and schooling outcomes, informal caregiving time, and the effects on caregiver's quality-adjusted life-years (QALYs).[1] In other words, in addition to the treatments of illness that may or may not be covered by health insurance or government programs, families of affected children might pay out-of-pocket payments for medical and non-medical costs related to the child's illness, spend time or even quit jobs to provide informal care to the child, and the quality of life of the family members might be affected as well.

However, this concept has been recognized by the society only recently that it is too narrow to focus only on the effects of the illness on the patient, and that effects on the families of the patient should be considered as well.[2] In the paper titled "Health as a Family Affair", the authors stated that recognizing and considering the potential support for time, finances, and health that the families of the patient might need will be beneficial not only to the families of the patient, but in turn, to the patient as well.[2] As stated in the paper, through recognizing these effects, potential interventions and policies can be developed to support the patient and the their families.[2]

This is especially important when it comes to the pediatric population, where when the child is affected by illness, it often affects the child's family. Therefore, in this dissertation, I will

focus on two pediatric chronic conditions: spinal muscular atrophy (SMA) and complex chronic conditions (CCC) and provide economic evidence for interventions and policies that would potentially support both patients and their families.

For the pediatric population with SMA, I will be exploring the value and effect of the interventions: newborn screening and high-cost treatments, which would potentially be a financial burden for the affected individuals and their families if not covered by health insurance or government programs. For the pediatric population with CCC, I will be taking a step back and explore what would be considered as the most important family spillover effects for families with children that has complex chronic conditions. The results of these research studies would provide important evidence for potential interventions and policies that would support both the children and their families.

1.1 Newborn screening and high-cost treatments

Newborn screening (NBS), which occurs shortly after birth, is one of the earliest health care interventions that a newborn will receive. NBS consists of a blood test typically done within 24 to 48 hours of birth along with hearing screening and pulse oximetry.[3] The screening process is extremely important because it can identify genetic and metabolic disorders before symptoms appear. This is critical because some symptoms are irreversible and can lead to very different health outcomes in the long term, including survival.

Given the benefits of NBS, the governments worldwide have established NBS programs, including North America, Latin America, Europe, Middle East and North Africa, and Asia Pacific, with increasing newborn screening activities taking place in Sub-Saharan Africa.[4] Most NBS programs in developed countries have successfully adopted tandem mass spectrometry (MS/MS),[5] which is an advanced screening method developed in the 1990s to

test multiple conditions using a single blood test. Those in developing countries, which lack resources, however, are still evaluating the possibility of adopting tandem mass spectrometry,[6] and some are even evaluating whether newborn screening are feasible at all.[7] Despite the process used, given the improved efficiency, NBS can detect over 50 different conditions,[4] providing benefits to the newborns, their caregivers, and even the society.

Although there are many benefits of NBS, many important decisions must be made for each condition screened. For example, is there an efficient screening method for this disorder if not tandem mass spectrometry? Is there an efficient treatment for this disorder? Should a condition be added to the current NBS program? If a condition is added, what would the clinical and economic impact be? These questions are medical and healthcare decisions which health policy decision makers must face. These decisions are complex as they involve uncertainties and trade-offs, such as the benefit and harm of these decisions, and can have various outcomes, ranging from more benefit than harm to more harm than benefits.[8] To facilitate these decision-making processes on the basis of scientific evidence, research methodologies, such as decision analysis, have been developed and applied to decision settings.

Decision analysis is a methodology that can assist medical and health care decision-making process by analyzing individual parameters within the decision, identify parameters with the most impact on the decision, and recombine these variables systematically to suggest a favorable decision.[8] Common decision analysis analytic methods under constrained resources include cost-minimization analysis, cost-effectiveness analysis, cost-benefit analysis, and so forth. This dissertation will be looking at two NBS decisions that can be supported by research using this methodology.

As stated earlier, most developed countries have successfully adopted tandem mass spectrometry. However, this leads to the question of how many NBS conditions should be screened. This involves exploring the question of whether a new condition should be added to the existing newborn screening program. Governments worldwide are continually faced with whether the newborn screening program should be expanded to identify more rare disorders.

To address the many questions, government worldwide have their own unique decision-making strategies. For example, many carry out research regarding a possible new NBS condition or establish advisory committee. In the United States, for example, the Secretary of Health and Human Services (HHS) makes the final decision of whether to include a new condition to the Recommended Uniform Screening Panel (RUSP), which is the list of recommended conditions approved by the HHS for states to include in their NBS programs.[9] In making this decision, the secretary receives recommendation from the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), which was established under the HHS to review clinical and economic evidence of the new nominated conditions and provide an evidence report to support HHS in making these decisions.[9]

In the United States, each state will decide whether to include a newborn screening condition or not through their own newborn screening program.[10] Based on the Association of Public Health Laboratories (APHL), for both federal and state newborn screening advisory committees to consider a new condition, the key considerations can include (1) screening is necessary for diagnosis, (2) a significant risk of severe outcome (disability or death) is present if not treated early, (3) there are effective treatments, (4) compared to treated later, treatment in newborn phase is more beneficial, (5) treatment and counseling are broadly available, and (6) the benefits to the society are greater than the risks and burdens of screening and treatment.[11]

However, each state may have their own criteria for making the final decision. For example, for SMA, the Oregon Northwest Regional Newborn Bloodspot Screening (NWRNBS) recommended the addition of SMA but decided against carrier screening as part of the screening for SMA due to the lack of enough genetic counselors to follow-up with the carriers identified through screening, and therefore, as of January 23, 2022, is not screening for SMA.[12, 13]

However, with limited resources available, resource allocation decisions must be made and, therefore, one of the most important considerations in deciding whether to include a new NBS condition or not is the evidence of economic impact of adding a new NBS condition. This impact can be evaluated using an analytic method known as the cost-effectiveness analysis (CEA). Cost-effectiveness analysis systematically compares the cost and effect of the candidate strategies. In the case of considering a new NBS condition, the analysis would involve comparing a new setting with the new NBS condition with the current setting (without the new NBS condition).

The first research of this dissertation will use the NBS for spinal muscular atrophy (SMA) to illustrate the evaluation of a new NBS condition. In July 2018, newborn screening for SMA was officially added to the RUSP after being recommended by the ACHDNC.[9] While, as of August 2021, it is reported that 38 states in the U.S. are screening for SMA.[13], the challenge lies in the high costs treatments available for SMA.

This includes the first treatment approved by U.S. Food and Drug Administration (FDA), nusinersen, estimated to be $510,000 for the first year and $382,500 for the subsequent years.[14], as well as onasemnogene abeparvovec-xioi, a one-time gene therapy, approved later in 2019 with an estimated cost of $2,092,965 per individual.[14] The F.D.A. recently approved risdiplam as the first drug that can be taken orally with an estimation of annual costs between

$99,278 and $341,955 based on age and weight.[14-16] The high costs of these treatments raises the question of whether newborn screening for SMA will be considered economically favorable. Therefore, the first research question for this dissertation is ***(1) Is newborn screening and treatment for spinal muscular atrophy considered cost-effective?*** The study will be incorporating both individual and caregiver health outcomes as SMA will require long-term care that would most likely have significant family spillover effects. The results of this research will be important evidence for relevant policies in the future for the U.S. and potentially for countries outside of the U.S. as well.

If newborn screening for a new condition is cost-effective, the next phase in decision-making is to determine whether a condition should be implemented into the screening protocol. This aspect of decision-making needs to consider the resources required for screening. In addition, information such as the impact of the new NBS condition to the existing NBS program, the predicted number of disorders detected, and the impact of the new NBS program on the incidence and prevalence of the disorder are also needed.

Answers to these questions can be obtained through an analytic method, budget impact analysis. Budget impact analysis (BIA) is a systematic estimation of changes in costs and resources of a setting before and after a new intervention has been introduced to the population of interest from the perspective of the budget holder over a specific time period.[9] The differences between the settings of before and after a new intervention has been introduced would reflect the budget impact of the new NBS condition implication.

In the case of SMA however, while the additional costs of newborn screening for SMA may be covered through funds from state budgets, fundings, or increased screening fees, the real challenge for many rare conditions such as SMA lies in the costs for treatment. One program that

could potentially fund these high-cost treatments would be through the Medicaid program/The Children's Health Insurance Program (CHIP) in each state. However, it is unclear how much budget would be needed if they do. Therefore, using Michigan as an example, the second research question of this dissertation is: ***(2) What is the budget impact of newborn screening and treatment for spinal muscular atrophy from the perspective of the Medicaid/Children's Health Insurance Program in Michigan?*** This research will provide important evidence for making relevant policy decisions in the future.

1.2 Family spillover effect for families with children with serious or chronic conditions

In addition to polices that mostly provides support related to the illness of treatment, another important aspect would be the family spillover effects that are borne by the family. For families with children with serious or chronic conditions, the family spillover effects are often significant and long-term. For example, children with complex chronic conditions (CCCs). often require specialty pediatric care due to the complexity in treatment. These challenging treatment process not only has significant impact on the child, but also on the child's primary caregiver and other family members. These family spillover effects include challenges such as paying out-of-pocket for the child's treatment and care, spending additional time taking care of the child, and their well-being being affected. While these spillover effects are important and recommended to be included in studies, they are usually partially included or not included at all. This would potentially underestimate the impact of the condition, such as the long-term family spillover effect that the family of children with CCCs face. Therefore, the third research question for this dissertation is: ***(3) What are the most important items when measuring family spillover effects for children with complex chronic conditions from an economic perspective?*** Concurrently

with identifying the most important items, this study will develop a core outcome set (COS) in measuring family spillover effects for children with CCC.

To develop the COS, this study uses the methodology developed by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative.[17] This includes identifying a list of candidate outcome measures, literature review, expert panels, and best-worst scaling (BWS). Best-worst scaling is a type of stated preference methods where it is based on the concept that when people are asked to select among three or more options, they can identify the best and worst options.[18] Using this idea and through experimental design, the data from a BWS survey can generate information on the relative importance weights for a list of items for a particular individual, in other words, how the individual ranks the items in a particular list including strength of preference. This would be an appropriate methodology for this research as the goal is to identify the most important items when measuring family spillover effects for children with CCC.

1.3 Research questions

To summarize, in this dissertation, I will be exploring the following research questions: (1) Is newborn screening and treatment for spinal muscular atrophy considered cost-effective? (2) What is the budget impact of newborn screening and treatment for spinal muscular atrophy from the perspective of the Medicaid/Children's Health Insurance Program in Michigan? (3) What are the most important items when measuring family spillover effects for children with complex chronic conditions from an economic perspective?

The next three chapters describes these three research questions, methodologies, results, discussions of the three research. Chapter 2 is the first research: The Costs and Health Outcomes of Newborn Screening and Treatment of Spinal Muscular Atrophy; Chapter 3 is the second

research: Budget Impact Analysis of Newborn Screening and Treatment for Spinal Muscular Atrophy (SMA) in the US – using Michigan as an example; and Chapter 4 is the third research: Chapter 1 Developing a Best-Worst Scaling for Measuring Family Spillover Effects for Children with Complex Chronic Conditions – from an economic perspective. This is followed by Chapter 5, which is summarizes the conclusion of this dissertation.

Chapter 2 The Costs and Health Outcomes of Newborn Screening and Treatment of Spinal Muscular Atrophy

Abstract

Over the last few years in the U.S., the timeline of diagnosis and treatment has significantly decreased for individuals with spinal muscular atrophy (SMA), a rare pediatric genetic disorder, with the recommendation of newborn screening and approval of new treatments, yielding benefits for individuals with SMA as well as their caregivers and family. However, new treatments, such as nusinersen and onasemnogene abeparvovec-xioi, carry high costs raising the question of whether newborn screening for SMA will be considered economically favorable. The objective is to evaluate the long-term cost-effectiveness of newborn screening and treatment of SMA in the U.S. while incorporating both individual and caregiver health outcomes.

A state-transition model was developed to compare the costs and health outcomes of newborn screening (NBS) with clinical identification (CI) from a healthcare sector and societal perspective. Treatments included usual (supportive) care, drug treatment (nusinersen, estimated $510,000 first year, $382,500 annually/individual with SMA), or gene therapy (onasemnogene abeparvovec-xioi, estimated $2,092,965/individual with SMA as one-time cost). Three main strategies were compared: (1) CI with drug treatment (CI/drug), (2) NBS with drug treatment (NBS/drug), and (3) NBS with gene therapy (NBS/gene therapy). The target population was a hypothetical cohort of 4,000,000 newborns. Model inputs (state-transition probabilities, costs,

and health utilities) were derived from published literature. The primary outcomes were costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICER). The model simulation time frame of the newborns was lifetime. Both costs and health outcomes were discounted at 3%.

From a societal perspective, when compared to CI/drug, NBS/gene therapy had an ICER of $103,669/QALY, while NBS/drug was dominated. Analyses from the healthcare sector perspective yield similar results, with higher ICERs for the NBS/gene therapy ($207,909/QALY). Using conventional willingness-to-pay thresholds of $100,000-$150,000/QALY, newborn screening strategies with gene therapy was considered cost-effective. Sensitivity analysis revealed that if gene therapy was assumed lower treatment effects, NBS/drug switched from a dominated strategy to having an ICER of $260,000 and $11,000,000/QALY. When compared with CI/drug, NBS/drug had an ICER of $263,382/QALY.

When compared with clinical identification strategies, newborn screening with gene therapy, onasemnogene abeparvovec-xioi, had a favorable cost-effectiveness ratio under conventional willingness-to-pay thresholds, while newborn screening with drug, nusinersen, did not. Future research should explore conditions under which nusinersen would be more economically attractive.

2.1 Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disorder which causes the weakening of skeletal muscle due to the deficiency of survival motor neuron (SMN) proteins.[19] It is a progressive disease which leads to the loss of motor and pulmonary function over time, resulting in hospitalization and premature death.[19] The genotype prevalence of SMA at birth is estimated to range from 8.5 to 10.3 per 100,000 live births globally.[20-24] While SMA is considered a rare disorder, given the severe outcome of SMA, newborn screening (NBS) for SMA has been topic of interest worldwide.[25]

In the United States, the incidence of SMA is estimated to be 1 in 11,000.[23] If individuals with SMA are not diagnosed early through newborn screening but in the clinical settings when symptoms are present, the outcome can be severe if they have early SMA onset. For example, individuals with SMA onset at less than a week will typically have a life span of less than a month. For those with SMA onset less than half year, the individual will never sit and have a life span less than two month. For those with SMA onset after half year, the life span is predicted to be more than 2 years, and will be able to sit independently, however, based on the condition, they might lose the ability to sit. For SMA onset over 3 years of age, individuals typically can walk independent and have a life span as an adult. However, most of the newborns are SMA type 1 and most will die by the age of two if not early diagnosed and treated.[25] Therefore, early diagnosis is very important as it leads to early treatment and the stopping of irreversible disease progression.

A SMA screening pilot test was carried out in New York state between 2016 and 2017.[26] The screening was done using a custom TaqMan real-time quantitative polymerase chain reaction (qPCR) assay to detect deficiency of SMN proteins in carriers and infants.[26]

The pilot test demonstrated the feasibility of screening for SMA and provided evidence that SMA should be considered for national screening.[26] In July 2018, newborn screening for SMA was officially added to the Recommended Uniform Screening Panel (RUSP) by the Secretary of Health and Human Services (HHS), after being recommended by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC).[9] As of August 2021, it is reported that 38 states in the U.S. are screening for SMA, as it may take several years to fully implement new recommendations by the RUSP and each state, such as Oregon, may have their own decision criteria. [10, 12, 13]

As stated above, each state may have their own criteria in deciding whether to include a newborn screening condition or not. Aside from ethical, legal, and social issues in genetic testing in children and adolescents discussed in the statement of the American Society of Human Genetics (ASHG), as well as the availability of screening and treatments, one of the key considerations is whether the benefits to the society are greater than the risks and burdens of screening and treatment.[10, 11, 27] One aspect of consideration is the costs of screening and treatment, and while the newborn screening costs are typically covered by insurance,[28] treatment for SMA is extremely costly.

The first treatment approved by U.S. Food and Drug Administration (FDA) was nusinersen in 2016. This drug is given via intrathecal injection for both children and adult with SMA. It is estimated to be $510,000 for the first year and $382,500 for the subsequent years.[14] Later in 2019, onasemnogene abeparvovec-xioi, a one-time gene therapy given via intravenous infusion, was approved for individuals with SMA that are less than 2 years of age. This gene therapy has an estimated cost of $2,092,965 per individual.[14] The F.D.A. recently approved risdiplam as the first drug that can be taken orally and daily for patients two months and older,

with an estimation of annual costs between $99,278 and $341,955 based on age and weight.[14-16]

While early diagnosis through newborn screening is critical, with the high cost of nusinersen, onasemnogene abeparvovec-xioi, and the recently approved risdiplam, it is unclear if newborn screening and the treatments for SMA is a health policy where the benefits to the society are greater than the costs of screening and treatment. This can be evaluated using the methodology of cost-effectiveness analysis, which systematically compares the cost and effect of the candidate strategies, in this case, a strategy with newborn screening and treatment versus a strategy without newborn screening and treatment. In addition, potential family spillover effects may have impact on this consideration in the long-term as well. Therefore, the objective of this study is to evaluate the cost-effectiveness of newborn screening for SMA with high-cost treatments: nusinersen and onasemnogene abeparvovec-xioi. This study will not be including risdiplam as it was just recently approved. The results of this study will provide evidence for health policy decision makers when making related decisions.

2.2 Methods

To evaluate the cost-effectiveness of newborn screening and treatment for SMA, a state-transition model was developed to simulate the lifetime cost and health outcomes of a hypothetical cohort of 4 million newborns. In the model, different intervention strategies were compared, where the hypothetical cohort are diagnosed through either newborn screening (NBS) or clinical identification (CI), and treated with either usual (supportive) care, drug (nusinersen), or gene therapy (onasemnogene abeparvovec-xioi).

Four intervention strategies were created and compared in the model: (1) Clinical identification with drug treatment (nusinersen) (CI/drug); (2) Newborn screening with drug treatment (nusinersen) (NBS/drug); and (3) Newborn screening with gene therapy (onasemnogene abeparvovec-xioi) (NBS/gene therapy), and (4) Clinical identification with usual (supportive) care (CI/usual care); however, the analysis results will mainly focus on the comparison between CI/drug, NBS/gene therapy, and NBS/drug, as CI/support is seldom practiced now in clinical settings.

Model inputs included state-transition probabilities, costs, and health-related quality of life associated with SMA as well as the non-SMA population. Data were derived from published literature and reports. The analytic perspectives were from a societal perspective and a healthcare sector perspective. The cycle length for the model is 1 year. Primary outcomes included costs (2021 USD), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). Costs and QALYs are discounted at 3%.[29]

2.2.1 Model structure and assumptions

The model framework is shown in Figure 2.1 with three submodels: SMA submodel, clinical identification (CI) submodels, and newborn screening (NBS) submodels. The lifetime trajectories through health states of these submodels are shown in Appendix Table 2. With limited data available, extrapolations for the long-term were assumed based on extending the function using existing data from published literature and reports.

The SMA submodel consists of four health states and serves as a base submodel for adding on treatments in other intervention strategies. The four health states included alive/non-ventilator dependent, motor deficits, ventilator-dependent, and dead, which reflected potential condition progression of individuals with SMA. In the model, it is assumed that individuals can move to worsen health states without passing through the intermediate health state (e.g., from alive/non-ventilator dependent to permanent ventilation), but they cannot recover to a better health state from a worse health state, as the symptoms of SMA are irreversible.

Utilizing the SMA health state submodel as base submodel, the CI submodel and NBS model added treatments as well as adjustments to simulate the disorder progression of SMA. In addition to the submodels, the diagnostic process of SMA has also been added to the CI and NBS submodels, which are built into the four intervention strategies of CI and NBS strategies stated earlier.

In the CI strategies, newborns are identified through the clinical setting when symptoms are present. They are assumed to receive usual (supportive) care or drug treatment. For the NBS strategies, newborns will receive an initial screening test at birth. If screened positive, an additional confirmation test will be conducted. If diagnosed with SMA, individuals with symptomatic SMA will receive treatment immediately; Individuals with asymptomatic SMA

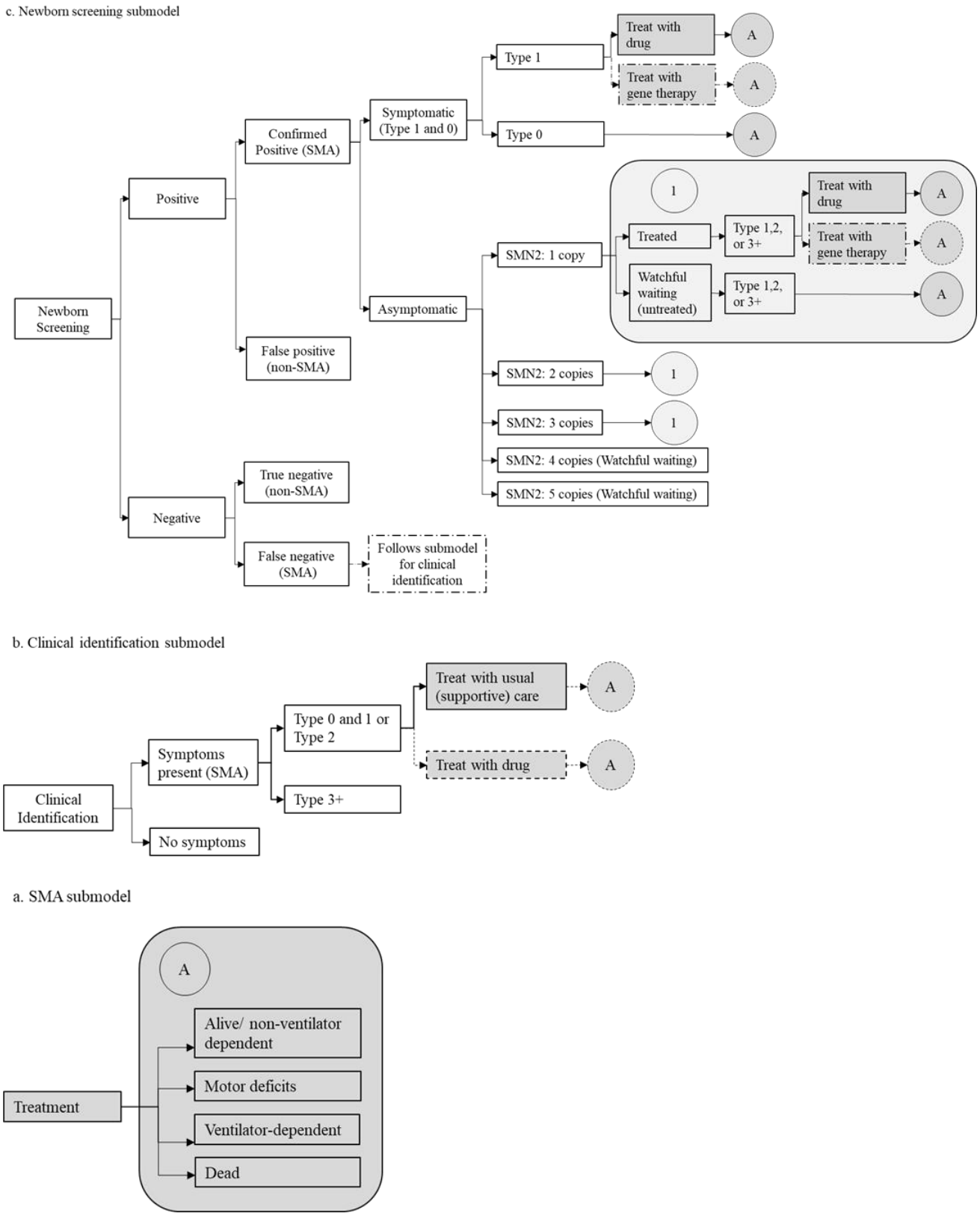


Figure 2.1 Model framework for cost-effectiveness analysis

will receive treatment based on the severity of their condition or remain on watchful waiting. This is determined by the copy number of their survival motor neuron-2 (SMN2) gene. Treatments for NBS strategies include drug treatment (nusinersen) or gene therapy (onasemnogene abeparvovec-xioi).

There are a few model assumptions in this study. It is assumed that the number of individuals with SMA identified through CI and NBS strategies are identical, and CI strategies can only identify symptomatic cases. This is assumed to make sure the severity of the populations is the same at baseline and the strategies are only comparing the costs and health outcomes of early diagnosis and early treatment with late diagnosis and late treatment.

For assumptions related to treatment, in the base-case, it is assumed that symptomatic type 1 SMA are treated with either drug or gene therapy. For asymptomatic individuals with SMA, those with 2 and 3 copies SMN2 of type 1 and type 2 SMA are treated with drug or gene therapy in the base-case. It is assumed in the base-case that all individuals with 1 copy of SMN2 are all symptomatic, and therefore, there are no individual with 1 copy of SMN2 that are asymptomatic. For individuals with 4 or 5 copies of SMN2, it is assumed in the base-case that they are on watchful waiting. Different assumptions are explored in the scenario analysis.

2.2.2 Epidemiology and transition probabilities

Epidemiology and state-transition probabilities in the model are shown in Table 2.1 and were derived from published literature and reports[14, 23, 26, 28, 30-55]. Transition probabilities are annual probabilities. It is assumed individuals with SMA have a SMA specific mortality rate as well as an all-cause mortality rate derived from the life table from the Centers for Disease Control and Prevention (Appendix Table 1).[30, 38, 55]

Table 2.1 Epidemiology and transition probabilities

	Most likely	Range (Low - High)	Source
Probability of NBS and CI results			
NBS test: positive	0.0132	0.0118 - 0.0164	[26, 30][5]
NBS follow-up test: positive	0.0069	0.0002 - 0.0378	[26, 30][5]
NBS test: false negative	0	0 - 0.00005	Assumption[5,6]
Probability of being diagnosis SMA through CI	0.000091	0.00004 - 0.00019	[23, 30] [5]
Probability of different SMA types and SMN2 copies			
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1	0.125	0.003 - 0.527	[26, 30, 35]
Probability of SMN2 copies, asymptomatic			
1 copy	0	--	Assumption[8]
2 copies	0.4755	0.419 – 0.531	[30, 33] [8]
3 copies	0.4725	0.416 – 0.528	[30, 33] [8]
4 copies	0.046	0.027 - 0.077	[30, 33] [8]
5 copies	0.006	0.059 - 0.138	Assumption[8]
If 2 SMN2 copies, type 1	0.84615	0.84615 - 0.953	Assumption[1,9]
If 2 SMN2 copies, type 2	0.12821	0.047 - 0.12821	Assumption[1,9]
If 3 SMN2 copies, type 1	0.15226	0.03817 - 0.15226	Assumption[1,4,9]
If 3 SMN2 copies, type 2	0.30635	0.27481 - 0.30635	Assumption[1,4,9]
CI: Probability of being type 0 and 1	0.54	0.48 - 0.75	Assumption[7]
CI: Probability of being type 2	0.18	0.1 - 0.21	Assumption[7]
Transition Probabilities			
CI: Drug; NBS: Drug/Gene therapy[11]			
Probability of death	0.183	0.079 - 0.356	[30, 38][10]
Probability of ventilator dependence	0.265	0.089 - 0.532	[30, 38] [10]
CI: Usual (supportive) care, type 1			
Probability of death	0.356	0.3204 - 0.3916	Assumption[2,10]
Probability of motor deficit	0	--	Assumption[10]
Probability of permanent ventilation	0.532	0.4788 - 0.5852	Assumption[2,10]
CI: Usual (supportive) care, type 2			
Probability of death	0.1068	0.0961 - 0.1175	Assumption[3,10]
Probability of motor deficit	0	--	Assumption[10]
Probability of permanent ventilation	0.1596	0.1436 - 0.1756	Assumption[3,10]

Abbreviations: NBS: Newborn screening; CI: clinical identification

[1] Assumed and calculated from **[33].** This data source summarized data from 33 papers, and data from three U.S. studies **[36, 39, 45]** were included for the calculation (case number of different SMA types with different number copies of SMN2); Range derived from **[30, 33]**.

[2] Value assumed using high value of **[30, 38].** Range calculated as plus/minus 10%.

[3] Value assumed using high value of **[30, 38]** with adjustment assuming a 70% probability of reduction for type 2 to reflect that type 2 are generally less severe when compared to type 1 (multiply 0.3). Range calculated as plus/minus 10%.

[4] Base-case values adjusted to have the same incidence rate in both CI and NBS strategies.
[5]These variables are run together in sensitivity analysis to ensure case numbers are the same across strategies, where 0.455 was used in one scenario as the high value instead of highest value of the range (0.0164) for the probability of "NBS test: positive".
[6] The base-case value assumed from **[26, 30]**, range assumed based on assumption that all strategies have the same case number.
[7] Base -case value from **[30]**, range assumed as conditional probability set of "Probability of different SMA types and SMN2 copies"
[8] Probability of 5 copies is conditional on the probability of 1 copy to 4 copies. The sensitivity analyses of these parameters are run as a set.
[9] The sensitivity analyses of these parameters are run as a set.
[10] The sensitivity analyses of these parameters are run as a set.
[11] These probabilities do not include the treatment effect of Drug and Gene therapy.

2.2.3 Treatment effectiveness

The treatment effectiveness is reflected in the model by incorporating parameters that reflect a relative reduction of transferring to a worse health state. For example, for a given probability of a health state, p_1, the probability with the treatment effect p_2 will be p_1* (1-treatment effect). These probabilities are shown in Table 2.2. The values are sourced from the report of Advisory Committee on Heritable Disorders in Newborns and Children where they estimated the treatment effects based on two clinical trials evaluating the treatment effect of nusinersen.[30, 40, 49] The treatment effect for gene therapy was assumed using the higher value of the drug treatment based on the study by Dabbous et al[37], suggesting that gene therapy may be more effective than drug treatment. The treatment effects are assumed to be the same throughout the years and extends the use of the above annual values beyond the original one-year time frame of these parameters. In addition, given the uncertainty of the parameters, sensitivity analysis was conducted to test the robustness of these values. In addition, it is assumed that if the individuals did not respond to gene therapy, they will receive drug treatment.

Table 2.2 Treatment effects

	Most likely (%)	Range (%, low-high)	Source
Drug treatment			
Relative reduction of ventilator dependence between treated early and treated late, symptomatic, drug treatment	65.1	39.1 - 86.2	[30, 49]
Relative reduction of death between treated early and treated late, symptomatic, drug treatment	63.8	45.8 - 79.3	[30, 49]
Relative reduction of ventilator dependence and death, asymptomatic, drug treatment	100	70.1 - 100	[30, 40]
Gene therapy			
Probability of responding to gene therapy	80	50 - 100	Assumption
Relative reduction of ventilator dependence, symptomatic, gene therapy	86.2	39.1 - 100	Assumption
Relative reduction of death, symptomatic, gene therapy	79.3	45.8 - 100	Assumption
Relative reduction of ventilator dependence and death, asymptomatic, gene therapy	100	70.1 - 100	Assumption

2.2.4 Cost and resource use

Table 2.3 includes the values of costs and resource use related to SMA. Newborn screening costs were derived from the Michigan Department of Health and Human Services,[28] with the follow-up test estimated from Prevention Genetics.[47] The current Physician Fee Schedule does not price the CPT/HCPCS code 81329 (Smn1 gene dos/deletion alys) and 81336 (Smn1 gene full gene sequence) and therefore, were not used. It is assumed in the model that individuals receive yearly outpatient, prescription, and inpatient cost when they are treated. Annual heath care costs are assumed based on a study that evaluated the economic burden of SMA using the data of the US Department of Defense Military Healthcare System data from 2003 to 2012, with a sample size of 239 individuals with SMA,[31] However, this study does not include costs for drug treatment and gene therapy, therefore, treatment costs were calculated separately from these costs. For treatment costs, the costs from the Department of Veterans Affairs (VA) Federal Supply Schedule (FSS) price was used as the base-case value, with the

Department of Veterans Affairs (VA) Big4 price as the lower bound and the REDBOOK Average Wholesale Price (AWP) price as the higher bound.[14, 42] Informal care costs were assumed based on health states. For the "alive/non-ventilator-dependent" health state, it was assumed to be 14 hours per week at an average hourly wage of $29.90.[41, 45] For the "motor deficits" and "permanent ventilation" health states, it was assumed to be 16 hours per day, 7 days a week at an average hourly wage of $29.90.[41, 45] Informal care costs are included in the analysis from a societal perspective.

Table 2.3 Costs and Resource Use

	Most likely	Range	Source
Newborn screening test costs			
First test	137.10	69 - 206	Assumed from [28][1]
Confirmation test	540	270 - 810	Assumed from [47][1]
Treatment costs			
Drug (nusinersen)			
First year	510,000	370,028 - 612,000	[14, 42]
Subsequent years	382,500	277,521 - 459,000	
Administration cost	1,306	653 – 1,959	Assumed from [41][2,4]
Gene therapy (onasemnogene abeparvovec-xioi)	2,092,965	1,598,394 - 2,550,000	[14, 42]
Administration cost	148	74 - 222	Assumed from [41][2,4]
Annual healthcare costs			
Alive/non-ventilator-dependent			
Cost of inpatient visits	0	0 - 9,768	Assumed from [31][2,3]
Cost of outpatient visits	4,398	4,398 - 25,551	
Cost of prescription	168	168 - 2,268	
Motor deficits			
Cost of inpatient visits	2,296	0 - 9,768	
Cost of outpatient visits	11,048	4,398 - 25,551	
Cost of prescription	585	168 - 2,268	
Permanent ventilation			
Cost of inpatient visits	9,768	0 - 9,768	
Cost of outpatient visits	25,551	4,398 - 25,551	
Cost of prescription	2,268	168 - 2,268	
Informal care costs			

Alive/non-ventilator-dependent	21,768	15,549 - 21,768	Assumed from [48, 53]
Motor deficits	174,147	119,726 - 174,147	
Permanent ventilation	174,147	119,726 - 174,147	

[1] Range assumed as +/- 50% of base-case value.
[2] Adjusted using the Gross Domestic Product (GDP) deflator to 2021 US dollars, range calculated based on same data source.
[3] This is for usual (supportive) care, assuming the value of the 25th percentile, median, and 75th percentile costs from **[31]**. Ranges assumed. The healthcare costs for drug treatment and gene therapy
[4] Range assumed as +/- 50% of base-case value.

2.2.5 Health-related quality of life

Table 2.4 shows the health-related utilities of individuals with SMA and the health-related disutilites of caregivers based on health states. For individuals with SMA, the base-case health utility weight for "alive/non-ventilator-dependent" was assumed to be preference-based EQ-5D index scores for chronic conditions in the United States.[51] For "motor deficit", values were from a study that interviewed clinical experts to provide a proxy assessment of the health utility weights of SMA type 1 and type 2.[43, 54] For "permanent ventilation", data were from a study that developed health utilities for infants and young children with SMA through methodologies such as parent-proxy assessment and physician proxy assessments.[41, 52] Sensitivity analysis was conducted using values from two very recent published studies to test the robustness of these results. One collected baseline quality of life results among individuals affected by SMA using the Health Utilities Index Questionnaire (HUI)[32] and the other estimated time-trade off (TTO) social tariff score for individuals with SMA type 1, 2, and 3.[34] The base-case analysis from the societal perspective included both the utilities of individuals with SMA and the disutilites of the caregivers, while analysis from the healthcare sector perspective included only the former. Caregiver disutilities for health states "alive/non-ventilator-dependent" and "motor deficit" were approximated using values from a study that utilized a stated-preference survey using a time trade-off approach elicited health utilities for Pompe disease.[50] For "Permanent ventilation", base-case caregiver disutility value was

sourced from a study that collected EQ-5D social tariff score for caregivers of individuals with SMA in Spain.[44]. Sensitivity analysis for this parameter was conducted using values from two studies that estimated caregiver utilities in Australia and Canada.[34, 46]

Table 2.4 Health-related utilities/disutilities

	Utility/Disutility	Range	Source
Non- SMA individuals (Utility)	1	--	Assumption
Individuals with SMA (Utility)			
Watchful waiting	1	-	Assumption
Alive/non-ventilator-dependent	0.84	-0.04 - 1	Assumed from [32, 51][1]
Motor deficits	0.52	-0.16 - 0.71	Assumed from [32, 43, 54][2]
Permanent ventilation	0.19	-0.20 - 0.31	Assumed from [32, 34, 41, 52][3]
Dead	0	--	Assumption
Caregiver (Disutility)			
Alive/non-ventilator-dependent	0.072	0.042 – 0.103	Assumed from [50][4]
Motor deficits	0.131	0.09 – 0.173	Assumed from [50][4]
Permanent ventilation	0.516	0.16 – 0.614	Assumed from [34, 44, 46][5]
Dead	1	--	Assumption

[1] Range assumed from [51] (Preference-Based EQ-5D index scores: 0.736-0.922) and [32] (HUI3 Scores, SMA, walk independently: -0.04-1)
[2] Base-case value based on [43, 54], range assumed from [43, 54] (Health-state utility values, SMA Walks with assistance: 0.33-0.71) and [32] (HUI3 Scores, SMA, Non-Sitters : -0.16-0.41).
[3] Base-case value based on [41, 52], range assumed from [34] (HRQoL (TTO social tariff score), SMA: 0.104-0.252) and [32] (HUI3 Scores, SMA, Permanent Ventilation: -0.20 - 0.31).
[4] Assumption based on [50], approximated the health states "alive/non-ventilator-dependent" to Pompe mild symptoms and "motor deficits" to severe symptoms.
[5] Assumption calculated based on [44]. This source has a mean of 0.484 (Standard Deviation=0.448) for SMA caregivers in Spain (N=81, SMA type 1 n=8, type2 n=60, type3 n=13; therefore, the disutility is calculated as 1-0.484=0.516). Range calculated as the 95% confidence interval assuming a normal distribution (0.418-0.614) and from [34] (HRQoL (TTO social tariff score), SMA caregivers: 0.703-0.715 (disutility: 0.285-0.297)) and [46] (mean health utility index, SMA caregivers: 0.84 (disutility: 0.16))

2.2.6 Analysis plan

The base-case analytic perspectives were from a societal perspective and a healthcare sector perspective. The base-case results included results of three comparisons: (1) Using

CI/drug as the reference comparator, (2) using CI/drug as the reference comparator assuming if gene therapy is not available, and (3) using CI/usual (supportive care) as the reference comparator. Primary outcomes included costs (2021 USD), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). Costs and QALYs are discounted at 3%.[29] One-way sensitivity analyses were conducted to test the robustness of the parameters and additional scenario analyses were conducted to test different assumptions. This includes the following scenarios: (1) Assuming only type 1 SMA individuals receive gene therapy, i.e., type 2 does not receive gene therapy; (2) Assuming individuals with 4 copies of SMN2 and are type 1 and type 2 SMA individuals are treated, based on recent revised treatment recommendation.[56]; (3) Using the healthcare sector perspective and including informal care costs; and (4) Using the healthcare sector perspective and including caregiver disutility. The analyses were conducted using TreeAge Pro 2021 (TreeAge Software, Inc., Williamstown, MA, USA). The impact inventory is included in the Appendix Table 4.

2.3 Results

2.3.1 Base-case results

For a cohort of 4,000,000 newborns, the model projected a total of 364 SMA cases in all strategies. For simplicity, the results are presented as 1,000 newborns. As shown in Table 2.5, NBS strategies had higher costs and QALYs than CI strategies. From a societal perspective, when CI/drug was the reference comparator, NBS/gene therapy had an ICER of $103,669/QALY. NBS/drug was dominated when compared to NBS/gene therapy due to its slightly lower QALYs and significantly higher costs. However, if assuming gene therapy is not available, NBS/drug had an ICER of $263,382/QALY when compared to CI/drug.

When CI/usual care was the reference comparator, NBS/gene therapy had an ICER of $154,670/QALY. NBS/drug was still dominated when compared to NBS/gene therapy. CI/drug was extended dominated due to its slightly higher QALY but significantly higher cost.

Analyses from the healthcare sector perspective yield similar results, with less favorable ICERs for the NBS/gene therapy: when compared with CI/drug it was $207,909/QALY, when compared with CI/usual care it was $307,354/QALY. Similarly, NBS/drug also had a less favorable ICER when compared with CI/drug from healthcare perspective, the ICER increased to $539,466/QALY. Undiscounted and disaggregated results are presented in Appendix Table 5 and Appendix Table 6.

Table 2.5 Base-case results (Assuming a cohort of 1,000 newborns)

Strategies	Cost ($USD)	Incremental Costs	QALYs	Incremental QALYs	ICER ($/QALY)
Societal perspective					
(1) Reference comparator: CI/drug					
CI/drug	192,986	--	30,439.65	--	--
NBS/gene therapy	472,189	279,203	30,442.35	2.693	103,669

NBS/drug	883,950	411,761	30,442.28	-0.070	dominated
(2) Reference comparator: CI/drug (if gene therapy is not available)					
CI/drug	192,986	--	30,439.65	--	--
NBS/drug	883,950	690,964	30,442.28	2.623	263,382
(3) Reference comparator: CI/usual (supportive) care					
CI/usual (supportive) care	32,869	--	30,439.51	--	--
CI/drug	192,986	160,117	30,439.65	0.147	Extended dominated[1]
NBS/gene therapy	472,189	439,320	30,442.35	2.840	154,670
NBS/drug	883,950	411,761	30,442.28	-0.070	dominated
Healthcare sector perspective (Excludes informal care costs and caregiver QoL)					
(1) Reference comparator: CI/drug					
CI/drug	153,972	--	30,439.40	--	--
NBS/gene therapy	423,910	269,938	30,440.70	1.298	207,909
NBS/drug	836,472	412,562	30,440.66	-0.033	dominated
(2) Reference comparator: CI/drug (if gene therapy is not available)					
CI/drug	153,972	--	30,439.40	--	--
NBS/drug	836,472	682,500	30,440.66	1.265	539,466
(3) Reference comparator: CI/usual (supportive) care					
CI/usual (supportive) care	5,823	--	30,439.34	--	--
CI/drug	153,972	148,149	30,439.40	0.062	Extended dominated[2]
NBS/gene therapy	423,910	418,087	30,440.70	1.360	307,354
NBS/drug	836,472	412,562	30,440.66	-0.033	dominated

Abbreviations: NBS: Newborn screening; CI: Clinical identification; QALY: Quality adjusted life year; ICER: incremental cost effectiveness ratio; QoL: Quality of life

[1] Extended dominated: $1,088,179/QALY

[2] Extended dominated: $2,392,035/QALY

2.3.2 Sensitivity analysis

For sensitivity analysis, the base-case case scenario of societal perspective and using CI/drug as reference comparator for NBS/gene therapy, and NBS/drug was compared with NBS/gene therapy. The detailed sensitivity analysis results are shown in Appendix Table 3. One-

way sensitivity analysis was conducted, with parameters that were dependent on the parameters run as a set. For NBS/gene therapy, Table 2.6 shows the ranking of the parameters that had the most impact (widest range of differences). The three parameters that had the most impacts were: the relative reduction of ventilator dependence and death (asymptomatic) for gene therapy, the probability of responding to gene therapy, and the health utility of individuals with SMA.

For NBS/drug, the results remain the same as base-case, dominated, except for two parameters: (1) When using all minimum values for the relative reduction of ventilator dependence (symptomatic) and the relative reduction of death (symptomatic) for gene therapy: NBS/drug went from dominated to having an ICER of $11,714,425/QALY. (2) When using the minimum value for the relative reduction of ventilator dependence and death (asymptomatic) for gene therapy: NBS/drug went from dominated to having an ICER of $263,382/QALYs. (These results are shown in Appendix Table 3)

Also Shown in Table 2.6, when NBS/drug was compared with CI/drug, the three parameters that had the most impact were the relative reduction of ventilator dependence and death (asymptomatic) for drug treatment, the health utilities of individuals with SMA, and the probability of being diagnosed SMA through clinical identification.

Additional scenarios of treatment effects were tested, such as using all low or high values for drug and gene therapy, the preferred strategies did not change but the ICER for NBS/gene therapy were $662,944/QALY and $44,171/QALY. Assuming gene therapy has perfect treatment effect resulted in a ICER of $44,171/QALY. NBS/drug remain dominated in these scenarios. (These results are shown in Appendix Table 3)

Table 2.6 Sensitivity analysis ranking

	Using low value(s) ($/QALY)	Using high value(s) ($/QALY)	Differences
NBS/gene therapy vs. CI/drug			
Relative reduction of ventilator dependence and death, asymptomatic, gene therapy	299,725	103,669	196,056
Probability of responding to gene therapy	181,864	52,377	129,487
Individuals with SMA (Utility) (Set)	205,212	95,341	109,871
Probability of being diagnosis SMA through CI	171,948	75,765	96,183
Probability of NBS follow-up test: positive	192,251	101,505	90,746
Transition Probabilities (Set)	57,827	125,419	67,592
Probability of NBS test: false negative	103,669	167,093	63,424
Newborn screening test costs: First test	78,383	129,251	50,868
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1	95,894	140,290	44,396
Costs of Gene therapy (onasemnogene abeparvovec-xioi)	91,637	114,787	23,150
Relative reduction of ventilator dependence/death, symptomatic (Set), gene therapy	106,845	91,745	15,100
Relative reduction of ventilator dependence and death, asymptomatic, drug treatment	91,729	103,669	11,940
Probability of when 2 or 3 SMN2 copies, type 1 or type 2 (Set)*	114,574	103,669	10,905
Annual healthcare costs (Set)*	103,669	113,344	9,675
Probability of SMN2 copies, asymptomatic (Set)	110,960	102,127	8,833
Newborn screening test costs: Confirmation test	102,345	104,992	2647
Costs of Drug (nusinersen) (Set)	104,922	102,755	2,167
Relative reduction of ventilator dependence/death between treated early and treated late, symptomatic (Set), drug treatment	102,969	104,473	1,504
Caregiver (Disutility) (Set)*	103,669	105,026	1,357
Probability of NBS test: positive	103,388	104,310	922
Informal care costs (Set)	102,936	103,669	733
Drug: Administration cost	103,674	103,664	10
Gene therapy: Administration cost	103,667	103,671	4
NBS/drug vs. CI/drug			
Relative reduction of ventilator dependence and death, asymptomatic, drug treatment	651,091	263,382	387,709
Individuals with SMA (Utility) (Set)	521,291	242,243	279,048
Probability of being diagnosis SMA through CI	333,478	234,736	98,742
Costs of Drug (nusinersen) (Set)	207,345	304,217	96,872

Probability of NBS follow-up test: positive	354,321	261,161	93,160
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1	252,864	321,317	68,453
Probability of NBS test: false negative	263,382	328,494	65,112
Newborn screening test costs: First test	237,424	289,646	52,222
Transition Probabilities (Set)	251,907	271,301	19,394
Probability of when 2 or 3 SMN2 copies, type 1 or type 2 (Set)	274,593	262,921	11,672
Probability of SMN2 copies, asymptomatic (Set)	271,256	261,303	9,953
Annual healthcare costs (Set)*	263,382	273,066	9,684
Caregiver (Disutility) (Set)*	263,382	266,801	3,419
Newborn screening test costs: Confirmation test	262,024	264,741	2,717
Relative reduction of ventilator dependence between treated early and treated late, symptomatic (Set), drug treatment	263,382	262,262	1,120
Probability of NBS test: positive	263,094	264,041	947
Drug: Administration cost	263,035	263,730	695
Informal care costs (Set)	262,716	263,382	666
Costs of Gene therapy (onasemnogene abeparvovec-xioi)	263,382	263,382	0
Gene therapy: Administration cost	263,382	263,382	0
Relative reduction of ventilator dependence and death, asymptomatic, gene therapy	263,382	263,382	0
Relative reduction of ventilator dependence, symptomatic (Set), gene therapy	263,382	263,382	0
Probability of responding to gene therapy	263,382	263,382	0
CI: Clinical identification, NBS: newborn screening *Base-case ICER value was used when set had a higher ICER to reflect the widest differences.			

2.3.3 Scenario analysis

As shown in Table 2.7, four scenarios were conducted to test different assumptions. While the values of cost and effect may have changed, the conclusion of NBS/gene therapy with a ICER between $100,229 to $215,045/QALYs when compared to CI/drug did not change, and NBS/drug remained dominated.

Table 2.7 Scenario analysis (Assuming a cohort of 1,000 newborns)

Strategies	Cost ($USD)	Incremental Costs	QALYs	Incremental QALYs	ICER ($/QALY)
(1) Assuming only type 1 SMA individuals receive gene therapy, i.e., type 2 does not receive gene therapy					
CI/drug	192,986	--	30,439.65	--	--
NBS/gene therapy	626,961	433,974	30,442.35	2.693	161,136
NBS/drug	883,950	256,989	30,442.28	-0.070	dominated
(2) Assuming individuals with 4 copies of SMN2 and are type 1 and type 2 SMA individuals are treated, based on recent revised treatment recommendation.					
CI/drug	199,081	--	30,439.62	--	--
NBS/gene therapy	480,903	281,822	30,442.39	2.769	101,770
NBS/drug	905,020	424,117	30,442.32	-0.070	dominated
(3) Healthcare sector perspective + informal care costs					
CI/drug	192,986	--	30,439.40	--	--
NBS/gene therapy	472,189	279,203	30,440.70	1.298	215,045
NBS/drug	883,950	411,761	30,440.66	-0.033	dominated
(4) Healthcare sector perspective + caregiver disutility					
CI/drug	153,972	--	30,439.65	--	--
NBS/gene therapy	423,910	269,938	30,442.35	2.693	100,229
NBS/drug	836,472	412,562	30,442.28	-0.070	dominated

2.4 Discussion

The objective of this study was to evaluate whether newborn screening with the high-cost treatments for SMA is a health policy that is considered economically favorable, specifically nusinersen (drug) and onasemnogene abeparvovec-xioi (gene therapy). The base-case results show that, overall, when compared to clinical identification strategies, newborn screening strategies had slightly higher QALYs but significantly higher costs. From a societal perspective, base-case results show that newborn screening with gene therapy (NBS/gene therapy) yielded an ICER of $103,669 per QALY when compared to clinical identification with drug (CI/drug). This is considered a favorable cost-effective ratio when using the conventional threshold of 100,000–$150,000 per QALY as well as guidelines used by the National Institute for Health and Care Excellence (NICE) in the UK for very rare conditions (highly specialized technologies) at £100,000 (around $131,340).[57, 58] On the other hand, newborn screening with drug (NBS/drug) was considered as an unfavorable strategy for its significantly higher costs and slightly lower QALYs when compared to NBS/gene therapy. However, if gene therapy was assumed lower treatment effects, NBS/drug switched from a dominated strategy to having an ICER of $$263,382 and $11,714,425/QALYs.

When NBS/drug was compared with CI/drug, it had an ICER of $263,382/QALY, which is consider less favorable when using the conventional threshold, as well as using the guidelines used by the NICE stated above. However, if using the willingness-to-pay thresholds ($50,000 per QALY to $500,000 per QALY) for ultra-rare diseases proposed by the Institute for Clinical and Economic Review (ICER), it would be considered as a favorable strategy.[59]

The societal perspective included parameters additional to those from the healthcare sector perspective, including informal time costs and caregiver disutility. This is an important

aspect of SMA that should be captured as individuals with SMA are often diagnosed and treated at a young age and families are often the main caregiver. In this study, the results are more favorable from the societal perspective when compared to the healthcare sector perspective.

In the literature, there are a few studies that explored the economic values of newborn screening (NBS) and treatments for SMA. Jalali et al [60] evaluated the cost-effectiveness of nusinersen and universal NBS for SMA and concluded that it is a preferred strategy when compared with no screening with treatment. In a conference abstract, Arjunji et al [61] evaluated the cost-effectiveness analysis of NBS with gene therapy and concluded that compared to no NBS and symptomatic treatment, NBS with pre-symptomatic treatment is a cost-effective option from the U.S. payer perspective with a willingness-to-pay threshold of $150,000/QALY. A more recent study by Shih et al [62] evaluated the cost-effectiveness analysis of NBS for both nusinersen and onasemnogene abeparvovec-xioi and concluded NBS with gene therapy would be considered value-for-money in the Australia setting. While the results are limited to their setting, Shih et al did state that their results are comparable to the conference abstract of the preliminary results of this study.[63] The key differences between this study is that Jalali et al [60] and Arjunji et al [61] only focused on newborn screening with either drug treatment or gene therapy only and also focused on type 1 SMA or only restricting treatment to SMA type 1. In addition, while Shih et al [62] evaluated both drug and gene therapy treatment with newborn screening, they focused on individuals with 2 copies and 3 copies, while based on recent revised treatment recommendation, it is recommended that 4 copies of SMN2 are treated as well.[56] Therefore, this study provides a broader perspective in evaluating this research question.

Overall, more studies explored the economic evaluation of the treatments only (without newborn screening). A recent systematic literature review summarized literature from 1998 to

2020 that looked at the economic burden of SMA and economic evaluations of treatments.[64] Of the six economic evaluations, the authors concluded that the ICER for nusinersen when compared to standard of care ranged from $210,095-$1,150,455/QALY, and $32,464-$251,403/QALY for onasemnogene abeparvovec-xioi for individuals with SMA type 1. While there are many differences between these studies and the model assumptions, the results of this study were broadly similar: For the NBS/drug(nusinersen) strategy, it had a ICER of $625,925/QALY when compared with CI/usual care from a healthcare perspective, and $307,187/QALY when compared with CI/usual care from a societal perspective. For the NBS/gene therapy (onasemnogene abeparvovec-xioi) strategy, it had an ICER of $307,354/QALY when compared to CI/usual care from a healthcare perspective, and $154,670/QALY when compared to CI/usual care from a societal perspective.

There are several limitations in this study. One limitation is the scarcity of data available for few parameters and long-term outcomes. While assumptions were made for these parameters, sensitivity analyses that tested different parameter values and scenario analyses that tested different assumptions were carried out and revealed the robustness of the model results.

The main uncertainty revolved around the treatment effectiveness of gene therapy. For example, assuming gene therapy has perfect treatment effect resulted in a much lower ICER of $44,171/QALYs for NBS/gene therapy, although the overall conclusions did not change. Setting the treatment effects of drug and gene therapy all at low value resulted in a ICER of $662,944/QALY for NBS/gene therapy. In addition, when gene therapy was assumed to have lower treatment effects, NBS/drug went from being a dominated strategy to having a ICER of $11,714,425/QALYs (assuming lower value for parameters: “Relative reduction of ventilator dependence, symptomatic, gene therapy” and “Relative reduction of death, symptomatic, gene

therapy") and $263,382/QALYs (assuming lower value for parameter "Relative reduction of ventilator dependence and death, asymptomatic, gene therapy").

Another limitation is the simplified assumptions in the model as well as the assumption of treatment. In the base-case, it is assumed that individuals with SMA type 1 and type 2 are treated, and assumed to have the option of receiving gene therapy. Given that many studies focus on individuals with type 1 SMA solely, this study conducted scenario analysis assuming only type 1 SMA will receive gene therapy. The conclusion remained the same, with a slightly higher ICER of $161,136/QALY for NBS/gene therapy. In addition, this study also tested the scenario where individuals with 4 copies of SMN2 and are type 1 and type 2 SMA individuals are treated, based on recent revised treatment recommendation.[56] The overall conclusions for preferred strategies of NBS/gene therapy did not change, thought the ICER was slightly lower at $101,770/QALY. In addition, the health utilities for watchful waiting are assumed to be the same as non-SMA population, however, it is possible that they have different health utility weights.

One other limitation is that probability sensitivity analysis (PSA) was not feasible due to the limited data available of SMA, the computational limitations given the hypothetical cohort size of 4 million newborns of the model, and the complexity of running a PSA the model as most inputs are correlated. However, the conclusions are unlikely to change given the robustness of the sensitivity analysis results. In addition, this study did not include risdiplam, the drug recently approved by the FDA, for limited data are available for this drug. Risdiplam is the first treatment that is administer orally and has an estimated costs between $99,278 and $341,955 annually based on age and weight.[14-16], this might have an impact on the choice of treatment, as the gene therapy (onasemnogene abeparvovec-xioi) is given through intravenous (IV) infusion and drug treatment (nusinersen) is given through intrathecal (IT) injection. Given that the costs are

lower than drug treatment (nusinersen), which is $510,000 for the first year and $382,500 for the subsequent years, if the treatment effect is better, it might be a more favorable option than nusinersen. However, the reoccurring costs might be a factor that would make it a less favorable option than gene therapy if the treatment effects are not better than gene therapy. Additional research is needed to confirm this conclusion.

An additional limitation is that possible education resources needed for individuals with SMA, and that formal care was not included in the study. For example, for individuals requiring ventilators, there might be nurses that takes care of them 8 hours a day at the hospital or at home, which are typically considered as direct medical costs and are covered by health insurance. However, given the robustness of the sensitivity analysis, it is estimated that it will not likely change the conclusion.

Another limitation is that the possible effects of siblings were not considered in this study. For example, if there is an affected sibling in the family already, other siblings will be screened, typically during pregnancy, while newborn screening is designed to screening for infants that are not at higher risk for the condition. In addition, this study also did not consider additional aspects of the policy, such as the ethics of not screening, or the ethics of not having an available treatment when diagnosed. Finally, another limitation is that there might be alternative ways to incorporate the quality of life of caregivers as there are still many discussions around the issue of incorporating caregiver QALYs. For example, a very recent study by Al-Janabi et al, estimated a social value of 0.74 for carer *health-related* quality of life effects and 0.69 for carer *care-related* quality of life effects, distinguishing the two types of quality of life.[65]

2.5 Conclusion

When compared with clinical identification strategies, newborn screening with gene therapy, onasemnogene abeparvovec-xioi, had a favorable cost-effectiveness ratio under conventional willingness-to-pay thresholds, while newborn screening with drug, nusinersen, did not. Future research should explore conditions under which nusinersen would be more economically attractive.

Chapter 3 Budget Impact Analysis of Newborn Screening and Treatment for Spinal Muscular Atrophy (SMA) in the US – Using Michigan as an Example

Abstract

Spinal muscular atrophy (SMA), a rare pediatric disorder, was recommended for national screening in the U.S in 2018. The benefit of NBS for SMA is that earlier diagnosis would potentially lead to earlier treatments. However, for many rare conditions such as SMA, the real challenge lies in the costs for treatment. For example, the drug treatment, nusinersen, has an estimation of around $510,000 for the first year and $382,500 for the subsequent years. The gene threapy, onasemnogene abeparvovec-xioi, has an estimated one-time cost of $2,092,965 per individual. One program that could potentially fund these high-costs treatments would be through the Medicaid program/The Children's Health Insurance Program (CHIP) in each state. However, it is unclear how much budget would be needed for the program. Therefore, the goal of this study is to estimate the budget impact of NBS and treatment for SMA on a middle size state in the U.S. using budget impact analysis, using Michigan as an example.

A state-transition model and a spreadsheet model were developed for the budget impact analysis of newborn screening and treatments for SMA for this study. A hypothetical population with cohorts of 111,507 newborns per year was used to compare the budget impact of two scenarios: (1) clinical identification with drug treatment, nusinersen (CI/drug), and (2) newborn screening with gene therapy, onasemnogene abeparvovec-xioi (NBS/gene therapy). Model inputs include epidemiology and transition probabilities, treatment effectiveness, costs and resource

use, and health-related quality of life. These parameters were derived from published literature and reports. Results from the state-transition model were then transferred to the spreadsheet model. The base-case results are presented as annual costs and total 5-year costs. Sensitivity analyses and scenario analyses were conducted to explore the possible projected changes to the results. The time horizon of the analysis is assumed to be a five-year period and costs are in USD2021.

In the base-case analysis, assuming 80% of individual with SMA receiving gene therapy and 20% receiving drug treatment, the model projected that clinical identification with drug had lower annual costs than newborn screening with gene therapy. Both strategies had increasing costs each year: CI/drug started with $3.5 million in the first year and increased to $11 million in the fifth year; and NBS/gene therapy started with $16 million in the first year and increased to $18 million in the fifth year. CI/drug had more costs in all costs categories than NBS/gene therapy, excluding gene therapy costs. The budget impact of NBS/gene therapy started at an estimation of $12 million in the first year and decreased to $7 million in the fifth year. The total budget impact over a five-year period is estimated to be $48 million. Sensitivity analyses and scenario analyses revealed a range of differences between $21 million and nearly $100 million.

In conclusion, the budget impact on the Medicaid/CHIP program if implemented the strategy of newborn screening with onasemnogene abeparvovec-xioi is estimated to be $12 million in the first year and decreased to $7 million in the fifth year. Over a five-year period, the budget impact is projected to be $48 million, with a potential range between $21 million to near $100 million using alternative assumptions.

3.1 Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disorder. In the United States, the incidence of SMA is estimated to be 1 in 11,000.[23] This disorder causes the weakening of skeletal muscle due to the deficiency of the survival motor neuron (SMN) proteins, which are produced by survival motor neuron (SMN) genes.[19] Individuals with more severe SMA will lose motor and pulmonary function over time, resulting in hospitalization and early death.[19]

SMA is classified clinically based on the age of disease onset in Type I, II, III, and IV.[19, 25] The earlier the age of diseases onset, the worse the motor development and expected life span. The most severe type is SMA type I, without healthcare intervention, they have an estimated life span of less than two years.[25] SMA type I also have the highest estimated incidence rate among all subgroups, at approximately 60%.[66] With this severe outcomes and the development of screening test for SMA, newborn screening (NBS) for SMA was recommended by the Secretary of Health and Human Services (HHS) in 2018, and as of August 2021, it is reported that 38 states in the U.S. are screening for SMA.[9, 13]

The benefit of NBS for SMA is that earlier diagnosis would potentially lead to earlier treatments. While the additional costs of newborn screening for SMA may be covered through funds from state budgets, fundings, or increased screening fees, the real challenge for many rare conditions such as SMA lies in the costs for treatment.

In the United States, a study using costs for years 2003-2012 estimated that the total medical expenditure for an individual with SMA diagnosed before one year of age was $507,580 (standard deviation $741,027). For individuals diagnosed after one year of age, it was $229,410 (standard deviation: $564,242).[31] This, however, does not include the high costs treatments

that were approved by the U.S. Food and Drug Administration (FDA) starting in 2016. Nusinersen, the first drug approved to treat SMA, is estimated to be around $510,000 for the first year and $382,500 for the subsequent years.[14] A few years later, onasemnogene abeparvovec-xioi, a one-time gene therapy, was approved and has an estimated one-time cost of $2,092,965 per individual.[14]

As newborn screening is made available, more individuals with SMA will be diagnosed through screening at an early stage of SMA or pre-symptomatic SMA. This will require treatment, possibly these high-costs treatments as they would most likely provide benefit in preventing worse symptoms when given at an early stage. For example, the gene therapy is currently approved by the FDA for individuals with SMA less than two-years of age. The high costs of these treatments, however, if not covered by the insurance, will remain a challenge for many individuals with SMA and their families to access these treatments.

One program that could potentially fund these high-costs treatments would be through the Medicaid program/The Children's Health Insurance Program (CHIP) in each state. However, it is unclear how much budget would be needed if they do. Therefore, the goal of this study is to estimate the budget impact of NBS and treatment for SMA on a middle size state in the US using budget impact analysis. Budget impact analysis (BIA) is a systematic estimation of changes in costs and resources of a setting before and after a new intervention has been introduced to the population of interest from the perspective of the budget holder over a specific time period.[67] This study will be using Michigan as an example, and the results of this study would provide information for states when making decisions related to providing financial support for high-costs treatments for SMA.

3.2 Methods

To estimate the potential budget impact of newborn screening and treatment for SMA on a middle size state in the U.S., a state-transition model and a spreadsheet model was developed. The analytic perspective of this study is from the perspective of the Medicaid program/The Children's Health Insurance Program (CHIP) at the Michigan Department of Health and Human Services (MDHHS).

In the analysis, the targeted eligible population is assumed to be hypothetical cohorts of 111,507 newborns per year, where a new cohort added to the population each year for five years. This is assumed to have around 10 individuals with SMA per year. The targeted population will then receive diagnosis and treatment with either (1) the current intervention mix or (2) the new intervention mix.

As shown in Figure 3.1, (1) the current intervention mix is assumed to be diagnosis through clinical identification and treatment with drug, i.e., nusinersen (CI/drug) (marked in yellow). (2) The new intervention mix is assumed to be diagnosis through newborn screening and treatment with gene therapy, i.e., onasemnogene abeparvovec-xioi (NBS/gene therapy) (marked in blue). For NBS/gene therapy, if individuals with SMA do not respond to gene therapy, they will receive drug (nusinersen) treatment. The response rate to gene therapy is assumed to be 80% in the base-case analysis. The primary outcome for the analysis is the costs for five years in 2021 USD. The costs differences between CI/drug and NBS/gene therapy will be the budget impact if the Medicaid program/CHIP were to pay for the high-cost treatments, in this case, gene therapy.

Figure 3.2 shows the number of individuals in each cohort for 5 years for the two strategies CI/drug (marked in yellow) and NBS/gene therapy (marked in blue). This is multiplied

by the costs for each strategy in each year, and the costs for each year for each cohort are added up. The final costs for each strategy are then compared and the costs differences (marked in orange) are the budget impact between the two strategies.

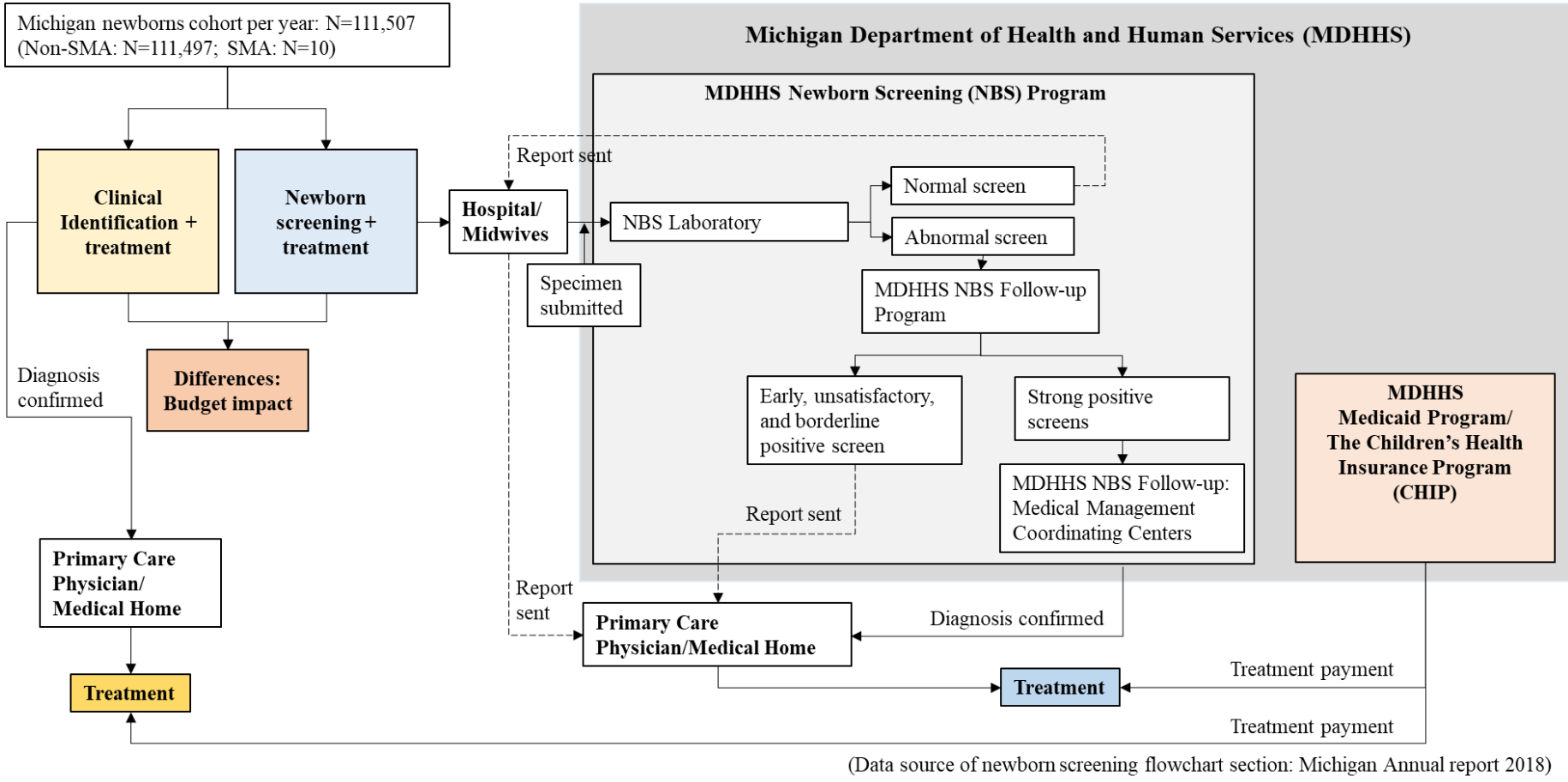


Figure 3.1 Study framework for budget impact analysis (1)

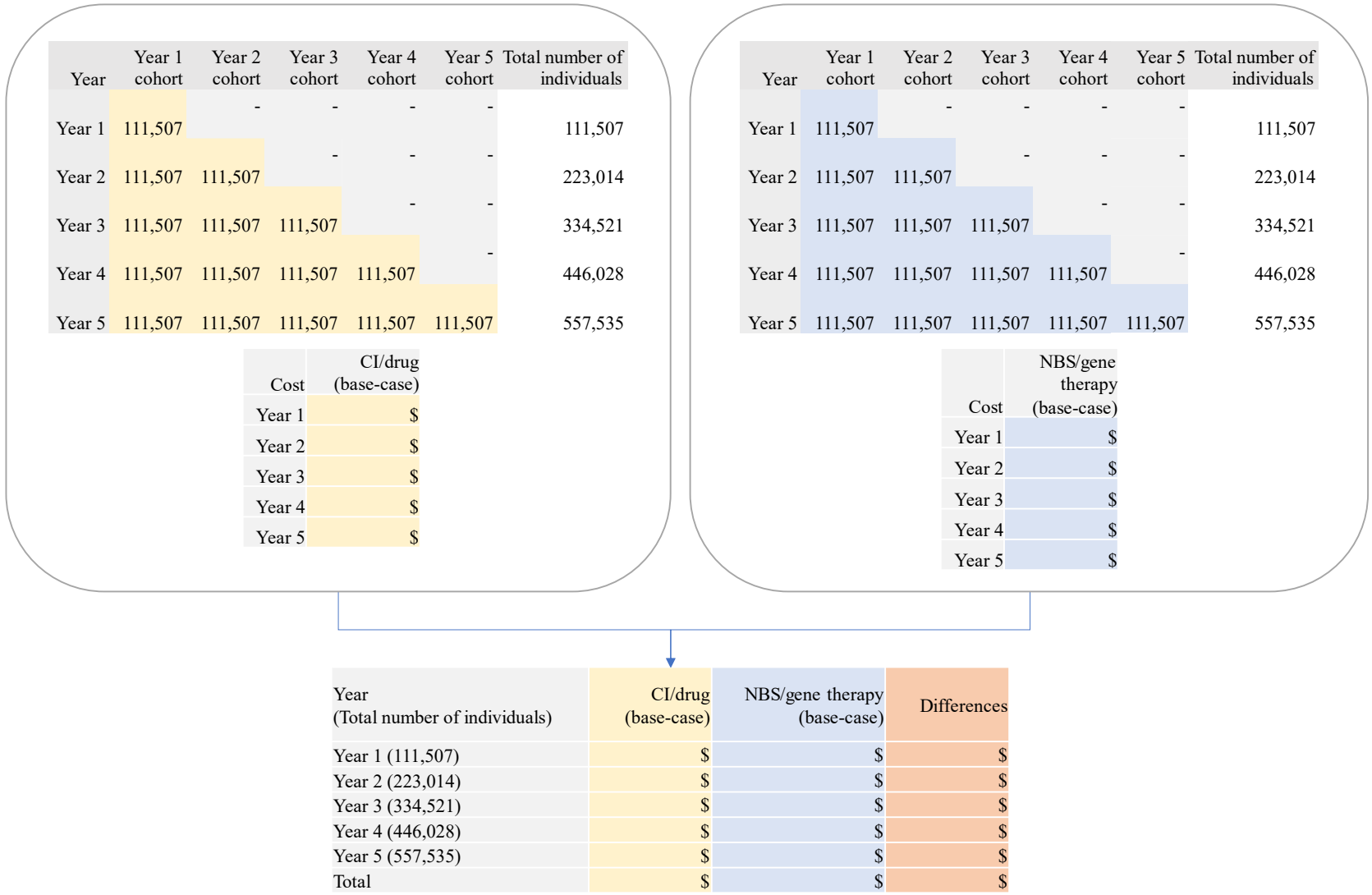


Figure 3.2 Study framework for budget impact analysis (2)

Model inputs for the state-transition model include epidemiology and transition probabilities, treatment effectiveness, costs and resource use, and health-related quality of life. These parameters were derived from published literature and reports.[14, 23, 26, 30-46, 48-55] The model inputs are listed in Appendix Table 7 to 11. Note that newborn screening costs are not included in this analysis as Michigan and most states has already implemented newborn screening for SMA.[13] In addition, the costs are in USD2021 and are undiscounted. This is based on the guidelines by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report of the 2012 Budget Impact Analysis Good Practice II Task Force where they stated that discount is not recommended for budget impact analyses as the budget holder's interest is generally the expected impact at each budget period and not the net present value.[68]

Model assumptions include the following: (1) The number of individuals with SMA identified through CI and NBS strategy are identical, and CI strategy can only identify symptomatic cases. (2) In the NBS strategy, it is assumed that symptomatic type 1 SMA are treated with gene therapy. For asymptomatic individuals with SMA, those with 2 and 3 copies SMN2 of type 1 and type 2 SMA are treated with gene therapy in the base-case. (3) In the NBS strategy, it is also assumed in the base-case that all individuals with 1 copy of SMN2 are all symptomatic, and therefore, there are no individual with 1 copy of SMN2 that are asymptomatic. (4) It is also assumed for individuals with 4 or 5 copies of SMN2, in the base-case that they are on watchful waiting. (5) It is assumed if the individuals did not respond to gene therapy, they will receive drug treatment.

The primary outcomes include the costs of the CI/drug and NBS/gene therapy, this includes annual costs from the first year to the fifth year, total 5-year costs, and the differences

between the two strategies. In the base-case analysis, results are presented in an aggregated and disaggregated form. Disaggregated results include the following categories of costs: inpatient costs, outpatient costs, prescription costs, drug costs, and gene therapy costs. The aggregate costs include all the categories stated above.

Sensitivity analyses and scenario analyses were conducted to explore the possible changes to the results. For example, the following were explored in the scenario analyses: (1) Assuming only type 1 SMA individuals receive gene therapy, i.e., type 2 does not receive gene therapy (2) Assuming individuals with 4 copies of SMN2 and are type 1 and type 2 SMA individuals are treated, based on recent revised treatment recommendation.[56]. (3) Comparing NBS/gene therapy with NBS/drug as this is another likely scenario for those that have already implemented newborn screening. (4) Comparing NBS/gene therapy with CI/usual care to explore the scenario when drug treatment is not available. The analyses were conducted using TreeAge Pro 2021 (TreeAge Software, Inc., Williamstown, MA, USA) and Microsoft Excel Version 2110 (Microsoft Corporation, USA).

3.3 Results

3.3.1 Base-case results: aggregated

The aggregated base-case results are shown in Table 3.1. Overall, the model projected that clinical identification with drug had lower annual costs than newborn screening with gene therapy. Both strategies had increasing costs each year: CI/drug started with $3.5 million in the first year and increased to $11 million in the fifth year; and NBS/gene therapy started with $16 million in the first year and increased to $18 million in the fifth year.

The budget impact on the Medicaid/CHIP program if implemented the NBS/gene therapy strategy started at an estimation of $12 million in the first year and decreased to $7 million in the fifth year. Over a five-year period, it is estimated that NBS/gene therapy had a budget impact of $48 million when compared with CI/drug.

Table 3.1 Base-case results: aggregated

Cost Year	Number of newborns	CI/drug	NBS/gene therapy	Differences
Year 1	111,507	3,519,373	16,055,949	12,536,576
Year 2	223,014	5,900,477	16,624,602	10,724,125
Year 3	334,521	7,919,755	17,187,777	9,268,022
Year 4	446,028	9,632,112	17,745,810	8,113,698
Year 5	557,535	11,085,445	18,299,001	7,213,555
Total		38,057,162	85,913,138	47,855,976
Abbreviations: CI: Clinical identification, NBS: Newborn screening				

3.3.2 Base-case results: disaggregated

Table 3.2 shows the disaggregated results of the base-case analysis, including inpatient costs, outpatient costs, prescription costs, drug costs, and gene therapy costs. Overall, CI/drug had more costs in all categories than NBS/gene therapy, excluding gene therapy costs. This highlights the significant costs of gene therapy in this budget impact analysis.

Table 3.2 Base-case results: disaggregated

Cost Year	Number of newborns	CI/drug	NBS/gene therapy	Differences
Inpatient costs				
Year 1	111,507	0	0	0
Year 2	223,014	8,274	296	-7,978
Year 3	334,521	19,924	840	-19,084
Year 4	446,028	32,464	1,592	-30,872
Year 5	557,535	44,663	2,518	-42,146
Total		105,325	5,245	-100,080
Outpatient costs				
Year 1	111,507	16,066	16,066	0
Year 2	223,014	47,385	32,560	-14,826
Year 3	334,521	83,891	49,470	-34,421
Year 4	446,028	120,558	66,717	-53,841
Year 5	557,535	155,019	84,234	-70,786
Total		422,919	249,046	-173,873
Prescription costs				
Year 1	111,507	614	614	0
Year 2	223,014	2,904	1,283	-1,622
Year 3	334,521	5,840	2,001	-3,839
Year 4	446,028	8,899	2,759	-6,140
Year 5	557,535	11,829	3,551	-8,278
Total		30,086	10,207	-19,879
Drug costs				
Year 1	111,507	3,502,693	747,114	-2,755,579
Year 2	223,014	5,841,913	1,298,308	-4,543,605
Year 3	334,521	7,810,101	1,843,312	-5,966,789
Year 4	446,028	9,470,191	2,382,587	-7,087,604
Year 5	557,535	10,873,933	2,916,543	-7,957,390
Total		37,498,832	9,187,865	-28,310,967
Gene therapy costs				
Year 1	111,507	0	15,292,155	15,292,155
Year 2	223,014	0	15,292,155	15,292,155
Year 3	334,521	0	15,292,155	15,292,155
Year 4	446,028	0	15,292,155	15,292,155
Year 5	557,535	0	15,292,155	15,292,155
Total		0	76,460,776	76,460,776

Abbreviations: CI: Clinical identification, NBS: Newborn screening; Note: The disaggregated shown above costs are rounded to nearest dollar and may have +/- $1 dollar difference when added up directly. However, it is confirmed that these disaggregated results add up to the aggregated results.

3.3.3 Sensitivity analyses

The summarized one-way sensitivity results are shown in Table 3.3, with more detailed annual results and the range of differences shown in shown in Appendix Table 12 and Appendix Table 13, respectively. Compared with the base-case results of a five-year $48 million budget impact between CI/drug and NBS/gene therapy, sensitivity analysis revealed a range of differences between $21 million and almost $100 million. The parameter that had the most impact on the budget impact results is the probability of being diagnosed SMA through CI, i.e., the incidence rate of SMA, which had a range of differences of $79 million, ranging from $21 million to almost $100 million of differences. The was followed by the costs of gene therapy (Range of differences: $35 million) and probability of receiving a false negative test result for NBS (Range of differences: $26 million).

Table 3.3 Sensitivity analysis

Parameter	Differences ($million) between CI/drug and NBS/gene therapy using low/ high value		Range of Differences ($million)
Base-case result	47.86		--
Sensitivity analysis results			
Incidence of SMA (diagnosis through CI) (0.00004-0.00019)	21.04	99.92	78.88
Cost of Gene therapy (onasemnogene abeparvovec-xioi) (1598394-2550000))	29.79	64.55	34.76
Probability of NBS test: false negative (0-0.00005)	21.91	47.86	25.95
Probability of responding to gene therapy (50-100)	38.66	61.64	22.98
Costs of Drug (nusinersen) (All low/high))	42.21	55.60	13.39
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1 (0.003-0.527))	45.39	55.98	10.59
Transition Probabilities (All low/high))	43.86	51.78	7.93
Probability of when 2 or 3 SMN2 copies, type 1 or type 2 (All low/Adjusted high[1])	41.57	48.53	6.96

Probability of SMN2 copies, asymptomatic (All low/Adjusted high[1])	43.13	49.48	6.35
Relative reduction of ventilator dependence and death, asymptomatic (drug) (All low/high)	47.40	47.86	0.46
Healthcare costs (All low/high[2])	48.19	48.52	0.32
Relative reduction of ventilator dependence/death between treated early and treated late, symptomatic (drug) (70.1-100)	47.80	47.90	0.1
Relative reduction of ventilator dependence and death, asymptomatic (gene therapy) (70.1-100)	47.86	47.95	0.1
Drug: Administration cost (653-1959)	47.81	47.90	0.09
Relative reduction of ventilator dependence/death, symptomatic (gene therapy) (All high/low)	47.85	47.88	0.04
Gene therapy: Administration cost (74-222)	47.85	47.86	0.01
Probability of NBS follow-up test: positive 0.0002-0.0378)	47.86	47.86	0
Probability of NBS test: positive (0.0118-0.0164)	47.86	47.86	0
Abbreviations: CI: Clinical identification, NBS: Newborn screening [1] Several combinations of the parameter values were tested, and this was the lowest/highest value. [2] The healthcare costs for drug treatment and gene therapy are assumed to be 50% of these values, therefore they change with these variables			

3.3.4 Scenario Analysis

Table 3.4 shows the results of three scenario analyses. In the first scenario, when assuming only individual with SMA type 1 receives gene therapy, the differences between CI/drug and NBS/gene therapy increased from the five-year base-case budget impact of $48 million to $57 million. In the second scenario, when assuming individuals with 4 copies and are type 1 or type 2 SMA receives treatment, the budget impact also increased to $49 million. In the third scenario, however, where NBS/gene therapy was compared with NBS/drug, the budget impact decreased to $40 million. On the other hand, when NBS/gene therapy was compared with CI/usual, the budget impact increased to $85 million.

Table 3.4 Scenario analysis

(1) Assuming only type 1 SMA individuals receive gene therapy, i.e., type 2 does not receive gene therapy				
Cost Year	Number of newborns	CI/drug	NBS/gene therapy	Differences
Year 1	111,507	3,519,373	16,803,063	13,283,690
Year 2	223,014	5,900,477	17,929,360	12,028,883
Year 3	334,521	7,919,755	19,049,973	11,130,218
Year 4	446,028	9,632,112	20,165,298	10,533,187
Year 5	557,535	11,085,445	21,275,676	10,190,231
Total		38,057,162	95,223,370	57,166,208
(2) Assuming individuals with 4 copies of SMN2 and are type 1 and type 2 SMA individuals are treated, based on recent revised treatment recommendation				
Cost Year	Number of newborns	CI/drug	NBS/gene therapy	Differences
Year 1	111,507	3,599,618	16,467,582	12,867,963
Year 2	223,014	6,044,362	17,050,957	11,006,595
Year 3	334,521	8,119,986	17,628,848	9,508,862
Year 4	446,028	9,882,274	18,201,593	8,319,319
Year 5	557,535	11,379,908	18,769,494	7,389,585
Total		39,026,148	88,118,473	49,092,325
(3) Comparing NBS/gene therapy with NBS/drug				
Cost Year	Number of newborns	NBS/gene therapy	NBS/drug	Differences
Year 1	111,507	16,055,949	3,752,250	12,303,699
Year 2	223,014	16,624,602	6,526,550	10,098,051
Year 3	334,521	17,187,777	9,271,206	7,916,572
Year 4	446,028	17,745,810	11,988,178	5,757,632
Year 5	557,535	18,299,001	14,679,242	3,619,758
Total		85,913,139	46,217,426	39,695,713
(4) Comparing NBS/gene therapy with CI/drug				
Cost Year	Number of newborns	NBS/gene therapy	CI/usual care	Differences
Year 1	111,507	16,055,949	33,359	16,022,590
Year 2	223,014	16,624,602	162,616	16,461,986
Year 3	334,521	17,187,777	267,298	16,920,480
Year 4	446,028	17,745,810	346,501	17,399,309
Year 5	557,535	18,299,001	407,610	17,891,390
Total		85,913,139	1,217,384	84,695,755
Abbreviations: CI: Clinical identification, NBS: Newborn screening				

3.4 Discussion

The objective of this study is to estimate the budget impact of newborn screening (NBS) and treatment if the Medicaid program/The Children's Health Insurance Program (CHIP) implemented the NBS/gene therapy strategy, using Michigan as an example. Assuming a population with cohorts of 111,507 newborns and around 10 individuals with SMA (range: 4 - 21) per year, the base-case results showed that CI/drug had annual costs of between $3.5 million to $11 million for the first 5 years, while NBS/gene therapy was between $16 million to $18 million per year. The budget impact of NBS/gene therapy, when compared to CI/drug, was $12 million in the first year and decreased to $7 million to the fifth year, with a five-year total budget impact of $48 million. With the assumption of 111,507 newborns per year, this averages to a budget impact of $86 per newborn per year for 5 years.

Based on the Michigan Department of Health and Human Services Health budget briefing for Fiscal Year (FY) 2020 to 2021, the budget for medical services and behavioral health in FY 2020-21 is around $22.1 billion.[69] A potential part that would cover budget impact would be the medical services, which supports the Children's Special Health Care Services where they cover special medical care and treatment for children, although around 70% of the enrollees are also enrolled in Medicaid. For special payments in medical services, the budget is around $551 million.[69] Compared this budget, the budget impact of NBS/gene therapy of $7 to $12 million per year for the first five years seem to be a policy to consider.

Based on the results of the previous cost-effectiveness analysis using a societal analytic perspective, these base-case results also map to an incremental cost effectiveness ratio (ICER) of $103,669/QALY for NBS/gene therapy when compared with CI/drug. From a healthcare sector perspective, the ICER was $207,909/QALY.

While the base-case analysis projected a five-year total budget impact of $48 million, sensitivity analysis and scenario analysis revealed a possible range of $21 million to nearly $100 million. The parameter with the most impact was the probability of being diagnosed SMA through clinical identification, i.e., the incidence rate of SMA. Assuming the same population with 111,507 newborns per year but with around 4 individuals with SMA each year, the budget impact decreased to around $21 million, at approximately $38 per newborn per year for 5 years. However, it increased to nearly $100 million when assuming around 21 individuals with SMA per year, with an estimation of $179 per newborn per year for 5 years.

In the U.S., several studies have explored the budget impact analysis for the high-cost treatments of SMA. For example, the Institute for Clinical and Economic Review (ICER) estimated the potential budget impact of onasemnogene abeparvovec-xioi compared with best supportive care and nusinersen in two scenarios. They assumed there were 215 eligible individuals with type 1 SMA per year and assumed a price holder of $2 million per one-time treatment for onasemnogene abeparvovec-xioi.[41] In the first scenario, onasemnogene abeparvovec-xioi was compared with best supportive care and yielded an average annual per-patient budget impact of $946,300 ($1,113,600 versus $167,400). This was estimated to be 45% of the threshold when using a five-year annualized potential budget impact threshold of $991 million per year for new drugs. In the second scenario, onasemnogene abeparvovec-xioi was compared with a mix of best supportive care (25%) and nusinersen (75%). This resulted in an average annual per-patient budget impact of $573,100 ($1,113,600 versus $540,600), reaching only 24% of the threshold. They also included a scenario analysis estimating the budget impact of assuming 370 pre-symptomatic individuals with SMA per year receiving nusinersen compared

with best supportive care. The potential budget impact was $573,900 which reached 58% of the threshold.

Based on the results from ICER, they estimated the budget impact of onasemnogene abeparvovec-xioi were all below the threshold that would trigger policy actions to manage access and affordability. While the results between the study by ICER and this study are not directly comparable given different population assumptions and treatment groups, in a scenario of assuming a population with cohorts of 4 million newborns with around 364 individuals with SMA per year, this study projected a five-year budget impact of $1,717 million with annual average of $343 million per year. This would also be below the threshold provided by ICER of $991 million per year for new drugs.

Based on the results form ICER, a follow-up conference abstract compared the budget impact of onasemnogene abeparvovec-xioi with nusinersen and concluded that onasemnogene abeparvovec-xioi would have acceptable budget impact and cost-effectiveness at a price up to $2.915 million.[70] Another conference abstract estimated a five-year per-member-per-month budget impact of $0.05 to $0.11 for onasemnogene abeparvovec-xioi compared with nusinersen. This was under the assumption of a US payer covering 1 million individuals per year and treating an average of 0.68 patients per year and assuming the price point of onasemnogene abeparvovec-xioi was $2 million to $3 million.[71] The authors also concludes that the budget impact deceases each year as it is a one-time single dose therapy and installment plans for onasemnogene abeparvovec-xioi would reduce the budget even more. While the results of these two abstracts is based on different population and treatment assumptions than this study, this study also have similar conclusion that the budget impact of NBS/gene therapy decreases each year within the 5-year framework.

For budget impact results beyond five years, additional analyses were conducted and shown in Appendix Table 14 and Appendix Table 15. While there are even more uncertainties associated with a longer time frame, such as new treatments or new guidelines for treatment, these additional analyses provide an idea of the long-term budget impact differences. For example, as shown in Appendix Table 14, while the trend of between the differences of CI/drug and NBS/gene therapy in the first 5 years has deceased, the results showed an increase in differences starting at the 12th year. This is possibly due to that in the hypothetical cohort, most individuals with SMA type 1 and type 2 in the CI/drug has died around that period but most individuals in the NBS/gene therapy strategy continues to receive early diagnosis and treatment, which is a benefit that is not captured in the budget impact as it only includes costs. In addition, when NBS/gene therapy was compared with NBS/drug (shown in Appendix Table 15), the differences between the two strategies decreased in the first 5 years and continued to decrease throughout the longer-term, where the costs of NBS/drug was larger than NBS/gene therapy in the 7th year. This is possibly due to that while both have cohorts added each year, gene therapy is a one-time cost, but drug treatment will require continued treatment each year for all individuals with SMA.

There are a few limitations to this study. First, while this study uses Michigan as an example, the data is limited to publicly available data. However, this study has developed a general framework that can be updated and tailored to Michigan if a collaboration with the Michigan Department of Health and Human Services (MDHHS) is initiated. In addition, while every state has different newborn screening programs [10] and different budget for the Medicaid program/The Children's Health Insurance Program (CHIP), the model of this study can

potentially be tailored and adapted for different states in the U.S. as well. Given the differences in newborn screening program and other factors, the results might be different among states.

Another limitation is the model assumptions for the base-case analysis might differ across clinical settings, such as assuming individuals with both type 1 and type 2 SMA are treated with gene therapy. This was tested in the scenario analyses, for example, assuming only individuals with type 1 SMA receive gene therapy yield a five-year budget impact of $57 million. The assumptions of parameters were also tested through sensitivity analysis (Appendix Table 12 and 13). A common uncertainty in the literature revolved around the price point of gene therapy. Using the costs from the Department of Veterans Affairs (VA) Big4 price as a lower bound ($1,598,394) and the REDBOOK Average Wholesale Price (AWP) price as a higher bound ($2,550,000), the five-year budget impact was projected to be near $30 million and $65 million, respectively.

In addition, this study did not include potential polices or negotiations around the costs of gene therapy that might potentially affect the budget impact. For example, the installment plans for gene therapy that was stated in the above conference abstract might reduce the annual budget within the five-year period. In addition, negotiations between the Medicaid program and the pharmaceutical company may also alter the results of the budget impact. For example, the Massachusetts Medicaid program, MassHealth, has reached a deal with the drug manufacturer that they will pay for onasemnogene abeparvovec-xioi if it works, and if not, they will receive most of their money, if not all, back.[72] In addition, while it is unlikely there is off-label use of the high-cost treatments, this may be a potential limitation if there are new treatments in the future.

Due to limited data available, this study also did not include risdiplam, a drug treatment that was recently approved F.D.A., in the analysis, which has an estimated costs between $99,278 and $341,955 annually based on age and weight.[14-16] However, as this is the first treatment that is administer orally, it might have an impact on the intervention mix if it more widely used, although it is uncertain how it will affect the use of to the onasemnogene abeparvovec-xioi (given through intravenous (IV) infusion) and nusinersen (given through intrathecal (IT) injection).

In addition, this study assumed the model started with newborns, however, there might be different age group combinations that are of interest to the budget holder. This may be calculated using Appendix Table 14. where the costs for each year (age) is presented. For example, if the starting population consists of different age groups, the budget impact can be calculated using the costs of the different years weighted by the proportion of the population. However, this study only accounted for the different severity of SMA and age and did not include additional characteristics such as comorbidities, sex, and/or ethnicity.

A potential cost not included would be that early diagnosis and treatment of newborn screening with gene therapy might improve the productivity of these individuals, which might have impact if Medicaid/Chip were funded by tax subsidies. In addition, another potential cost not included is costs related to follow-up genetic consulting programs for individuals with SMA, their families, and carriers that were identified through screening if the state does not already have that program.

3.5 Conclusion

The budget impact on the Medicaid/CHIP program if implemented the strategy of newborn screening with onasemnogene abeparvovec-xioi started at an estimation of $12 million

in the first year and decreased to $7 million in the fifth year. Over a five-year period, the budget impact is projected to be $48 million, with a potential range between $21 million to near $100 million using alternative assumptions.

Chapter 4 Developing a Best-Worst Scaling Survey for Measuring Family Spillover Effects for Children with Complex Chronic Conditions – From an Economic Perspective

Abstract

Children with complex chronic conditions (CCCs) often require specialty pediatric care due to the complexity in treatment. These challenging treatment process not only has significant impact on the child, but also on the child's primary caregiver and other family members. These effects, known as family spillover effects, include challenges such as paying out-of-pocket for the child's treatment and care, spending additional time taking care of the child, and their well-being being affected. While these spillover effects are important and recommended to be included in studies, they are usually partially included or not included at all. This would potentially underestimate the impact of the condition, such as the long-term family spillover effect that the family of children with CCCs face. Therefore, the objective of this study is to develop a best-worst scaling survey to explore what would be considered as important items when measuring family spillover effects for children with complex chronic condition. This is a part of a larger study where the final goal is to develop a core outcome set for measuring family spillover effects for children with complex chronic illness.

A best-worst scaling survey was developed for this study and was a part of the methodology developed by the COMET (Core Outcome Measures in Effectiveness Trials). Stakeholder meetings, pretests, and pilot tests of the best-worst scaling survey was conducted.

Based on the best-worst scaling survey results of 30 respondents, overall, items in the quality of life and time categories were chosen more frequently as relatively most impact on families of children with complex chronic condition, while items in the cost category were chosen more frequently as relatively least impact. The items that were chosen most frequently as relatively most impact include: “Quit jobs or did not pursue a job in order to care for the child”, followed by “Caregivers’ quality of life” and “Family member’s quality of life”.

The results of this study are important finding because these items are rarely collected in current studies. The next step would be to conduct additional pilot survey for different stakeholder population. The final COS can be used in clinical trials and registries or other observational studies to measure the substantial burden on the family for CCC. In addition, these measures can be incorporated into economic evaluations and/or used to develop family/caregiver interventions.

4.1 Introduction

Children with complex chronic conditions (CCCs) have medical conditions foreseen to be long-term (at least 12 months unless death intervenes) and have one of their organ systems severely affected or multiple affected that would require specialty pediatric care and hospitalization.[73, 74] CCCs is a classification system that was developed by Feudtner et al. to identify children facing higher mortality rates and would likely require greater medical care.[74] The prevalence rate of children with more than one CCCs is estimated to be around 1,200 to 1,938 per 100,000 persons.[75]

Due to the complexity in treatment, children with CCCs are less likely to have favorable health outcomes and often require more health care resources. This includes higher pediatric intensive care unit mortality and longer length of stay,[76] higher costs when undergoing surgery,[77] and a hospital costs of around $60,000 to $341,000 during the last year of life for those with life-threating complex chronic conditions.[78]

CCCs and associated treatments not only have impacts on the child various ways physically and mentally, but also have impact on the child's family, particularly the caregiver, which is often the parent or guardian of the child. These family caregivers are often the designated and only person to communicate with the healthcare professionals on behalf of the child, and, moreover, provide unpaid care, short term or long term.[79] Therefore, it is important to highlight the effects an ill child may have on their caregiver and family, physically, mentally, and financially. This is especially critical for the families of children with chronic complex conditions, where it is a relatively complicated treatment process, possibly across the child's lifespan.

The effects that a child's disease or condition has on their primary caregiver or family is known as family spillover effect. This typically include the direct effects on caregiver activities such as healthcare utilization, employment, and schooling outcomes, the informal caregiving time, and the effects on caregiver's quality-adjusted life-years (QALYs).[1]

One of the most important effects is the direct costs that are paid by the family and not covered by insurance, or in other words, out-of-pocket payments. According to the 2016-2017 National Survey of Children's Health, around 38% of families pay more than $250 out-of-pocket cost for one child's health care over the past year.[80] Of these families, 2% are paying more than $5,000, and with an estimation of population size around 1,410,000 people, it is estimate of at least $7 billion dollars spent per year out-of-pocket.[80] However, of these, around 30% of these are families with children with special health care needs (CSHCN) and more complex health needs.[80] This highlights the important financial impact this group has on family, as well as the potential long-term impact if the conditions were chronic.

Another important effect is the informal caregiving time provided by the primary caregiver and family members. In the United States, it is estimated that 18.2% or 43.5 million adults have provide unpaid care to any age of care receiver for the past 12 months, based on a survey collected in late 2014.[81] This points out the importance of family caregivers to our society, without them, the society would have to pay for the patient care needed at an extremely high price.

In addition, the impact of providing care to an ill family member on the quality of life of the caregivers and family members are also important family spillover effects. A recent literature review examined the spillover effects on the caregivers' and family member's utility and concluded that, based on 80 studies, generally, the reported utilities showed a loss in the quality

of life associated with the role as a caregiver or a family member of an ill individual.[82] This highlights the impact of caregiving have on the quality of life of the caregiver or family member.

While these spillover effects are important and had been recommended to be included in evaluating the value of new healthcare interventions or treatments, they are seldom included in studies.[1] This would potentially underestimate the impact of the condition, such as the long-term family spillover effect that the family of children with CCCs face. In economic evaluations studies for example, family spillover effects were recommended for inclusion by the first and second US Panel on Cost-Effectiveness in Health and Medicine.[83, 84] However, according to a review of pediatric cost-utility analysis studies by Lavelle et al,[85] the authors pointed out that the majority of studies included caregiving time costs, with a few including QALYs, and no studies incorporated all the possible family spillover effects: "*family QALY impacts, caregiving time costs, family out-of-pocket costs, and potential direct healthcare costs for a health condition, such as depression or anxiety, resulting from a family member's illness*".[85] It is important to include these effects as not including would potentially result in different conclusions.[85]

In addition, one of the challenges is defining the scope of effects being included.[1] For example, the spillover effects for children may be on the primary caregiver but could also further expand to their siblings and grandparents, or even beyond the family.[1, 86] When studies use different scope and outcome measures, this inconsistency in outcomes can be problematic when these data are used for decision making. For example, it is difficult to compare across studies when different outcome measures are used. Moreover, it may lead to potential bias as researchers can choose to report only the outcomes that support their hypotheses.[17] Developing a core

outcome set, which is a standardized set of outcomes that should be measured and reported in all studies in a given research area, reduces these problems.

There is currently no defined core outcome set for measuring family spillover effects for children with complex chronic conditions. Therefore, as a first step in developing a core outcome set for measuring family spillover effects for children with complex chronic conditions, the objective of this study is to develop a best-worst scaling survey to explore what would be considered as important items when measuring family spillover effects for children with complex chronic condition.

Best-worst scaling (BWS), a type of stated preference methods, was developed by Louviere in 1980s, where it is based on the concept that when people are asked to select among three or more options, they can identify the best and worst options.[18] Using this idea and through experimental design, the data from a BWS survey can generate information on the relative importance weights for a list of items of a particular individual, in other words, how the individual ranks the items in a particular list. There are three types of BWS, the object case (Case 1), the profile case (Case 2), and the multi-profile case (Case 3), and they differ in the level of information the researcher wish to obtain. For this study, the goal is to rank the list of outcome measures by their importance, therefore, the object case (Case 1) is used.

The study results obtained from the best-worst scaling survey would provide important information in developing the core outcomes set, which would provide a framework for incorporating family spillover effects into studies, such as in clinical trials or registries, as well as in economic evaluation studies.

4.2 Methods

This study uses the methodology developed by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative to develop the best-worst scaling survey in identifying what would be considered as important items when measuring family spillover effects for children with complex chronic condition, which is a part in developing the core outcome set (COS) in measuring family spillover effects for children with complex chronic conditions.[17] The COS development steps are shown in Figure 4.1 with a detailed description of the steps presented in Appendix Table 17. In addition, a systematic review protocol has been developed to review studies and provide data of potentially overlooked outcome measures (Appendix Table 19). This study has been registered at the COMET Initiative website, available at: https://www.comet-initiative.org/Studies/Details/1928.

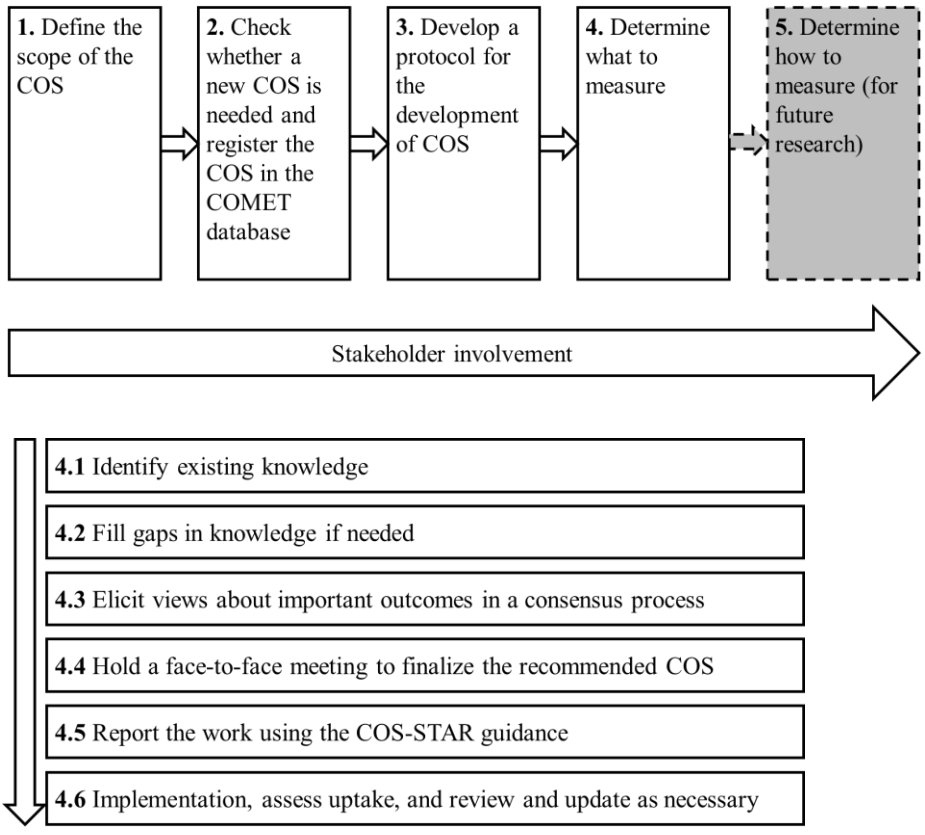


Figure 4.1 COS development steps developed by the COMET Initiative.

Stakeholder engagement was planned to be included throughout the study period. Key stakeholders listed in the COMET handbook include participants such as health service users, health care practitioners, trialists, regulators, industry representatives, policymakers, researchers, patients and public.[17] For this study, main stakeholder groups include members of the dissertation committee and the Outcomes Research Section faculty investigators at the Susan B. Meister Child Health Evaluation and Research (CHEAR) Center at the University of Michigan. The latter group consists of six pediatric subspecialists. Regular meetings were and will continue to be held throughout the study period for main stakeholders. Future meetings will include expert panels and the consensus meetings for finalizing the COS.

For the pilot survey phase, the main stakeholders stated above that were included. In addition, healthcare provider (e.g., physician, nurse, physician's assistant, nurse practitioner, care technician) in pediatric physician divisions at two hospitals in Michigan were invited to take the survey. Members of the Decision Sciences for Child Health Collaborative (DSCCo) were invited to take the survey as well. For future full field survey phase, potential survey groups such as the Courageous Parents Network, the Patient and Family Centered Care Program at C.S. Mott Children's Hospital, and the Partners for Children group at C.S. Mott Children's Hospital.

Following the COS development process, this study first identified a list of candidate outcome measures and then developed a best-worst scaling survey.

4.2.1 Identifying outcome measures: List of candidate outcome measures

The COMET initiative has developed a taxonomy that provides a comprehensive list of four core areas (38 categories) in which the outcome measures of interest may potentially be classified into.[87] The four core areas included: Death; physiological or clinical, life impact, resource use, and adverse events. However, the authors did note in their study that this taxonomy

relates to outcome measures measured at the individual patient level and does not intend to those measured at a broader level, such as family or community. Therefore, for this study, this taxonomy is used as a framework to identify the categories that are most relevant to our topic.

From the four core areas and 38 categories, we identified that the categories that were the most relevant to our study (Figure 4.2). A list of category definition is included in the Appendix Table 18.[87] We further group the identified categories into three main categories, including: A. Direct medical and non-medical costs that are borne by the family; B. Informal caregiving time, and C. Impact on family members' quality of life.

List of candidate outcome measures

As a base for our study, a list of candidate outcome measures items for each of the three category was derived from the study by Rose et al which surveys the family spillover effects of individuals with Phenylketonuria (PKU).[88] Based on the study, the following items (attributes) in each category have been identified as candidates of the core outcome set (Table 4.1).

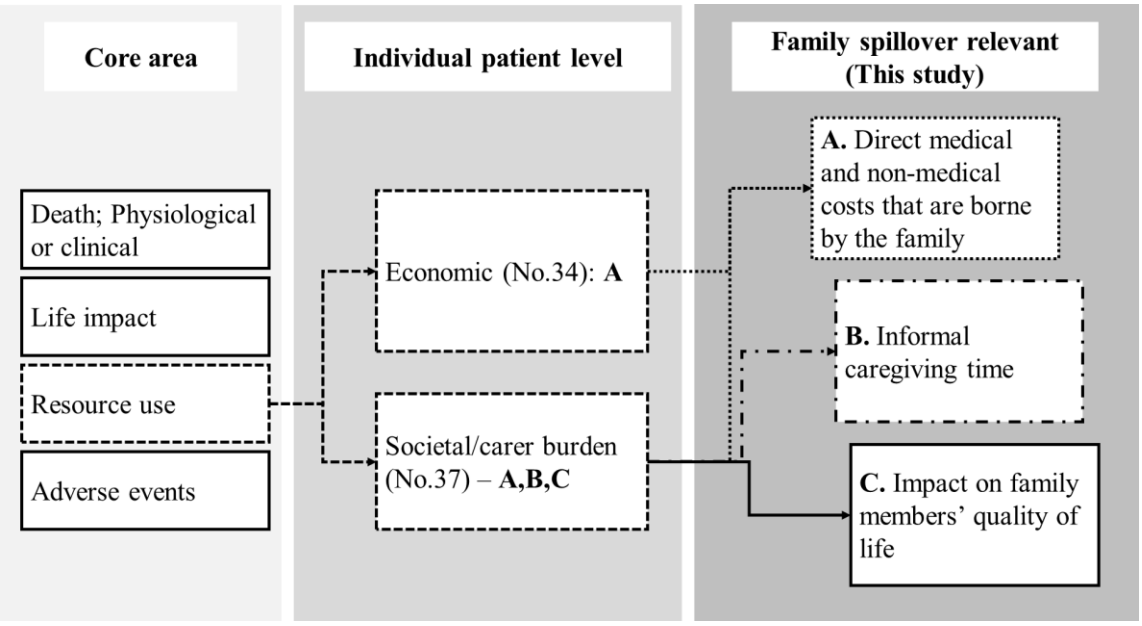


Figure 4.2 COMET initiative taxonomy of categories and this study

Table 4.1 List of candidate outcome measures

Item number	Item name	Definition
A. Direct medical and non-medical costs that are borne by the family		
1	Costs for medications	Out-of-pocket costs for your child's medicine. This includes the cost of over-the-counter, prescription, and infused medications as well as medical foods.
2	Costs for treatments	Out-of-pocket costs directly related to your child's treatments. This includes the cost of surgeries or procedures that help improve your child's condition.
3	Costs for doctor's visits	Out-of-pocket medical costs directly related to your child's specialist or primary care provider visits. This includes specialist visits required for diagnosis.
4	Costs for emergency room visits and hospitalizations	Out-of-pocket medical costs directly related to your child's emergency room visits and hospitalizations.
5	Costs for other medical visits	Out-of-pocket costs for other medical visits. This includes physical therapy, occupational therapy, speech therapy and counseling.
6	Costs for special equipment and supplies	Out-of-pocket costs of your child's special equipment and supplies directly related to your child's condition such as wheelchairs, bathroom equipment, and breathing machines (e.g., CPAP, nebulizers).
7	Costs related to travel to medical visits and hospitalization	Out-of-pocket non-medical costs directly related to your child's medical visits and hospitalizations including gas, parking, hotel stays, and meals.
8	Costs related to household renovations for your child's condition	Out-of-pocket non-medical costs spent on household modifications and renovations directly related to your child's condition such as ramps and enlarged doorways.
9	Costs of extra daily household supplies	Out-of-pocket non-medical costs spent on extra daily household supplies directly related to your child's condition such as extra toilet paper, cleaning supplies, diapers etc.
10	Costs of childcare	Out-of-pocket costs of childcare for other children in your household so that you can take your child to their medical appointments, ER visits, and hospitalizations.
B. Informal caregiving time		
11	Time spent at treatment-related visits	Caregiver time spent for your child's treatment-related medical visits, including the time spent traveling and waiting for the visit.

12	Time spent at doctor's visits	Caregiver time spent related to your child's specialist and primary care provider visits, including the time spent traveling and waiting for the visit. This includes time spent at specialist visits required for diagnosis.
13	Time spent at emergency room visits and hospitalizations	Caregiver time spent related to your child's emergency room visits and hospitalizations including the time spent traveling and waiting in the emergency room.
14	Time spent at other medical visits	Caregiver time spent related to your child's physical therapy, occupational therapy, speech therapy and counseling, including the time spent traveling and waiting for the visit.
15	Time spent coordinating your child's care	Caregiver time spent coordinating your child's care including contacting the insurance company, care coordinator, doctor's office, school, child care provider, and pharmacy.
16	Extra caregiving time spent caring for your child	Caregiver time spent on providing extra care related to your child's condition when compared to other children of same age.
17	Days of missed work in order to care for your child	Missed workdays spent on care of your child. This includes days of missed work by any caregiver in the household.
18	Quit jobs or did not pursue a job in order to care for your child	Quitting a job or deciding not to pursue a job to provide care for your child. This includes jobs quit by any caregiver in the household.
19	Reduced hours of paid work in order to care for your child	Reducing hours of paid work to provide care of your child. This includes a reduced work schedule for any caregiver in the household.
C. Impact on family members' quality of life.		
20	Caregivers' quality of life	Your physical, mental, and social health.
21	Family member's quality of life	The quality of life of other family members, such as siblings. This includes your family member's physical, mental, and social health.

4.2.2 Best-worst scaling survey

Expert panels were held for discussions of the list of candidate outcome measures and the development of the best-worst scaling survey. The best-worst scaling survey is used to explore the ranking of the items in the list of candidate outcome measures based on their importance by a broader stakeholder group. This study has yet to conduct the full field survey and consensus meeting to finalize the COS.

Stated preference methods - best-worst scaling survey

To design the BWS survey, a list of relatively essential outcome measures (objects/attributes) is generated. The outcome measures on this list are then put into different choice sets, and each choice set is a BWS task where the survey participant will choose the best and the worst option in each set. For this study, there are a total of 21 items. To generate the set of BWS tasks, this study used the balanced incomplete block designs (BIBDs) to determine the number choice sets. BIBDs is a design that takes the considers the number of objects, number of sets, number of occurs, set size, and co-occurs of each item, thus preventing the survey and number of tasks being too long or unrealistic to complete.[18] This study used a design of that includes 21 items, and 21 questions, which each question consisted of 5 items, and each items occurs 5 times and co-occurs with other items 1 time. To reduce the cognitive loading of respondents taking the survey, the original survey with 21 questions was randomized to three different versions of the surveys where each version included 7 questions and adjusted (exchanging 1 choice set in version 1 with 1 choice set version 2) so that 21 items occur at least once in each version.

Table 4.2 illustrates an example task derived from the survey of this study. In this survey, the respondents are asked to imagine themself in the role of the parent of a child with a complex

chronic condition. If they have a child with a severe health condition, they are asked to consider that child as they complete the survey. In each question, they are asked the following: "Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) Most impact and (2) Least impact on you and your family?" Additional questions asking the respondents characteristics, such as age and gender, and experiences with the survey were included as well. The full survey is shown in Appendix Section 21.

Table 4.2 Example survey BWS task

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) Most impact and (2) Least impact on you and your family?		
Most impact (select one)	Items	Least impact (select one)
□	Quit jobs or did not pursue a job in order to care for your child	□
□	Reduced hours of paid work in order to care for your child	□
□	Costs of extra daily household supplies	□
□	Costs related to household renovations for your child's condition	□
□	Costs for treatments	□

Survey administration – pilot survey

This survey has received UM IRB approval for exemption: IRB#HUM0019875. While there is not a formally established method in calculating the minimum required sample size for BWS and at the individual level, there are ways of estimation in other stated preference methods.[89, 90] Therefore, the sample size of this study is estimated using these methods as well as considering factors such as the BWS survey design, way of selecting sample, and budget. For survey development, a total of 10 pre-tests were completed for the survey. The pilot survey

period was from November 11, 2021, to December 2, 2021, and a total of 30 respondents were included in the final data analysis.

For the pilot survey phase, the focus is on two main stakeholder groups as recommended by the COMET handbook[17]: health care partitioners and researchers. This included the main stakeholders in this study as well as healthcare providers (e.g., physician, nurse, physician's assistant, nurse practitioner, care technician) in pediatric physician divisions at two hospitals in Michigan were invited to take the survey. Members of the Decision Sciences for Child Health Collaborative (DSCCo), where consists of mostly health care practitioners and researchers, were invited to take the survey as well. For future next steps, other stakeholder groups such as health service users, trialists, regulators, industry representatives, policymakers, patients and public, will considered for additional pilot study and full field survey phase. Potential survey groups include groups such as the Courageous Parents Network, the Patient and Family Centered Care Program at C.S. Mott Children's Hospital, and the Partners for Children group at C.S. Mott Children's Hospital.

4.2.3 Data analysis

The results of the best-worst scaling pilot survey include the characteristics of the respondents, the results of the best-worst scaling survey, and the respondents' experience of survey. For the data analysis of the best-worst scaling survey, various methods that can be used, common methods include count analysis, multinomial logit model, mixed logit model, latent class analysis, and hierarchical Bayes estimation.[18, 91, 92] The primary outcome of this study is the count analysis for the survey respondents (N=30), which ranks the items (outcome measures) based on the final score that reflects the frequency of times an outcomes was selected

as most or least impact. The final score is calculated as the count of each item selected as most impact minus the count of each item selected as least impact.

In addition to count analysis, conditional (multinomial) logistic (MNL) regression model was conducted. This was done by combining the dataset of 30 respondents into a combined dataset of 9 synthetic respondents. This was needed for the BIBD design for the survey in which the respondents only received a subset of the total best-worst scaling questions. This combined dataset included what each synthetic respondent selected as best and worst for each question. Using this combined dataset and the BIBD dataset, a new simulated dataset with 3781 observations was generated for the MNL model. An example of this simulated dataset is in Appendix Table 20 (Table 21a). The analysis was performed using the support.BWS package in R software.[93, 94], the key R code are included in Appendix Table 20 as well. However, given the small sample size and high similarity of the respondents, the results are limited, and therefore, the results are included in Appendix Table 20 for additional reference.

The survey was developed and coded in R Statistical Software version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) and Qualtrics software versions October to December 2021 (Qualtrics, Provo, UT). Analyses were performed using R Statistical Software version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel Version 2110 (Microsoft Corporation, USA).

4.3 Results

This section presents the results of the pilot survey, including the characteristics of the respondents, the results of the best-worst scaling survey, and the respondents' experience of survey.

4.3.1 Pilot survey results: respondents characteristics

The respondents' characteristics for the pilot study of the best-worst scaling survey are shown in Table 4.3. A total of 30 respondents completed the survey, the number of respondents that took the first, second, and third version of the survey were 11, 9, and 10 respondents, respectively. For their connection to children with CCC, around 70% were healthcare providers, and 13% did not know a child with CCC, while around 9% was an affected individual or family member.

The mean age of the respondents were 40.3 years old and 77% were female, with the other 23% male. The majority of race/ethnicities were white (83%) followed by 7% of Asian and another 7% choosing not to disclose, and 97% of the respondents' native language was English. Nearly all of the respondents completed graduate/professional training and are employed full-time (both at 97%). The majority (87%) of the respondents also had a total household income of more than $100,000 that supplied a mean of 3 people. Around 80% of the respondents are married and around half of the respondents has children under 18 years old in their household with a mean of 2 years old. All of the respondents were covered by private insurance, with 13% having self-pay or out-of-pocket for doctor's visits and health care. For those with children, their child's health care expenses were mostly paid through private insurance and self-pay or pay out-of-pocket as well.

Table 4.3 Pilot survey results: respondents characteristics

Respondent's characteristics	All (N=30)	Percentage or Range
Current connection to children with CCC		
Healthcare provider	21	70%
I don't know a child with complex chronic conditions	4	13%
Affected individual or family member	1 [b]	3%
Childcare provider	1	3%
Other professional	1	3%
Affected individual or family member; Healthcare provider	1 [c]	3%
Affected individual or family member; Other professional	1 [a]	3%
Other choice options: Patient or family advocacy, resource, or support organization member or leader; Teacher; Physical, occupational, or speech therapist; Counselor	0	0%
Type of CCC for affected individual or family member: [a] Cerebral palsy (self), cancer (family member); [b] Developmental delay, consequences of prematurity; [c] Family with cerebral palsy, cancer, Crohn's disease		
Age (mean)	40.3	30 – 67
Gender		
Female	23	77%
Male	7	23%
Other choice options: Transgender; Gender-variant or gender-nonconforming; Prefer not to disclose; Prefer to self-describe:	0	0%
Races/ethnicities		
White	25	83%
Asian	2	7%
Prefer not to disclose	2	7%
Prefer to self-describe:	1 [d]	3%
Other choice options: American Indian or Alaska Native; Black or African American; Hispanic or Latino; Native Hawaiian or Pacific Islander	0	0%
[d] Arab-American		
Native language		
English	29	97%
Other (Please specify):	1 [e]	3%
Other choice options: Spanish; Mandarin; Hindi; Arabic	0	0%
[e] Russian		
Highest level of education		
Completed graduate/professional training	29	97%
4-year college or university graduate	1	3%

Other choice options: Less than 7th grade; Completed more than 7th grade, but did not graduate high school; High school graduate; Some college or at least one year of specialized training	0	0%
Current primary employment status		
Employed full-time	29	97%
Stay-at-home parent	1	3%
Other choice options: Employed part-time; Out of work and looking for work; Out of work but not currently looking for work; Student; Military; Retired; Unable to work	-	-
Total household income before taxes in 2020		
More than $100,000	26	87%
More than $75,000 up to $100,000	2	7%
More than $25,000 up to $50,000	1	3%
More than $50,000 up to $75,000	1	3%
$25,000 or less	0	0%
Including respondent, number of people that income support in 2020 (mean)	3.0	1 – 8
Marital status		
Married or living with partner	24	80%
Single	6	20%
Other choice options: Divorced or separated; Widowed	0	0%
Have children under 18 years old in household		
Yes	16	53%
No	14	47%
How many children under 18 years old are in household (mean)	2.1	1 – 7
How doctor's visits and other health care paid for		
Private insurance (e.g., HMO, PPO, POS, etc.)	26	87%
Private insurance (e.g., HMO, PPO, POS, etc.); Self-pay or out-of-pocket	4	13%
Other choice options: Public insurance (e.g., Medicaid, Medicare, CHIP); Children's Special Health Care Services; Self-pay or out-of-pocket; Other (Please explain):	0	0%
If respondents have children, how are their children's doctor's visits and other health care paid for		
Private insurance (e.g., HMO, PPO, POS, etc.)	16	53%
I don't have children	10	33%
Private insurance (e.g., HMO, PPO, POS, etc.) AND Self-pay or out-of-pocket	3	10%
Other (Please explain):	1 [f]	3%
Other choice options: Public insurance (e.g., Medicaid, Medicare, CHIP); Children's Special Health Care Services; Self-pay or out-of-pocket	0	0%

[f] My children are adults and they have their own insurance

4.3.2 Pilot survey results: best-worst scaling results

In the best-worst scaling survey, the respondents were asked to select the items that they thought had the relatively most impact and relatively least impact on the family of children with complex chronic condition (For simplicity, "most impact/best" and "least impact/worst" will be used hereafter, however, these are still relatively most impact and relatively least impact). The results from the pilot survey are shown in Table 4.4 and Figure 4.3.

As shown in Table. 4.4, for the results of all 30 respondents, among the categories of cost, time, and quality of life of the items, overall, items in the quality of life and time categories were chosen more frequently as most impact, while items in the cost category were chosen more frequently as least impact. Shown in Figure 4.3 as well, "Quit jobs or did not pursue a job in order to care for the child" was the item with the highest frequency chosen as most impact. This was followed by "Caregivers' quality of life" and "Family member's quality of life".

Both of the items in the quality of life category were selected most frequently. Items in the time category were next. Among the items in the time category, items that affected the respondent's work and spending time taking of child were chosen more frequently as most impact, while items related to visits were chosen more frequently as less impact. On the other hand, items in the cost category were more frequently selected as less impact overall. Among the items in the cost category, "Costs for emergency room visits and hospitalizations" and "Costs related to household renovations for the child's condition" were more frequently selected as more impact, compared to items that were related to costs for visits or extra daily household supplies.

Table 4.4 Pilot survey results: best-worst scaling results

Item	Best (B)/Most impact	Worst (W)/Least impact	Best-Worst	Rank	Standardized B-W*	Square root of B/W	Mean B-W	Category
Quit jobs or did not pursue a job in order to care for the child	30	2	28	1	0.19	3.87	0.93	time
Caregivers' quality of life	23	4	19	2	0.13	2.40	0.63	Quality of life
Family member's quality of life	23	5	18	3	0.12	2.14	0.60	Quality of life
Extra caregiving time spent caring for child	21	4	17	4	0.11	2.29	0.57	time
Days of missed work in order to care for the child	18	1	17	5	0.11	4.24	0.57	time
Reduced hours of paid work in order to care for child	13	1	12	6	0.08	3.61	0.40	time
Time spent at emergency room visits and hospitalizations	16	4	12	7	0.08	2.00	0.40	time
Time spent coordinating the child's care	17	6	11	8	0.07	1.68	0.37	time
Costs for emergency room visits and hospitalizations	9	6	3	9	0.02	1.22	0.10	costs
Costs related to household renovations for the child's condition	10	12	-2	10	-0.01	0.91	-0.07	costs
Time spent at treatment-related visits	3	5	-2	11	-0.01	0.77	-0.07	time
Time spent at doctor's visits	7	13	-6	12	-0.04	0.73	-0.20	time
Costs for special equipment and supplies	2	11	-9	13	-0.06	0.43	-0.30	costs
Costs of childcare	2	11	-9	14	-0.06	0.43	-0.30	costs
Time spent at other medical visits	4	13	-9	15	-0.06	0.55	-0.30	time
Costs for treatments	3	13	-10	16	-0.07	0.48	-0.33	costs
Costs for medications	2	16	-14	17	-0.09	0.35	-0.47	costs
Costs for other medical visits	0	14	-14	18	-0.09	0.00	-0.47	costs
Costs for doctor's visits	4	19	-15	19	-0.10	0.46	-0.50	costs
Costs related to travel to medical visits and hospitalization	1	22	-21	20	-0.14	0.21	-0.70	costs
Costs of extra daily household supplies	2	28	-26	21	-0.17	0.27	-0.87	costs

*Calculated by dividing B minus W score with the product of frequency of occurrence of the item*sample size, see Mühlbacher et al. (2016) for more information.

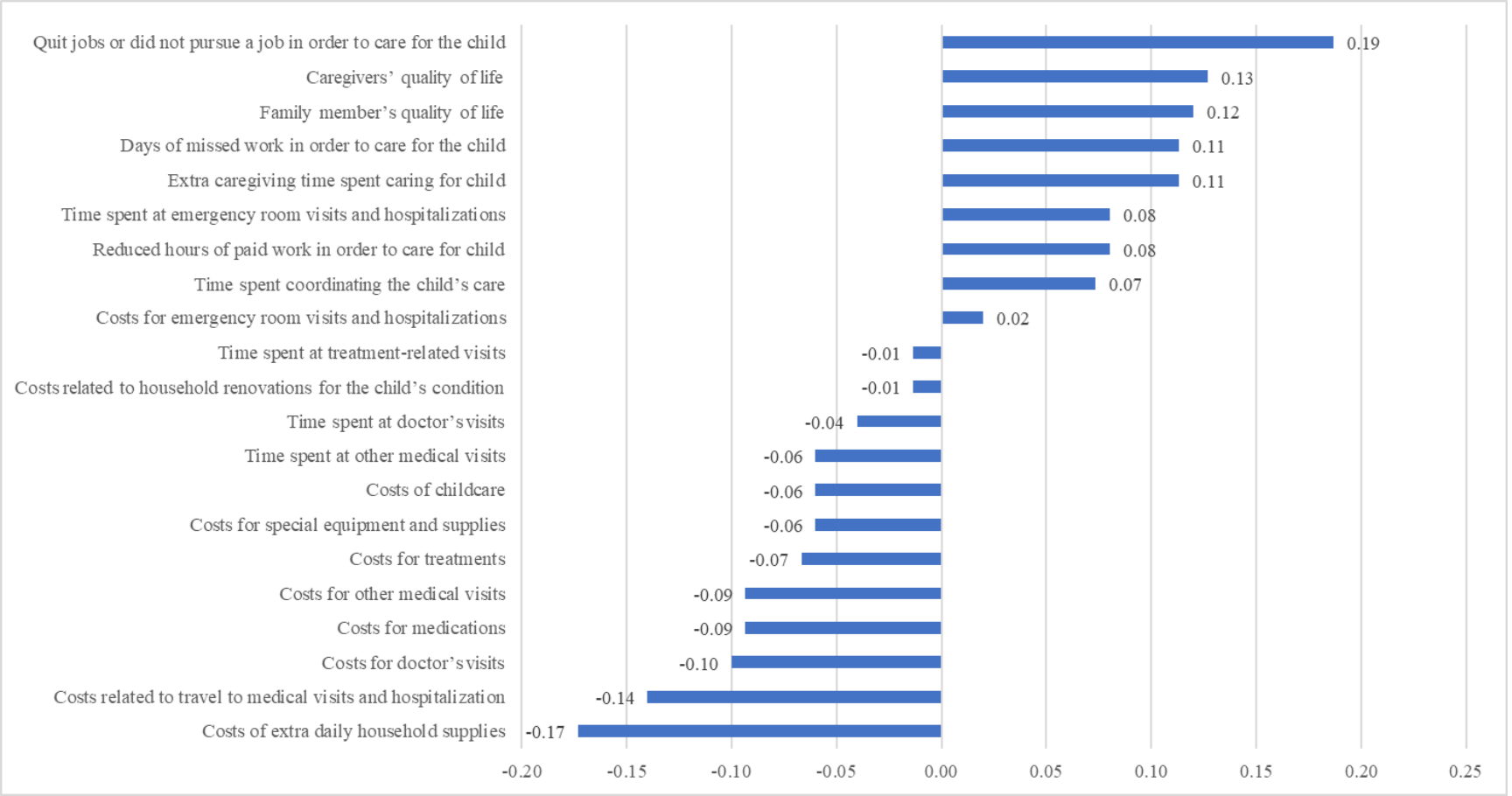


Figure 4.3 Pilot survey results: best-worst scaling results: standardized best-worst scores

4.3.3 Pilot survey results: respondents' experience of survey

The respondents were also asked questions regarding their experiences while taking the survey (Table 4.5). Based on the results, 63% felt they were somewhat confident in answering the questions, while 13% were very confident, and 23% not confident. Those who answered not confident were followed up and asked for the reason. Among these respondents, 43% had specific reasons revolving around the imagining of the scenario, while 29% felt there were too much information to consider in each question and 29% other felt they needed more information about the terms. Additional feedback on several challenges were also brought up as well, such as the difficulty of comparing "family members' quality of life" to the rest of the items, comparing between cost items, as well as comparing lost time to lost productivity.

Table 4.5 Pilot survey results: respondents' experience of survey

	All (N=30)	**Percentage**
How confident are you in your answers to the questions?		
Somewhat confident	19	63%
Not confident	7	23%
Very confident	4	13%
They were total guesses	0	0%
Please indicate the most important reason that you were not confident in your answers to these questions		
other (please specify)	3 [a, b, c]	43%
There was too much information to consider in each question	2	29%
I felt like I needed more information about the terms	2	29%
The items were too hard to imagine	0	0%
I did not understand what was being asked	0	0%
[a] Not sure because I am a provider [b] I struggle with hypotheticals [c] Because I am imagining the scenarios, it can imagine the impacts to be very different for each family		
Do you have any additional thoughts about the survey you would like to share?		
If this took a long time, sorry I got distracted the survey wasn't that long		
It is hard to rank other people's quality of life compared to any other item listed		
Comparing costs- it was hard to determine which was more important without knowing the amount of money that would be paid out of pocket, I think the dollar amount and not what it is associated with is most important. Also comparing lost time to lost productivity – lost time often translates into lost productivity, but it was not clear if this relationship should be assumed based on the descriptions of the attributes.		

4.4 Discussion

Based on the best-worst scaling survey results of 30 respondents, overall, items in the quality of life and time categories were chosen more frequently as relatively most impact on families of children with complex chronic condition, while items in the cost category were chosen more frequently as relatively least impact. The items that were chosen most frequently as relatively most impact include: “Quit jobs or did not pursue a job in order to care for the child”, followed by “Caregivers’ quality of life” and “Family member’s quality of life”.

This result may be representing a limited group of respondents. For example, the costs items are selected as relatively least impact on the family, and possible reasons might be that this group of respondents 100% have private insurance. In addition, 97% of them are employed full-time and 87% have total household income of more than $100,000, and therefore, work and time related items in the time category might have more impact than items in the cost category.

In addition, the results from the multinomial logit regression model were similar to the results from the count analysis based on the data of 30 respondents, where the items in the quality of life and time categories were more frequently chosen as most impact when compared to items in the cost categories (Appendix Table 20). However, given the small sample size of only 9 synthetic respondents combined and high similarity of the respondents, this result only provides limited information. Further collection of data is needed to address this question.

A limitation to this pilot survey is that the respondents are less diverse in characteristics, for example, 77% are female, 83% are white, 97% has English as their native language, and 97% competed graduate/professional training, and 97% are also employed full-time with 87% with a total household income of more than $100,000. In addition, 100% of them have private

insurance. This limits the generalizability of the results of this survey, and future steps to include a larger survey sample and more diverse population should be taken.

For next steps, this study will conduct additional pilot studies for different stakeholder groups, full field study and based on the results from the best-worst scaling survey, consensus meetings with the key stakeholders will be held to finalized core outcome set. A few important issues will also be incorporated into the consideration of the samples for future pilot and full field survey studies. This includes the issues of gender differences in caregiving,[95] differences among one caregiver and two caregivers (for example, married couple), the readability and health literacy differences among different stakeholder groups

In addition, the final results of this study will be reported using the COS-STAR guidance.[16] The results are planned to be disseminated through journal publication as well as presenting the results at different platforms such as conferences. The results will be available in the COMET database where it will be available for implementation. The authors will also consider assessing the uptake of COS as well as review and update the COS as necessary. This study will determine a standardized core outcome set of outcomes that should be measured and reported for all studies of family spillover effects for children with complex chronic conditions. This would provide a framework for studies to incorporate family spillover effects, which could be included in clinical trials or registries, as well as in economic evaluation studies.

The results of this study are important finding because these items are rarely collected in current studies. The final COS can be used in clinical trials and registries or other observational studies to measure the substantial burden on the family for CCC. These measures can be incorporated into economic evaluations and/or used to develop family/caregiver interventions.

4.5 Conclusion

Based on the best-worst scaling survey results of 30 respondents, overall, items in the quality of life and time categories were chosen more frequently as relatively most impact on families of children with complex chronic condition, while items in the cost category were chosen more frequently as relatively least impact. The items that were chosen most frequently as relatively most impact include: “Quit jobs or did not pursue a job in order to care for the child”, followed by “Caregivers’ quality of life” and “Family member’s quality of life”.

Chapter 5 Conclusion

In this dissertation, the following research questions were explored: (1) Is newborn screening and treatment for spinal muscular atrophy considered cost-effective? (2) What is the budget impact of newborn screening and treatment for spinal muscular atrophy from the perspective of the Medicaid/CHIP program in Michigan? (3) What are the most important items when measuring family spillover effects for children with complex chronic conditions from an economic perspective?

First, whether newborn screening and treatment for spinal muscular atrophy considered cost-effective, the results showed that when compared with clinical identification strategies, newborn screening with gene therapy, onasemnogene abeparvovec-xioi, had an incremental cost-effectiveness ratio of $103,669/QALY, which is considered favorable under conventional willingness-to-pay thresholds, while newborn screening with drug, nusinersen, did not.

Next, the budget impact on the Medicaid/Children's Health Insurance Program if implemented the strategy of newborn screening with onasemnogene abeparvovec-xioi started at an estimation of $12 million in the first year and decreased to $7 million in the fifth year. Over a five-year period, the budget impact is projected to be $48 million, with a potential range between $21 million to near $100 million using alternative assumptions.

Finally, based on the best-worst scaling survey results of 30 respondents, overall, items in the quality of life and time categories were chosen more frequently as relatively most impact on families of children with complex chronic condition, while items in the cost category were chosen more frequently as relatively least impact. The items that were chosen most frequently as

relatively most impact include: “Quit jobs or did not pursue a job in order to care for the child”, followed by “Caregivers’ quality of life” and “Family member’s quality of life”.

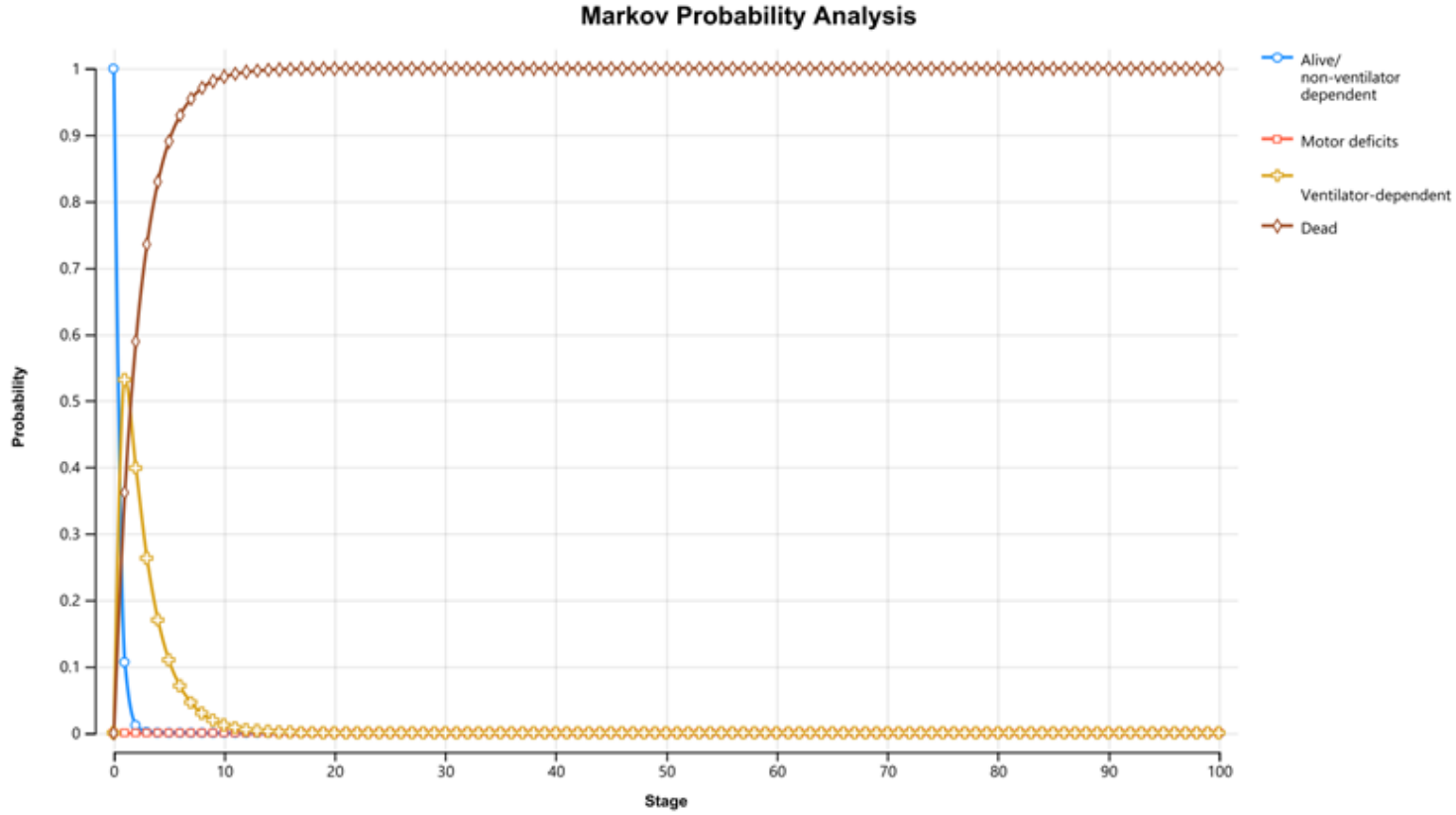
Appendix

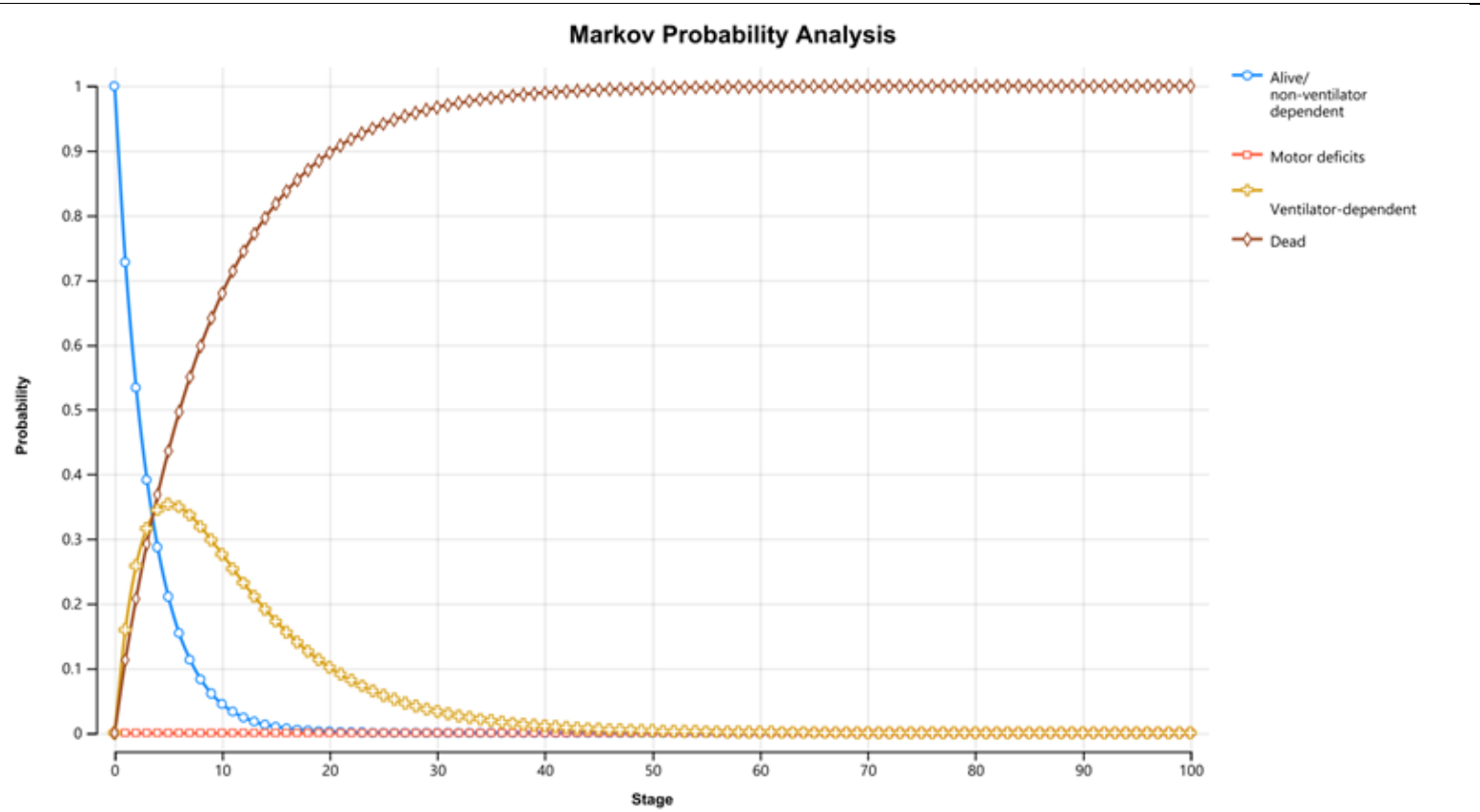
Appendix Table 1. Life table for the total population: United States, 2018 (CEA)

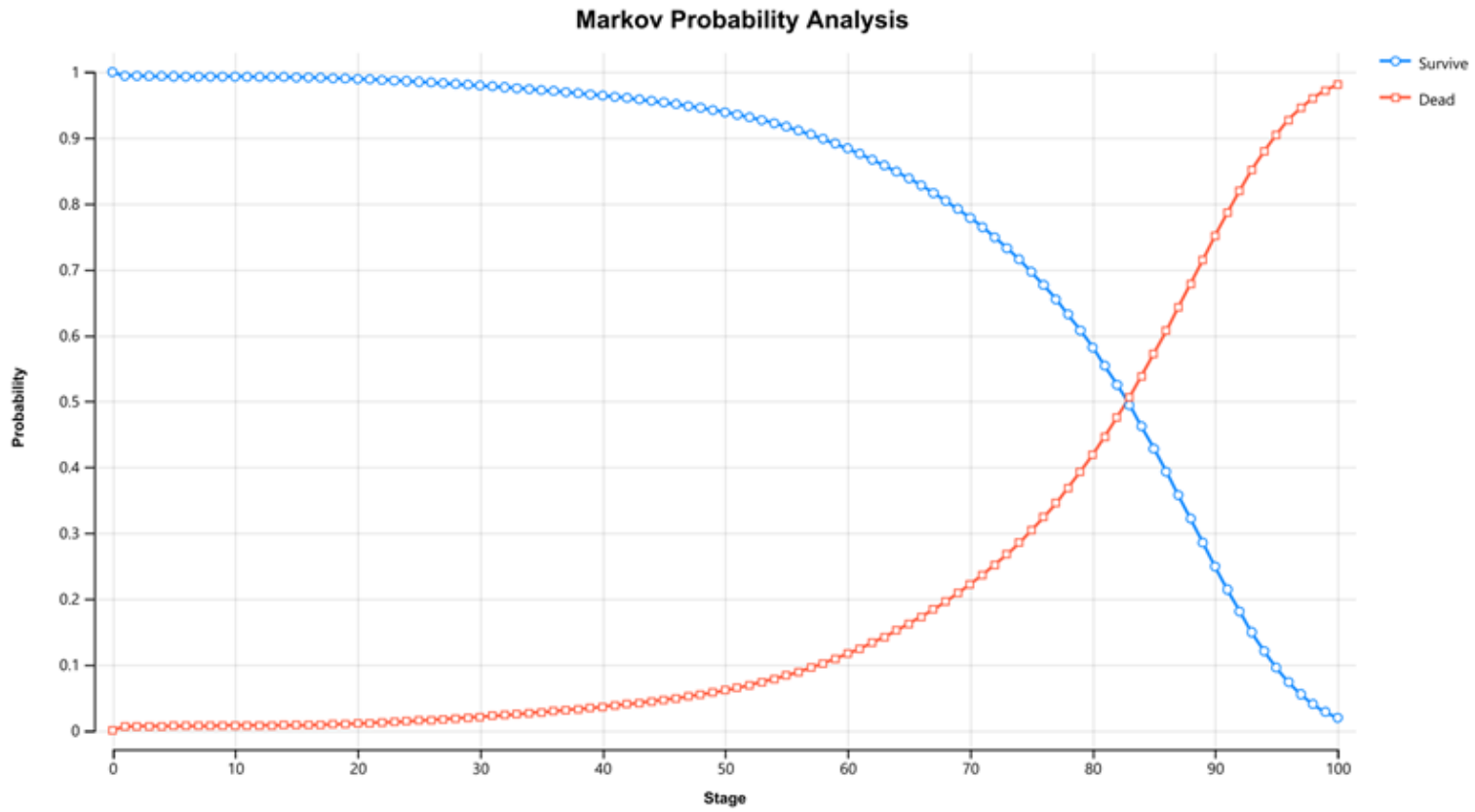
Age	Mortality	Age	Mortality	Age	Mortality
0–1	0.00565	34–35	0.00154	68–69	0.01572
1–2	0.00037	35–36	0.00161	69–70	0.01700
2–3	0.00026	36–37	0.00169	70–71	0.01839
3–4	0.00019	37–38	0.00175	71–72	0.01983
4–5	0.00015	38–39	0.00181	72–73	0.02191
5–6	0.00014	39–40	0.00186	73–74	0.02380
6–7	0.00013	40–41	0.00193	74–75	0.02619
7–8	0.00011	41–42	0.00202	75–76	0.02869
8–9	0.00010	42–43	0.00214	76–77	0.03179
9–10	0.00009	43–44	0.00229	77–78	0.03514
10–11	0.00009	44–45	0.00246	78–79	0.03867
11–12	0.00010	45–46	0.00265	79–80	0.04275
12–13	0.00013	46–47	0.00286	80–81	0.04720
13–14	0.00018	47–48	0.00309	81–82	0.05260
14–15	0.00025	48–49	0.00335	82–83	0.05859
15–16	0.00033	49–50	0.00364	83–84	0.06512
16–17	0.00041	50–51	0.00395	84–85	0.07340
17–18	0.00049	51–52	0.00430	85–86	0.08164
18–19	0.00058	52–53	0.00471	86–87	0.08981
19–20	0.00066	53–54	0.00519	87–88	0.10090
20–21	0.00075	54–55	0.00570	88–89	0.11308
21–22	0.00084	55–56	0.00622	89–90	0.12641
22–23	0.00091	56–57	0.00674	90–91	0.14090
23–24	0.00098	57–58	0.00728	91–92	0.15658
24–25	0.00103	58–59	0.00785	92–93	0.17342
25–26	0.00107	59–60	0.00845	93–94	0.19140
26–27	0.00112	60–61	0.00911	94–95	0.21044
27–28	0.00116	61–62	0.00979	95–96	0.23047
28–29	0.00121	62–63	0.01049	96–97	0.25134
29–30	0.00126	63–64	0.01119	97–98	0.27293
30–31	0.00131	64–65	0.01192	98–99	0.29505
31–32	0.00136	65–66	0.01269	99–100	0.31752

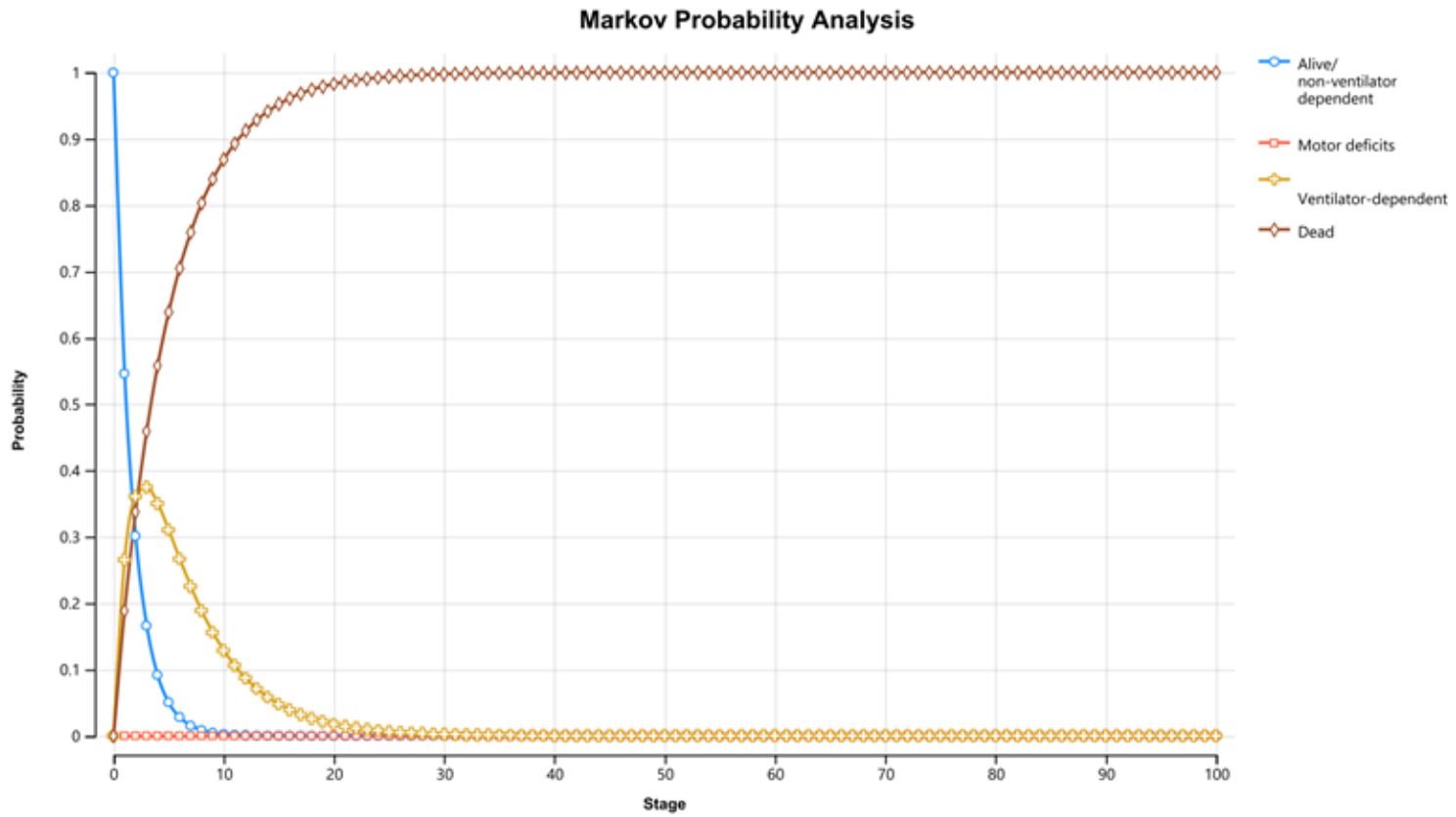
32–33	0.00141	66–67	0.01361	100+	1.00000
33–34	0.00147	67–68	0.01461		
Data source: [55]					

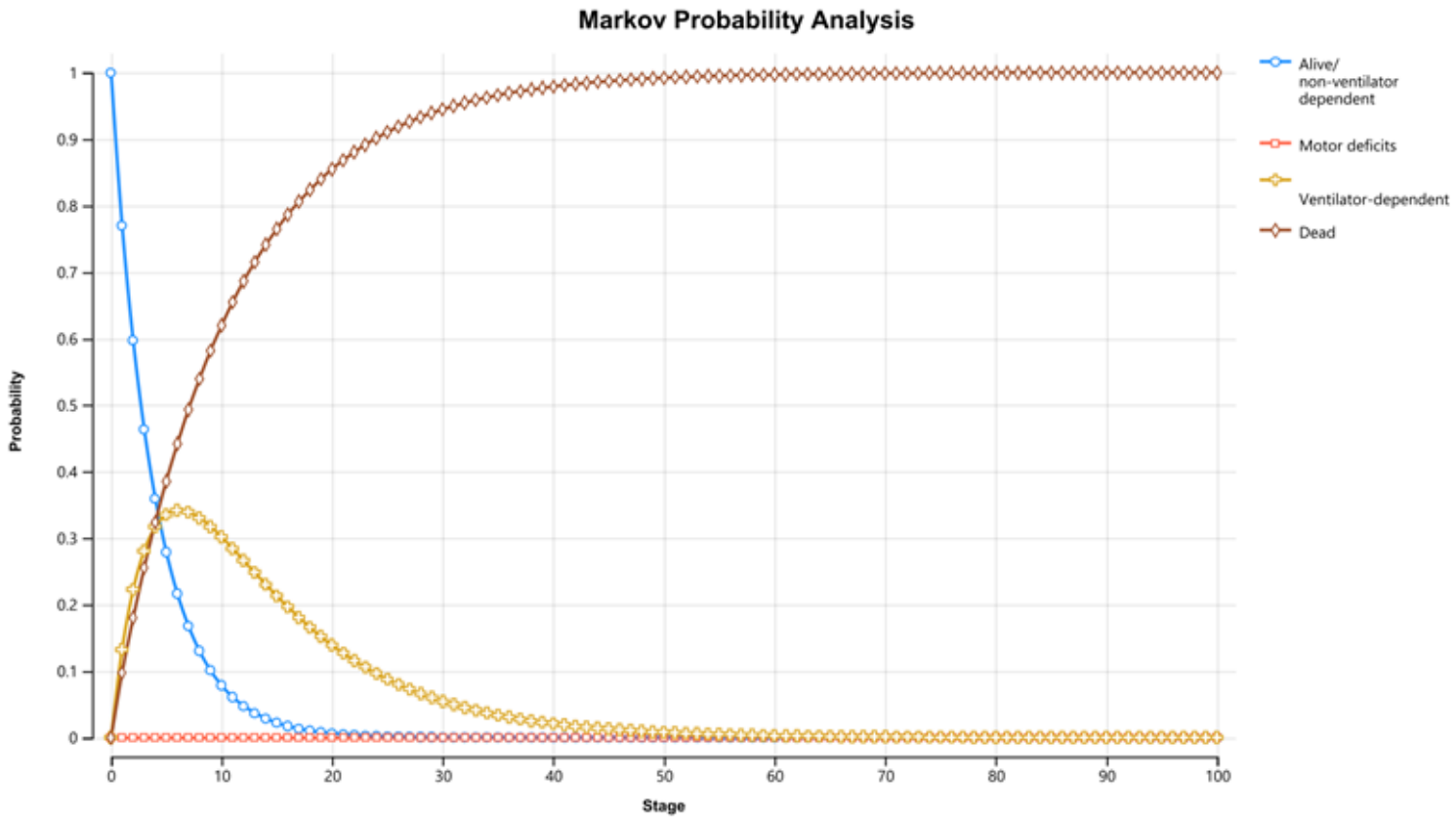
Appendix Table 2. Lifetime trajectories of submodels

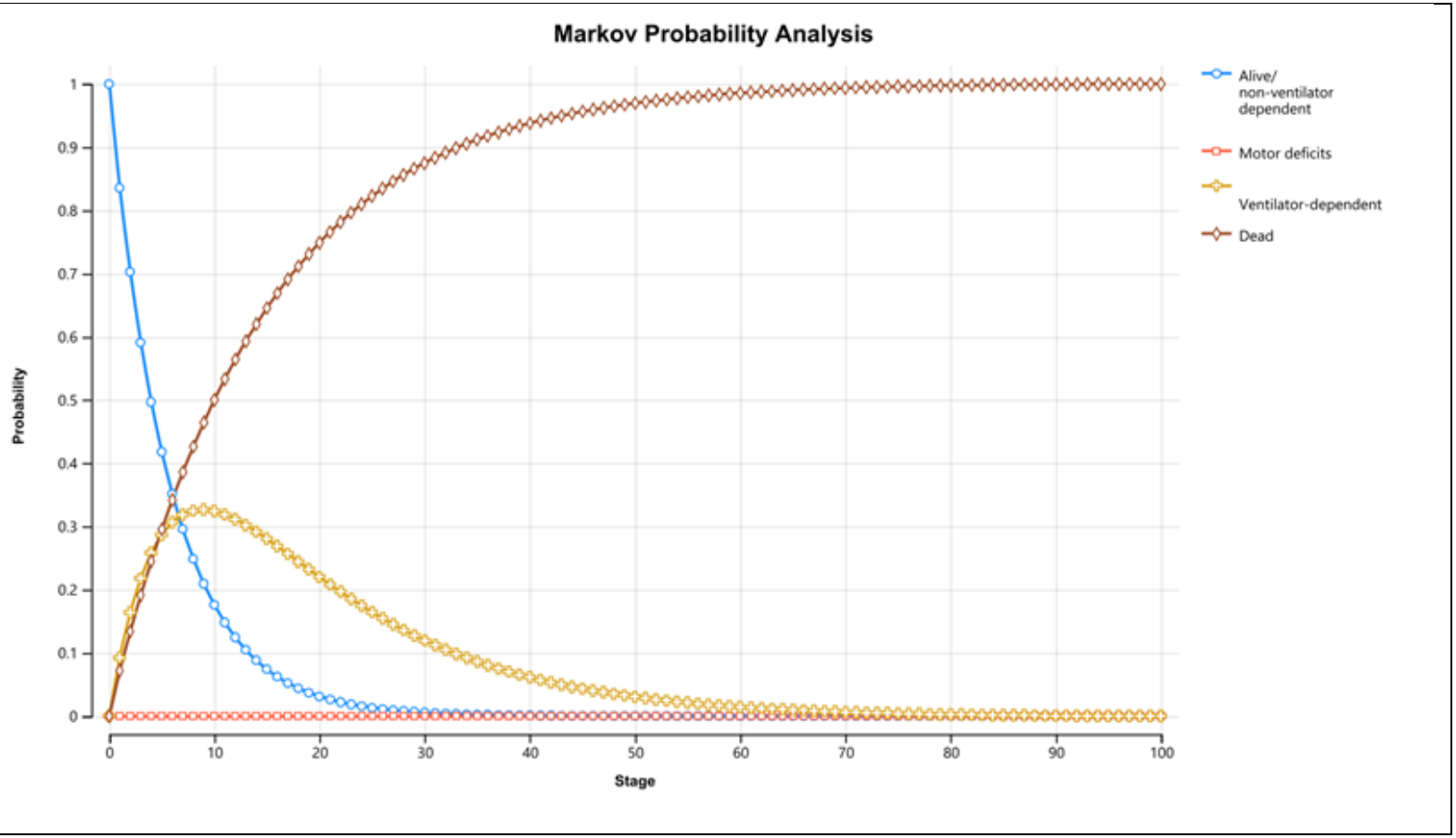
A. Clinical Identification strategies	
A1. CI/Usual care – type 1 and 0	

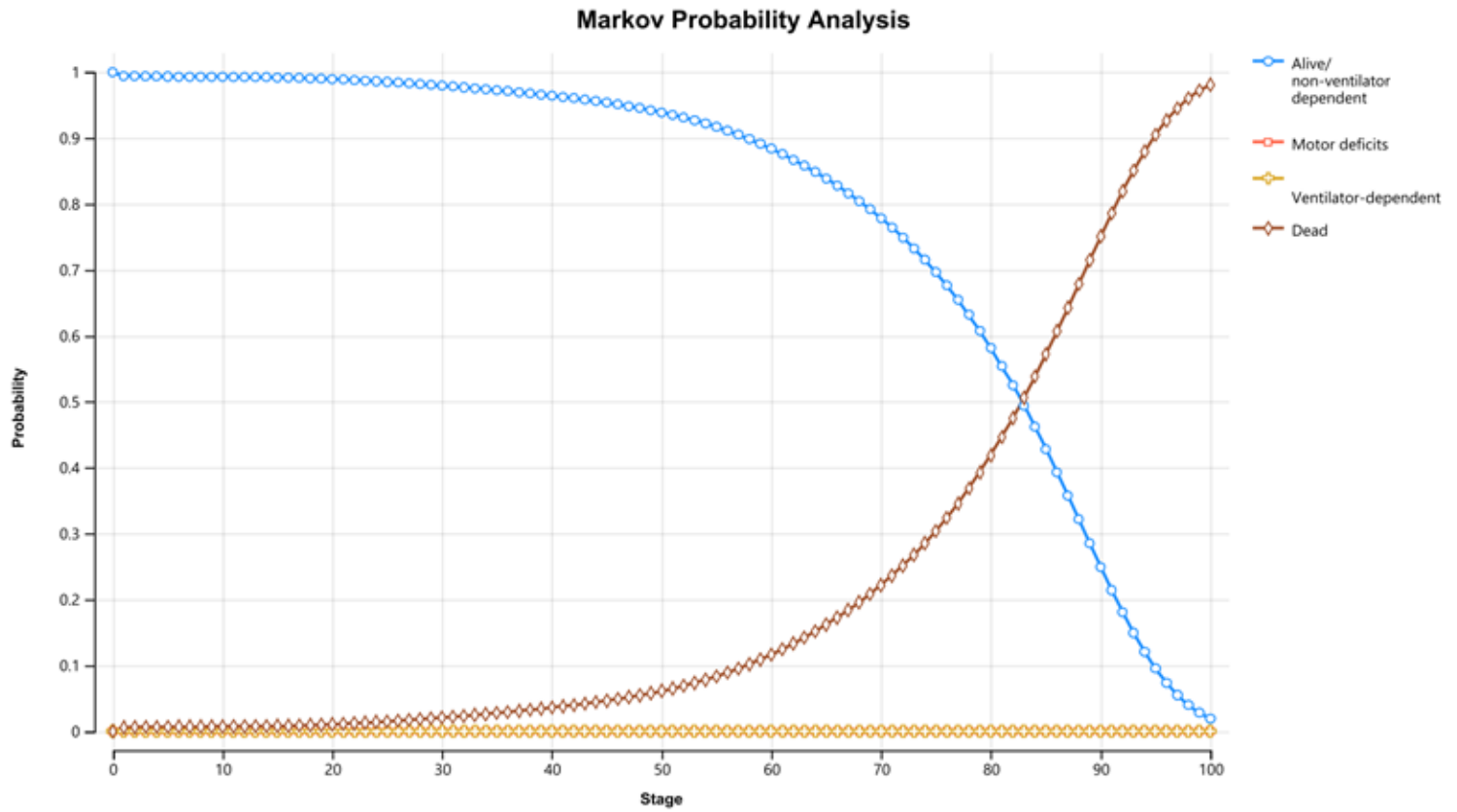
A2. CI/Usual care - type 2	

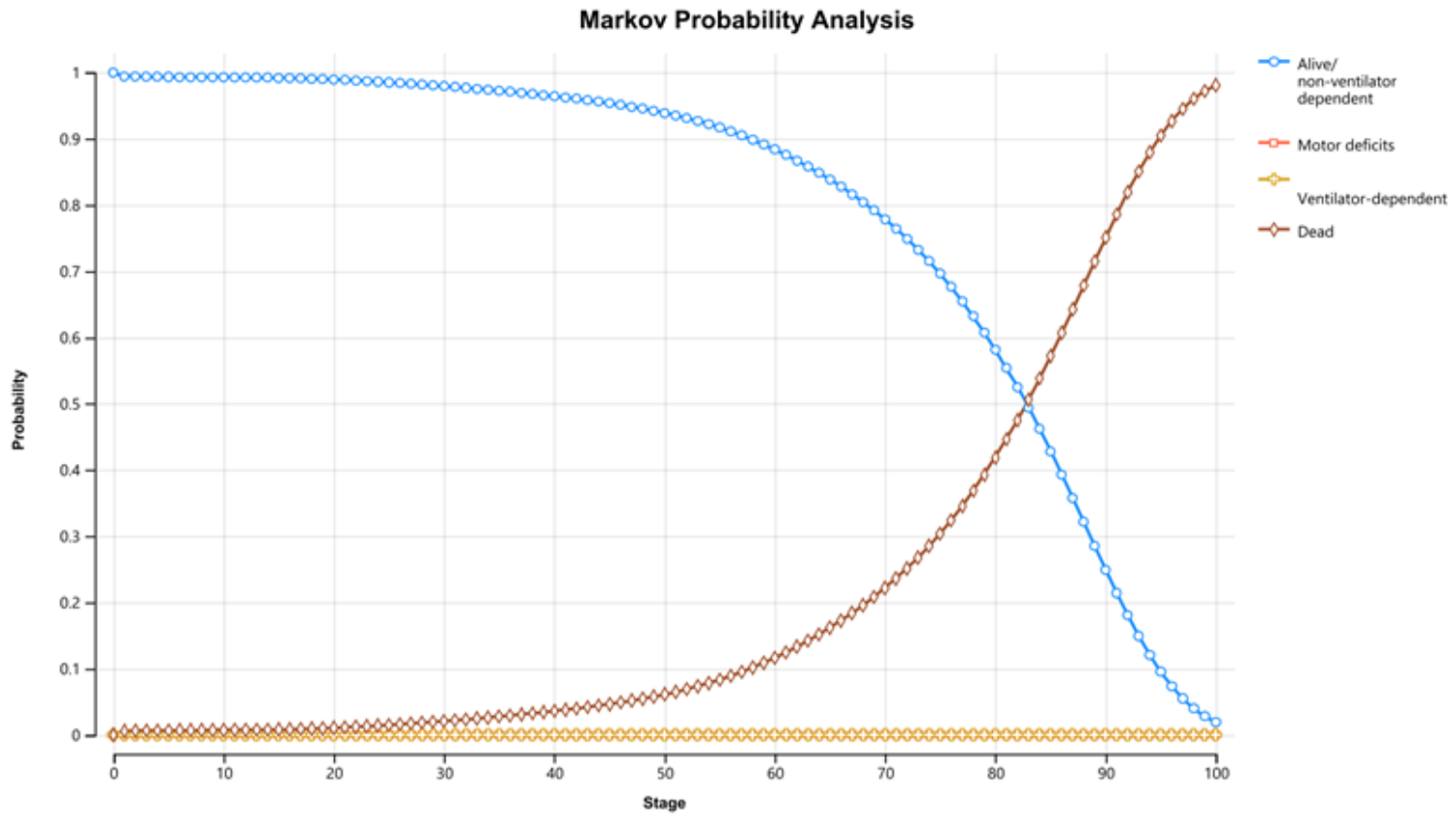
A3. CI/Usual care – type 3+	

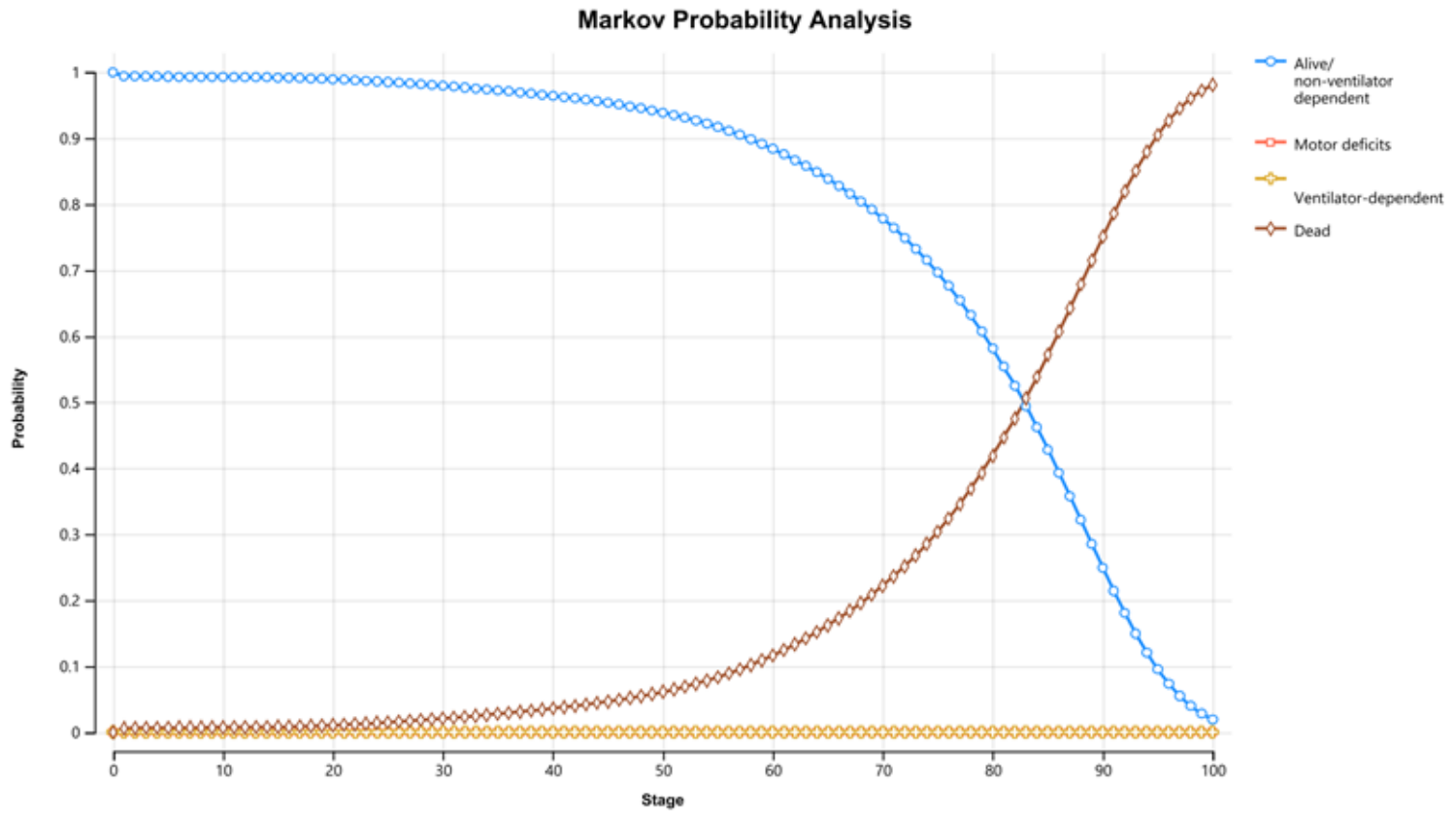
A4. CI/drug – type 1 and 0	

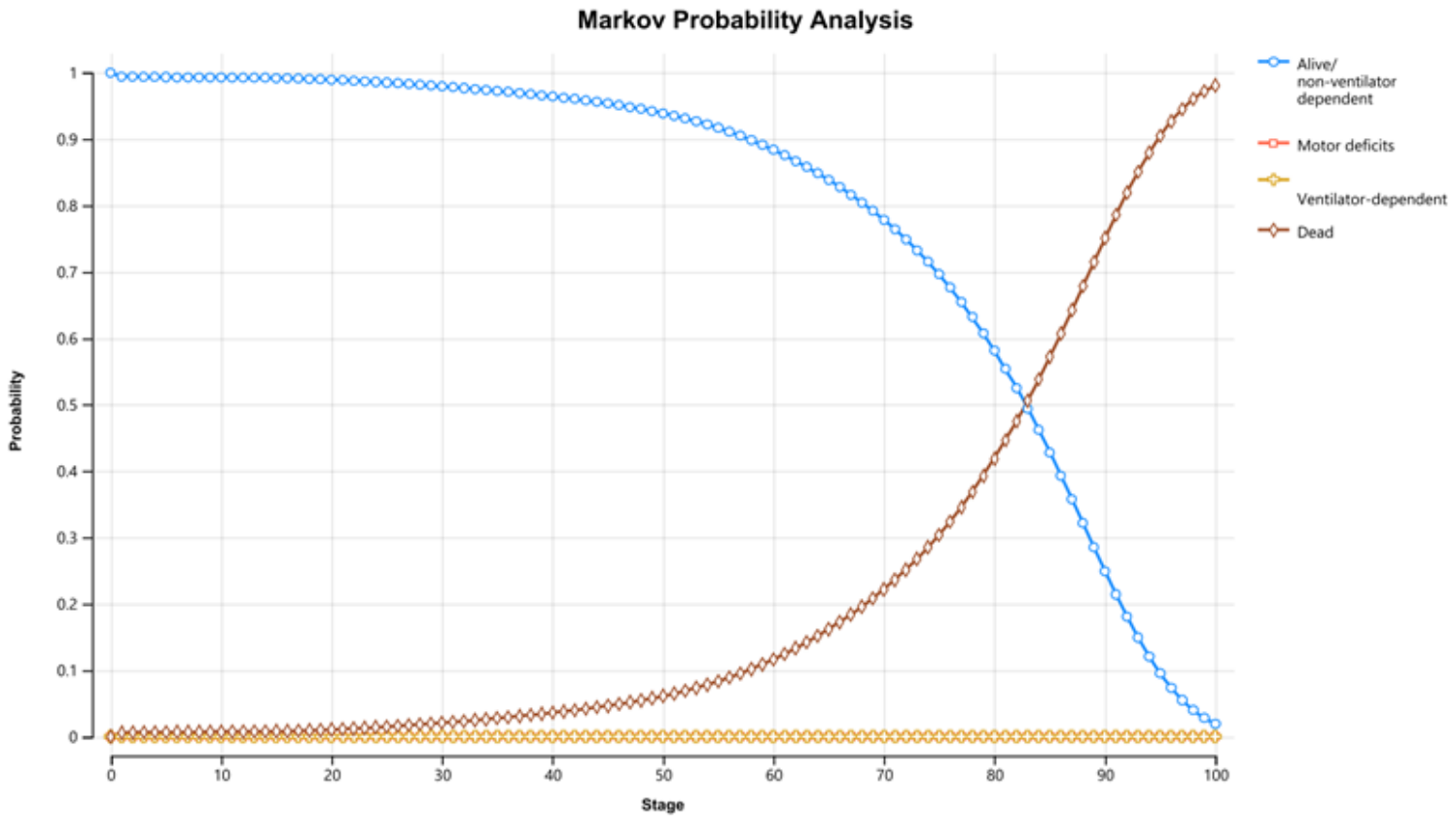
A5. CI/drug – type 2	
B. Newborn screening strategies	

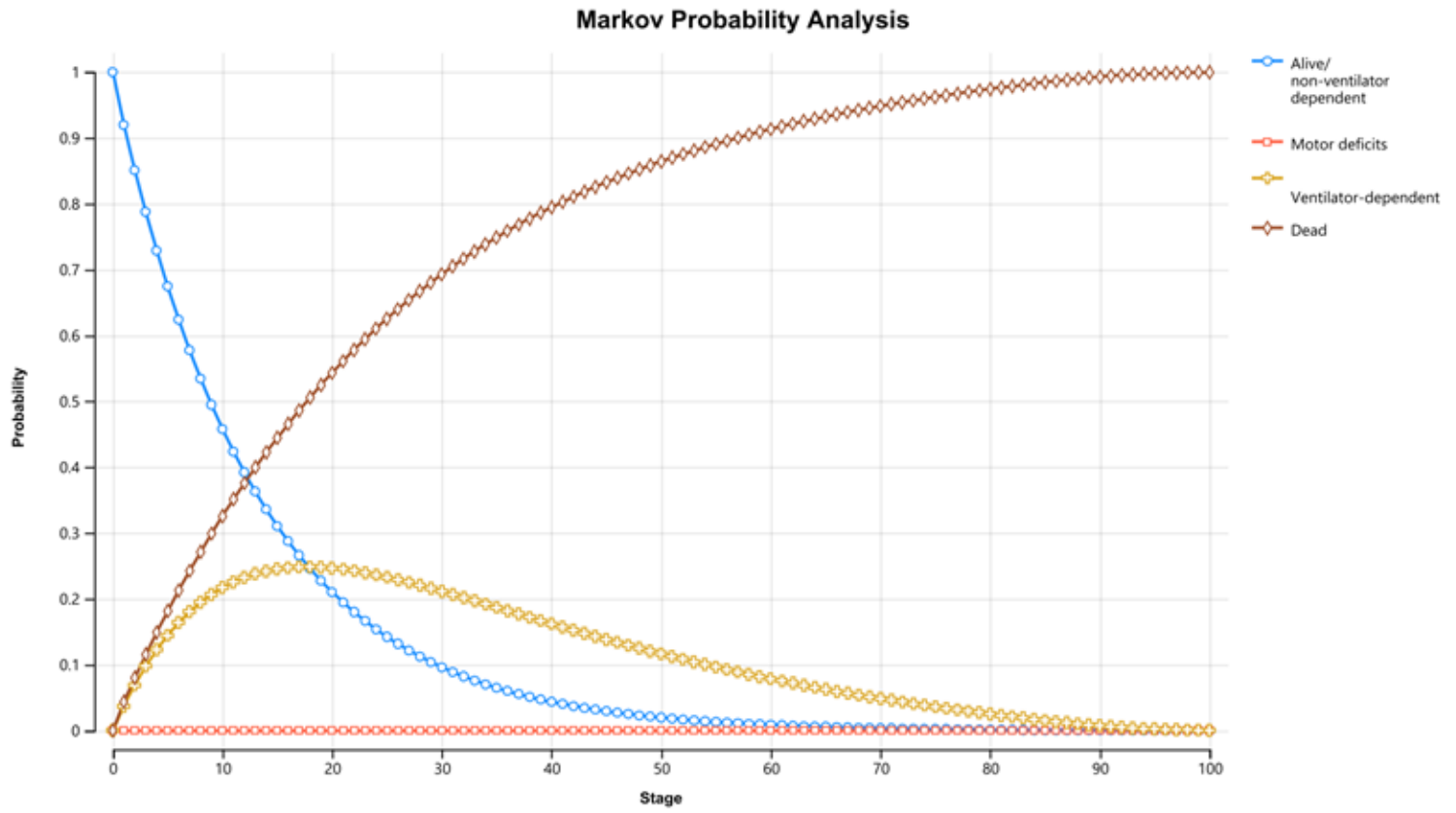
B1. NBS/drug – sym type 1	

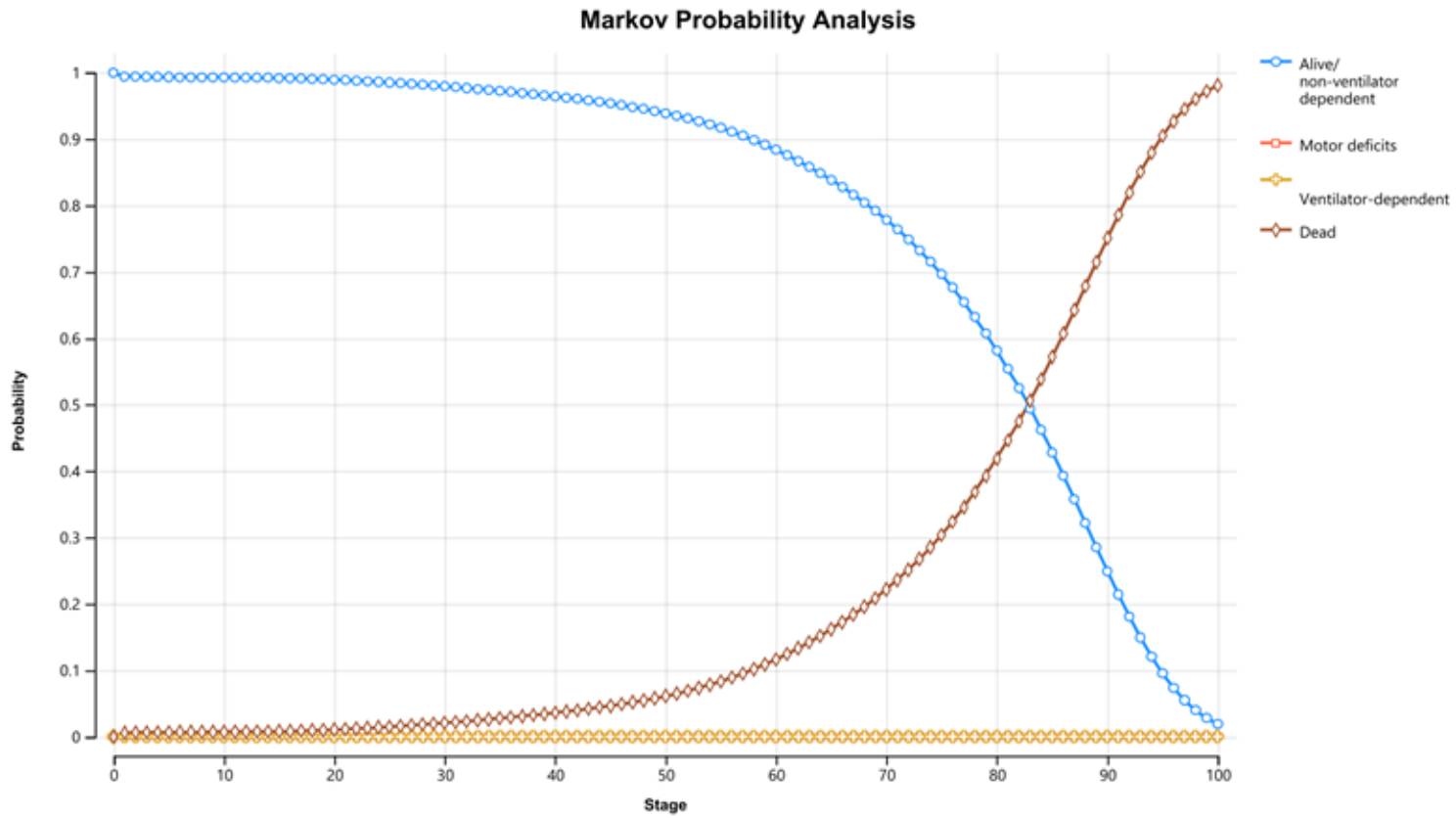
B2. NBS/drug asym – 2 copies type 1	

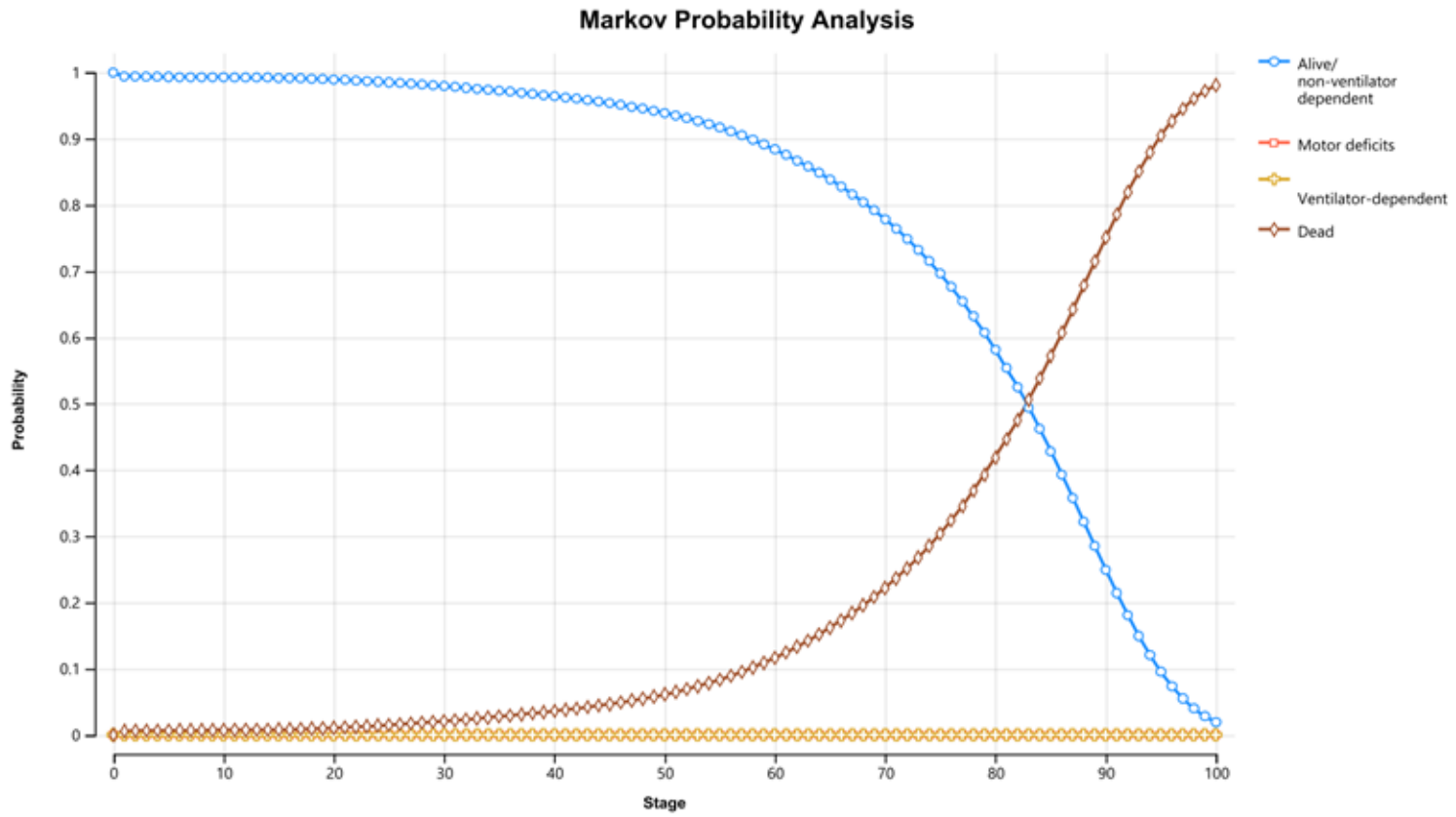
B3. NBS/drug asym – 2 copies type 2	

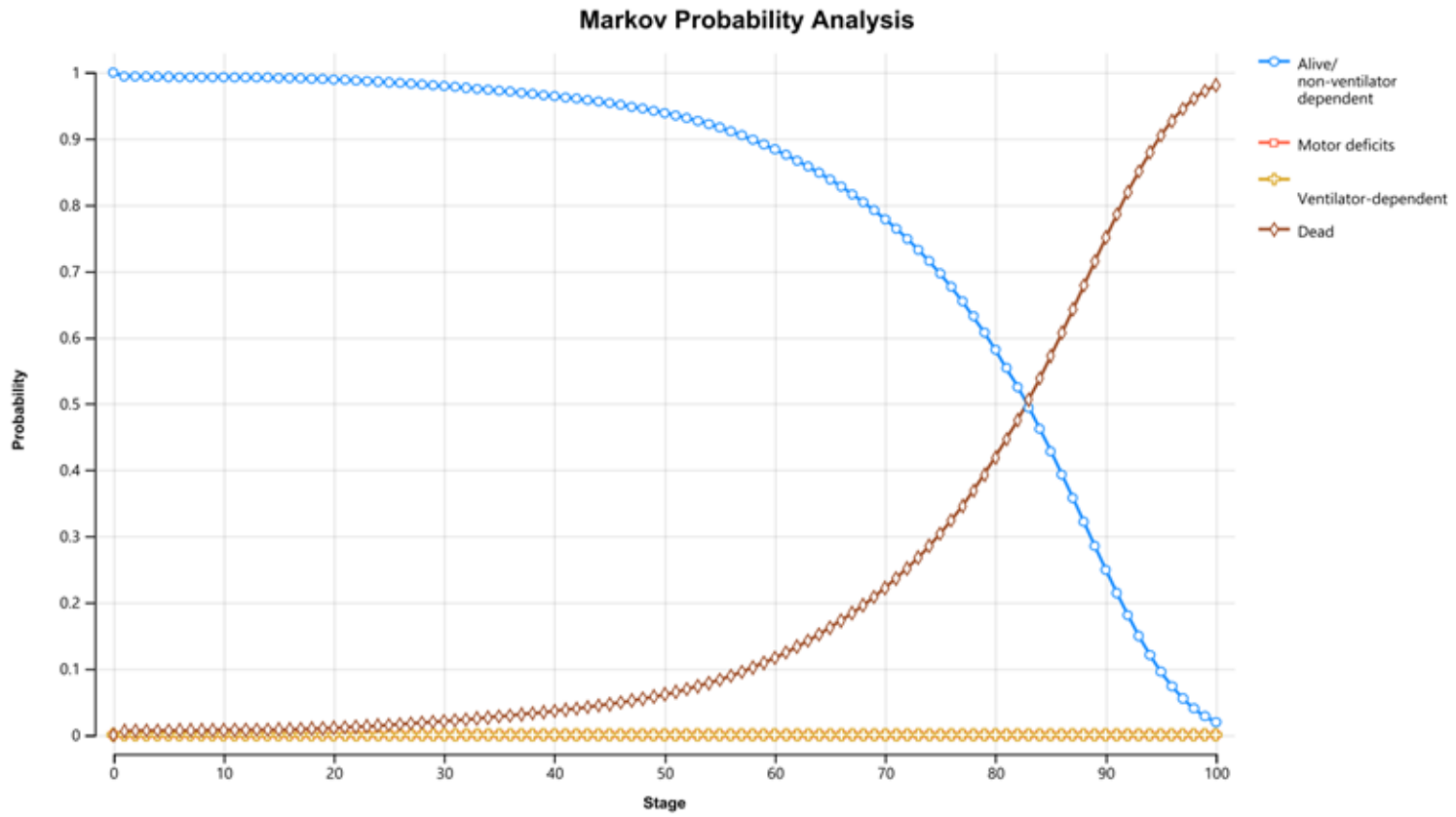
B4. NBS/drug asym – 3 copies type 1	

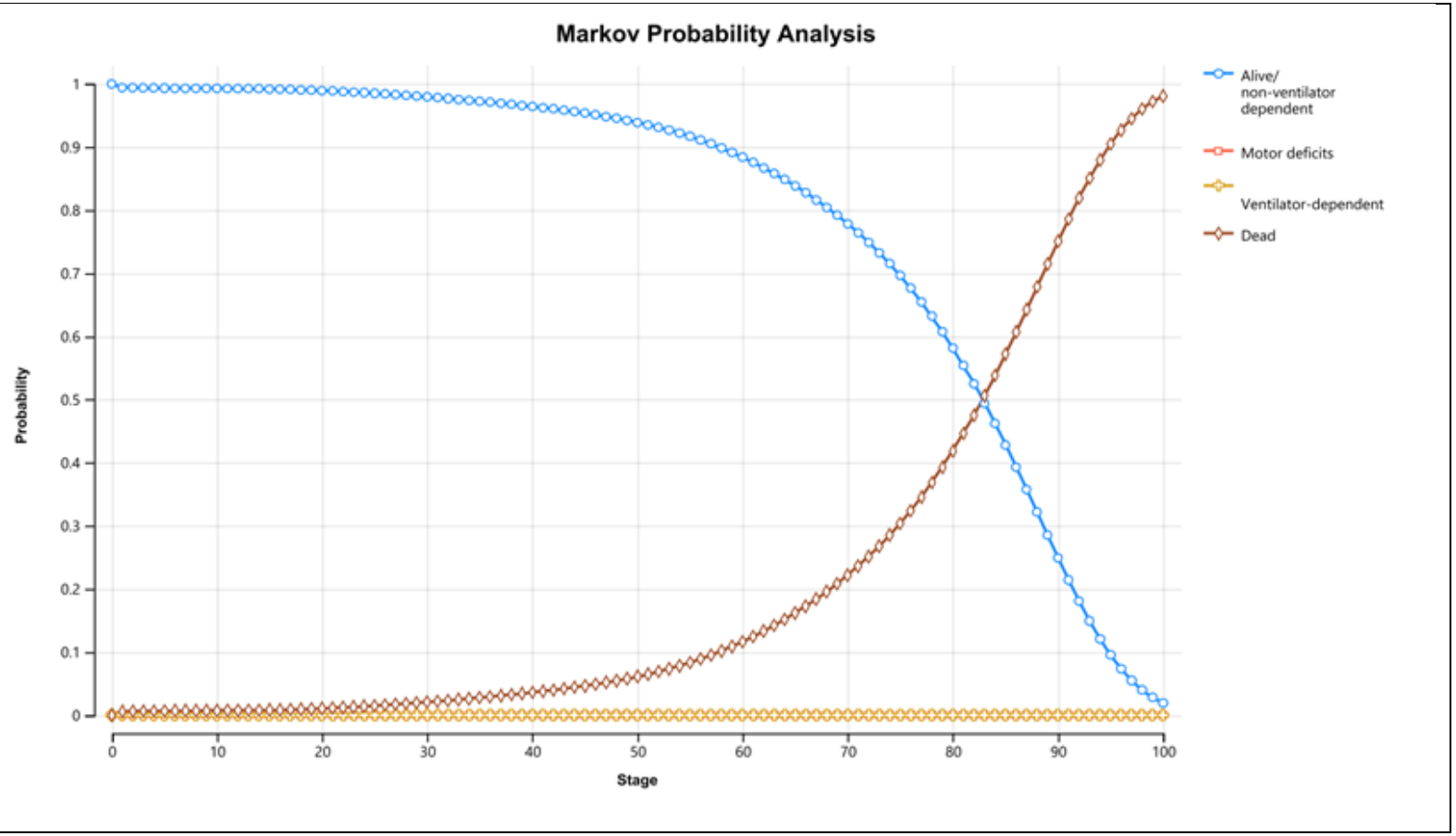
B5. NBS/drug asym – 3 copies type 2	

B6. NBS/gene therapy – sym type 1	

B7. NBS gene therapy asym – 2 copies type 1	

B8. NBS gene therapy asym – 2 copies type 2	

B9. NBS gene therapy asym – 3 copies type 1	

B10. NBS gene therapy asym – 3 copies type 2	

Appendix Table 3. Sensitivity analysis detailed results

Parameters	Range (Low- High)	ICER ($/QALY) range		
		NBS/gene therapy (vs. CI/drug)	NBS/drug (vs. NBS/gene therapy)	NBS/drug (vs. CI/drug)
Probability of NBS and CI results				
NBS test: positive	0.0118 – 0.0164	103,388; 104,310	dominated	263,094; 264,041
NBS follow-up test: positive	0.0002 – 0.0378	192,251; 101,505	dominated	354,321; 261,161
Probability of being diagnosis SMA through CI	0.00004 – 0.00019	171,948; 75,765	dominated	333,478; 234,736
NBS test: false negative	0 – 0.00005	103,669; 167,093	dominated	263,382; 328,494
Probability of different SMA types and SMN2 copies				
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1	0.003 – 0.527	95,894; 140,290	dominated	252,864; 321,317
Probability of SMN2 copies, asymptomatic		All low: 110,960; Adjusted high[1]:102,127	dominated	All low: 271,256; Adjusted high[1]: 261,303
2 copies	0.419 – 0.531			
3 copies	0.416 – 0.528			
4 copies	0.027 – 0.077			
If 2 SMN2 copies, type 1	0.84615 – 0.953	All low:114,574; Adjusted high[1]:104,144	dominated	All low: 274,593; Adjusted high[1]: 262,921
If 2 SMN2 copies, type 2	0.047 – 0.12821			
If 3 SMN2 copies, type 1	0.03817 – 0.15226			
If 3 SMN2 copies, type 2	0.27481 – 0.30635			
Transition Probabilities				
CI: Drug; NBS: Drug/Gene therapy				
Probability of death	0.079 – 0.356	All low: 57,827; All high: 125,419	dominated	All low: 251,907; All high: 271,301
Probability of ventilator dependence	0.089 – 0.532			
CI: Usual (supportive) care, type 1				
Probability of death	0.3204 – 0.3916			
Probability of permanent ventilation	0.4788 – 0.5852			

CI: Usual (supportive) care, type 2				
Probability of death	0.0961 – 0.1175			
Probability of permanent ventilation	0.1436 – 0.1756			
Treatment effect				
Relative reduction of ventilator dependence between treated early and treated late, symptomatic, drug treatment	39.1 – 86.2	All low: 102,969; All high: 104,473	All low: dominated All high: N/A[2]	All low: 262,480; All high: 262,262
Relative reduction of death between treated early and treated late, symptomatic, drug treatment	45.8 – 79.3			
Relative reduction of ventilator dependence and death, asymptomatic, drug treatment	70.1 – 100	91,729; 103,669	dominated	651,091;263,382
Probability of responding to gene therapy, gene therapy	50 – 100	181,864; 52,377	dominated	263,382;263,382
Relative reduction of ventilator dependence, symptomatic, gene therapy	39.1 – 100	All low: 106,845; All high: 91,745	All low: 11,714,425; All high: dominated	All low: 263,382; All high: 263,382
Relative reduction of death, symptomatic, gene therapy	45.8 – 100			
Relative reduction of ventilator dependence and death, asymptomatic , gene therapy	70.1 – 100	299,725; 103,669	263,382; dominated	263,382; 263,382
All drug and gene therapy low value		662,944	N/A[2]	682,395
All drug and gene therapy high value		44,171	dominated	262,262
All gene therapy high value (assuming gene therapy has perfect treatment effect)		44,171	dominated	263,382
Costs				
Newborn screening test costs: First test	69 – 206	78,383; 129,251	dominated	237,424; 289,646

Newborn screening test costs: Confirmation test	270 – 810	102,345; 104,992	dominated	262,024; 264,741
Drug (nusinersen): First year	370,028 – 612,000	All low: 104,922; All high: 102,755	dominated	All low: 207,345; All high: 304,217
Drug (nusinersen): Subsequent years	277,521 – 459,000			
Drug: Administration cost	653 – 1,959	103,674; 103,664	dominated	263,035; 263,730
Gene therapy (onasemnogene abeparvovec-xioi)	1,598,394 – 2,550,000	91,637; 114,787	dominated	263,382; 263,382
Gene therapy: Administration cost	74 – 222	103,667; 103,671	dominated	263,382; 263,382
Alive/non-ventilator-dependent				
Cost of inpatient visits	0 – 9,768	All low[3]: 104,552; All high[3]: 113,344	dominated	All low[3]: 264,287; All high[3]: 273,066
Cost of outpatient visits	4,398 – 25,551			
Cost of prescription	168 – 2,268			
Motor deficits				
Cost of inpatient visits	0 – 9,768			
Cost of outpatient visits	4,398 – 25,551			
Cost of prescription	168 – 2,268			
Permanent ventilation				
Cost of inpatient visits	0 – 9,768			
Cost of outpatient visits	4,398 – 25,551			
Cost of prescription	168 – 2,268			
Informal care costs				
Alive/non-ventilator-dependent	15,549 – 21,768	All low: 102,936; All high: 103,669	dominated	All low: 262,716; All high: 263,382
Motor deficits	119,726 – 174,147			
Permanent ventilation	119,726 – 174,147			
Health-related utilities/disutilities				
Individuals with SMA (Utility)				
Alive/non-ventilator-dependent	-0.04 – 1	All low: 205,212; All high 95,341	dominated	All low: 521,291; All high: 242,243
Motor deficits	-0.16 – 0.71			
Permanent ventilation	-0.20 – 0.31			
Caregiver (Disutility)				
Alive/non-ventilator-dependent	0.042 – 0.103	All low: 103,821;	dominated	All low: 263,886;

Motor deficits	0.090 – 0.173	All high: 105,026		All high: 266,801
Permanent ventilation	0.16 – 0.614			

[1] Several combinations of the parameter values were tested, and this was the lowest ICER value.
[2] Because effect is the same as gene therapy, therefore the difference in effect is zero.
[3] The healthcare costs for drug treatment and gene therapy are assumed to be 50% of these values, therefore they change with these variables

Appendix Table 4. Impact Inventory

Sector	*Type of Impact (list category within each sector with unit of measure if relevant*)*	*Included in This Reference Case Analysis from … perspective?*		*Notes on Sources of Evidence*
		Healthcare Sector	*Societal*	
Formal Healthcare sector				
Health	*Health outcomes (effects)*			
	Longevity effects	☐	☐	
	Health-related quality-of-life effects	☑	☑	Utility Weight
	Other health effects (e.g., adverse events and secondary transmissions of infections)	☐	☐	
	Medical costs			
	Paid for by third-party payers	☑	☑	Newborn screening and follow-up cost. Formal care is not included as a limitation but is estimated that it will not change the conclusion.
	Paid for by patients Out-of-pocket	☐	☐	
	Future related medical costs (payers and patients)	☐	☐	
	Future unrelated medical costs (payers and patients)	☐	☐	
Informal Healthcare sector				
Health	Patient time costs	NA	☑	Caregiver informal care time costs are included

	Unpaid caregiver time costs	NA	☑	Informal caregiving time costs (Wage cost)
	Transportation costs	NA	☐	
Non-healthcare sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	☐	Utility weights included productivity loss for both patients and caregivers
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	NA	☐	
Consumption	Further consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	Not 109ncluded and listed as limitation
Housing	Cost of intervention on home improvements (e.g., removing lead paint)	NA	☐	
Environment	Production of toxic waste or pollution by intervention	NA	☐	
Other (specify)	Other impacts	NA	☐	
*Categories listed are intended as examples for analysts. Abbreviation: NA = Not applicable				

Appendix Table 5. Base-case results: undiscounted

Strategies	Cost ($USD)	Incremental Costs	QALYs	Incremental QALYs	ICER ($/QALY)
Societal perspective					
(1) Reference comparator: CI/drug					
CI/drug	231,625	--	79,183.05	--	--
NBS/gene therapy	755,306	523,681	79,190.45	7.404	70,729
NBS/drug	1,986,613	1,231,307	79,190.32	-0.130	dominated
(2) Reference comparator: CI/drug (if gene therapy is not available)					
CI/drug	231,625	--	79,183.05	--	--
NBS/drug	1,986,613	1,754,988	79,190.32	7.274	241,265
(3) Reference comparator: CI/usual (supportive) care					
CI/usual (supportive) care	39,714	--	79,182.87	--	--
CI/drug	231,625	191,911	79,183.05	0.176	Extended dominated[1]
NBS/gene therapy	755,306	715,592	79,190.45	7.580	94,405
NBS/drug	1,986,613	1,231,307	79,190.32	-0.130	dominated
Healthcare sector perspective (Excludes informal care costs and caregiver QoL)					
(1) Reference comparator: CI/drug					
CI/drug	181,998	--	79,182.75	--	--
NBS/gene therapy	637,532	455,534	79,186.29	3.536	128,833
NBS/drug	1,874,740	1,237,209	79,186.23	-0.058	dominated
(2) Reference comparator: CI/drug (if gene therapy is not available)					
CI/drug	181,998	--	79,182.75	--	--
NBS/drug	1,874,740	1,692,742	79,186.23	3.48	486,774
(3) Reference comparator: CI/usual (supportive) care					
CI/usual (supportive) care	7,037	--	79,182.68	--	--
CI/drug	181,998	174,961	79,182.75	0.072	Extended dominated[2]
NBS/gene therapy	637,532	630,494	79,186.29	3.608	174,757
NBS/drug	1,874,740	1,237,209	79,186.23	-0.058	dominated

Abbreviations: NBS: Newborn screening; CI: Clinical identification; QALY: Quality adjusted life year; ICER: incremental cost effectiveness ratio; QoL: Quality of life

[1] Extended dominated: $ 1,090,442/QALY

[2] Extended dominated: $ 2,429,713/QALY

Appendix Table 6. Base-case results: disaggregated

	CI/usual care	CI/drug	NBS/gene therapy	NBS/drug
Inpatient Costs	1,381	990	286	288
Outpatient Costs	4,102	2,965	4,595	4,513
Prescription Costs	339	244	213	210
Drug Costs	-	149,773	137,447	687,234
Gene therapy Costs	-	-	137,141	-

CI: Clinical identification, NBS: newborn screening
Note: this is the lifetime costs of each category but does not include the full costs such as newborn screening costs.

Appendix Table 7. Epidemiology and transition probabilities

	Most likely	Range (Low – High)	Source
Probability of NBS and CI results			
NBS test: positive	0.0132	0.0118 – 0.0164	[26, 30][5]
NBS follow-up test: positive	0.0069	0.0002 – 0.0378	[26, 30][5]
NBS test: false negative	0	0 – 0.00005	Assumption[5,6]
Probability of being diagnosis SMA through CI	0.000091	0.00004 – 0.00019	[23, 30] [5]
Probability of different SMA types and SMN2 copies			
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1	0.125	0.003 – 0.527	[26, 30, 35]
Probability of SMN2 copies, asymptomatic			
1 copy	0	--	Assumption[8]
2 copies	0.4755	0.419 – 0.531	[30, 33] [8]
3 copies	0.4725	0.416 – 0.528	[30, 33] [8]
4 copies	0.046	0.027 – 0.077	[30, 33] [8]
5 copies	0.006	0.059 – 0.138	Assumption[8]
If 2 SMN2 copies, type 1	0.84615	0.84615 – 0.953	Assumption[1,9]
If 2 SMN2 copies, type 2	0.12821	0.047 – 0.12821	Assumption[1,9]
If 3 SMN2 copies, type 1	0.15226	0.03817 – 0.15226	Assumption[1,4,9]
If 3 SMN2 copies, type 2	0.30635	0.27481 – 0.30635	Assumption[1,4,9]
CI: Probability of being type 0 and 1	0.54	0.48 – 0.75	Assumption[7]
CI: Probability of being type 2	0.18	0.1 – 0.21	Assumption[7]
Transition Probabilities			
CI: Drug; NBS: Drug/Gene therapy[11]			
Probability of death	0.183	0.079 – 0.356	[30, 38][10]
Probability of ventilator dependence	0.265	0.089 – 0.532	[30, 38] [10]
CI: Usual (supportive) care, type 1			
Probability of death	0.356	0.3204 – 0.3916	Assumption[2,10]
Probability of motor deficit	0	--	Assumption[10]
Probability of permanent ventilation	0.532	0.4788 – 0.5852	Assumption[2,10]
CI: Usual (supportive) care, type 2			
Probability of death	0.1068	0.0961 – 0.1175	Assumption[3,10]
Probability of motor deficit	0	--	Assumption[10]
Probability of permanent ventilation	0.1596	0.1436 – 0.1756	Assumption[3,10]

Abbreviations: NBS: Newborn screening; CI: clinical identification

[1] Assumed and calculated from **[33]**. This data source summarized data from 33 papers, and data from three U.S. studies **[36, 39, 45]** were included for the calculation (case number of different SMA types with different number copies of SMN2); Range derived from **[30, 33]**.

[2] Value assumed using high value of **[30, 38]**. Range calculated as plus/minus 10%.

[3] Value assumed using high value of **[30, 38]** with adjustment assuming a 70% probability of reduction for type 2 to reflect that type 2 are generally less severe when compared to type 1 (multiply 0.3). Range calculated as plus/minus 10%.
[4] Base-case values adjusted to have the same incidence rate in both CI and NBS strategies.
[5]These variables are run together in sensitivity analysis to ensure case numbers are the same across strategies, where 0.455 was used in one scenario as the high value instead of highest value of the range (0.0164) for the probability of "NBS test: positive".
[6] The base-case value assumed from **[26, 30]**, range assumed based on assumption that all strategies have the same case number.
[7] Base -case value from **[30]**, range assumed as conditional probability set of "Probability of different SMA types and SMN2 copies"
[8] Probability of 5 copies is conditional on the probability of 1 copy to 4 copies. The sensitivity analyses of these parameters are run as a set.
[9] The sensitivity analyses of these parameters are run as a set.
[10] The sensitivity analyses of these parameters are run as a set.
[11] These probabilities do not include the treatment effect of Drug and Gene therapy.

Appendix Table 8. Treatment effect

	Most likely (%)	Range (%, low-high)	Source
Drug treatment			
Relative reduction of ventilator dependence between treated early and treated late, symptomatic, drug treatment	65.1	39.1 – 86.2	[30, 49]
Relative reduction of death between treated early and treated late, symptomatic, drug treatment	63.8	45.8 – 79.3	[30, 49]
Relative reduction of ventilator dependence and death, asymptomatic, drug treatment	100	70.1 – 100	[30, 40]
Gene therapy			
Probability of responding to gene therapy	80	50 – 100	Assumption
Relative reduction of ventilator dependence, symptomatic, gene therapy	86.2	39.1 – 100	Assumption
Relative reduction of death, symptomatic, gene therapy	79.3	45.8 – 100	Assumption
Relative reduction of ventilator dependence and death, asymptomatic, gene therapy	100	70.1 – 100	Assumption

Appendix Table 9. Costs and Resource Use

	Most likely	Range	Source
Newborn screening test costs			
First test	137.10	69 – 206	Assumed from [28][1]
Confirmation test	540	270 – 810	Assumed from [47][1]
Treatment costs			
Drug (nusinersen)			
First year	510,000	370,028 – 612,000	[14, 42]
Subsequent years	382,500	277,521 – 459,000	
Administration cost	1,306	653 – 1,959	Assumed from [41][2,4]
Gene therapy (onasemnogene abeparvovec-xioi)	2,092,965	1,598,394 – 2,550,000	[14, 42]
Administration cost	148	74 – 222	Assumed from [41][2,4]
Annual healthcare costs			
Alive/non-ventilator-dependent			
Cost of inpatient visits	0	0 – 9,768	Assumed from [31][2,3]
Cost of outpatient visits	4,398	4,398 – 25,551	
Cost of prescription	168	168 – 2,268	
Motor deficits			
Cost of inpatient visits	2,296	0 – 9,768	
Cost of outpatient visits	11,048	4,398 – 25,551	
Cost of prescription	585	168 – 2,268	
Permanent ventilation			
Cost of inpatient visits	9,768	0 – 9,768	
Cost of outpatient visits	25,551	4,398 – 25,551	
Cost of prescription	2,268	168 – 2,268	
Informal care costs			
Alive/non-ventilator-dependent	21,768	15,549 – 21,768	Assumed from [48, 53]
Motor deficits	174,147	119,726 – 174,147	
Permanent ventilation	174,147	119,726 – 174,147	

[1] Range assumed as +/- 50% of base-case value.
[2] Adjusted using the Gross Domestic Product (GDP) deflator to 2021 US dollars, range calculated based on same data source.
[3] This is for usual (supportive) care, assuming the value of the 25th percentile, median, and 75th percentile costs from **[31]**. Ranges assumed. The healthcare costs for drug treatment and gene therapy
[4] Range assumed as +/- 50% of base-case value.

Appendix Table 10. Health-related utilities/disutilities

	Utility/Disutility	Range	Source
Non- SMA individuals (Utility)	1	--	Assumption
Individuals with SMA (Utility)			
Watchful waiting	1	-	Assumption
Alive/non-ventilator-dependent	0.84	-0.04 – 1	Assumed from [32, 51][1]
Motor deficits	0.52	-0.16 – 0.71	Assumed from [32, 43, 54][2]
Permanent ventilation	0.19	-0.20 – 0.31	Assumed from [32, 34, 41, 52][3]
Dead	0	--	Assumption
Caregiver (Disutility)			
Alive/non-ventilator-dependent	0.072	0.042 – 0.103	Assumed from [50][4]
Motor deficits	0.131	0.09 – 0.173	Assumed from [50][4]
Permanent ventilation	0.516	0.16 – 0.614	Assumed from [34, 44, 46][5]
Dead	1	--	Assumption

[1] Range assumed from [51] (Preference-Based EQ-5D index scores: 0.736-0.922) and [32] (HUI3 Scores, SMA, walk independently: -0.04-1)
[2] Base-case value based on [43, 54], range assumed from [43, 54] (Health-state utility values, SMA Walks with assistance: 0.33-0.71) and [32] (HUI3 Scores, SMA, Non-Sitters : -0.16-0.41).
[3] Base-case value based on [41, 52], range assumed from [34] (HRQoL (TTO social tariff score), SMA: 0.104-0.252) and [32] (HUI3 Scores, SMA, Permanent Ventilation: -0.20 – 0.31).
[4] Assumption based on [50], approximated the health states "alive/non-ventilator-dependent" to Pompe mild symptoms and "motor deficits" to severe symptoms.
[5] Assumption calculated based on [44]. This source has a mean of 0.484 (Standard Deviation=0.448) for SMA caregivers in Spain (N=81, SMA type 1 n=8, type2 n=60, type3 n=13; therefore, the disutility is calculated as 1-0.484=0.516). Range calculated as the 95% confidence interval assuming a normal distribution (0.418-0.614) and from [34] (HRQoL (TTO social tariff score), SMA caregivers: 0.703-0.715 (disutility: 0.285-0.297)) and [46] (mean health utility index, SMA caregivers: 0.84 (disutility: 0.16))

Appendix Table 11. Life table for the total population: United States, 2018 (BIA)

Age	Mortality	Age	Mortality	Age	Mortality
0–1	0.00565	34–35	0.00154	68–69	0.01572
1–2	0.00037	35–36	0.00161	69–70	0.01700
2–3	0.00026	36–37	0.00169	70–71	0.01839
3–4	0.00019	37–38	0.00175	71–72	0.01983
4–5	0.00015	38–39	0.00181	72–73	0.02191
5–6	0.00014	39–40	0.00186	73–74	0.02380
6–7	0.00013	40–41	0.00193	74–75	0.02619
7–8	0.00011	41–42	0.00202	75–76	0.02869
8–9	0.00010	42–43	0.00214	76–77	0.03179
9–10	0.00009	43–44	0.00229	77–78	0.03514
10–11	0.00009	44–45	0.00246	78–79	0.03867
11–12	0.00010	45–46	0.00265	79–80	0.04275
12–13	0.00013	46–47	0.00286	80–81	0.04720
13–14	0.00018	47–48	0.00309	81–82	0.05260
14–15	0.00025	48–49	0.00335	82–83	0.05859
15–16	0.00033	49–50	0.00364	83–84	0.06512
16–17	0.00041	50–51	0.00395	84–85	0.07340
17–18	0.00049	51–52	0.00430	85–86	0.08164
18–19	0.00058	52–53	0.00471	86–87	0.08981
19–20	0.00066	53–54	0.00519	87–88	0.10090
20–21	0.00075	54–55	0.00570	88–89	0.11308
21–22	0.00084	55–56	0.00622	89–90	0.12641
22–23	0.00091	56–57	0.00674	90–91	0.14090
23–24	0.00098	57–58	0.00728	91–92	0.15658
24–25	0.00103	58–59	0.00785	92–93	0.17342
25–26	0.00107	59–60	0.00845	93–94	0.19140
26–27	0.00112	60–61	0.00911	94–95	0.21044
27–28	0.00116	61–62	0.00979	95–96	0.23047
28–29	0.00121	62–63	0.01049	96–97	0.25134
29–30	0.00126	63–64	0.01119	97–98	0.27293
30–31	0.00131	64–65	0.01192	98–99	0.29505
31–32	0.00136	65–66	0.01269	99–100	0.31752
32–33	0.00141	66–67	0.01361	100+	1.00000
33–34	0.00147	67–68	0.01461		
Data source: [55]					

Appendix Table 12. Sensitivity analysis detailed results

Parameter	Values	Costs	CI/drug	NBS/gene therapy	Differences
Probability of NBS and CI results					
NBS test: positive	0.0118	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,624,602	10,724,125
		Year 3	7,919,755	17,187,777	9,268,022
		Year 4	9,632,112	17,745,810	8,113,698
		Year 5	11,085,445	18,299,001	7,213,555
		Total	**38,057,162**	**85,913,138**	**47,855,976**
	0.0164	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,624,602	10,724,125
		Year 3	7,919,755	17,187,777	9,268,022
		Year 4	9,632,112	17,745,810	8,113,698
		Year 5	11,085,445	18,299,001	7,213,555
		Total	**38,057,162**	**85,913,138**	**47,855,976**
NBS follow-up test: positive	0.0002	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,624,602	10,724,125
		Year 3	7,919,755	17,187,777	9,268,022
		Year 4	9,632,112	17,745,810	8,113,698
		Year 5	11,085,445	18,299,001	7,213,555
		Total	**38,057,162**	**85,913,138**	**47,855,976**
	0.0378	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,624,602	10,724,125
		Year 3	7,919,755	17,187,777	9,268,022
		Year 4	9,632,112	17,745,810	8,113,698
		Year 5	11,085,445	18,299,001	7,213,555
		Total	**38,057,162**	**85,913,138**	**47,855,976**
Probability of being diagnosis SMA through CI	0.00004	Year 1	1,546,977	7,057,560	5,510,583
		Year 2	2,593,616	7,307,517	4,713,901
		Year 3	3,481,211	7,555,067	4,073,856
		Year 4	4,233,895	7,800,356	3,566,461

		Year 5	4,872,723	8,043,517	3,170,794
		Total	**16,728,423**	**37,764,017**	**21,035,594**
	0.00019	Year 1	7,348,141	33,523,409	26,175,268
		Year 2	12,319,677	34,710,707	22,391,031
		Year 3	16,535,753	35,886,568	19,350,815
		Year 4	20,111,002	37,051,690	16,940,688
		Year 5	23,145,435	38,206,704	15,061,270
		Total	**79,460,008**	**179,379,079**	**99,919,071**
NBS test: false negative	0	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,624,602	10,724,125
		Year 3	7,919,755	17,187,777	9,268,022
		Year 4	9,632,112	17,745,810	8,113,698
		Year 5	11,085,445	18,299,001	7,213,555
		Total	**38,057,162**	**85,913,138**	**47,855,976**
	0.00005	Year 1	3,519,373	9,258,645	5,739,272
		Year 2	5,900,477	10,810,005	4,909,528
		Year 3	7,919,755	12,162,676	4,242,921
		Year 4	9,632,112	13,346,580	3,714,469
		Year 5	11,085,445	14,387,827	3,302,382
		Total	**38,057,162**	**59,965,733**	**21,908,571**
Probability of different SMA types and SMN2 copies					
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1	0.003	Year 1	3,283,448	15,185,359	11,901,912
		Year 2	5,547,164	15,728,319	10,181,154
		Year 3	7,477,628	16,270,951	8,793,323
		Year 4	9,124,382	16,813,322	7,688,940
		Year 5	10,530,723	17,355,477	6,824,753
		Total	**35,963,346**	**81,353,428**	**45,390,082**
	0.527	Year 1	4,296,765	18,924,611	14,627,846
		Year 2	7,064,670	19,577,928	12,513,258
		Year 3	9,376,601	20,208,795	10,832,194
		Year 4	11,305,122	20,818,432	9,513,310
		Year 5	12,913,298	21,407,989	8,494,691

		Total	**44,956,456**	**100,937,757**	**55,981,300**
Probability of SMN2 copies, asymptomatic	All low	Year 1	3,177,976	14,476,170	11,298,194
		Year 2	5,323,529	14,988,324	9,664,795
		Year 3	7,141,889	15,495,021	8,353,132
		Year 4	8,682,814	15,996,589	7,313,775
		Year 5	9,989,707	16,493,326	6,503,619
		Total	**34,315,915**	**77,449,430**	**43,133,515**
	Adjusted high[1]	Year 1	3,659,348	16,605,530	12,946,182
		Year 2	6,116,884	17,193,838	11,076,954
		Year 3	8,196,336	17,776,662	9,580,326
		Year 4	9,955,518	18,354,337	8,398,819
		Year 5	11,444,835	18,927,167	7,482,332
		Total	**39,372,922**	**88,857,535**	**49,484,613**
Probability of when 2 or 3 SMN2 copies, type 1 or type 2 (Set)	All low	Year 1	3,090,101	13,959,842	10,869,741
		Year 2	5,152,506	14,453,530	9,301,024
		Year 3	6,894,330	14,941,767	8,047,437
		Year 4	8,364,903	15,424,881	7,059,978
		Year 5	9,607,213	15,903,168	6,295,954
		Total	**33,109,054**	**74,683,187**	**41,574,133**
	Adjusted high[1]	Year 1	3,618,682	16,293,841	12,675,159
		Year 2	6,022,806	16,871,002	10,848,196
		Year 3	8,050,381	17,442,682	9,392,301
		Year 4	9,759,613	18,009,217	8,249,604
		Year 5	11,201,211	18,570,909	7,369,699
		Total	**38,652,694**	**87,187,652**	**48,534,958**
Transition Probabilities	All low	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	6,138,588	16,627,675	10,489,087
		Year 3	8,584,442	17,196,761	8,612,319
		Year 4	10,868,724	17,763,329	6,894,605
		Year 5	13,002,402	18,327,478	5,325,076
		Total	**42,113,529**	**85,971,192**	**43,857,663**
	All high	Year 1	3,519,373	16,055,949	12,536,576

		Year 2	5,501,668	16,619,393	11,117,725
		Year 3	8,584,442	17,196,761	8,612,319
		Year 4	7,874,486	17,717,594	9,843,108
		Year 5	8,580,345	18,254,348	9,674,003
		Total	**34,060,313**	**85,844,044**	**51,783,731**
Treatment effect					
Relative reduction of ventilator dependence/death between treated early and treated late, symptomatic, drug treatment	All low	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,621,664	10,721,188
		Year 3	7,919,755	17,179,360	9,259,604
		Year 4	9,632,112	17,729,734	8,097,622
		Year 5	11,085,445	18,273,431	7,187,986
		Total	**38,057,162**	**85,860,138**	**47,802,976**
	All high	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,627,146	10,726,669
		Year 3	7,919,755	17,195,175	9,275,419
		Year 4	9,632,112	17,760,159	8,128,048
		Year 5	11,085,445	18,322,202	7,236,757
		Total	**38,057,162**	**85,960,630**	**47,903,468**
Relative reduction of ventilator dependence and death, asymptomatic, drug treatment	70.1	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,600,672	10,700,195
		Year 3	7,919,755	17,117,230	9,197,475
		Year 4	9,632,112	17,607,028	7,974,917
		Year 5	11,085,445	18,071,401	6,985,956
		Total	**38,057,162**	**85,452,280**	**47,395,118**
	100	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,624,602	10,724,125
		Year 3	7,919,755	17,187,777	9,268,022
		Year 4	9,632,112	17,745,810	8,113,698
		Year 5	11,085,445	18,299,001	7,213,555
		Total	**38,057,162**	**85,913,138**	**47,855,976**
	50	Year 1	3,519,373	17,176,620	13,657,247
		Year 2	5,900,477	18,572,391	12,671,914

Probability of responding to gene therapy		Year 3	7,919,755	19,953,621	12,033,866
		Year 4	9,632,112	21,321,256	11,689,144
		Year 5	11,085,445	22,676,149	11,590,704
		Total	**38,057,162**	**99,700,037**	**61,642,875**
	100	Year 1	3,519,373	15,308,835	11,789,462
		Year 2	5,900,477	15,326,076	9,425,599
		Year 3	7,919,755	15,343,882	7,424,126
		Year 4	9,632,112	15,362,179	5,730,067
		Year 5	11,085,445	15,380,901	4,295,456
		Total	**38,057,162**	**76,721,872**	**38,664,710**
Relative reduction of ventilator dependence/death, symptomatic, gene therapy	All low	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,626,551	10,726,074
		Year 3	7,919,755	17,192,728	9,272,973
		Year 4	9,632,112	17,754,208	8,122,096
		Year 5	11,085,445	18,310,879	7,225,434
		Total	**38,057,162**	**85,940,314**	**47,883,153**
	All high	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,624,077	10,723,600
		Year 3	7,919,755	17,186,271	9,266,516
		Year 4	9,632,112	17,742,926	8,110,814
		Year 5	11,085,445	18,294,396	7,208,951
		Total	**38,057,162**	**85,903,618**	**47,846,456**
Relative reduction of ventilator dependence and death, asymptomatic, gene therapy	70.1	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,630,317	10,729,840
		Year 3	7,919,755	17,203,730	9,283,974
		Year 4	9,632,112	17,775,543	8,143,431
		Year 5	11,085,445	18,345,233	7,259,788
		Total	**38,057,162**	**86,010,772**	**47,953,610**
	100	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,900,477	16,624,602	10,724,125
		Year 3	7,919,755	17,187,777	9,268,022
		Year 4	9,632,112	17,745,810	8,113,698

		Year 5	11,085,445	18,299,001	7,213,555
		Total	**38,057,162**	**85,913,138**	**47,855,976**
Costs					
Costs of Drug (nusinersen)	All low	Year 1	2,560,660	15,851,423	13,290,763
		Year 2	4,301,938	16,269,313	11,967,375
		Year 3	5,782,876	16,683,419	10,900,543
		Year 4	7,041,163	17,093,948	10,052,785
		Year 5	8,110,544	17,501,091	9,390,547
		Total	**27,797,182**	**83,399,194**	**55,602,013**
	All high	Year 1	4,218,003	16,204,990	11,986,986
		Year 2	7,065,359	16,883,507	9,818,148
		Year 3	9,476,936	17,555,312	8,078,376
		Year 4	11,520,180	18,220,832	6,700,652
		Year 5	13,253,307	18,880,451	5,627,144
		Total	**45,533,785**	**87,745,092**	**42,211,307**
Drug: Administration cost	653	Year 1	3,514,602	16,054,995	12,540,392
		Year 2	5,891,726	16,622,710	10,730,984
		Year 3	7,907,656	17,184,958	9,277,302
		Year 4	9,617,188	17,742,073	8,124,885
		Year 5	11,068,133	18,294,355	7,226,222
		Total	**37,999,305**	**85,899,091**	**47,899,786**
	1,959	Year 1	3,524,144	16,056,903	12,532,759
		Year 2	5,909,227	16,626,494	10,717,266
		Year 3	7,931,855	17,190,597	9,258,742
		Year 4	9,647,035	17,749,546	8,102,511
		Year 5	11,102,757	18,303,646	7,200,889
		Total	**38,115,018**	**85,927,185**	**47,812,167**
Gene therapy (onasemnogene abeparvovec-xioi)	1,598,394	Year 1	3,519,373	12,442,643	8,923,270
		Year 2	5,900,477	13,011,297	7,110,820
		Year 3	7,919,755	13,574,472	5,654,717
		Year 4	9,632,112	14,132,504	4,500,393
		Year 5	11,085,445	14,685,695	3,600,250

		Total	**38,057,162**	**67,846,611**	**29,789,449**
	2,550,000	Year 1	3,519,373	19,395,018	15,875,645
		Year 2	5,900,477	19,963,672	14,063,195
		Year 3	7,919,755	20,526,847	12,607,092
		Year 4	9,632,112	21,084,879	11,452,768
		Year 5	11,085,445	21,638,070	10,552,625
		Total	**38,057,162**	**102,608,486**	**64,551,325**
Gene therapy: Administration cost	74	Year 1	3,519,373	16,055,408	12,536,035
		Year 2	5,900,477	16,624,061	10,723,585
		Year 3	7,919,755	17,187,237	9,267,481
		Year 4	9,632,112	17,745,269	8,113,157
		Year 5	11,085,445	18,298,460	7,213,015
		Total	**38,057,162**	**85,910,435**	**47,853,273**
	222	Year 1	3,519,373	16,056,489	12,537,116
		Year 2	5,900,477	16,625,143	10,724,666
		Year 3	7,919,755	17,188,318	9,268,563
		Year 4	9,632,112	17,746,350	8,114,239
		Year 5	11,085,445	18,299,541	7,214,096
		Total	**38,057,162**	**85,915,841**	**47,858,679**
Healthcare costs	All low[2]	Year 1	3,519,373	16,055,949	12,536,576
		Year 2	5,872,507	16,623,602	10,751,095
		Year 3	7,852,403	17,184,939	9,332,537
		Year 4	9,522,367	17,740,429	8,218,063
		Year 5	10,934,459	18,290,489	7,356,030
		Total	**37,701,108**	**85,895,409**	**48,194,300**
	All high[2]	Year 1	3,639,998	16,176,573	12,536,576
		Year 2	6,093,760	16,863,258	10,769,498
		Year 3	8,158,323	17,542,718	9,384,395
		Year 4	9,899,700	18,215,475	8,315,775
		Year 5	11,372,179	18,881,995	7,509,816
		Total	**39,163,959**	**87,680,019**	**48,516,060**
Abbreviations: CI: Clinical identification, NBS: Newborn screening;					

[1] Several combinations of the parameter values were tested, and this was the lowest/highest value.
[2] The healthcare costs for drug treatment and gene therapy are assumed to be 50% of these values, therefore they change with these variables

Appendix Table 13. Sensitivity analysis differences range

Parameter	CI/drug ($million)	NBS/gene therapy ($million)	Differences ($million)	Differences range ($million)
Cost of Gene therapy (onasemnogene abeparvovec-xioi) (1598394)	38.06	67.85	29.79	34.76
Cost of Gene therapy (onasemnogene abeparvovec-xioi) (2550000)	38.06	102.61	64.55	
Costs of Drug (nusinersen) (All high)	45.53	87.75	42.21	13.39
Costs of Drug (nusinersen) (All low)	27.80	83.40	55.60	
Drug: Administration cost (1959)	38.12	85.93	47.81	0.09
Drug: Administration cost (653)	38.00	85.90	47.90	
Gene therapy: Administration cost (222)	38.06	85.92	47.86	0.01
Gene therapy: Administration cost (74)	38.06	85.91	47.85	
Healthcare costs (All high[2])	39.16	87.68	48.52	0.32
Healthcare costs (All low[2])	37.70	85.90	48.19	
Incidence of SMA (diagnosis through CI) (0.00004)	16.73	37.76	21.04	78.88
Incidence of SMA (diagnosis through CI) (0.00019)	79.46	179.38	99.92	
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1 (0.003)	35.96	81.35	45.39	10.59
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assuming type 1 (0.527)	44.96	100.94	55.98	
Probability of NBS follow-up test: positive (0.0002)	38.06	85.91	47.86	-
Probability of NBS follow-up test: positive (0.0378)	38.06	85.91	47.86	
Probability of NBS test: false negative (0)	38.06	85.91	47.86	25.95
Probability of NBS test: false negative (0.00005)	38.06	59.97	21.91	
Probability of NBS test: positive (0.0118)	38.06	85.91	47.86	-
Probability of NBS test: positive (0.0164)	38.06	85.91	47.86	

Relative reduction of ventilator dependence and death, asymptomatic (gene therapy) (100)	38.06	85.91	47.86	0.10
Relative reduction of ventilator dependence and death, asymptomatic (gene therapy) (70.1)	38.06	86.01	47.95	
Relative reduction of ventilator dependence and death, asymptomatic (drug) (100)	38.06	85.91	47.86	0.46
Relative reduction of ventilator dependence and death, asymptomatic (drug) (70.1)	38.06	85.45	47.40	
Relative reduction of ventilator dependence/death between treated early and treated late, symptomatic (drug) (All high)	38.06	85.96	47.90	0.10
Relative reduction of ventilator dependence/death between treated early and treated late, symptomatic (drug) (All low)	38.06	85.86	47.80	
Relative reduction of ventilator dependence/death, symptomatic (gene therapy) (All high)	38.06	85.90	47.85	0.04
Relative reduction of ventilator dependence/death, symptomatic (gene therapy) (All low)	38.06	85.94	47.88	
Probability of responding to gene therapy (100)	38.06	76.72	38.66	22.98
Probability of responding to gene therapy (50)	38.06	99.70	61.64	
Probability of SMN2 copies, asymptomatic (Adjusted high[1])	39.37	88.86	49.48	6.35
Probability of SMN2 copies, asymptomatic (All low)	34.32	77.45	43.13	
Probability of when 2 or 3 SMN2 copies, type 1 or type 2 (Set) (Adjusted high[1])	38.65	87.19	48.53	6.96
Probability of when 2 or 3 SMN2 copies, type 1 or type 2 (Set) (All low)	33.11	74.68	41.57	
Transition Probabilities (All high)	34.06	85.84	51.78	7.93
Transition Probabilities (All low)	42.11	85.97	43.86	

Abbreviations: CI: Clinical identification, NBS: Newborn screening

[1] Several combinations of the parameter values were tested, and this was the lowest/highest value.

[2] The healthcare costs for drug treatment and gene therapy are assumed to be 50% of these values, therefore they change with these variables

Appendix Table 14. Projected long-term budget impact (NBS/gene therapy vs. CI/drug)

Year	CI/drug	NBS/gene therapy	Assuming 111,507 newborns			
			CI/drug	NBS/gene therapy	Differences	Accumulated Differences
1	31.56	143.99	3,519,373	16,055,949	12,536,576	12,536,576
2	21.35	5.10	5,900,477	16,624,602	10,724,125	23,260,701
3	18.11	5.05	7,919,755	17,187,777	9,268,022	32,528,723
4	15.36	5.00	9,632,112	17,745,810	8,113,698	40,642,421
5	13.03	4.96	11,085,445	18,299,001	7,213,555	47,855,976
6	11.08	4.92	12,320,755	18,847,625	6,526,870	54,382,846
7	9.43	4.88	13,372,729	19,391,932	6,019,203	60,402,050
8	8.05	4.84	14,270,543	19,932,159	5,661,617	66,063,666
9	6.89	4.81	15,038,646	20,468,540	5,429,895	71,493,561
10	5.91	4.78	15,697,459	21,001,293	5,303,834	76,797,395
11	5.08	4.75	16,264,035	21,530,623	5,266,588	82,063,983
12	4.38	4.72	16,752,605	22,056,724	5,304,119	87,368,102
13	3.79	4.69	17,175,054	22,579,771	5,404,717	92,772,818
14	3.28	4.66	17,541,317	23,099,922	5,558,605	98,331,424
15	2.86	4.64	17,859,710	23,617,315	5,757,605	104,089,028
16	2.49	4.62	18,137,208	24,132,068	5,994,861	110,083,889
17	2.17	4.59	18,379,674	24,644,287	6,264,614	116,348,503
18	1.90	4.57	18,592,052	25,154,071	6,562,019	122,910,522
19	1.67	4.55	18,778,518	25,661,509	6,882,992	129,793,514
20	1.47	4.53	18,942,606	26,166,681	7,224,075	137,017,589
21	1.30	4.51	19,087,318	26,669,665	7,582,347	144,599,936
22	1.15	4.49	19,215,207	27,170,525	7,955,319	152,555,255
23	1.02	4.47	19,328,449	27,669,323	8,340,874	160,896,128
24	0.90	4.46	19,428,911	28,166,122	8,737,211	169,633,339
25	0.80	4.44	19,518,192	28,660,982	9,142,790	178,776,130
26	0.71	4.42	19,597,668	29,153,966	9,556,298	188,332,428
27	0.64	4.40	19,668,527	29,645,137	9,976,610	198,309,038
28	0.57	4.39	19,731,795	30,134,550	10,402,755	208,711,794
29	0.51	4.37	19,788,362	30,622,260	10,833,898	219,545,692
30	0.45	4.36	19,839,000	31,108,310	11,269,311	230,815,002
31	0.41	4.34	19,884,381	31,592,743	11,708,362	242,523,364
32	0.37	4.33	19,925,096	32,075,597	12,150,501	254,673,866
33	0.33	4.32	19,961,657	32,556,905	12,595,248	267,269,113
34	0.29	4.30	19,994,518	33,036,698	13,042,180	280,311,293
35	0.27	4.29	20,024,077	33,515,000	13,490,923	293,802,216
36	0.24	4.28	20,050,684	33,991,825	13,941,142	307,743,357
37	0.21	4.26	20,074,648	34,467,187	14,392,539	322,135,896
38	0.19	4.25	20,096,245	34,941,091	14,844,846	336,980,742
39	0.17	4.24	20,115,719	35,413,550	15,297,831	352,278,574

40	0.16	4.22	20,133,286	35,884,575	15,751,289	368,029,862
41	0.14	4.21	20,149,140	36,354,178	16,205,038	384,234,900
42	0.13	4.20	20,163,454	36,822,363	16,658,908	400,893,809
43	0.12	4.19	20,176,381	37,289,119	17,112,738	418,006,546
44	0.10	4.17	20,188,058	37,754,422	17,566,364	435,572,910
45	0.09	4.16	20,198,607	38,218,232	18,019,624	453,592,534
46	0.09	4.15	20,208,140	38,680,499	18,472,359	472,064,893
47	0.08	4.13	20,216,753	39,141,162	18,924,409	490,989,302
48	0.07	4.12	20,224,536	39,600,152	19,375,616	510,364,918
49	0.06	4.10	20,231,569	40,057,388	19,825,819	530,190,737
50	0.06	4.08	20,237,923	40,512,777	20,274,854	550,465,591
51	0.05	4.07	20,243,664	40,966,212	20,722,548	571,188,139
52	0.05	4.05	20,248,849	41,417,577	21,168,728	592,356,867
53	0.04	4.03	20,253,531	41,866,738	21,613,208	613,970,075
54	0.04	4.01	20,257,757	42,313,537	22,055,780	636,025,855
55	0.03	3.98	20,261,571	42,757,786	22,496,215	658,522,070
56	0.03	3.96	20,265,010	43,199,283	22,934,273	681,456,343
57	0.03	3.93	20,268,111	43,637,830	23,369,719	704,826,062
58	0.03	3.90	20,270,905	44,073,229	23,802,324	728,628,386
59	0.02	3.87	20,273,422	44,505,277	24,231,856	752,860,241
60	0.02	3.84	20,275,687	44,933,765	24,658,078	777,518,319
61	0.02	3.81	20,277,724	45,358,472	25,080,748	802,599,068
62	0.02	3.77	20,279,555	45,779,162	25,499,606	828,098,674
63	0.01	3.73	20,281,200	46,195,593	25,914,392	854,013,066
64	0.01	3.69	20,282,677	46,607,525	26,324,847	880,337,914
65	0.01	3.65	20,284,002	47,014,725	26,730,723	907,068,637
66	0.01	3.61	20,285,189	47,416,956	27,131,767	934,200,403
67	0.01	3.56	20,286,252	47,813,976	27,527,724	961,728,127
68	0.01	3.51	20,287,203	48,205,492	27,918,289	989,646,416
69	0.01	3.46	20,288,054	48,591,195	28,303,142	1,017,949,558
70	0.01	3.40	20,288,812	48,970,747	28,681,935	1,046,631,493
71	0.01	3.35	20,289,489	49,343,766	29,054,277	1,075,685,770
72	0.01	3.28	20,290,090	49,709,849	29,419,759	1,105,105,529
73	0.00	3.22	20,290,625	50,068,602	29,777,977	1,134,883,506
74	0.00	3.15	20,291,099	50,419,430	30,128,331	1,165,011,837
75	0.00	3.07	20,291,519	50,761,847	30,470,328	1,195,482,165
76	0.00	2.99	20,291,889	51,095,240	30,803,352	1,226,285,517
77	0.00	2.90	20,292,214	51,419,017	31,126,803	1,257,412,320
78	0.00	2.81	20,292,499	51,732,453	31,439,954	1,288,852,274
79	0.00	2.71	20,292,748	52,034,831	31,742,083	1,320,594,356
80	0.00	2.61	20,292,965	52,325,477	32,032,512	1,352,626,868
81	0.00	2.49	20,293,153	52,603,661	32,310,508	1,384,937,376
82	0.00	2.38	20,293,314	52,868,681	32,575,367	1,417,512,743
83	0.00	2.25	20,293,453	53,119,732	32,826,279	1,450,339,022
84	0.00	2.12	20,293,570	53,356,047	33,062,477	1,483,401,499

85	0.00	1.98	20,293,669	53,576,949	33,283,280	1,516,684,778
86	0.00	1.84	20,293,752	53,781,616	33,487,864	1,550,172,642
87	0.00	1.69	20,293,820	53,969,555	33,675,735	1,583,848,377
88	0.00	1.53	20,293,876	54,140,599	33,846,723	1,617,695,100
89	0.00	1.38	20,293,922	54,294,371	34,000,450	1,651,695,549
90	0.00	1.22	20,293,958	54,430,743	34,136,785	1,685,832,335
91	0.00	1.07	20,293,986	54,549,866	34,255,880	1,720,088,215
92	0.00	0.92	20,294,007	54,652,196	34,358,189	1,754,446,404
93	0.00	0.77	20,294,024	54,738,497	34,444,474	1,788,890,878
94	0.00	0.64	20,294,036	54,809,827	34,515,791	1,823,406,669
95	0.00	0.52	20,294,044	54,867,499	34,573,455	1,857,980,124
96	0.00	0.41	20,294,050	54,913,032	34,618,982	1,892,599,106
97	0.00	0.31	20,294,054	54,948,069	34,654,015	1,927,253,120
98	0.00	0.24	20,294,057	54,974,298	34,680,241	1,961,933,361
99	0.00	0.17	20,294,059	54,993,367	34,699,308	1,996,632,669
100	0.00	0.12	20,294,060	55,006,809	34,712,749	2,031,345,418

Appendix Table 15. Projected long-term budget impact (NBS/gene therapy vs. NBS/drug)

Year	NBS/gene therapy	NBS/drug	Assuming 111,507 newborns			
			NBS/gene therapy	NBS/drug	Differences	Accumulated Differences
1	143.99	33.65	16,055,949	3,752,250	12,303,699	12,303,699
2	5.10	24.88	16,624,602	6,526,550	10,098,051	22,401,750
3	5.05	24.61	17,187,777	9,271,206	7,916,572	30,318,322
4	5.00	24.37	17,745,810	11,988,178	5,757,632	36,075,954
5	4.96	24.13	18,299,001	14,679,242	3,619,758	39,695,712
6	4.92	23.92	18,847,625	17,346,016	1,501,609	41,197,321
7	4.88	23.71	19,391,932	19,989,964	-598,032	40,599,290
8	4.84	23.52	19,932,159	22,612,476	-2,680,317	37,918,973
9	4.81	23.34	20,468,540	25,214,901	-4,746,360	33,172,613
10	4.78	23.17	21,001,293	27,798,488	-6,797,196	26,375,417
11	4.75	23.01	21,530,623	30,364,423	-8,833,800	17,541,617
12	4.72	22.86	22,056,724	32,913,798	-10,857,074	6,684,543
13	4.69	22.72	22,579,771	35,447,617	-12,867,846	-6,183,303
14	4.66	22.59	23,099,922	37,966,776	-14,866,854	-21,050,157
15	4.64	22.47	23,617,315	40,472,064	-16,854,749	-37,904,906
16	4.62	22.35	24,132,068	42,964,167	-18,832,099	-56,737,005
17	4.59	22.24	24,644,287	45,443,697	-20,799,410	-77,536,415
18	4.57	22.13	25,154,071	47,911,220	-22,757,149	-100,293,564
19	4.55	22.03	25,661,509	50,367,256	-24,705,746	-124,999,310
20	4.53	21.93	26,166,681	52,812,259	-26,645,577	-151,644,888
21	4.51	21.83	26,669,665	55,246,669	-28,577,004	-180,221,892
22	4.49	21.74	27,170,525	57,670,864	-30,500,338	-210,722,230

23	4.47	21.65	27,669,323	60,085,184	-32,415,861	-243,138,092
24	4.46	21.57	28,166,122	62,489,988	-34,323,866	-277,461,958
25	4.44	21.48	28,660,982	64,885,601	-36,224,619	-313,686,577
26	4.42	21.40	29,153,966	67,272,365	-38,118,399	-351,804,976
27	4.40	21.33	29,645,137	69,650,618	-40,005,481	-391,810,456
28	4.39	21.25	30,134,550	72,020,648	-41,886,098	-433,696,554
29	4.37	21.18	30,622,260	74,382,740	-43,760,481	-477,457,034
30	4.36	21.11	31,108,310	76,737,133	-45,628,823	-523,085,857
31	4.34	21.05	31,592,743	79,084,042	-47,491,298	-570,577,156
32	4.33	20.98	32,075,597	81,423,662	-49,348,065	-619,925,220
33	4.32	20.92	32,556,905	83,756,168	-51,199,264	-671,124,484
34	4.30	20.86	33,036,698	86,081,719	-53,045,021	-724,169,505
35	4.29	20.79	33,515,000	88,400,431	-54,885,432	-779,054,937
36	4.28	20.73	33,991,825	90,712,383	-56,720,558	-835,775,495
37	4.26	20.67	34,467,187	93,017,639	-58,550,452	-894,325,946
38	4.25	20.61	34,941,091	95,316,225	-60,375,134	-954,701,080
39	4.24	20.55	35,413,550	97,608,204	-62,194,654	-1,016,895,734
40	4.22	20.50	35,884,575	99,893,625	-64,009,050	-1,080,904,784
41	4.21	20.44	36,354,178	102,172,548	-65,818,370	-1,146,723,154
42	4.20	20.38	36,822,363	104,444,979	-67,622,616	-1,214,345,770
43	4.19	20.32	37,289,119	106,710,869	-69,421,750	-1,283,767,520
44	4.17	20.26	37,754,422	108,970,091	-71,215,669	-1,354,983,190
45	4.16	20.20	38,218,232	111,222,446	-73,004,214	-1,427,987,404
46	4.15	20.14	38,680,499	113,467,681	-74,787,183	-1,502,774,587
47	4.13	20.07	39,141,162	115,705,497	-76,564,335	-1,579,338,922
48	4.12	20.00	39,600,152	117,935,544	-78,335,392	-1,657,674,314
49	4.10	19.93	40,057,388	120,157,426	-80,100,038	-1,737,774,352
50	4.08	19.85	40,512,777	122,370,678	-81,857,901	-1,819,632,253
51	4.07	19.77	40,966,212	124,574,771	-83,608,559	-1,903,240,811
52	4.05	19.68	41,417,577	126,769,131	-85,351,554	-1,988,592,365
53	4.03	19.59	41,866,738	128,953,101	-87,086,362	-2,075,678,728
54	4.01	19.49	42,313,537	131,125,897	-88,812,359	-2,164,491,087
55	3.98	19.38	42,757,786	133,286,592	-90,528,806	-2,255,019,893
56	3.96	19.26	43,199,283	135,434,205	-92,234,922	-2,347,254,815
57	3.93	19.13	43,637,830	137,567,751	-93,929,920	-2,441,184,735
58	3.90	19.00	44,073,229	139,686,257	-95,613,028	-2,536,797,763
59	3.87	18.86	44,505,277	141,788,729	-97,283,452	-2,634,081,215
60	3.84	18.70	44,933,765	143,874,131	-98,940,367	-2,733,021,581
61	3.81	18.54	45,358,472	145,941,388	-100,582,916	-2,833,604,497
62	3.77	18.37	45,779,162	147,989,327	-102,210,165	-2,935,814,662
63	3.73	18.18	46,195,593	150,016,768	-103,821,175	-3,039,635,837
64	3.69	17.99	46,607,525	152,022,527	-105,415,002	-3,145,050,839
65	3.65	17.78	47,014,725	154,005,459	-106,990,735	-3,252,041,574
66	3.61	17.57	47,416,956	155,964,402	-108,547,446	-3,360,589,020
67	3.56	17.34	47,813,976	157,898,160	-110,084,184	-3,470,673,204

68	3.51	17.10	48,205,492	159,805,301	-111,599,808	-3,582,273,013
69	3.46	16.85	48,591,195	161,684,302	-113,093,107	-3,695,366,120
70	3.40	16.58	48,970,747	163,533,512	-114,562,765	-3,809,928,884
71	3.35	16.30	49,343,766	165,351,053	-116,007,287	-3,925,936,171
72	3.28	16.00	49,709,849	167,134,956	-117,425,107	-4,043,361,278
73	3.22	15.68	50,068,602	168,883,289	-118,814,687	-4,162,175,965
74	3.15	15.33	50,419,430	170,593,138	-120,173,708	-4,282,349,673
75	3.07	14.97	50,761,847	172,262,129	-121,500,282	-4,403,849,955
76	2.99	14.57	51,095,240	173,887,262	-122,792,021	-4,526,641,976
77	2.90	14.15	51,419,017	175,465,635	-124,046,618	-4,650,688,594
78	2.81	13.70	51,732,453	176,993,710	-125,261,257	-4,775,949,850
79	2.71	13.22	52,034,831	178,467,979	-126,433,147	-4,902,382,998
80	2.61	12.71	52,325,477	179,885,139	-127,559,662	-5,029,942,660
81	2.49	12.17	52,603,661	181,241,627	-128,637,967	-5,158,580,627
82	2.38	11.59	52,868,681	182,534,011	-129,665,330	-5,288,245,956
83	2.25	10.98	53,119,732	183,758,345	-130,638,613	-5,418,884,570
84	2.12	10.34	53,356,047	184,910,885	-131,554,838	-5,550,439,408
85	1.98	9.66	53,576,949	185,988,317	-132,411,368	-5,682,850,776
86	1.84	8.95	53,781,616	186,986,619	-133,205,003	-5,816,055,779
87	1.69	8.22	53,969,555	187,903,379	-133,933,824	-5,949,989,603
88	1.53	7.48	54,140,599	188,737,772	-134,597,172	-6,084,586,775
89	1.38	6.73	54,294,371	189,487,944	-135,193,573	-6,219,780,348
90	1.22	5.97	54,430,743	190,153,264	-135,722,521	-6,355,502,869
91	1.07	5.21	54,549,866	190,734,460	-136,184,594	-6,491,687,463
92	0.92	4.48	54,652,196	191,233,750	-136,581,554	-6,628,269,017
93	0.77	3.78	54,738,497	191,654,849	-136,916,352	-6,765,185,369
94	0.64	3.12	54,809,827	192,002,911	-137,193,084	-6,902,378,454
95	0.52	2.52	54,867,499	192,284,346	-137,416,847	-7,039,795,301
96	0.41	1.99	54,913,032	192,506,551	-137,593,519	-7,177,388,819
97	0.31	1.53	54,948,069	192,677,540	-137,729,471	-7,315,118,290
98	0.24	1.15	54,974,298	192,805,550	-137,831,252	-7,452,949,542
99	0.17	0.83	54,993,367	192,898,620	-137,905,253	-7,590,854,795
100	0.12	0.59	55,006,809	192,964,228	-137,957,420	-7,728,812,215

Appendix Table 16. Projected long-term budget impact (NBS/gene therapy vs. CI/usual care)

Year	NBS/gene therapy	CI/usual care	Assuming 111,507 newborns			
			NBS/gene therapy	CI/usual care	Differences	Accumulated Differences
1	143.99	0.30	16,055,949	33,359	16,022,590	16,022,590
2	5.10	1.16	16,624,602	162,616	16,461,986	32,484,575
3	5.05	0.94	17,187,777	267,298	16,920,480	49,405,055
4	5.00	0.71	17,745,810	346,501	17,399,309	66,804,364
5	4.96	0.55	18,299,001	407,610	17,891,390	84,695,754

6	4.92	0.44	18,847,625	456,229	18,391,396	103,087,151
7	4.88	0.36	19,391,932	496,051	18,895,881	121,983,032
8	4.84	0.30	19,932,159	529,478	19,402,681	141,385,713
9	4.81	0.26	20,468,540	558,090	19,910,451	161,296,164
10	4.78	0.22	21,001,293	582,940	20,418,352	181,714,517
11	4.75	0.20	21,530,623	604,754	20,925,869	202,640,386
12	4.72	0.17	22,056,724	624,044	21,432,680	224,073,066
13	4.69	0.15	22,579,771	641,186	21,938,585	246,011,651
14	4.66	0.14	23,099,922	656,468	22,443,454	268,455,105
15	4.64	0.12	23,617,315	670,119	22,947,196	291,402,301
16	4.62	0.11	24,132,068	682,327	23,449,742	314,852,043
17	4.59	0.10	24,644,287	693,249	23,951,039	338,803,082
18	4.57	0.09	25,154,071	703,022	24,451,049	363,254,130
19	4.55	0.08	25,661,509	711,768	24,949,741	388,203,872
20	4.53	0.07	26,166,681	719,592	25,447,090	413,650,961
21	4.51	0.06	26,669,665	726,590	25,943,075	439,594,036
22	4.49	0.06	27,170,525	732,847	26,437,679	466,031,715
23	4.47	0.05	27,669,323	738,439	26,930,884	492,962,599
24	4.46	0.04	28,166,122	743,437	27,422,685	520,385,284
25	4.44	0.04	28,660,982	747,902	27,913,080	548,298,364
26	4.42	0.04	29,153,966	751,889	28,402,077	576,700,441
27	4.40	0.03	29,645,137	755,450	28,889,688	605,590,128
28	4.39	0.03	30,134,550	758,628	29,375,922	634,966,051
29	4.37	0.03	30,622,260	761,466	29,860,794	664,826,845
30	4.36	0.02	31,108,310	763,998	30,344,312	695,171,157
31	4.34	0.02	31,592,743	766,258	30,826,486	725,997,642
32	4.33	0.02	32,075,597	768,274	31,307,323	757,304,965
33	4.32	0.02	32,556,905	770,073	31,786,832	789,091,797
34	4.30	0.01	33,036,698	771,677	32,265,021	821,356,818
35	4.29	0.01	33,515,000	773,108	32,741,892	854,098,710
36	4.28	0.01	33,991,825	774,384	33,217,441	887,316,151
37	4.26	0.01	34,467,187	775,523	33,691,665	921,007,815
38	4.25	0.01	34,941,091	776,537	34,164,554	955,172,369
39	4.24	0.01	35,413,550	777,442	34,636,108	989,808,477
40	4.22	0.01	35,884,575	778,248	35,106,326	1,024,914,804
41	4.21	0.01	36,354,178	778,967	35,575,211	1,060,490,015
42	4.20	0.01	36,822,363	779,608	36,042,755	1,096,532,769
43	4.19	0.01	37,289,119	780,179	36,508,939	1,133,041,709
44	4.17	0.005	37,754,422	780,688	36,973,734	1,170,015,442
45	4.16	0.004	38,218,232	781,141	37,437,090	1,207,452,532
46	4.15	0.004	38,680,499	781,545	37,898,953	1,245,351,486
47	4.13	0.003	39,141,162	781,905	38,359,257	1,283,710,743
48	4.12	0.003	39,600,152	782,225	38,817,927	1,322,528,669
49	4.10	0.003	40,057,388	782,510	39,274,878	1,361,803,547
50	4.08	0.002	40,512,777	782,764	39,730,013	1,401,533,561

51	4.07	0.002	40,966,212	782,990	40,183,223	1,441,716,783
52	4.05	0.002	41,417,577	783,190	40,634,387	1,482,351,170
53	4.03	0.002	41,866,738	783,369	41,083,370	1,523,434,540
54	4.01	0.001	42,313,537	783,527	41,530,010	1,564,964,550
55	3.98	0.001	42,757,786	783,668	41,974,118	1,606,938,668
56	3.96	0.001	43,199,283	783,793	42,415,491	1,649,354,159
57	3.93	0.001	43,637,830	783,903	42,853,927	1,692,208,086
58	3.90	0.001	44,073,229	784,002	43,289,227	1,735,497,314
59	3.87	0.001	44,505,277	784,089	43,721,189	1,779,218,502
60	3.84	0.001	44,933,765	784,166	44,149,599	1,823,368,101
61	3.81	0.001	45,358,472	784,234	44,574,238	1,867,942,340
62	3.77	0.001	45,779,162	784,294	44,994,868	1,912,937,207
63	3.73	0.0005	46,195,593	784,347	45,411,246	1,958,348,453
64	3.69	0.0004	46,607,525	784,394	45,823,130	2,004,171,584
65	3.65	0.0004	47,014,725	784,436	46,230,289	2,050,401,872
66	3.61	0.0003	47,416,956	784,472	46,632,484	2,097,034,356
67	3.56	0.0003	47,813,976	784,504	47,029,472	2,144,063,828
68	3.51	0.0003	48,205,492	784,533	47,420,960	2,191,484,788
69	3.46	0.0002	48,591,195	784,557	47,806,638	2,239,291,426
70	3.40	0.0002	48,970,747	784,579	48,186,168	2,287,477,594
71	3.35	0.0002	49,343,766	784,598	48,559,168	2,336,036,762
72	3.28	0.0001	49,709,849	784,615	48,925,234	2,384,961,996
73	3.22	0.0001	50,068,602	784,630	49,283,973	2,434,245,968
74	3.15	0.0001	50,419,430	784,642	49,634,787	2,483,880,756
75	3.07	0.0001	50,761,847	784,653	49,977,194	2,533,857,949
76	2.99	0.0001	51,095,240	784,663	50,310,577	2,584,168,527
77	2.90	0.0001	51,419,017	784,671	50,634,346	2,634,802,872
78	2.81	0.0001	51,732,453	784,678	50,947,775	2,685,750,647
79	2.71	0.0001	52,034,831	784,685	51,250,147	2,737,000,794
80	2.61	0.00005	52,325,477	784,690	51,540,787	2,788,541,580
81	2.49	0.00004	52,603,661	784,694	51,818,966	2,840,360,547
82	2.38	0.00003	52,868,681	784,698	52,083,983	2,892,444,530
83	2.25	0.00003	53,119,732	784,701	52,335,031	2,944,779,561
84	2.12	0.00002	53,356,047	784,704	52,571,343	2,997,350,904
85	1.98	0.00002	53,576,949	784,706	52,792,243	3,050,143,147
86	1.84	0.00002	53,781,616	784,708	52,996,908	3,103,140,055
87	1.69	0.00001	53,969,555	784,709	53,184,846	3,156,324,900
88	1.53	0.00001	54,140,599	784,710	53,355,889	3,209,680,789
89	1.38	0.00001	54,294,371	784,711	53,509,660	3,263,190,449
90	1.22	0.00001	54,430,743	784,712	53,646,031	3,316,836,480
91	1.07	0.000005	54,549,866	784,713	53,765,153	3,370,601,634
92	0.92	0.000004	54,652,196	784,713	53,867,483	3,424,469,117
93	0.77	0.000003	54,738,497	784,713	53,953,784	3,478,422,901
94	0.64	0.000002	54,809,827	784,714	54,025,113	3,532,448,014
95	0.52	0.000001	54,867,499	784,714	54,082,786	3,586,530,799

96	0.41	0.000001	54,913,032	784,714	54,128,318	3,640,659,118
97	0.31	0.000001	54,948,069	784,714	54,163,355	3,694,822,473
98	0.24	0.0000004	54,974,298	784,714	54,189,584	3,749,012,056
99	0.17	0.0000003	54,993,367	784,714	54,208,653	3,803,220,709
100	0.12	0.0000001	55,006,809	784,714	54,222,095	3,857,442,804

Appendix Table 17. COS development steps

COS development steps	**This study**
1. Define the scope of the COS	The scope includes health conditions, target population, interventions, and settings. The health condition included in this study is pediatric complex chronic conditions (CCC). The target population is the family of ill children. This study does not target any specific interventions or settings.
2. Check whether a new COS is needed and register the COS in the COMET database	After searching within the COMET database [96], there were no studies identified that developed COS to measure family spillover effects. This study will be registered with the following data: Name, Organization, Email address, Phone, Study title, Abstract, Collaborators, Stage of work, State date, End date (actual or estimated), Comments.
3. Develop a protocol for the development of COS	This table serves as the protocol for the development of COS.
4. Determine what to measure	Following the COS development process, this study includes the following steps: (1) Identifying outcome measures, (2) Expert panels and best-worst scaling survey, and (3) Consensus meetings to finalize the COS.
4.1 Identify existing knowledge	See Methods (1) Identifying outcome measures
4.2 Fill gaps in knowledge if needed	See Methods (1) Identifying outcome measures
4.3 Elicit views about important outcomes in a consensus process	See Methods (2) Expert panels and best-worst scaling survey
4.4 Hold a face-to-face meeting to finalize the recommended COS	See Methods (3) Consensus meetings to finalize the COS
4.5 Report the work using the COS-STAR guidance[97]	See Methods (3) Consensus meetings to finalize the COS
4.6 Implementation, assess uptake, and review and update as necessary	See Methods (3) Consensus meetings to finalize the COS
5. Determine how to measure	Not included in this study, for future research

5.1 Identifying existing measurement in instruments or definitions for each outcome in the COS	Not included in this study, for future research
5.2 Quality assess instruments and definitions	Not included in this study, for future research
5.3 Use a consensus process to finalize the recommended outcome measurement instruments and definition	Not included in this study, for future research
Stakeholder involvement	See Methods

Appendix Table 18. The COMET initiative outcome measures: taxonomy of categories

Core area		**Individual patient level**	**Family spillover relevant (Our study)**	**Definitions (Individual patient level)**
Death Physiological or clinical	1	Mortality/survival	N/A	
	2 – 24: Physiological/clinical			
	2	Blood and lymphatic system outcomes	N/A	
	3	Cardiac outcomes	N/A	
	4	Congenital, familial and genetic outcomes	N/A	
	5	Endocrine outcomes	N/A	
	6	Ear and labyrinth outcomes	N/A	
	7	Eye outcomes	N/A	
	8	Gastrointestinal outcomes	N/A	
	9	General outcomes	N/A	
	10	Hepatobiliary outcomes	N/A	
	11	Immune system outcomes	N/A	
	12	Infection and infestation outcomes	N/A	
	13	Injury and poisoning outcomes	N/A	

	14	Metabolism and nutrition outcomes	N/A	
	15	Musculoskeletal and connective tissue outcomes	N/A	
	16	Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps)	N/A	
	17	Nervous system outcomes	N/A	
	18	Pregnancy, puerperium, and perinatal outcomes	N/A	
	19	Renal and urinary outcomes	N/A	
	20	Reproductive system and breast outcomes	N/A	
	21	Psychiatric outcomes	N/A	
	22	Respiratory, thoracic and mediastinal outcomes	N/A	
	23	Skin and subcutaneous tissue outcomes	N/A	
	24	Vascular outcomes	N/A	
Life impact	Functioning			
	25	Physical functioning	N/A	impact of disease/condition on physical activities of daily living (for example, ability to walk, independence, self-care, performance status, disability index, motor skills, sexual dysfunction. Health behavior and management)
	26	Social functioning	N/A	impact of disease/condition on social functioning (e.g., ability to socialize, behavior within society, communication, companionship, psychosocial development, aggression, recidivism, participation)
	27	Role functioning	N/A	impact of disease/condition on role (e.g. ability to care for children, work status)

	28	Emotional functioning/well-being	N/A	impact of disease/condition on emotions or overall wellbeing (e.g., ability to cope, worry, frustration, confidence, perceptions regarding body image and appearance, psychological status, stigma, life satisfaction, meaning and purpose, positive affect, self-esteem, self-perception and self-efficacy)
	29	Cognitive functioning	N/A	impact of disease/condition on cognitive function (e.g., memory lapse, lack of concentration, attention); outcomes relating to knowledge, attitudes and beliefs (e.g., learning and applying knowledge, spiritual beliefs, health beliefs/knowledge)
	30	Global quality of life	N/A	Includes only implicit composite outcomes measuring global quality of life
	31	Perceived health status	N/A	Subjective ratings by the affected individual of their relative level of health
	32	Delivery of care, including - Satisfaction/patient preference - Acceptability and availability - Adherence/compliance - Withdrawal from treatment - Appropriateness of treatment – Process, implementation, and service outcomes	N/A	Includes outcomes relating to the delivery of care, including adherence/compliance; patient preference; tolerability/acceptability of intervention; withdrawal from intervention (e.g. time to treatment failure, reason for stopping therapy); appropriateness of intervention; accessibility, quality and adequacy of intervention; patient/carer satisfaction (emotional rather than financial burden); process, implementation and service outcomes (e.g. overall health system performance and the impact of service provision on the users of services)
	33	Personal circumstances	N/A	Outcomes relating to patient's finances, home and environment

Resource use	**34**	**Economic**	**A. Direct medical and non-medical costs that are borne by the family**	**General outcomes (e.g., cost, resource use) not captured within other specific resource use domains**
	35	Hospital	N/A	Outcomes relating to inpatient or day case hospital care (e.g., duration of hospital stays, admission to ICU)
	36	Need for further intervention	N/A	Need for further intervention: outcomes relating to medication (e.g., concomitant medications, pain relief), surgery (e.g., caesarean delivery, time to transplantation) and other procedures (e.g., dialysis-free survival, mode of delivery)
	37	**Societal/carer burden**	**A. Direct medical and non-medical costs that are borne by the family** **B. Informal caregiving time** **C. Impact on family members' Quality of life**	**Outcomes relating to financial or time implications on carer or society as a whole (e.g., need for home help, entry to institutional care, effect on family income)**
Adverse events	38	Adverse events/effects	N/A	

Appendix Table 19. Spillover COS Project Systematic Review Protocol

Project title	Systematic review of outcomes for study "Developing a Core Outcome Set for Measuring Family Spillover Effects for Children with Complex Chronic Conditions – from an economic perspective"
Introduction	As recommended by the COMET (Core Outcome Measures in Effectiveness Trials) initiative in their handbook for developing a core outcome set (COS)[17], this study plans to conduct a systematic review to understand the types of outcomes that previous researchers focused on when they measure family spillover effects. The results of the systematic review will provide data of potentially overlooked outcomes, if any.
Methods	The systematic review will focus on the two topics of family spillover effects: (1) direct medical and non-medical costs and (2) informal caregiving time. This study will not focus on spillover effects on caregivers'

and family members' quality of life as a recent published systematic review has done so.[82] The databases used to perform the search will include PubMed (MEDLINE), Embase, and EconLit. While the COMET handbook did not recommend a time window, they did state that a recent search is recommended as a minimum, such as the past 24 months. For this study, a time frame of 10 years seems to be appropriate for the topic, therefore, the time frame will be from January 2010 to August 2021. For data extraction, the COMET handbook recommended considering the following: (1) Study characteristics, (2) Outcomes, (3) Outcome measurement instruments and/or definitions provided by the authors for each outcome. It is also recommended that the data is extracted verbatim, i.e., the same words as were used originally. The search terms and limitations are shown in Table 1 and Table 2 below.

Search Terms

Table 1. Search 1: direct medical and non-medical costs

Database	Search term	Results (Number of papers)
PubMed (MEDLINE)	(spillover) AND (health) AND (cost[MeSH Terms]), 2010-2021	115
Embase	spillover AND health AND cost AND [2010-2021]/py	228
EconLit	spillover AND health AND cost, Date: From January 01 2010 to August 31 2021; Language: English	148
Duplicated		85
Total		406

Table 2. Search 2: Informal caregiving time

Database	Search term	Results (Number of papers)
PubMed (MEDLINE)	(spillover) AND (health) AND (informal) AND (care), 2010-2021	74
Embase	spillover AND health AND informal AND care AND [2010-2021]/py	22
EconLit	spillover AND health AND informal AND care	11
Duplicated		15
Total		92

Analysis Plan

The articles will be included if they listed potential outcome measure items, such as cost items or items related to spending time on informal caregiving (e.g., quit job, missed workdays, etc.) The results of the systematic review will provide data of potentially overlooked outcomes, if any.

Appendix Table 20 Best-worst scaling analysis - MNL regression model preliminary results

Best-worst scaling analysis - MNL regression model preliminary results

Table 21a. Example of simulated dataset (first 10 rows of data, total observation N=3,781)

id	Q	PAIR	BEST	WORST	RES.B	RES.W	RES	t_coordinatecare	c_medication	c_ervisithosp	q_familymembers	c_travelmedvisithosp	c_specequipsup	t_extracaregiving
1	1	1	2	11	15	2	FALSE	0	1	0	0	0	0	0
1	1	2	2	15	15	2	FALSE	0	1	0	0	0	0	0
1	1	3	2	18	15	2	FALSE	0	1	0	0	0	0	0
1	1	4	2	19	15	2	FALSE	0	1	0	0	0	0	0
1	1	5	11	2	15	2	FALSE	0	-1	0	0	0	0	0
1	1	6	11	15	15	2	FALSE	0	0	0	0	0	0	0
1	1	7	11	18	15	2	FALSE	0	0	0	0	0	0	0
1	1	8	11	19	15	2	FALSE	0	0	0	0	0	0	0
1	1	9	15	2	15	2	TRUE	0	-1	0	0	0	0	0

t_docvisits	t_quitjobs	t_missedworkday	c_childcare	t_reducedhours	c_extrahouseholdsup	q_caregivers	t_ervisithosp	c_householdreno	c_medvisit	c_treatment	t_treatmentvisit	c_docvisits	t_medvisits	STR
0	0	0	-1	0	0	0	0	0	0	0	0	0	0	101
0	0	0	0	0	0	0	-1	0	0	0	0	0	0	101
0	0	0	0	0	0	0	0	0	0	-1	0	0	0	101
0	0	0	0	0	0	0	0	0	0	0	-1	0	0	101
0	0	0	1	0	0	0	0	0	0	0	0	0	0	101
0	0	0	1	0	0	0	-1	0	0	0	0	0	0	101
0	0	0	1	0	0	0	0	0	0	-1	0	0	0	101
0	0	0	1	0	0	0	0	0	0	0	-1	0	0	101
0	0	0	0	0	0	0	1	0	0	0	0	0	0	101

The "BEST" and "WORST" are possible pairs the respondent can choose and "RES.B" and "RES.W" indicates what the respondent choice as the response. RES is coded as FALSE if these two do not match, and "TRUE" if these matches. For the regression analysis, RES is the dependent variable, and the 21 items are the independent variables (these are coded as 1 if listed as "BEST" but coded as -1 if listed as "WORST" in the possible pairs).

Preliminary results of count analysis and MNL regression using the simulated dataset

(1) Count analysis

As shown in the table and figures below, the items selected as the most important items are "Quit jobs or did not pursue a job in order to care for the child", "Caregivers' quality of life", and "Extra caregiving time spent caring for child". The result is similar to the results of 30 respondents, where the items in the time and quality of life categories are more likely to be selected more important and items in the cost categories are more likely to be selected as least important.

Table 21b. Count analysis results – best-worst scores and ranking

	Best (B)	Worst (W)	Best-Worst (B-W)	Rank	Standardized B-W*	Square root of B/W	Mean B-W
Quit jobs or did not pursue a job in order to care for the child	27	2	25	1	0.56	3.67	2.78
Caregivers' quality of life	21	4	17	2	0.38	2.29	1.89
Extra caregiving time spent caring for child	19	3	16	3	0.36	2.52	1.78
Days of missed work in order to care for the child	16	1	15	4	0.33	4.00	1.67
Family member's quality of life	18	5	13	5	0.29	1.90	1.44
Reduced hours of paid work in order to care for child	12	1	11	6	0.24	3.46	1.22
Time spent at emergency room visits and hospitalizations	14	4	10	7	0.22	1.87	1.11
Time spent coordinating the child's care	15	6	9	8	0.20	1.58	1.00
Costs for emergency room visits and hospitalizations	9	6	3	9	0.07	1.22	0.33
Costs related to household renovations for the child's condition	9	10	-1	10	-0.02	0.95	-0.11

Time spent at treatment-related visits	3	5	-2	11	-0.04	0.77	-0.22
Time spent at doctor's visits	7	11	-4	12	-0.09	0.80	-0.44
Costs for special equipment and supplies	2	9	-7	13	-0.16	0.47	-0.78
Costs of childcare	2	9	-7	13	-0.16	0.47	-0.78
Time spent at other medical visits	4	11	-7	13	-0.16	0.60	-0.78
Costs for treatments	3	11	-8	16	-0.18	0.52	-0.89
Costs for other medical visits	0	13	-13	17	-0.29	0.00	-1.44
Costs for medications	1	15	-14	18	-0.31	0.26	-1.56
Costs for doctor's visits	4	18	-14	18	-0.31	0.47	-1.56
Costs related to travel to medical visits and hospitalization	1	20	-19	20	-0.42	0.22	-2.11
Costs of extra daily household supplies	2	25	-23	21	-0.51	0.28	-2.56
*Calculated by dividing B minus W score with the product of frequency of occurrence of the item*sample size, see Mühlbacher et al. (2016) for more information.							

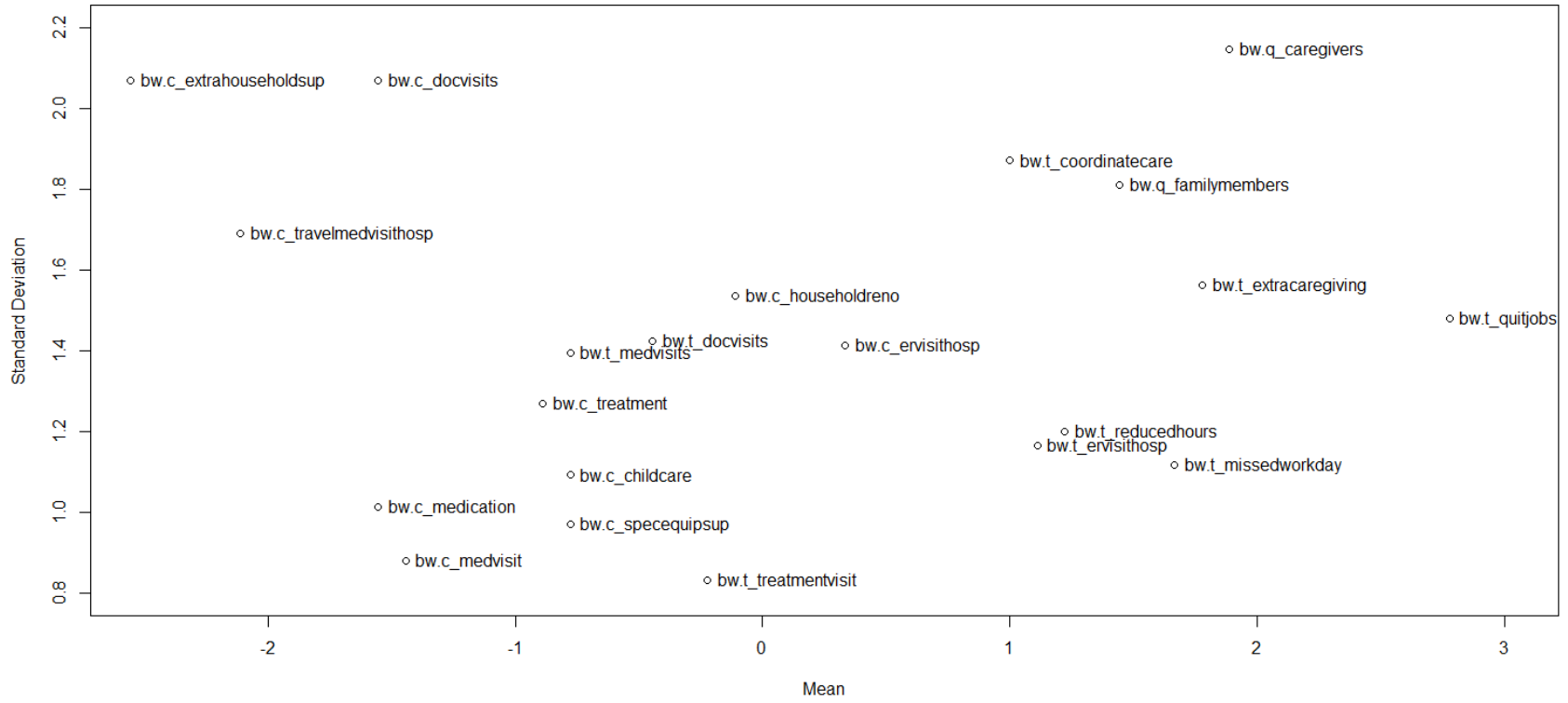


Figure 21a. Count analysis result – mean best-worst score

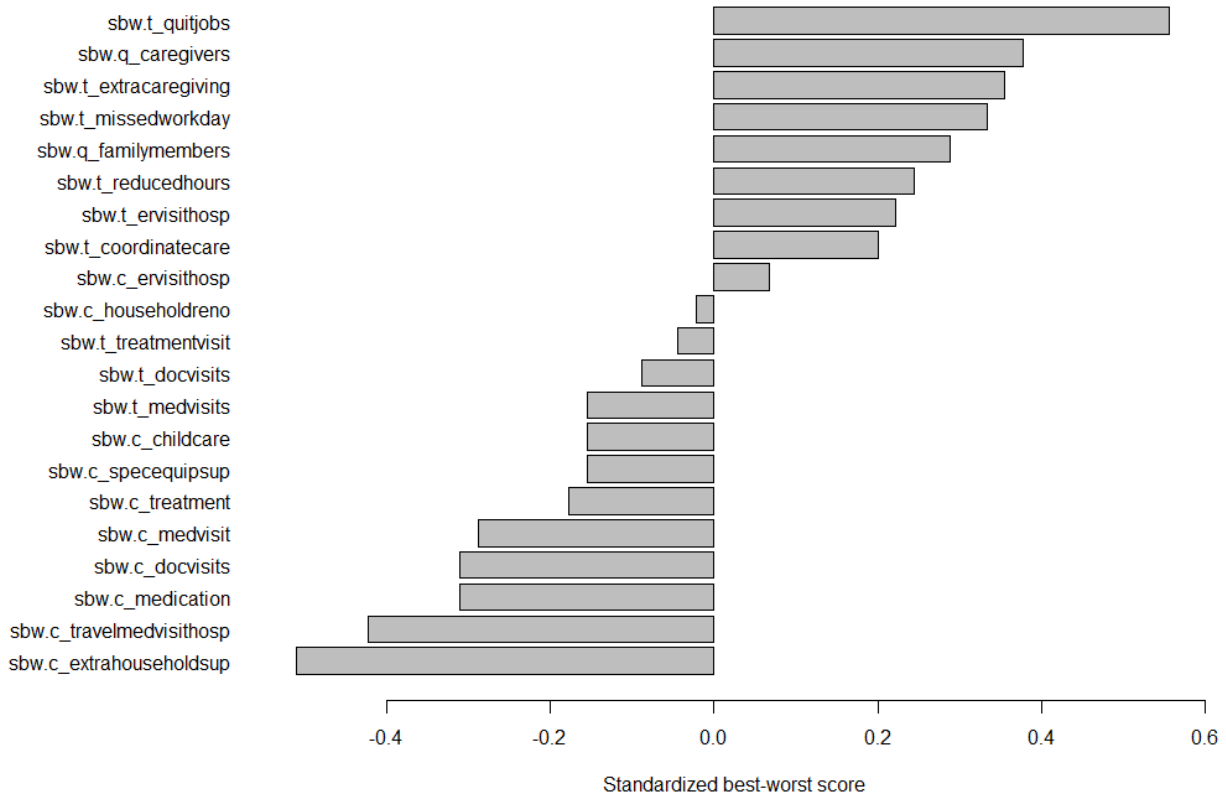


Figure 21b. Count analysis result – standardized best-worst score

(2) MNL regression

For the MNL regression results, the model is set as the following utility function using "Costs of extra daily household supplies" (c_extrahouseholdsup) as the reference variable as it was considered as the least important item in the count analysis:

Utility = β_1 t_coordinatecare + β_2 c_medication + β_3 c_ervisithosp + β_4 q_familymembers + β_5 c_travelmedvisithosp + β_6 c_specequipsup + β_7 t_extracaregiving + β_8 t_docvisits + β_9 t_quitjobs + β_{10} t_missedworkday + β_{11} c_childcare + β_{12} t_reducedhours + β_{13} q_caregivers + β_{14} t_ervisithosp + β_{15} c_householdreno

$+ \beta_{16}$ c_medvisit $+ \beta_{17}$ c_treatment $+ \beta_{18}$ t_treatmentvisit $+ \beta_{19}$ c_docvisits $+ \beta_{20}$ t_medvisits

In the table below, the results show the same ranking as count analysis. Based on the results of all the coefficients are positive and most of them are statistically significant, most of them are significantly more important than the reference variable (c_extrahouseholdsup).

As shown above, compared to the count analysis based on the data of 30 respondents, the results of combined data with 9 respondents were similar. However, given the small sample size and high similarity of the respondents, this result only provides limited information. Further collection of data is needed to address this question.

Table 21c. MNL regression results

Coefficients	Estimate	Std. Error	z-value	Pr(>|z|)	Significant level
t_coordinatecare	2.32	0.399	5.8	0.00000001	***
c_medication	0.64	0.378	1.7	0.092	.
c_ervisithosp	1.76	0.388	4.5	0.000006	***
q_familymembers	2.44	0.393	6.2	0.000000001	***
c_travelmedvisithosp	0.30	0.376	0.8	0.422	
c_specequipsup	1.09	0.375	2.9	0.004	**
t_extracaregiving	2.79	0.400	7.0	0.000000000003	***
t_docvisits	1.30	0.381	3.4	0.001	***
t_quitjobs	3.40	0.414	8.2	0.0000000000000002	***
t_missedworkday	2.70	0.403	6.7	0.00000000002	***
c_childcare	1.09	0.380	2.9	0.004	**
t_reducedhours	2.46	0.401	6.1	0.000000001	***
q_caregivers	2.83	0.401	7.1	0.000000000002	***
t_ervisithosp	2.22	0.389	5.7	0.00000001	***
c_householdreno	1.53	0.379	4.0	0.00005	***
c_medvisit	0.72	0.378	1.9	0.058	.
c_treatment	1.02	0.376	2.7	0.007	**
t_treatmentvisit	1.39	0.380	3.7	0.0002	***
c_docvisits	0.63	0.376	1.7	0.095	.
t_medvisits	1.08	0.378	2.9	0.004	**

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
Log-Likelihood: -458.09

Key code in R software

Generating new dataset

```
mdcos.data <- bws.dataset(  data = cosdata1, response.type = 1,   choice.sets = testbibd,
  design.type = 2,   item.names = items.cos,   id = "id",   model = "maxdiff")
```

Count analysis

```
cscos <- bws.count(mdcos.data, cl = 2)
summary(cscos)
```

MNL regression (using c_extrahouseholdsup as reference)

```
regbws <- RES ~ t_coordinatecare+c_medication+c_ervisithosp+q_familymembers+c_travelmedvisithosp+c_specequipsup+t_extracaregiving
+t_docvisits+t_quitjobs+t_missedworkday+c_childcare+t_reducedhours+q_caregivers+t_ervisithosp+c_householdreno
+c_medvisit+c_treatment+t_treatmentvisit+c_docvisits+t_medvisits -1
mdcos.data.dfidx <- dfidx(data = mdcos.data, idx = list(c("STR", "id"), "PAIR"), choice = "RES")
mdcos.out <- mlogit(formula = regbws, data = mdcos.data.dfidx)
summary(mdcos.out)
```

Appendix Section 21. Survey

STUDY TITLE

Developing a Core Outcome Set for Measuring Family Spillover Effects for Children with Complex Chronic Conditions – from an economic perspective

GENERAL INFORMATION

We are conducting a survey to understand what is important to families with a child with complex chronic conditions. We expect this survey will take approximately 10-15 minutes to complete. We welcome anyone to take the survey. You do not have to have a child with complex chronic conditions to take the survey.

Taking part in this study is completely voluntary. There are no right or wrong answers to the survey questions we will be asking you. You do not have to participate if you do not want to. If you choose to participate, you do not have to answer any questions you do not want to answer. In addition, there will be no penalty or loss of benefits if you choose not to participate in this research study at any time.

Your responses will be kept confidential, and only the research team will have access to the survey data. The results of this study may be published in an article but would not include any information that would let others know you have participated in the survey.

There are no direct benefits to you for participating in this survey.

To thank you for taking part in our study, we will send you $20 after you take the survey. At the end of the survey, you will have the opportunity to enter your contact information to receive this payment.

Institutional Review Board Compliance

This study received IRB Exempt from the University of Michigan Medical School Institutional Review Board (IRBMED): IRB#HUM00198755.

CONTACT INFORMATION

Please contact the person listed below to get more information about the study, ask a question about the study, or express a concern about the study.

Coordinator: Angela Rose, MS, MPH
University of Michigan
300 North Ingalls
Ann Arbor, MI 48109
angmrose@med.umich.edu

You may also express concern about the study (IRB#HUM00198755) by contacting the Institutional Review Board.

University of Michigan Medical School
Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768
E-mail: irbmed@umich.edu

What country do you live in?

- ◉ United States
- ○ Outside of the United States

STUDY INFORMATION

Children with complex chronic conditions have severe medical problems needing special medical care. These problems last at least 1 year. They visit the doctor or hospital often and may take many medications. The goal of this survey is to measure family effects. Examples of family effects are paying for the child's treatment, spending time taking care of the child, and changes to the family's quality of life. The impact of family effects includes changes in the family's stress level and how family members interact with each other.

In this survey, we would like to learn which family effects could be most important to the families of children with complex chronic conditions. We welcome anyone to take the survey. You do not have to have a child with complex chronic conditions to take the survey.

It will take about 10-15 minutes to finish this survey.

Now, imagine yourself in the role of the parent of a child with a complex chronic condition. Taking care of your child requires a lot of care and coordination from the family. If you have a child with a severe health condition, consider that child as you complete the survey.

On the next few pages are items that might be important to you when thinking about how your child's condition affects your family.

These items are related to the out-of-pocket costs for medical care which is the amount you pay for medical care after insurance. This includes costs like co-pays, co-insurance, and deductibles. If you are not insured, out-of-pocket costs are the full amounts that hospitals and doctors charge for care. This does not include any other costs related to medical care, such as parking or transportation, or to the premiums that families have to pay to buy health insurance.

Item	Definition
Costs for medications	Out-of-pocket costs for your child's medicine. This includes the cost of over-the-counter, prescription, and infused medications as well as medical foods.

Costs for treatments	Out-of-pocket costs directly related to your child's treatments. This includes the cost of surgeries or procedures that help improve your child's condition.
Costs for doctor's visits	Out-of-pocket medical costs directly related to your child's specialist or primary care provider visits. This includes specialist visits required for diagnosis.
Costs for emergency room visits and hospitalizations	Out-of-pocket medical costs directly related to your child's emergency room visits and hospitalizations.
Costs for other medical visits	Out-of-pocket costs for other medical visits. This includes physical therapy, occupational therapy, speech therapy and counseling.
Costs for special equipment and supplies	Out-of-pocket costs of your child's special equipment and supplies directly related to your child's condition such as wheelchairs, bathroom equipment, and breathing machines (e.g., CPAP, nebulizers).

Families with a child with a complex chronic condition may have other, non-medical costs related to caring for their child. The items below describe these costs.

Item	**Definition**
Costs related to travel to medical visits and hospitalization	Out-of-pocket non-medical costs directly related to your child's medical visits and hospitalizations including gas, parking, hotel stays, and meals.
Costs related to household renovations for your child's condition	Out-of-pocket non-medical costs spent on household modifications and renovations directly related to your child's condition such as ramps and enlarged doorways.
Costs of extra daily household supplies	Out-of-pocket non-medical costs spent on extra daily household supplies directly related to your child's condition such as extra toilet paper, cleaning supplies, diapers etc.
Costs of childcare	Out-of-pocket costs of childcare for other children in your household so that you can take your child to their medical appointments, ER visits, and hospitalizations.

Item	Definition
Time spent at treatment-related visits	Caregiver time spent for your child's treatment-related medical visits, including the time spent traveling and waiting for the visit.
Time spent at doctor's visits	Caregiver time spent related to your child's specialist and primary care provider visits, including the time spent traveling and waiting for the visit. This includes time spent at specialist visits required for diagnosis.
Time spent at emergency room visits and hospitalizations	Caregiver time spent related to your child's emergency room visits and hospitalizations including the time spent traveling and waiting in the emergency room.
Time spent at other medical visits	Caregiver time spent related to your child's physical therapy, occupational therapy, speech therapy and counseling, including the time spent traveling and waiting for the visit.
Time spent coordinating your child's care	Caregiver time spent coordinating your child's care including contacting the insurance company, care coordinator, doctor's office, school, child care provider, and pharmacy.
Extra caregiving time spent caring for your child	Caregiver time spent on providing extra care related to your child's condition when compared to other children of same age.

These items describe how caregivers of children with complex chronic conditions may need to miss work to care for their child.

Item	Definition
Days of missed work in order to care for your child	Missed workdays spent on care of your child. This includes days of missed work by any caregiver in the household.
Quit jobs or did not pursue a job in order to care for your child	Quitting a job or deciding not to pursue a job to provide care for your child. This includes jobs quit by any caregiver in the household.
Reduced hours of paid work in order to care for your child	Reducing hours of paid work to provide care of your child. This includes a reduced work schedule for any caregiver in the household.

Item	Definition
Caregivers' quality of life	Your physical, mental, and social health.
Family member's quality of life	The quality of life of other family members, such as siblings. This includes your family member's physical, mental, and social health.

Now you will be asked which of these items might have the biggest impact and which might have the least impact on your family. You will have 5 items to choose from in each question. There will be 7 questions.

The following question is a practice question. To see the definitions of each item, hover your cursor over the item. Please respond to the questions imagining yourself in the role of the parent of a child with a complex chronic condition.

PRACTICE QUESTION

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) **Most impact** and (2) **Least impact** on you and your family?

Most impact (select one)		**Least impact (select one)**
○	Time spent coordinating your child's care	○
○	Costs for medications	○
○	Costs for emergency room visits and hospitalizations	○
○	Family member's quality of life	○
○	Costs related to travel to medical visits and hospitalization	○

Now, the official survey questions will begin.

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) **Most impact** and (2) **Least impact** on you and your family?

Most impact (select one)		**Least impact (select one)**
○	Cost for medications	○
○	Extra caregiving time spent caring for your child	○
○	Reduced hours of paid work in order to care for your child	○
○	Costs for other medical visits	○
○	Time spent at other medical visits	○

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) **Most impact** and (2) **Least impact** on you and your family?

Most impact (select one)		**Least impact (select one)**
○	Quit jobs or did not pursue a job in order to care for your child	○
○	Reduced hours of paid work in order to care for your child	○
○	Costs of extra daily household supplies	○

○	Costs related to household renovations for your child's condition	○
○	Costs for treatments	○

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) **Most impact** and (2) **Least impact** on you and your family?

Most impact (select one)		**Least impact (select one)**
○	Costs related to travel to medical visits and hospitalization	○
○	Extra caregiving time spent caring for your child	○
○	Quit jobs or did not pursue a job in order to care for your child	○
○	Costs of childcare	○
○	Costs for doctor's visits	○

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) **Most impact** and (2) **Least impact** on you and your family?

Most impact (select one)		**Least impact (select one)**
○	Time spent coordinating your child's care	○

○	Reduced hours of paid work in order to care for your child	○
○	Time spent at treatment-related visits	○
○	Costs for doctor's visits	○

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) **Most impact** and (2) **Least impact** on you and your family?

Most impact (select one)		**Least impact (select one)**
○	Costs for medications	○
○	Costs for emergency room visits and hospitalizations	○
○	Costs for special equipment and supplies	○
○	Costs related to household renovations for your child's condition	○
○	Costs for doctor's visits	○

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) **Most impact** and (2) **Least impact** on you and your family?

Most impact (select one)		**Least impact (select one)**

○	Costs for medications	○
○	Family member's quality of life	○
○	Time spent at doctor's visits	○
○	Quit jobs or did not pursue a job in order to care for your child	○
○	Days of missed work in order to care for your child	○

Imagine you are a caregiver or a family member taking care of your child that has a complex chronic condition now. Of the items in the list below, which item do you think has the (1) **Most impact** and (2) **Least impact** on you and your family?

Most impact (select one)		**Least impact (select one)**
○	Family member's quality of life	○
○	Extra caregiving time spent caring for your child	○
○	Caregivers' quality of life	○
○	Time spent at emergency room visits and hospitalizations	○
○	Costs related to household renovations for your child's condition	○

You completed the last question this section. If you would like to change any of your answers, please use the back arrow return to the previous questions and make changes now. Otherwise, use the forward arrow to move to the next section.

In the next part, we would like to ask some information about you and your current status.

How confident are you in your answers to the questions?

- ○ Very confident
- ○ Somewhat confident
- ○ Not confident
- ○ They were total guesses

Please indicate the most important reason that you were not confident in your answers to these questions

1 There was too much information to consider in each question
2 I felt like I needed more information about the terms
3 The items were too hard to imagine
4 I did not understand what was being asked
5 other (please specify)

What is your current connection to children with complex chronic conditions? Select all that apply.

- ☐ Affected individual or family member
- ☐ Healthcare provider (e.g., physician, nurse, physician's assistant, nurse practitioner, care technician)
- ☐ Patient or family advocacy, resource, or support organization member or leader
- ☐ Childcare provider
- ☐ Teacher
- ☐ Physical, occupational, or speech therapist
- ☐ Counselor
- ☐ Other professional
- ☐ I don't know a child with complex chronic conditions

Do you have children under 18 years old in your household?

- ○ No
- ○ Yes

How many children under 18 years old are in your household?

What is your age?

What is your gender?

- ○ Male
- ○ Female
- ○ Transgender
- ○ Gender-variant or gender-nonconforming
- ○ Prefer not to disclose
- ○ Prefer to self-describe:

Choose one or more races/ethnicities that you consider yourself to be:

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Hispanic or Latino
- ☐ Native Hawaiian or Pacific Islander
- ☐ White
- ☐ Prefer not to disclose
- ☐ Prefer to self-describe:

What is your native language?

- ○ English
- ○ Spanish
- ○ Mandarin
- ○ Hindi
- ○ Arabic
- ○ Other (Please specify):

What is the highest level of education you have completed?

- Less than 7th grade
- Completed more than 7th grade, but did not graduate high school
- High school graduate
- Some college or at least one year of specialized training
- 4-year college or university graduate
- Completed graduate/professional training

What is your current primary employment status?

- Employed full-time
- Employed part-time
- Out of work and looking for work
- Out of work but not currently looking for work
- Stay-at-home parent
- Student
- Military
- Retired
- Unable to work

Which of the following categories best describes your total household income, from all sources, before taxes in 2020?

- $25,000 or less
- More than $25,000 up to $50,000
- More than $50,000 up to $75,000
- More than $75,000 up to $100,000
- More than $100,000

Including yourself, how many people did that income support in 2020?

How are your doctor's visits and other health care paid for at this time? Select all that apply.

- Private insurance (e.g., HMO, PPO, POS, etc.)
- Public insurance (e.g., Medicaid, Medicare, CHIP)

- ☐ Children’s Special Health Care Services
- ☐ Self-pay or out-of-pocket
- ☐ Other (Please explain):

If you have children, how are your child’s doctor’s visits and other health care paid for at this time? Select all that apply.

- ☐ I don't have children
- ☐ Private insurance (e.g., HMO, PPO, POS, etc.)
- ☐ Public insurance (e.g., Medicaid, Medicare, CHIP)
- ☐ Children’s Special Health Care Services
- ☐ Self-pay or out-of-pocket
- ☐ Other (Please explain):

What is your marital status?

- ○ Married or living with partner
- ○ Single
- ○ Divorced or separated
- ○ Widowed

Do you have any additional thoughts about the survey you would like to share?

In appreciation of your time, we'd like to mail you a $20 check card for completing this survey. If you would like to receive this incentive, please click the link below to enter your contact information. This information will be stored separately from your survey answers. [Link]

If you would like to skip this part or you have already completed this part, please click the next button to end the survey.

We thank you for your time spent taking this survey.
Your response has been recorded.

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