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ORIGINAL ARTICLE

Financial cost and quality of life of patients with spinal muscular atrophy identified by symptoms or newborn screening

Tamara Dangouloff[1] | **Mickael Hiligsmann**[2] | **Nicolas Deconinck**[3] | **Adèle D'Amico**[4] | **Andreea M. Seferian**[5] | **François Boemer**[6] | **Laurent Servais**[1,7]

[1]Division of Child Neurology, Reference Center for Neuromuscular Diseases, Department of Paediatrics, University Hospital Liege & University of Liege, Belgium

[2]Department of Health Services Research, Care and Public Health Research Institute, Maastricht University, Maastricht, the Netherlands

[3]Neuromuscular Reference Center and Paediatric Neurology Department, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium

[4]Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Istituto di Ricovero e Cura a Carattere Scientifico Bambino Gesù Children's Hospital, Rome, Italy

[5]Institute of Myology, GH, Paris, France

[6]Biochemical Genetics Lab, Department of Human Genetics, CHU de Liège, University of Liege, Liege, Belgium

[7]Muscular Dystrophy UK Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, UK

Correspondence
Laurent Servais, CRMN Liege, CHR de la Citadelle, Boulevard du 12ème de Ligne, 4000 Liege, Belgium.
Email: laurent.servais@paediatrics.ox.ac.uk

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Abstract

Aim: To compare the societal financial costs and quality of life (QoL) of untreated patients with spinal muscular atrophy (SMA) and treated patients identified because they presented symptoms or were identified by early testing (sibling or newborn screening).

Method: Data from two different sources were used: data collected prospectively in untreated patients from 2016 to 2018 and data collected during a prospective follow-up study from 2018 to 2021. Patients or their caregiver completed a questionnaire that included questions on direct medical and non-medical costs, indirect non-medical costs, and health-related QoL.

Results: Data (median; range) were available for 149 patients (93 untreated – 10 years; 2 years–59 years), 42 patients (6 years 3 months; 9 months–58 years) treated after presenting with symptoms, and 14 patients (1 year 7 months; 5 months–2 years) treated after early diagnosis. Total costs were lower in untreated patients due to the high cost of drugs used in treated patients. Costs were lower for treated patients who were identified by early testing than for treated patients identified because they presented with symptoms. In all groups, patients with two *SMN2* copies had higher costs than those with more copies.

Interpretation: Early patient identification and treatment offer the opportunity to reduce the total societal costs of SMA where treatments are available for presymptomatic and postsymptomatic patients.

Spinal muscular atrophy (SMA) is an inherited autosomal recessive disease.[1] It is the most common genetic cause of infant mortality with an incidence of approximately 1 in 10 000 live births.[2,3] SMA is linked to a homozygous deletion of the survival motor neuron 1, telomeric (*SMN1)* gene. Survival of motor neuron 2, centromeric (*SMN2*) is a paralog gene

Abbreviations: GCS, Generic Core Scale; HUI, Health Utilities Index; NBS, Newborn screening; NMM, Neuromuscular module; NMRC, Neuromuscular reference centre; PedsQL, Pediatric Quality of Life Inventory; QoL, Quality of life; SMA, Spinal muscular atrophy.

that is present in a variable number of copies. The severity of SMA depends largely on the number of copies of *SMN2*: two copies usually lead to the most severe form and four or more copies to the less severe form.[4] SMA presents as progressive and generalized muscle weakness leading to respiratory insufficiency. Clinical phenotypes have been grouped into five different forms (types 0–4) depending on the severity of the disease and age at onset of the first symptoms. The most common and severe form, SMA type 1, accounts for 60% of cases; if untreated, it causes death or permanent ventilation in 94% of cases below 2 years of age.[5] SMA types 2 and 3, less common and less severe forms of the disease, are associated with severe motor disability; however, life expectancy is considerably longer, approaching that of the overall population.[5] The emergence of new phenotypes in treated patients and adoption of an international standard of care[6] has led to a tripartite classification system based on current functional ability: non-sitters; sitters; and walkers. Some patients are identified before the onset of symptoms because a sibling is diagnosed with SMA, or by newborn screening (NBS), which is now performed in several countries.[7] Patients who are not identified by symptoms, for whom no functional data are available at birth, are classified by the number of *SMN2* copies.

Since 2017, three drugs have been approved for use in SMA and are currently reimbursed in several countries based on the results of clinical trials that have demonstrated safety and efficacy.[8] Despite the substantial burden and cost of SMA,[9–12] these drugs are very expensive relative to the benefit that they bring to patients who are not treated until after they develop symptoms.[9] Experimental evidence shows that disease duration before treatment initiation is an important negative prognostic factor for treatment efficacy.[13] This has prompted several countries to initiate NBS for SMA.[7,14–16] Although drug treatment has a transformative effect on the condition of patients who are treated before symptom onset,[17] to our knowledge no published reports have compared the costs and quality of life (QoL) of treated patients with SMA identified by symptoms or before symptom onset. These data are necessary to assess the economic value of NBS.

The aim of this study was to assess and compare QoL and societal costs of untreated patients with SMA and treated patients with SMA identified by symptoms or by testing to evaluate the potential benefits of NBS on the costs and QoL of patients with SMA.

What this paper adds

- Untreated patients with spinal muscular atrophy had lower total financial costs than treated patients.
- Total financial costs were lower for treated patients identified by early screening than for treated patients identified after symptom onset.
- Direct financial costs excluding treatment were much lower in treated patients identified by early screening.
- Hospitalization costs were much lower in patients identified by early screening.

METHOD

Study participants

This study used data from two prospective studies and focused on the costs and health-related QoL of patients with SMA grouped according to whether they received treatment or not and according to the timing of treatment initiation (i.e. after symptom onset or due to early detection). The studies were the following: (1) a prospective study of 81 untreated patients conducted from 2016 to 2018 in Belgium, France, and Germany (NatHis-SMA; NCT02391831).[18] All patients or parents provided written informed consent. The study was approved in France (no. IDRCB-2014-A01263-44) by the regulatory health authority and the central ethics committee and was further approved in Liege, Leuven, and Essen by the local ethics committees. All patients between 2 and 30 years old who were followed up at the neuromuscular reference centres (NMRCs) taking part in the study were asked to participate. For inclusion, non-ambulant patients needed to tolerate sitting in a wheelchair for a minimum of 3 hours. Patients were excluded from the study if exposed at any time to an investigational SMA treatment or if they had a comorbid condition that could significantly interfere with disease assessment. Pregnant or breastfeeding females were excluded. More information on the inclusion and exclusion criteria can be found elsewhere;[18,19] and (2) a prospective study conducted in Liege (Liege NMRC study), Belgium between November 2018 and February 2021. Enrolment was open to all patients with SMA who were registered at the Liege NMRC (University Hospital of Liege) with or without treatment, without age restrictions. Additional treated patients not identified by symptoms were referred from the Brussels NMRC (Hôpital Universitaire des Enfants Reine Fabiola) and Rome (Bambino Gesù Children's Hospital). All study participants provided written informed consent. The study was approved by the Liege ethics committee (no. 1750).

Patients in both studies had a genetic confirmation of SMA (either a homozygous or heterozygous deletion and an unequivocally pathogenic mutation on the other allele); *SMN2* copy numbers were determined for all patients.

Study procedures

Data were collected from various questionnaires completed by the patients or their parents or guardians (henceforth referred to as parents since all minors were accompanied

by one of their actual parents) and by consulting medical and financial records in hospital accounting departments. In the NatHis-SMA study, patients or caregiver completed questionnaires during their hospital visits. In the Liege NMRC study, questionnaires could be completed either on paper or online using SurveyMonkey. Each participant had an identification number to ensure that confidentiality was maintained. The information was anonymized and stored. For children up to 18 years of age, medical and cost data were completed by the parents; QoL questionnaires were completed by both parents and children if aged older than 6 years. Some adolescents or adults with limited hand mobility due to the disease indicated the answers orally to their parents.

The questionnaires were filled out once a year from patient inclusion onwards during planned visits to the hospital or after contact with the investigator. Some patients were followed for 2 years. The most recent questionnaire for each individual was used for this cross-sectional study. Two patients completed the questionnaire the first time in 2017 when they were off treatment and were assigned to the untreated symptomatic group. They were given treatment in 2018 and have since been included in the treated symptomatic group.

Data collection

The NatHis-SMA participants responded to questionnaires concerning their health status: motor capacity; ventilation; number of hospitalizations. In the Liege NMRC study, patients or their caregiver completed a questionnaire including socio-demographic (age, occupation) and medical questions (motor evaluation and age at first symptom onset, diagnosis, and start of treatment). The data collected for costs and QoL are detailed in the next sections.

Assessment of costs of illness

Financial costs were collected from responses to a predefined cost questionnaire that included questions regarding direct medical and non-medical costs and indirect costs in the last year. All costs were then extrapolated to 2020 reference values using an inflation calculator when necessary (https://fxtop.com/fr/calculateur-inflation-entre-deux-dates.php). Treatment costs in US dollars were converted to euros using the Bureau of Labor Statistics' consumer price index obtained in October 2020 (https://www.officialdata.org/us/inflation/). Patients responded to questionnaires with the data for the previous year.

Direct medical costs

Direct medical costs are those used for medical care (consultation, examinations, medication, hospitalization). Data on direct medical costs were collected in a structured predefined way to capture the number of hospitalizations, hospitalization duration, numbers of medical and physical therapy consultations, concomitant medications, and medical care consumption respiratory data (use of physiotherapy, ventilation). For patients followed in the Liege NMRC study, we obtained the real costs of the hospital follow-up from the hospital's financial department. The costs for home care services were collected on the website of the Institut National d'Assurance Maladie-Invalidité (the Belgian social security organization that pays for these services; https://www.riziv.fgov.be/fr/themes/cout-remboursement/par-mutualite/prestations-individuelles/prix/). For patients not followed in the Liege NMRC study, only the number of hospitalization days and consultations were collected. For these individuals, we estimated the hospitalization (€1500 per night) and consultation (€68 per consultation) costs based on patients with SMA with the same motor and care course treated in Liege. The costs related to home ventilation were established by the type (invasive, €39.1 per day; non-invasive, €27.83 per day) and duration of respiratory support and the daily cost fixed by the health insurance according to the ventilation type. The costs of physiotherapy were established based on the number of visits (€26 per consultation). All these unitary costs are summarized in Table S1.

In Belgium, each patient followed by an NMRC is 'registered', which translates into a flat rate of €1535 in 2021 paid to the NMRC by the health insurance and which covers the annual follow-up of the patient. At the yearly visit, the patient is evaluated by a trained physiotherapist, speech therapist, social worker, and psychologist and multidisciplinary team consultations are held.

The costs of drug treatment (summarized in Table S2) were calculated separately because they are much higher than other costs. Three different treatments were administered to patients: nusinersen; onasemnogene abeparvovec (gene therapy); and risdiplam. The costs of drug treatment include the official cost of the treatment itself, the cost of hospitalization for treatment administration, and the medical consultation directly related to treatment delivery. It is important to note that the timing of administration was very different for the three treatments: gene therapy is a one-time cost; nusinersen requires four loading doses, resulting in a higher cost for the first year than in subsequent ones; and the cost of risdiplam is constant over the years. We calculated over 1, 2, and 10 years and considered as a yearly cost the total 10-year cost divided by 10. Several patients from our study were included in therapeutic trials or compassionate use programmes and received the treatment free of charge. Nevertheless, the cost of the treatment received was calculated as if treatment had been delivered during standard of care and paid through social security. (In Belgium, when expensive treatments are approved, they are paid entirely by the state.)

Nusinersen has been approved by the European Medicines Agency and is reimbursed in Europe. The official price of nusinersen in Belgium in 2020 was €88 300 per vial. In the first year, doses are given at days 0, 14, 28, and 64, and then

every 4 months for a total cost of €529 800. Subsequently, patients are given three injections per year for a cost of €264 900. The costs associated with administering the injection were estimated at €250. Nusinersen is reimbursed in Belgium for all patients, even for presymptomatic patients with four *SMN2* copies.

Onasemnogene abeparvovec is an adeno-associated virus serotype 9 gene therapy currently approved by the European Medicines Agency. Its reimbursement has just been authorized in Belgium. The estimated cost of treatment is €1.9 million (US$2.1 million); a single dose is given. The injection is currently performed as a single intravenous injection under close supervision in an intensive care unit for 3 days. The cost also includes strict medical follow-up during the first weeks and months after the injection for an average of 13 consultations during the first year. Further follow-up is not treatment-specific.

Risdiplam is also approved by the European Medicines Agency and its reimbursement has just been announced in Belgium. The price is currently not fixed in Belgium but is €289 000 per year in the USA (US$340 000). Follow-up is currently six medical consultations per year.

Direct non-medical costs

Direct non-medical costs are money spent by patients because of the disease but for non-health-related purposes; they include accommodation, domestic help, adaptation of houses/cars, special transport, and so on. Direct non-medical costs were collected directly in the questionnaire; prices used in the analysis were those reported by patients or their parents.

Indirect costs

Indirect costs represent the societal loss of patient or caregiver productivity caused by the disease, that is, money lost because they cannot work. Participants or their caregiver were asked if they were employed. For those who were employed, the number of days they were unable to work because of SMA were recorded. We did not examine presenteeism but examined absenteeism. We averaged loss of productivity considering the average annual full-time working time and salary in southern Belgium (i.e. 253 days and €43 068 respectively; statistical indicator provided by the Institut Wallon de l'Évaluation, de la Prospective et de la Statistique-Wallonia-Brussels Federation). We did not examine paid or unpaid informal care.

Assessment of QoL

Health-related QoL was measured using the EQ-5D, Health Utilities Index (HUI), and Pediatric Quality of Life Inventory (PedsQL) questionnaires completed either by the patients or their parents or caregiver. When both were available, we primarily considered patient-completed questionnaires.

The EQ-5D is a valid and reliable instrument used to describe and value health created by the EuroQol Research Foundation. The EQ-5D includes five dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression rated as no problems, slight problems, moderate problems, severe problems, and many problems. The adult version was used for patients over 18 years of age (EQ-5D-5L) and the youth version was used for patients aged 6 to 18 years (EQ-5D-Y). Patients under 6 years of age were not assessed with this tool. This questionnaire uses a Visual Analogue Scale that allows scoring of one's health status out of 100. To report the results of the EQ-5D descriptive system, we used a recently established EQ-5D-5L value set for Belgium.[20] Since a valuation set does not yet exist for the EQ-5D-Y, we converted the scoring of the child questionnaire to 5 levels (a score of 1 remained 1, a score of 2 became 3, and a score of 3 became 5). This provides a utility value expressed on a scale where 0 is the value for 'dead' and 1 is the value for 'full health'. Negative values are possible for health states considered worse than death by respondents, which can happen in cases of severe disability or suffering. The EQ-5D was not available for untreated symptomatic patients in the NatHis-SMA study.

The HUI is another well-known generic QoL instrument that produces utility scores.[21] Health-related QoL is scored between 0 (death) and 1 (perfect health). The HUI2 and HUI3 instruments combine a comprehensive generic health status classification system with a generic utility score system. HUI2 examines eight health attributes: vision; hearing; speech; mobility; dexterity; emotion; cognition; and pain/discomfort. In the HUI3, these attributes are structurally independent of each other and any combination of levels in the system is possible. This makes the classification system efficient because each attribute provides unique information. We used the HUI2 and HUI3 in all patients from 2 years of age; data were reported by parents when patients were under 6 years of age.

The PedsQL Measurement Model is a modular approach to measure health-related QoL in typically developing children and adolescents and in those with acute and chronic health conditions. The PedsQL integrates seamlessly both generic core scales (PedsQL Generic Core Scale [GCS]) and disease-specific modules (PedsQL neuromuscular module [NMM]) into one measurement system (http://www.pedsql.org). The PedsQL includes 23 items divided into four multidimensional scales: physical; emotional; social; and school functioning. We used the PedsQL GCS and PedsQL NMM. PedsQL GCS questionnaires were completed by parents for patients aged between 2 and 6 years (PedsQL GCS parent report) and by the patients themselves using the questionnaires dedicated to their ages (5–7 years old, 8–12 years old, 13–18 years old, 18–25 years old, adult). For the PedsQL NMM, we used the 13 to 18 years questionnaire for all patients older than 13 years since no adult version is available. The PedsQL Family Impact, which assesses the impact of

paediatric chronic illness on the QoL of caregiver and family functioning over the past month, was also used. It includes six scales of a caregiver's self-reported functioning: physical; emotional; social; cognitive functioning; communication; and worrying. In addition, it explores two scales of family functioning: daily activities and family relationships. The scoring algorithm permits health-related QoL between 0 and 100, with higher scores indicative of higher QoL. This questionnaire was not used in the NatHis-SMA study. Therefore, these data were not available for most untreated symptomatic patients.

Data analysis

Descriptive statistics (median, minimum, maximum) were used to report annual costs, QoL, and utilities for the groups of patients. Given the small sample size, we used non-parametric statistics for the descriptive statistics (median, range) and to compare the medians of the groups (Mann–Whitney *U* test). Comparison of socioeconomic status was conducted using a χ^2 test, considering five categories (unemployed, student, manual worker, employee, and manager). All tests were conducted using SPSS v28.0.0.0 (IBM Corp., Armonk, NY, USA). When sample size was less than five, no formal comparison was conducted, and no *p*-value is provided. We considered a $p < 0.05$ as clinically significant and provided a *p*-value each time a formal test was conducted.

Participants were divided into three groups based on treatment status (treated or untreated) and, for treated patients, whether treatment was initiated due to presenting with symptoms or before symptom onset by NBS or testing due to sibling diagnosis. Groups were the following: untreated symptomatic patients, that is, patients identified by symptoms who did not receive treatment; treated symptomatic patients, that is, patients identified by symptoms who received treatment; patients treated but not identified by symptoms, that is, patients not identified by symptoms who received treatment.

Each group was further subdivided into three categories according to the number of *SMN2* copies. We chose copy number classification rather than SMA type or functional status to be able to compare patients not identified by symptoms with other patients. The SMA type of symptomatic patients is provided in Table 1. We did not classify patients as presymptomatic and postsymptomatic as in therapeutics studies because some patients identified by NBS show clinical signs of the disease at the first consultation. These individuals were treated early but were not all strictly presymptomatic.

RESULTS

Patient characteristics

A total of 149 patients were enrolled in this study. Of these, 93 were untreated symptomatic patients (aged between 2 and 59 years, median 10 years), with 81 from the NatHis-SMA study conducted in Belgium, France, and Germany and 12 from the Liege NMRC study. In untreated symptomatic patients, there was no difference in terms of the frequency of SMA type or motor function between the NatHis-SMA and Liege NMRC groups ($p = 0.99$). Untreated symptomatic patients from the Liege NMRC study were older than those from the NatHis-SMA study since the Liege NMRC cohort had no age inclusion criteria (median age = 32 years vs 8 years, $p = 0.022$; Table S3). The treated symptomatic group included 42 patients from the Liege NMRC cohort (aged between 9 and 58 years, median 6 years 3 months). In the 14 patients from the 'not identified by symptoms' group, 10 were patients identified through NBS from Belgium and four were identified when testing was performed due to the diagnosis of siblings (aged between 5 months–2 years, median 1 year 7 months). Of the individuals identified because of their siblings, one was Belgian and three were Polish. Of the Polish patients, two were followed in Rome and one in Liege. We compared the socio-professional categories of the Polish and Belgian parents and found no difference ($p = 0.92$). Distribution by copy number in the different groups was not homogeneous ($p < 0.001$). Since recruitment for the NatHis-SMA study only included untreated patients older than 2 years, there were very few untreated symptomatic patients with two copies (3%). In treated symptomatic patients and patients not identified by symptoms, they were 26% and 43% respectively. The distribution is presented in Figure 1.

Of the treated patients, 38 were treated with nusinersen, 13 with risdiplam, and five with gene therapy. All patients treated with risdiplam or gene therapy were treated in the context of a clinical trial. At the time of this study, nusinersen was commercially available.

The study cohort included 33 non-sitters, 77 sitters, and 36 walkers. Patients described as sitters were always non-walkers. Three patients were younger than 9 months and thus were not categorized. In patients not identified by symptoms over the age of ambulation acquisition (18 months), 9 out of 11 were ambulant. All but four patients not identified by symptoms reached the maximum value of the scales applicable for their age. No untreated or treated symptomatic patients reached maximum values for their ages. Patient characteristics are reported in Table 1.

Costs

All costs (direct medical, direct non-medical, indirect non-medical, and treatment) for each group are reported in Table 2 and in Figure S1. The costs for treated patients were significantly higher than for untreated patients due to the high cost of SMA-specific treatment ($p < 0.001$). The total cost for patients not identified by symptoms was lower than the total cost for treated symptomatic patients ($p = 0.006$). When treatment costs were not considered, the direct costs for patients not identified by symptoms were statistically much lower than those for untreated and treated symptomatic patients ($p < 0.001$); no difference was observed between the

TABLE 1 Patient characteristics

	NIS				TS				UntS			
	***SMN2* copy number**			**All ($n = 14$)**	***SMN2* copy number**			**All ($n = 42$)**	***SMN2* copy number**			**All ($n = 93$)**
	2 ($n = 6$) 46% of NIS	**3 ($n = 5$) 36% of NIS**	**4 ($n = 3$) 21% of NIS**		**2 ($n = 11$) 26% of TS**	**3 ($n = 24$) 57% of TS**	**4 ($n = 7$) 17% of TS**		**2 ($n = 3$) 3% of UntS**	**3 ($n = 75$) 81% of UntS**	**4 ($n = 15$) 16% of UntS**	
Age, median (minimum–maximum), years:months	2:0 (1:2–2:11)	1:6 (0:5–2:10)	1:1 (0:6–1:5)	1:7 (0:5–2:11)	3:10 (0:9–20:0)	5:9 (2:5–45:0)	30:0 (11:0–58:0)	6:3 (0:9–58:0)	6:0 (4:0–18:0)	8:0 (2:0–44:0)	22:0 (6:0–59:0)	10:0 (2:0–59:0)
Delay between symptoms and diagnosis (minimum–maximum), months	20 days[a] (0–30 days)	18 days[a] (10–150 days)	18 days[a] (14–31 days)	18 days[a] (0–150 days)	1 (0.5–10)	5 (1–36)	24 (0.4–234)	5 (0.4–234)	11 (5–39)	7 (0.1–135)	23 (3–521)	7 (0.1–521)
Maximum motor development												
NA	0	2	1	3	0	0	0	0	0	0	0	0
Non-sitter	0	0	0	0	5	7	0	12	1	20	0	21
Sitter	2	0	0	2	5	15	2	22	2	42	7	51
Walker	4	3	2	9	1	2	5	8	0	13	8	21
Motor development scale												
CHOP INTEND/64	60	64	64	64	38	42	NA	38	NA	NA	NA	NA
HINE-2/26	18	25	26	24	5	14	NA	9	NA	10	NA	10
MFM32/96	NA	NA	NA	NA	53	45	73	48	39	38	73	44
Treatment												
Nusinersen	3	3	1	7	5	20	6	31	0	0	0	0
Gene therapy (OA)	3	1	0	4	2	4	0	6	0	0	0	0
Risdiplam	0	1	2	3	4	0	1	5	0	0	0	0
SMA types 1–3	NA	NA	NA	NA	SMA1: 8; SMA2: 2; SMA3: 1	SMA1: 8; SMA2: 14; SMA3: 2	SMA2: 2; SMA3: 5	SMA1: 16; SMA2: 18; SMA3: 8	SMA2: 2; SMA3: 1	SMA2: 57; SMA3: 18	SMA2: 2; SMA3: 13	SMA2: 61; SMA3: 32

[a]Age at diagnosis. Abbreviations: NIS, patients not identified by symptoms; TS, treated symptomatic patients; UntS, untreated symptomatic patients; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination-Part 2; MFM32, 32-item Motor Function Measure; NA, not applicable; OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy.

TABLE 2 Yearly median societal cost of illness in € per patient with SMA

	Patients not identified by symptoms				**Treated symptomatic patients**				**Untreated symptomatic patients**			
	***SMN2* copy number**				***SMN2* copy number**			**All (*n* = 42)**	***SMN2* copy number**			**All (*n* = 93)**
	2 (*n* = 6)	**3 (*n* = 5)**	**4 (*n* = 3)**	**All (*n* = 14)**	**2 (*n* = 11)**	**3 (*n* = 24)**	**4 (*n* = 7)**		**2 (*n* = 3)**	**3 (*n* = 75)**	**4 (*n* = 15)**	
Direct medical costs (without treatment costs)												
Consultations	*340*	*272*	*272*	*272*	*952*	*680*	*408*	*680*	*952*	*680*	*408*	*680*
Hospitalizations	0 (0–150)	0	77 (0–153)	0 (0–153)	5482 (407–21 529)	6760 (0–35 575)	2026 (788–3332)	3248 (0–35 575)	30 000 (12 000–64 500)	11 385 (0–57 000)	1582 (0–16 500)	4500 (0–64 500)
NMRC registration	1535	1535	1535	1535	1535	1535	1535	1535	1535	1535	1535	1535
Physiotherapy	2038 (0–4076)	0 (0–2718)	0	0 (0–4076)	8153 (1359–16 305)	5435 (0–12 229)	4076 (1359–5435)	*4576 (0–16 305)*	*8153*	5199 (0–8152)	0 (0–5435)	5435 (0–8152)
Ventilation	0	0	0	0	14 458 (0–14 458)	3649 (0–14 458)	*0*	0 (0–14 458)	10 158 (0–10 158)	5431 (0–14 272)	0 (0–14 272)	0 (0–14 272)
Total direct medical costs	**3913 (13%)**	**1807 (59%)**	**1884 (69%)**	**1807 (51%)**	**30 580 (34%)**	**18 059 (50%)**	**8045 (54%)**	**10 219 (64%)**	**50 798 (72%)**	**24 230 (50%)**	**3525 (42%)**	**12 510 (35%)**
Direct non-medical costs												
Adaptation to daily life	0	0	0	0	14 245 (0–34 000)	3227 (0–93 000)	4125 (0–14 500)	*3000 (0–93 000)*	*15 000*	21 196 (0–141 100)	4125 (0–23 200)	21 196 (0–141 100)
Adaptation of food/care	0 (0–1800)	0	0	0 (0–1800)	1700 (0–23 000)	350 (0–88 000)	150 (0–3400)	*175 (0–88 000)*	*1700*	600 (0–7600)	150 (0–3200)	600 (0–7600)
Total direct non-medical costs	**0**	**0**	**0**	**0**	**15 945 (18%)**	**3577 (10%)**	**4275 (29%)**	**3175 (20%)**	**16 700 (24%)**	**21 796 (45%)**	**4275 (50%)**	**21 796 (63%)**
Total direct costs	**3913**	**1807**	**1884**	**1807**	**46 525**	**21 636**	**12 320**	**13 394**	**67 498**	**46 026**	**7800**	**33 946**
Indirect non-medical costs												
Lost productivity	25 790 (511–43 068) (87%)	1702 (0–43 068) (41%)	1702 (0–4256) (31%)	1702 (0–43 068) (49%)	43 068 (511–43 068) (48%)	14 732 (0–43 068) (41%)	2553 (0–43 068) (17%)	2553 (0–43 068) (16%)	2894 (2894–5107) (4%)	2669 (0–43 068) (5%)	681 (0–43 068) (8%)	681 (0–43 068) (2%)
Societal total without treatment costs	**29 703**	**3509**	**3662**	**3509**	**89 593**	**36 368**	**14 873**	**15 948**	**70 392**	**48 695**	**8481**	**34 267**
Treatment costs	240 236	270 976	290 439	290 954	272 652	291 856	292 059	292 501	–	–	–	–
Societal total cost of illness	269 939	274 486	294 101	294 463	362 245	328 224	306 932	311 002	70 392	48 695	8481	34 267

Values in italics are extrapolated costs. Abbreviations: NMRC, neuromuscular reference centre; SMA, spinal muscular atrophy.

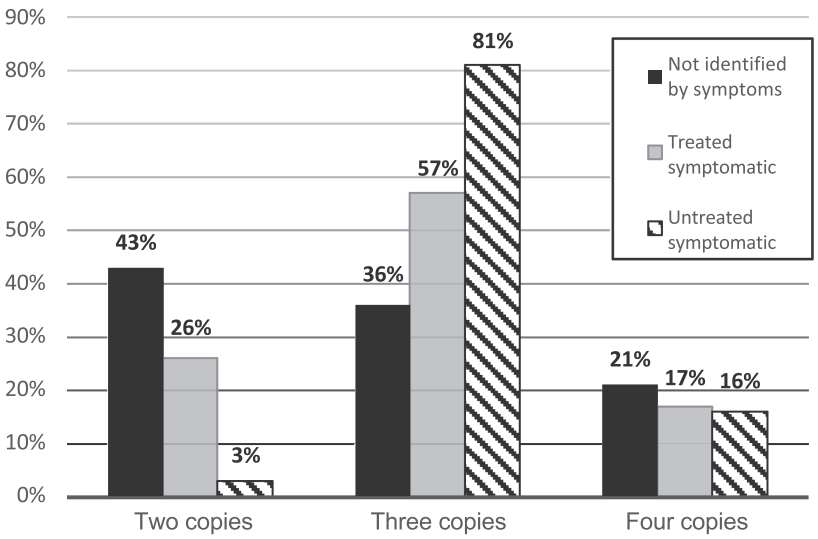

FIGURE 1 Distribution of patients according to the number of *SMN2* copies by category.

untreated and treated symptomatic groups ($p = 0.961$). Since treatment depended on the number of *SMN2* copies, we compared the total cost excluding treatment costs in patients not identified by symptoms and untreated and treated symptomatic patients. In all groups, patients with two copies of the *SMN2* gene had the highest costs; the difference was statistically significant in treated symptomatic patients ($p = 0.035$). When disease-modifying treatment costs were not considered, the direct medical costs for patients not identified by symptoms were statistically much lower than those for untreated and treated symptomatic patients ($p < 0.001$); no difference was observed between the untreated and treated symptomatic patients ($p = 0.961$). Specifically, hospitalization costs were much lower ($p < 0.001$) in patients not identified by symptoms.

QoL

QoL scores measured on the PedsQL GCS and PedsQL NMM subscales are reported in Table 3; they were higher in the group of patients not identified by symptoms than the other groups, but the sample size was too small to conduct a formal comparison ($n = 4$). On the PedsQL Family Impact scale, patients not identified by symptoms were as impacted as untreated and treated symptomatic patients. The difference between untreated and treated symptomatic patients was not significant on the PedsQL Family Impact ($p = 0.107$) or EQ-5D Visual Analogue Scale subscales ($p = 0.72$). The HUI was obtained only in three patients not identified by symptoms, who scored close to the maximum. Treated and untreated symptomatic cohorts had very similar values (0.52 and 0.54 for HUI2 and 0.26 and 0.28 for HUI3 respectively).

The results of the QoL and utility values for the different groups as a function of the number of *SMN2* copies are reported in Table 3. Health-related QoL and utility scores were much higher in patients not identified by symptoms than in the other groups; some patients not identified by symptoms reached full health as measured on the HUI scale. The range of values were also much narrower in patients not identified by symptoms. However, on the PedsQL Family Impact scale, patients not identified by symptoms were as impacted as untreated and treated symptomatic patients.

DISCUSSION

This study analysed disease-related costs and health-related QoL in three broad categories of patients with SMA: untreated symptomatic patients; treated symptomatic patients who were diagnosed because of the onset of symptoms and then treated; and patients not identified by symptoms who were identified due to early testing (either through NBS or due to the diagnosis of a sibling) and then treated. Patients not identified by symptoms had better motor development, better QoL, and much lower disease costs, especially in both direct medical and non-medical costs, than treated symptomatic patients. The cost of treatment with an approved drug for SMA (nusinersen, onasemnogene abeparvovec, or risdiplam) resulted in much higher total costs in the treated groups of patients than in untreated patients.

Patients not identified by symptoms were not all presymptomatic at the time of treatment initiation[22], which makes this population slightly different from the population described in drug efficacy studies, who are treated before the age of 42 days and who are strictly non-symptomatic.[17] For this population, indirect costs are probably country-dependent. Indeed, these costs are mainly related to state-supported parental leave in southern Belgium for any parent who stops working to raise their child under the age of 3 years; nine parents of patients not identified by symptoms reported that diagnosis of their child was an incentive to use this leave, even if their child remained non-symptomatic. This cost will likely decrease

TABLE 3 Median health-related quality of life scores of patients with SMA

		Patients not identified by symptoms				Treated symptomatic patients				Untreated symptomatic patients			
		SMN2 copy number			All ($n = 14$)	*SMN2* copy number			All ($n = 42$)	*SMN2* copy number			All ($n = 93$)
		2 ($n = 6$)	3 ($n = 5$)	4 ($n = 3$)		2 ($n = 11$)	3 ($n = 24$)	4 ($n = 7$)		2 ($n = 3$)	3 ($n = 75$)	4 ($n = 15$)	
PedsQL/100	Family impact	50 (F = 5)	73 (F = 5)	62 (F = 3)	62 ($n = 13$)	65 (F = 11)	52 (F = 19)	65 ($n = 2$)	57 ($n = 32$)	–	51 ($n = 4$)	–	51 ($n = 4$)
	GCS	80 (F = 1)	97 (F = 3)	–	93 ($n = 4$)	40 (P = 3, F = 4)	49 (P = 11, F = 11)	65 (P = 7)	51 ($n = 36$)	55 (P = 1, F = 2)	54 (P = 39, F = 34)	54 (P = 12, F = 3)	54 ($n = 91$)
	NMM	76 (F = 1)	89 (F = 3)	–	86 ($n = 4$)	65 (P = 3, F = 4)	55 (P = 11, F = 11)	80 (P = 7)	62 ($n = 36$)	67 (P = 1, F = 2)	65 (P = 39, F = 34)	69 (P = 11, F = 3)	66 ($n = 90$)
EQ-5D	VAS/100	79 (F = 1)	–	–	79 ($n = 1$)	56 (P = 2, F = 2)	78 (P = 7, F = 7)	60 (P = 6, F = 1)	73 ($n = 25$)	–	78 (P = 5, F = 3)	58 (P = 4)	75 ($n = 12$)
	Utility/1	1 (F = 1)	–	–	1 ($n = 1$)	0.34 (P = 2, F = 2)	0.45 (P = 7, F = 7)	0.70 (P = 6, F = 1)	0.52 ($n = 25$)	–	0.43 (P = 5, F = 3)	0.34 (P = 4)	0.40 ($n = 12$)
HUI/1	HUI2	1.00 (F = 1)	0.97 (F = 2)	–	1 ($n = 3$)	0.47 (P = 2, F = 4)	0.51 (P = 8, F = 14)	0.79 (P = 6, F = 1)	0.52 ($n = 35$)	0.42 (P = 1, F = 2)	0.52 (P = 36, F = 37)	0.69 (P = 12, F = 3)	0.54 ($n = 91$)
	HUI3	1.00 (F = 1)	0.96 (F = 2)	–	1 ($n = 3$)	0.19 (P = 2, F = 4)	0.19 (P = 8, F = 14)	0.74 (P = 6, F = 1)	0.26 ($n = 35$)	0.12 (P = 1, F = 2)	0.22 (P = 36, F = 37)	0.42 (P = 12, F = 3)	0.28 ($n = 91$)

F: information collected from the family; P: information collected from the patient. Abbreviations: GCS, Generic Core Scale; HUI, Health Utilities Index; NMM, neuromuscular model; PedsQL, Pediatric Quality of Life Inventory; VAS, Visual Analogue Scale.

after 3 years, when parents can no longer take advantage of state-funded leave. This hypothesis will be tested when these children reach 3 years of age (currently they are aged 5–35 months). This applies only to patients not identified by symptoms since most of the other patients, treated and untreated symptomatic patients older than 3 years, are not impacted by this parental leave.

The yearly total cost differences between treated symptomatic patients and patients not identified by symptoms were much lower in patients with four copies of the gene than in patients with two or three copies. Patients with four copies present with significantly less severe disability, regardless of whether they are treated early or indeed at all; thus, the difference due to early diagnosis is less. The positive impact of early treatment on the health status of patients with two and three copies of the *SMN2* gene also translates into substantial cost savings.

The NBS for SMA in southern Belgium is reimbursed by the regional Ministry of Childhood at €5 per infant (in 2021). Given the observed incidence during the pilot programme (1 in 15 149 tested infants),[22] we estimated that the cost from the payer's perspective of identifying one patient through NBS rather than by diagnosing symptoms is €75 745 (€5 × 15 149). This is probably an overestimate since the identification of patients who present with symptoms involves additional costs, beginning with at least a neurology consultation but also frequently including futile exams, such as neurography or brain magnetic resonance imaging (MRI). Indeed, a study conducted in Italy indicated that in patients ultimately diagnosed with SMA 12% had an MRI, 4.2% had a muscle biopsy, and 39% had an electromyogram.[23] The same study reported that the diagnostic journey took 1.94 plus or minus 1.84 months in patients with type 1 SMA, 5.28 plus or minus 4.68 months in patients with type 2 SMA, and 16.8 plus or minus 18.72 months in patients with type 3 SMA.[23] These long delays are in line with our population of treated patients identified based on symptoms and suggests that diagnostic costs in the absence of NBS are high. Even considering a conservative cost of €75 745 to identify a patient before symptom onset rather than after, the cost of screening is amortized after 2 to 6 years according to the number of *SMN2* copies as the yearly total cost difference between treated patients identified by screening or by symptoms is €92 306, €53 738, and €12 833 for patients with two, three, and four copies respectively. Considering a life expectancy greater than 60 years, since life expectancy is not considerably different in patients with SMA types 2 or 3 than in the general population,[5] the NBS is clearly cost-effective.

The medical costs of untreated patients per year (€50 798, €24 230, and €2325 for individuals with two, three, or four copies of the *SMN2* gene respectively) reported in southern Belgium are quite similar to the costs reported from other analyses in European countries (France, Germany,[10] the UK,[24] Spain[9,24]), which ranged from €3809 to €47 793. Medical costs (excluding the cost of treatment) in the USA[25–27] and Australia[28] were much higher, especially for patients with SMA type 1 (lifetime cost of €5 178 773), who

can be grossly considered as patients with two *SMN2* copies for comparison to the present study. For symptomatic patients with two or three *SMN2* copies, medical costs (excluding the cost of treatment) were lower in treated patients (€20 218 and €6171 respectively), which is in line with previous reports.[25] These data demonstrate the positive impact of treatment. Nevertheless, the prohibitive costs of treatment led to much higher overall costs in treated versus untreated patients, irrespective of the manner in which they were identified.

Our QoL data on the PedsQL GCS and NMM are very comparable with previous reports.[29] In contrast, the EQ-5D-3L utility scores reported by López-Bastida et al.[11] were much lower (average = 0.16, SD = 0.44, maximum = 1) than observed with the EQ-5D for treated and untreated symptomatic patients with two or three *SMN2* copies (between 0.34 and 0.45). This could be due, at least in part, to a difference in the populations studied: of the patients who responded to the EQ-5D in our study, 10%, 58%, and 32% of patients were classified as SMA types 1, 2, and 3 respectively, whereas the distribution was 10%, 74%, and 16% in the López-Bastida et al.[11] analysis. Thus, the previous study included fewer patients with a milder phenotype. A recent study that calculated the cost-effectiveness of NBS in SMA in Australia[28] classified utility scores in patients with SMA according to the motor skills affected from −0.20 to 0.64. The Australian study revealed a lower disease cost and higher QoL in presymptomatic patients, which is in agreement with our conclusion that NBS is of economic value.

Our study has several limitations. First, the cohort of patients not identified by symptoms was small. The size of this population is limited by the novelty of NBS. Southern Belgium was one of the first regions to perform NBS and treat patients immediately. A second limitation is that patients not identified by symptoms were much younger than other patients in the study, which is again related to the novelty of NBS. This had a direct impact on the QoL data because questionnaires were not valid before the age of 2 years (except for the PedsQL Family Impact scale) and were filled by the parents before the age of 6 years. We believe that this introduces a negative bias against patients not identified by symptom evolution since parents of very young children tended to rate the family impact of the disease as severe even if the child had no symptoms. This is likely due to the fear that the disease will get worse. For this reason, the comparison of QoL data between groups should be interpretated cautiously. In addition, the inclusion and exclusion criteria for the populations of the two studies were different: for instance, the NatHis-SMA study only collected data from patients older than 2 years of age who could maintain a sitting position in their wheelchair for 3 hours; no similar exclusion criteria were adopted in the other study. This could lead to a bias towards a better overall condition in untreated patients. A third limitation resides in the reliability of the estimation of indirect costs. For example, indirect costs are probably overestimated for individuals not identified by symptoms due to government support for a career break for parents. Another limitation could be the use of adult EQ-5D tables to analyse the responses of children. This may have limited the precision of the responses. Moreover, QoL and costs were only reported at one time point in this study. Collection of longitudinal data is ongoing and will provide relevant information to assess whether QoL and costs change over time. A final limitation could be that costs were collected from a single European country. Further data collected in other European Union and non-European Union countries are needed to generalize this conclusion.

Conclusions

This study showed that overall costs vary considerably between treated and untreated patients with SMA. If treatment costs are not considered, patients not identified by symptoms had better motor development and lower direct medical and non-medical costs than untreated patients or patients who began treatment after presenting with symptoms. This study clearly suggests the positive impact of NBS on disease-related costs. Furthermore, our data suggest that if a treatment is available, identifying patients early results in significant short-term savings. Longer follow-up and larger cohorts are needed to confirm the long-term cost-effectiveness of NBS.

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

François Boemer https://orcid.org/0000-0003-4470-9524
Laurent Servais https://orcid.org/0000-0001-9270-4061

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SUPPORTING INFORMATION

The following additional material may be found online.

Table S1: Unitary cost of illness in € in 2020.
Table S2: Estimation of cost in € of treatment in 2020.
Table S3: Comparison of the population by origin (NatHis-SMA or Liege NMRC study).
Figure S1: Yearly median societal cost in € per patient with SMA.

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