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Social/ economic burden and health-related quality of life in patients with Spinal Muscular Atrophy (SMA) in Greece

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Abstract

Objective

The objective of this study was to determine the economic burden and health-related quality of life (HRQoL) of patients with Spinal Muscular Atrophy SMA and their caregivers in Greece, which is still unknown, and explore the economic impact of the implementation of a reproductive carrier screening (RCS) program.

Methods

A cross-sectional study was conducted in which an online questionnaire was completed by caregivers of SMA patients. A cost of illness (COI) model was developed in which costs per patient were calculated from a societal perspective and extrapolated to the Greek SMA population. Parents'/caregivers' HRQoL was measured using the 36-item PedsQL™ Family Impact Module. Resources for the implementation of RCS program were estimated and its short-term impact was assessed.

Results

The COI was estimated at €261,785 per patient in 2022. When extrapolating this across all affected persons, the average annual cost ranged from €49,739,395 to €91,036,017 depending on the prevalence considered. Out-of-pocket expenses accounted for 8% of the total. Results of the analysis on HRQoL indicated a high burden on parents/ caregivers with the majority of scores falling below 50 and a mean total score of 45. Depending on the scenario used, an RCS program could save the Greek healthcare system at least €167,181 or increase its costs by €564,804.

Conclusions

SMA imposes a significant economic burden in affected patients, caregivers, and health care system. The cost-saving magnitude of a potential implementation of an CRS program is dependent on the parents' reproductive choices following a positive screening result.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by the degeneration of alpha motor neurons in the spinal cord which results in progressive proximal muscle weakness and paralysis [1]. The incidence of SMA ranges from 1 in 6,000 to 1 in 10,000 live births, and carrier frequency ranges from 1/40 to 1/60, making it the second most common fatal autosomal recessive disorder after cystic fibrosis.[2,3]

In Greece, its prevalence is estimated at 3.3/100,000 and 1.5/100,000 according to Orphanet[4] and Kekou et al. 2020[5], respectively. The debilitating nature and severity of the disease require a variety of healthcare resources, including frequent visits to medical practitioners and expensive treatments to increase life expectancy. Patients may have restricted access to early medication if SMA diagnosis is delayed for months or even years.

Various studies have been conducted worldwide in an effort to estimate the economic burden of SMA to the society as a whole.[6-18] To our knowledge, no study has been published in Greece delving into the economic burden of SMA.

Further, not many studies[19] have attempted to quantify the economic impact of introducing a reproductive carrier screening (RCS) program to the third-party payer's budget as well. The purpose of the RCS is to inform women who are about to give birth on the likelihood of giving birth to a child who will develop SMA.

Reproductive choices of couples who have been informed of a positive result differ between countries.[4, 5, 20, 21] Few real-world studies have shown that a high proportion of couples do not proceed with the pregnancy[22-24] while in an Israelian study this percentage dropped to around 50%.[25]

In Greece, a survey conducted in two hospitals among 533 women showed that 78% and 86% would not proceed with pregnancy in cases of lethal anomaly or developmental delay, respectively.[26] Real world Greek data from 88 pregnancies from a single hospital indicate an increase to this number to 96% and 100% for lethal anomalies and developmental delays, respectively.[26]

The present study aims to present results regarding the socio-economic burden of SMA in Greece and specifically estimate the cost of illness (COI) and health-related quality of life (HRQoL) of patients with SMA.

Further, it attempts to assess the economic impact to the Greek National Health System from the implementation of an RCS program.

2. Methodology

A cross-sectional study was conducted between October to December 2022. An online questionnaire with 21 queries was developed to assess patients' healthcare resource use (HCRU) (i.e., inpatient admissions, outpatient visits, surgical procedures, laboratory investigations, imaging tests and concomitant medications), equipment and services required for patients' daily activities, socio-demographic factors as well as parents'/ caregivers' loss of productivity and HRQoL. The questionnaire was reviewed and validated by members of the "95" Rare Alliance Greece, a Greek non-profit organization advocating for patients with rare diseases. Respondents' healthcare resource use was leveraged as input in the COI model while cost inputs were retrieved by publicly official sources.

A convenience sample of 19 families was identified while those eligible to participate in the study were patients diagnosed with SMA, and their main caregiver. The latter was responsible for the completion of the self-administered questionnaire. Participants were informed of the study objectives as well as confidentiality and anonymity of data and gave written consent to participate. The present study was conducted in accordance with the Declaration of Helsinki and the Greek legislation (Law 2328/1995, Presidential Decree 310/1996, Law 3603/2007, Law 2472/1997, Law 3471/2006), stating that there is no need for ethics approval in telephone and internet surveys such the one presented here.

Following the queries focused on assessing the economic burden of SMA, the 36-item PedsQL™ Family Impact Module (FIM) was used to evaluate HRQoL of parents/ caregivers. The 36-item PedsQL™ FIM Scales encompasses 6 scales measuring parent self-reported functioning: 1) physical functioning (6 items), 2) emotional functioning (5 items), 3) social functioning (4 items), 4) cognitive functioning (5 items), 5) communication (3 items), 6) worry (5 items), and 2 scales measuring parent reported family functioning; 7) daily activities (3 items) and 8) family relationships (5 items).[27] Each item is scored on a five-point response scale, then converted to a 0 to 100 scale. A 5-point response scale is utilized (0 = never a problem; 4 = always a problem). Items are reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better functioning (less negative impact). Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data).

2.1. Cost of illness analysis

A de novo COI model was developed to estimate the average annual economic burden of SMA in the Greek population from a societal perspective considering direct and indirect costs (productivity loss). The model adopted a prevalence approach and as such all prevalent cases in Greece were considered. Two approaches were explored to estimate the number of SMA patients; one using the prevalence value reported by Orphanet[4] and one using the prevalence recorded in 2020 by Kekou et al.[5] The prevalence rates were then applied to the total number of the Greek population (10,432,481)[20] and it was estimated that 348 and 190 patients, were respectively expected to suffer from SMA in Greece. Moreover, based on an 1:11,000 incidence rate[5] it was estimated that approximately eight births of babies with SMA could be expected every year. The resources used, as reported in the questionnaires, were multiplied by the unit costs[21] to estimate the annual cost per patient and per population

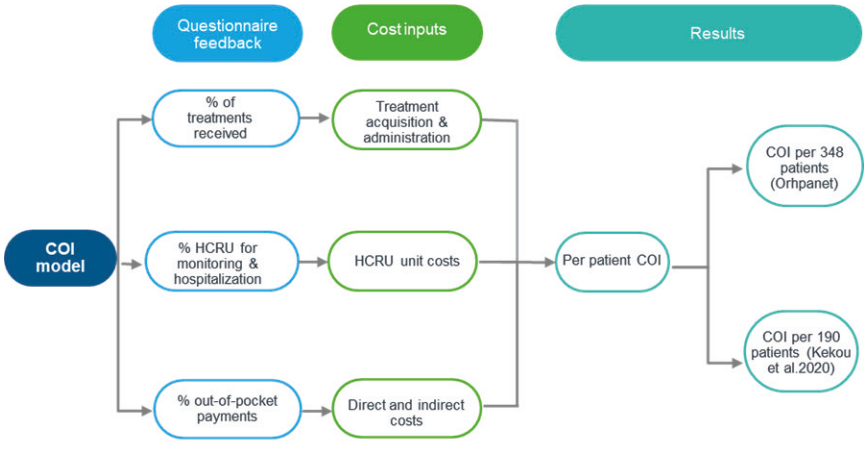

Figure 1. Model structure

using 2022 as the reference year. An overview of the model structure is illustrated in Figure 1.

2.1.1 Healthcare resource use inputs

Healthcare resource use of patients with the different types of SMA as reported by respondents is presented in Table 1. Overall, the healthcare resources with the highest usage for patients were visits to a healthcare practitioner, complete blood count testing, X-rays. Three hospitalizations were reported by patients during the previous year, each lasted approximately three days. The main reason of hospitalization was lower respiratory tract infections such as pneumonia and bronchitis, with pneumonia accounting for almost half of hospitalizations.

Table 1. Yearly healthcare resource use of patients with SMA

Resource	Average
Medical visit	5.3
Complete blood count	3.0
X-ray	2.3
Spirometry	1.4
Use of chest or limb support	0.9
DXA	0.4
Hospitalization	2.7
Sleep study	0.6
Eye test	0.7
Dental test	2.1
Physiotherapy	2.3
Speech and language therapy	1.0
Occupational therapy	1.3
Hydrotherapy	1.9
Psychotherapy	0.6

Abbreviations: DXA, dual-energy x-ray absorptiometry

Furthermore, a number of patients required surgery of the spine (33%), tracheostomy (17%), gastrostomy (11%) and orthopedic operations (17%). Some health services that considered in the analysis such as physiotherapy, speech therapy, occupational therapy, hydrotherapy, and psychotherapy are not fully reimbursed in Greece. As outlined in Table 2, up to 100% of patients reported not receiving full reimbursement for their treatments.

Patients with SMA require additional resources such as consumables for tracheostomy, breathing devices and medications besides the SMA related treatment. Moreover, some patients may also need adjustments to their home, an elevator, or a vehicle for transportation to improve their daily management of the disease. It is also common for patients to visit hospitals and clinics at regular intervals to undergo various treatments, which contributes to the already high out-of-pocket costs.

Last, more than half of respondents said that one of the two parents was unable to work because of the responsibility of caring for someone with SMA. The working parent had to take approximately 17 days off from work in order to assist with the activities.

2.1.2. Cost inputs

Cost inputs comprise of direct treatment acquisition and administration, direct monitoring and hospitalization (HCRU), out-of-pocket and indirect costs (productivity loss).

Treatment acquisition costs were based on the recommended dosing schemes as sourced from each treatment's Summary of Product Characteristics (SPC) issued by European Medicines Agency (EMA)[28-30] and the published unit prices as sourced from the latest Drug price bulletin issued by the Greek Ministry of Health[31] (Supplementary Table 1).

Administration costs were applied to the treatments requiring to be administered by a physician or health professional with experience in the management of SMA and therefore the cost of a day-case hospital setting was charged (€80 per infusion[32]).

Monitoring and hospitalization costs were inserted into the model based on the annual frequency of use reported by respondents and the unit costs reflecting the official reimbursed prices by budget payer and the relevant DRGs. The aforementioned unit costs are illustrated in Supplementary Table 2.

Physiotherapy, speech therapy, occupational therapy, and psychotherapy are partially reimbursed by the Government, so patients do have to cover a portion of them, representing direct out-of-pocket payments, illustrated in Supplementary Table 3. Further a breakdown among activities comprising out-of-pocket costs for SMA patients can be shown in Figure 2.

Table 2. Percentage of reimbursement of specific therapies

	Physiotherapy	Speech and language therapist	Occupational therapy	Hydrotherapy	Psychotherapy
% of patients reported not receiving full reimbursement	72.2%	88.9%	83.3%	100.0%	88.9%

Abbreviations: SMA, spinal muscular atrophy

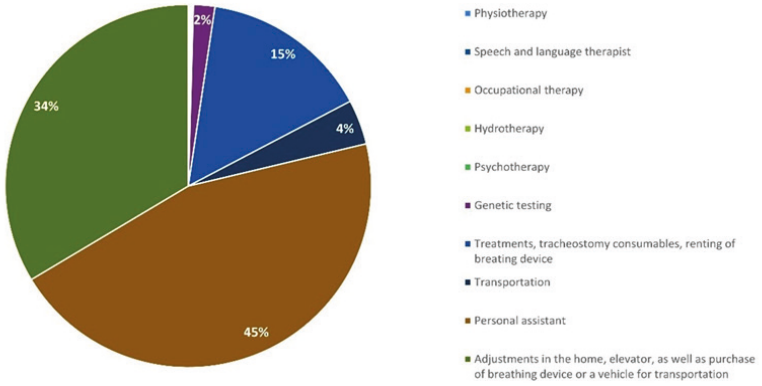

Figure 2. Percentage breakdown of out-of-pocket costs

Annual productivity loss for the working parent was calculated based on the daily wage of €56.7 as sourced from Hellenic Statistical Authority.[33] The annual productivity loss cost was estimated at €964.

2.2. Assessment of reproductive carrier screening program economic impact

We further aimed to evaluate the impact of the implementation of an RCS program into the healthcare system and specifically to the yearly budget. In Greece, 85,799 women were pregnant in 2021.[34] We assumed that all women who are pregnant would undertake the RCS program and also that following screening, women with positive test results will terminate the birth. Further, we assumed that the carrier frequency is 1/40 which was based on updated unpublished data from the Laboratory of Medical Genetics[35] leading to a possible detection of ~2,145 female carriers. In these cases, the father would also need to be screened aggravating the budget by another 2,145 tests. Moreover, using an incidence rate for SMA of 1:11,000[5] it is estimated that approximately 8 births of babies with SMA would be avoided with the use of an RCS program. The resources necessary for the implementation of the RCS program were assessed in the context of a massive screening for *SMN1* exon 7 deletions in up to 40,000 individuals in a period of 12 months and are presented in Supplementary Table 4. For the equipment, instead of paying off its total cost within the first year, an approach was used whereby the repayment of the costs was split among four installments across four years.

To be as inclusive as possible, our analysis considered a first scenario using the least extreme value of 78% from the Greek literature[26] and a second scenario using the value of 50%[25], as the percentage of cases in which the pregnancy would be terminated following a positive result.

3. Results

3.1. Cost of illness

Participants were 41 years old on average (SD = 11.86) (range: 9-55 years) and 61% were female. The main characteristics of participants are shown in Table 3.

Table 3. Demographic characteristics of the study participants

	Total n (%)	Type I n (%)	Type II n (%)	Type III n (%)	Type IV n (%)
No. of patients (%)	19 (100)	1 (5.3)	12 (63.2)	4 (21.1)	2 (10.5)
Gender					
Female	12 (63.2)	1 (100.0)	7 (58.3)	3 (75.0)	1 (50.0)
Male	7 (36.8)	0 (0.0)	5 (41.7)	1 (25.0)	1 (50.0)
% Disability					
<67%	1 (5.3)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)
>67%	18 (94.7)	1(100.0)	11 (91.7)	4 (100.0)	2 (100.0)
Treatment					
Onasemnogene abeparvovec	4 (21.1)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nusinersen	12 (63.2)	0 (0.0)	8 (66.7)	4 (33.3)	0 (0.0)
Risdiplam	3 (15.8)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)

Cost of illness comprise of the summary of direct treatment acquisition and administration costs, direct monitoring and hospitalization costs, out-of-pocket and indirect costs. Overall, the average annual cost of SMA was estimated at €261,785 per patient in 2022. Subsequently, the average annual out-of-pocket and indirect costs per patient were €20,846 (Table 4) which represents the 8% of the average annual cost.

Table 4. Per patient cost breakdown

Cost category	Average annual cost
Drug acquisition and administration costs	€236,568
Monitoring & hospitalization costs	€4,371
Out-of-pocket and indirect costs	€ 20,846
Total	€261,785

Based on the two population scenarios with either 348 or 190 SMA patients in Greece, average annual costs were estimated at €91,036,017 and €49,739,395, respectively (Table 5).

Table 5. Cost breakdown extrapolated to the whole population

Cost category	Average annual cost	
	n=348	n=190
Drug acquisition and administration cost	€82,266,204	€45,013,981
Monitoring & hospitalization costs	€1,520,475	€764,589
Out of pocket and indirect costs	€7,249,338	€3,960,825
Total	€91,036,017	€49,739,395

Abbreviations: HCRU, healthcare resource use

3.2. Health-related quality of life

The analysis indicated that the burden on the HRQoL of parents/ caregivers of SMA patients is high, with scores below 50 on most scales. "Worry" and "daily activities" scores were the lowest, while "cognitive functioning" scores were the highest (Table 6). It is evident that SMA contributes to the HRQoL burden of the families, even if parents of children without any health condition responded scores between 100 and 75.

Table 6. PedsQL™ FIM scores in different functioning categories

Scale	Mean	Median
Total scores	45.0	40.3
Parent HRQoL Summary Score	49.3	46.9
Family Functioning Summary Score	42.7	40.6
Physical functioning	41.7	39.6
Emotional functioning	41.5	37.5
Social functioning	45.9	40.6
Cognitive functioning	68.8	67.5
Communication	47.9	50.0
Worry	30.0	25.0
Daily activities	30.8	29.2
Family relationships	49.8	50.0

Abbreviations: FIM: family impact module; HRQoL: health-related quality of life; PedsQL™: Pediatric Quality of Life Inventory

3.3. Economic impact of reproductive carrier screening program implementation

The implementation of the RCS program when considering the first scenario (78% of cases tested positive opt to stop pregnancy[26]) indicates that investing €1,871,922 per year to test all pregnant women would lead to cost-savings up to €167,181 per year (Table 7). After the fourth year, which is when the disbursement of the equipment stops, the annual cost-savings are projected to increase by an additional €100,000.

However, considering the second scenario (50% of cases tested positive opt to stop pregnancy[25]) indicates that RCS may not prove as cost-saving as possibly expected. This is probably due to accumulative costs of both the implementation of the RCS and the early administration of therapies in the pregnancies to be continued, bringing on additional costs of up to €564,804.

4. Discussion

To our knowledge this is the first study conducted in Greece measuring the COI and HRQoL of patients with SMA and estimating the economic impact of the implementation of an RCS program. Our results revealed an average annual economic burden of €261,785 per patient in 2022. Applying this figure to the prevalence rates sourced from Orphanet[4] and Kekou et al.[5] resulted to average annual costs of €91,036,017 and €49,739,395 across all affected patients in Greece, respectively. Out-of-pocket costs were also very high representing approximately 8% of the total expenditure which is translated to €41,693 on average per patient.

Overall, the cost of SMA patients management accounts for 1.2% of the total health expenditure in Greece.[36] Based on the above results and considering that the total cost per patient with diabetes (patients with diabetes represent 10% of the total population) in Greece is equal to €7,111 per year[37, 38] we can conclude that the economic and humanistic burden of SMA in Greece is significantly high.

Our findings regarding the economic burden of SMA, are in line with those of other similar studies.[6, 11, 13, 14, 17, 18] In order for the comparison to be meaningful it should be noted that authors of those studies did not take into account expensive innovative medications such as Nusinersen, Risdiplam or Onasemnogene abeparvovec. On the contrary the treatment options were limited to general supportive measures.

Excluding treatment acquisition and administration costs, our analysis yield results at a average annual cost of SMA at €25,217 per patient in 2022. Lopez-Bastida et al.[13] estimated the economic costs related to SMA from a societal perspective in Spain and found that the average annual cost associated with SMA was €33,721. In Italy, Rumi et al.[18] surveyed 73 patients with SMA and developed an economic model to estimate the average annual cost per patient. Results showed that the annual costs per patient were €19,885 excluding drug-related therapies for SMA. A larger study in Italy by Marcellusi et al.[14] estimated an average annual per patient cost of €15,371. Klug et al.[11] in their four-month cross-sectional study conducted in Germany estimated that the total direct medical and non-medical costs per patient per year were €54,721. Pena-Longobardo et al.[17] also estimated the annual cost of SMA in UK, France and Germany and found an aver-

age total annual cost per patient of €54,295, €32,042 and €51,983, respectively. Armstrong et al.[6] in a similar study evaluating the resource utilization and costs associated with SMA in United States. The authors only included medical costs and estimated an annualized mean of total healthcare expenditure of $47,862 ± $88,607.

Our cost estimates (excluding the cost of treatments) are very similar to that of the study conducted for Italy and not very much different from those conducted for Spain and France, as described above. However, compared to the UK, German and US studies our costs are significantly lower which may be attributed to the different methods of accounting for direct healthcare resources and informal care and to the inclusion of more expensive resources (e.g., artificial nutrition systems, respiratory management) which were not considered in our analysis.

HRQoL is another indicator through which we can define the overall societal impact of a specific health problem. Overall, HRQoL of our sample was low with the majority of scores in the scales falling below 50. The scales of "Worry" and "Daily activities" were the ones with the lowest scores while the scale of "Cognitive functioning" was the one with the highest. No other study was identified in the literature exploring the HRQoL of parents/guardians of patients with SMA using the PedsQL™ Family Impact Module, thus making it difficult to compare our results with the wider literature. However, other studies in patients with juvenile localized scleroderma[39], developmental delays (gross motor, fine motor, speech language, cognition)[40], malignant neoplasm in active therapy[41], sickle cell disease[42] have been conducted using PedsQL™ Family Impact Module the results of which indicate a better HRQoL of parents/guardians of patients with other diseases.

Results of the economic impact of the implementation of an RCS program suggest that it would possibly be cost-saving for the Greek National Health System, dependent on the number of families that opt to terminate pregnancy following a positive screening result.

There are several limitations in this analysis which are highlighted below. The first and most important limitation relates to the sample size of our study which consisted of 19 patients. This is a relatively small sample size which does not allow us to make safe conclusions regarding the actual COI. However, in Greece, a single system or database capturing al those patients suffering from Rare Disease is missing thus making the identification of these patients very difficult. The majority of the patients in our sample size had type II SMA and were not evenly spread across the different types of SMA. For example, there was only one patient with type I SMA which is considered the most frequent type. As a result, we were not able to estimate COI per type of SMA, which would have been much more useful and informative. Furthermore, the absence of patients with type I SMA from our sample most likely underestimates the true COI since these patients tend to have higher costs compared to the other types.

In the absence of newborn screening findings, which would represent the actual prevalence of SMA in Greece, estimation of COI was based on prevalence rates from Orphanet[4] and Kekou et al..[5] Few simplifications were used in our model such as the accrual of the one-off costs in the first year. Our model also used a close cohort of patients and did not take into account any newly diagnosed patients or patients who have passed away. A few simplified assumptions were also used for the scenarios with the implementation of the RCS program. For example, it was assumed that pregnant participants with affected fetuses would discontinue their pregnancies. However, the actual number of couples to be screened and subsequently discontinue an affected pregnancy remains unknown and is influenced also by various social practices such as religion. To proceed, pilot studies of RCS program implementation will need to be performed and a cost analysis to be undertaken following the completion of those studies.

Table 7. Economic impact of a reproductive carrier screening program implementation

Economic impact of a reproductive carrier screening program		
Inputs to be consider	85,799 pregnant women	
	2,145 fathers will need to be examined	considering a mean carrier frequency of 1/40
	8 births will be terminated with the use of reproductive carrier screening program	using an incidence rate for SMA of 1:11,000
Cost of reproductive carrier screening program testing per year	€ 1,871,922	
Costs avoided per year	€ 2,039,103	
Cost-savings per year	€ 167,181	

5. Conclusion

In conclusion, a considerable economic burden exists for both healthcare system and families of SMA patients. Additionally, there is a notable impact in the QoL of those caring for SMA patients. The implementation of an RCS program could also have a positive impact to the healthcare system budget, as our research indicates, but more research and pilot tests are needed to confirm these results.

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CONFLICT OF INTEREST

Vasileios Kontogiannis, Mary Adamopoulou, Dimitris Athanasiou, Georgia Moraiti and Maria Kalogeropoulou report receiving financial support for the conduct of this study from Astrazeneca Greece, Genesis Pharma and Takeda Hellas. Maria Kalogeropoulou, Mary Adamopoulou and Dimitris Athanasiou conceived and designed the study. Maria Kalogeropoulou, Mary Adamopoulou, Dimitris Athanasiou, Georgia Moraiti and Vasileios Kontogiannis designed the study questionnaires. Vasileios Kontogiannis and Maria Kalogeropoulou analyzed the data and all authors contributed to the interpretation of the findings. Jan Traeger-Synodinos, Chrystallena Sofocleous and Kyriaki Kekou provided costing data for the reproductive carrier screening program. Vasileios Kontogiannis and Marios Athanasios Loupas drafted the first manuscript version and all authors commented on this version. Authors state no conflict of interest. All authors read and approved the final manuscript.

Supplementary materials

Supplementary Table 1. Treatment dosing schemes and cost inputs				
Treatment	Dosing scheme	Total doses	Reimbursed annual cost	Source
Nusinersen	The recommended dosage is 12 mg (5 ml) per administration. Four loading doses on Days 0, 14, 28 and 63. A maintenance dose once every 4 months thereafter	6	€ 58,644	Drug price bulletin issued by the Ministry of Health[31]
Risdiplam	5 mg daily dose (2 years of age (≥ 20 kg)	31	€ 6,834	
Onasemnogene abeparvovec	Mean of 185.25 total volume of dose (mL)	1	€ 1,686,257	

Supplementary Table 2. Unit costs of HCRU		
Resource	Unit cost	Source
Medical visit	€10.0	EOPYY reimbursed price based on physicians reimbursed fee
Complete blood count	€1.99	EOPYY reimbursed price of complete blood count based on Greek list of laboratory and imaging tests' prices (Geek reference: 157/18,157/24 - Γενική εξέταση αίματος-αιμοσφαιρίνη-αριθμός ερυθρών αιμοσφαιρίων, αριθμός λευκών και τύπος αυτών, μετά προσδιορισμού αιματοκρίτου ΗΤ)
X-ray	€4.1	EOPYY reimbursed price of hips X-ray based on Greek list of laboratory and imaging tests' prices (Greek reference: 157/39: Ακτινογραφία λεκάνης και κατ' ισχίον αρθρώσεων)
Spirometry	€4.1	EOPYY reimbursed price of spirometry based on Greek list of laboratory and imaging tests' prices (Greek reference ΣΤΡ. ΣΧΕΔ. ΔΒ3Ε/92/19-01-2017 - Απλή σπιρομέτρηση προ βρογχοδιαστολής)
Use of chest or limb support	€35.0	EOPYY reimbursed price of splint based on Greek list of laboratory and imaging tests' prices (Greek reference: 1502/11-10-2006 - Ναρθηκες από σκληρο ακρυλικο χειρουργικοι-συγκλισης-ανακουφισης - Τ.Α.Υ.Τ.Ε.Κ.Ω.)
DXA	€33.3	EOPYY reimbursed price of bone density test based on Greek list of laboratory and imaging tests' prices (Greek reference: 138/29 - Μέτρηση οστικής πυκνότητας με διπλή φωτονιακή απορροφησιομέτρηση (D.P.A.)-ΜΟΠ)
Hospitalisation	€200.0	One-day clinic
Sleep study	€146.7	EOPYY reimbursed price of sleep study based on Greek list of laboratory and imaging tests' prices (Greek reference: 427/7 - Πολυσωματοκαταγραφική μελέτη κατά την διάρκεια του ύπνου ή μελέτη κατά τη διάρκεια του ύπνου (test ύπνου). Κατά την διάρκεια του ύπνου επί 7 ώρες καταγράφονται: Ηλεκτροεγκεφαλογράφημα, Ηλεκτροκαρδιογράφημα, Καπνογράφημα, Κινήσεις θώρακος και κοιλιάς, Οξυμετρία)
Eye test	€10.0	EOPYY reimbursed price based on physicians reimbursed fee
Dental test	€10.0	EOPYY reimbursed price based on physicians reimbursed fee
Physiotherapy	€15.0	EOPYY reimbursed price based on physicians reimbursed fee
Speech and language therapy	€15.0	EOPYY reimbursed price of speech and language therapy based on Greek list of laboratory and imaging tests' prices (Greek reference: 138/43, 127/1, ΦΕΚ 2011 - 2456/14, ΣΧΔ69/26-3- 2014 - Αγωγή λόγου-λογοθεραπεία)
Occupational therapy	€15.0	EOPYY reimbursed price of occupational therapy based on Greek list of laboratory and imaging tests' prices (Greek reference: ΦΕΚ 1233/11-04-2012, ΣΧΔ69/26-3-2014, ΦΕΚ 38-28-03-2017 - Εργοθεραπεία ενηλίκων)
Psychotherapy	€15.0	EOPYY reimbursed price of psychotherapy based on Greek list of laboratory and imaging tests' prices (Greek reference: 138/43, 127/1 - Ατομική Ψυχοθεραπεία ενηλίκων από ψυχίατρο)
One-off costs		
Surgery of the spine*	€5,283.3	Government Gazette 946/2012 - DRGs List - 1/3/2012 (Average of Greek DRGs-KEN N03M, N03X, M06Μα, M06A, M06Μβ, M06Μγ, M06X, M09Μα, M09Χα, M09Μβ, M09Χβ, M09Μγ, M09X, M10Μα, M10Μβ, M10Χα, M10Χβ, M10Χγ, M10Χδ)
Tracheostomy	€12,000.0	Government Gazette 946/2012 - DRGs List - 1/3/2012 (Average of Greek DRGs-KEN E06M, E06Χα, E06Χγ)
Gastrostomy	€2,834.0	Government Gazette 946/2012 - DRGs List - 1/3/2012 (Average of Greek DRGs-KEN Θ09Μα, Θ09Μβ, Θ09X)
Orthopedic operations[a]	€5,623.5	Government Gazette 946/2012 - DRGs List - 1/3/2012 (Average of Greek DRGs-KEN Φ02M, Φ02X, M08M, M08X)

Abbreviations: DXA, dual-energy x-ray absorptiometry; HCRU, healthcare resource use
aCost is underestimated since patients conduct more advanced technology orthopedic operations that are not fully covered by the Social Security Fund and the respective expenditure is €40,000

Supplementary Table 3. Out-of-pocket costs		
Resource		Cost per visit/year
Direct	Physiotherapy	€28.6
	Speech and language therapy	€15.6
	Occupational therapy	€13.3
	Hydrotherapy	€30.6
	Psychotherapy	€24.4
	Treatments, tracheostomy consumables, renting of breathing devices	€3,738.9*
Indirect	Transportation	€1,000*
	Personal assistant	€11,310*
	Genetic tests	€474*
	One-off costs	
	Adjustments in the home, elevator, purchase of a breathing device or a vehicle for transportation	€8,422

**Resources with an asterisk indicate a yearly value*

Supplementary Table 4. Estimated total costs of a reproductive carrier screening program	
Equipment	Cost* (VAT 24% included)
Robotic DNA extraction system for extracting DNA from DBS	€80,000
Robotic system for high throughput Digital PCR analysis for the quantification of SMN1/SMN2 copies	€140,000
ABI automated sequencer (MLPA and sequencing analysis)	€160,000
Other	€20,000
Total	€400,000
Consumables	
DNA extraction & ddPCR (Quantification of SMN1 copies)	€720,000
Kit for MLPA	€16,500
Tips, tubes, 96-well plates, gloves etc	€33,500
Total	€770,000
Salaries	
2 Full time employees (biologists)	€50,000
1 Full time employee (technician)	€16,000
1 Full time employee (administrative)	€13,000
Total	€79,000

**Cost required for a massive screening for SMN1 exon 7 deletions in up to 40,000 individuals in a period of 12 months*

Abbreviations: DBS, Dried blood spot testing; PCR, polymerase chain reaction; ddPCR, Droplet digital polymerase chain reaction; MLPA, Multiplex-Ligation Dependent Probe Amplification.

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