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Investigating attitudes toward prenatal diagnosis and fetal therapy for spinal muscular atrophy

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Abstract

Objective: In utero SMA treatment could improve survival and neurologic outcomes. We investigated the attitudes of patients and parents with SMA regarding prenatal diagnosis, fetal therapies, and clinical trials.

Methods: A multidisciplinary team designed a questionnaire that Cure SMA electronically distributed to parents and patients (>18 years old) affected by SMA. Multivariable ordinal logistic regression was used to analyze associations between respondent characteristics and attitudes.

Results: Of 114 respondents (60% of whom were patients), only 2 were prenatally diagnosed. However, 91% supported prenatal testing and 81% felt there had been a delay in their diagnosis. Overall, 55% would enroll in a phase I trial for fetal antisense oligonucleotide (ASO) while 79% would choose an established fetal ASO/small molecule therapy. Overall, 61% would enroll in fetal gene therapy trials and 87% would choose fetal gene therapies. Patients were less likely to enroll in a fetal gene therapy trial than parents enrolling a child (OR 0.31, $p < 0.05$). Older parental

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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age and believing there had been excessive delay in diagnosis were associated with an interest in enrolling in a fetal ASO trial (OR 1.04, 7.38, respectively, $p < 0.05$).

Conclusion: In utero therapies are promising for severe genetic diseases. Patients with SMA and their parents view prenatal testing and therapies positively, with gene therapy being favored.

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is a debilitating neuromuscular disease that is caused by a deletion or loss of function mutation in the survival motor neuron 1 gene (*SMN1*). Carrier frequency ranges from 1 in 40 to 1 in 60 and is equally distributed across all populations. A near duplicate gene, *SMN2*, encodes the same protein as *SMN1*, but it is a nonfunctional variant.[1] SMA is a leading cause of neonatal death with the number of copies of *SMN2* correlating with the severity of disease. Patients having 0–2 copies of *SMN2* demonstrate the most severe phenotypes.[1] SMA is classified into five types depending on the timing of disease onset and highest level of motor function achieved.[2] Patients with type 0 typically present prenatally with characteristics of fetal akinesia deformation sequence and exhibit profound hypotonia, respiratory distress, and cranial nerve impairment at birth.[3] Patients with type 0 rarely survive the first month of life. Type 1 (Werdnig–Hoffmann disease) accounts for 50% of patients with SMA.[2] Type 1 patients exhibit symptoms prior to 6 months of age and natural history is typically death prior to 2 years of life. Patients with type 1 SMA suffer a rapid loss of motor function, impaired swallowing, compromised respiratory function, and cannot sit without support. Importantly, there is growing evidence that the onset of type 1 disease also begins in utero[4,5]

Patients with type 2 SMA present with symptoms between 6 and 18 months of age and never ambulate independently, experiencing proximal weakness, intercostal muscle weakness, progressive scoliosis, and respiratory compromise.[6] They account for 20% of SMA cases, and most patients survive past age 25[7]. Patients with type 3 SMA (Kugelberg–Welander) present with symptoms after 18 months of age and attain independent ambulation but may require a wheelchair with disease progression.[6–8] They account for 30% of SMA cases and have an unaltered lifespan. Patients with type 4 develop progressive proximal weakness in adulthood and remain ambulatory. They account for less than 5% of SMA cases.[6,7,9]

Given the correlation of disease severity with the number of copies of the *SMN2* gene, genetic testing has prognostic value and can be offered prenatally. Based on high morbidity and mortality, carrier frequency and ability to accurately identify carriers by molecular testing carrier screening has been recommended by the American College of Medical Genetics since 2008, and in 2017, the American College of Obstetrics and Gynecology recommended offering carrier screening to all women that are pregnant or considering pregnancy.[10,11] For couples identified to be at risk of an affected pregnancy, prenatal genetic testing can identify patients with mutations in *SMN1* and low copy numbers of *SMN2*, who are predicated to have a severe phenotype.[11] Newborn screening for SMA is implemented in multiple states,[12] concordant with the growing options for available therapies.

The landscape of available therapies for patients with SMA has dramatically expanded in the past 5 years. Antisense oligonucleotide (nusinersen), gene therapy (onasemnogene

abeparvovec), and a small molecule therapy (risdiplam) are approved for pediatric and adult patients with SMA. Multiple studies have demonstrated that these therapies have maximal benefit when initiated early, including improved survival, reduced need for ventilation support, better motor function, and attainment of motor milestones unseen in historical cohorts.[13–16] Thus, there is a strong rationale for treating patients with severe SMA, especially patients with types 0 and 1, even earlier, prior to birth.[5]

Postnatal therapeutic efficacy can be limited by the prenatal onset of axonal injury[5] and the inability to reverse the sequelae of the disease at the time of postnatal therapy.[17] Prenatal therapy could enable the treatment prior to disease onset or progression and result in improved neurologic outcomes. Moreover, delivering therapies prior to the closure of the blood–brain barrier could improve therapeutic efficacy. In a mouse model for severe SMA, fetal gene therapy using a single dose of AAV9-SMN successfully ameliorated the SMA phenotype.[18] Furthermore, an analog of the orally bioavailable SMN2 splice switching drug risdiplam was safely delivered to pregnant dams with sufficient bioavailability in SMA fetuses to improve axonal development, electrophysiology, and motor behavior.[5] Our group has launched two phase I clinical trials for fetuses with different genetic conditions: in utero hematopoietic stem cell transplantation for fetuses with alpha thalassemia (NCT02986698), and in utero intravenous enzyme replacement therapy (ERT) for fetuses with various lysosomal storage diseases (NCT04532047). We are now exploring the potential for prenatal therapies for fetuses with SMA.

As novel therapies are developed, it is crucial to engage the patient community for that disease.[19] The approval of nusinersen in 2016 brought hope to a community affected by a disease with a previously bleak prognosis,[20,21] with members of the SMA community feeling hopeful about the promise of novel therapies and future of living with SMA.[22] Having so recently witnessed the rapid proliferation of drugs that can alter the natural history of SMA, the SMA community may be predisposed to be optimistic about other novel approaches, such as fetal therapies. Historically, the SMA community has demonstrated a high interest in accessing clinical trials, despite a fear of receiving the placebo and lack of information about trial risks.[23–25] As the possibility of prenatal therapies emerges, it is also important to assess whether this population's historical interest in previous novel approaches also portends an interest in prenatal clinical trials. Gathering stakeholder views can help inform conversations with regulatory authorities regarding trials for fetal therapies and importantly, provide direction for future trials in considering their primary beneficiaries' priorities and needs. The aim of this study is to understand the beliefs of patients, carriers, and caregivers regarding prenatal diagnosis and therapy and discern which variables are associated with positive interest in participating in prenatal clinical trials.

2 | METHODS

2.1 | Instrument development

This study sought to assess the attitudes of patients and parents of patients with SMA toward fetal treatment and fetal clinical trials. No validated questionnaire was available on this topic; thus, two of the authors (MES and TCM) wrote sample questions about the topic of interest. The questionnaire was designed according to the principles outlined by

Dillman et al.[26] Simple, direct sentences were used for clarity and to minimize respondent burden. The survey was discussed during a virtual meeting by a multidisciplinary group (genetic counselor, neurologist, three patient advocacy leaders from Cure SMA, and fetal surgeon) (Appendix 1) that provided feedback on the questions and formatting. The survey was revised accordingly and circulated among all the team members via email in an iterative process to establish construct and content validity. Questions were written in a structured response format with a free text option where appropriate. After determining whether the respondent was a patient or a parent of a patient, the survey was divided into three sections. The first inquired about diagnostic details and therapies received by the affected individual (if the respondent was a patient themselves; if the respondent was a parent, their child/children). ASO and small molecule therapy were grouped together as they are considered chronic therapies, as opposed to the single dose gene therapy. The small molecule therapy, branaplam, available through clinical trials at the time of the survey, was included as a small molecule therapy that respondents could indicate receiving. The second section evaluated attitudes toward potential fetal therapies and trials, using a 5-point Likert scale. The third appraised respondents' demographics, socioeconomic status, and occupation.

2.2 | Survey distribution

This study was approved by the University of California, San Francisco's Institutional Review Board. A link to the electronic survey, on the survey platform, Qualtrics XM (SAP, Provo, UT), was distributed to parents and patients (aged 18 and older) via the monthly newsletter of Cure SMA, the leading national SMA patient advocacy group in the United States. Cure SMA is a nonprofit organization that has chapters throughout the United States and over 120,000 members and supporters. At the time of the survey, there were 8600 individuals affected with SMA in the member database. Cure SMA is invested in comprehensive research to shape the community's understanding of SMA. Cure SMA described the survey and provided the survey link in six monthly research newsletters. Subjects were told in the newsletter that they were eligible to participate if they were a patient with SMA or a parent who had a child affected by SMA. In addition to the newsletters, Cure SMA sent out a targeted eblast to 100 parents of children affected with SMA type I, inviting them to participate in the survey. The survey was anonymous and remained available from July 15, 2020, until April 10, 2021. There were no benefits or compensation for participating in the survey. Informed consent was obtained prior to patients filling out the survey. A cover letter explained the purpose of the survey, the rationale for fetal therapy for SMA, and the potential risks and benefits of fetal therapy for SMA (Appendix 2).

2.3 | Statistical analysis

Only surveys with completion rates greater than 80% were included. Descriptive statistics and Chi-squared test were used to assess the relationship between each of categorical variables and the different respondent types (parents vs. patients, severe vs. less severe disease type). Univariable ordinal logistic regression was used to analyze associations between respondent characteristics and the four outcome variables: (1) choose fetal ASO or small molecule therapy if it was an approved therapy, (2) choose fetal gene therapy if it was an approved therapy, (3) enroll in a phase one clinical trial for fetal ASO therapy,

and (4) enroll in a phase one clinical trial for fetal gene therapy. Multivariable ordinal logistic regression was then performed, incorporating all variables with a p-value of <0.1 in univariable regression, for each of the four outcome variables. A separate subanalysis was performed for only parents. A two-sided alpha of 0.05 was considered significant for all analyses. All the analyses were performed by using the statistical computing software, R version 4.0.

3 | RESULTS

3.1 | Respondent characteristics

One hundred and 14 people responded to the survey, including 46 parents and 68 patients (Table 1). Most respondents were white women with a bachelor's or graduate degree, with a median age of 37. Most respondents were affected by types 2 and 3 SMA. One parent of a type 0 patient, 25 parents of a type 1 child, and four type 1 patients responded. Overall, only two parents had received a prenatal diagnosis, and six had used preimplantation genetic diagnosis (PGD). The median age at the time of postnatal diagnosis was 15 months. Overall, 63.3% of patients had received antisense oligonucleotides (nusinersen), 28.3% had received gene therapy (zolgensma), and 14.7% received small molecule therapy (risdiplam and branaplam). Some patients had received more than one therapy.

3.2 | Attitudes toward SMA diagnosis

We sought to investigate patients' and parents' experience receiving a diagnosis of SMA and their attitudes toward prenatal testing for SMA. Since patients with the more severe types (0 and 1) are most likely to be offered prenatal therapy, we separated their responses from those with types 2 and 3. When asked about their opinion about prenatal testing for SMA, 80% of those affected by types 0% and 1% and 71.4% of those affected by types 2 and 3 strongly supported it (Figure 1A). Overall, 77% of respondents affected by SMA types 0 or 1% and 85% of those affected by types 2 or 3 subjectively felt that there had been a delay (moderate or excessive) in receiving the diagnosis of SMA. Only 23.1% of patients/parents affected by SMA types 0 and 1 felt that there had been no delay in their diagnosis and 15% of those were affected by types 2 and 3 (Figure 1B). When asked about the likelihood of having another pregnancy, 70% of respondents (in both the group affected by types 0–1 and the group affected types 2–3) reported being unlikely to have another pregnancy (Figure 1C).

3.3 | Attitudes toward fetal trials and therapies

When asked about the likelihood of enrolling in a phase I clinical trial for fetal ASO therapy, 55% of all respondents said they were likely to enroll. Respondents were divided into those (parents and patients) affected by types 0 and 1 and those affected by types 2 and 3: 60% of those affected by the more severe types were likely to enroll versus 57% of those affected by the less severe types ($p = 0.83$ by Chi square test) (Figure 2). Respondents were significantly more likely to enroll if they were older (OR 1.04, 95% CI 1.1–1.08, $p = 0.036$) and if they believed there had been an excessive delay in receiving the diagnosis of SMA (OR 7.38, 95% CI 1.44–37.77, $p = 0.016$). Respondents were less likely to want to enroll in this type of

fetal trial if the patient had received postnatal gene therapy (OR 0.2, 95% CI 0.05–0.75, p = 0.017).

When asked about the likelihood of choosing fetal ASO/small molecule therapy if this were to become an established therapy, 78.9% of all respondents said they were likely, 11% were unlikely, and 10.1% were neither likely nor unlikely. Of those affected by the more severe types of the disease, 73.3% were likely versus 81% of those affected by the less severe SMA types (p = 0.43) (Figure 3). Respondents were significantly more likely to choose an established fetal ASO or small molecule therapy if they believed there had been a moderate (OR 7.42, 95% CI 1.1–50.17, p = 0.04) or excessive delay (OR 4.47, 95% CI 0.88–22.64, p = 0.07) in diagnosis. Respondents were less likely if the patient had received postnatal gene therapy (OR 0.13, 95% CI 0.03–0.57, p = 0.007).

When asked about their attitude toward a phase I clinical trial for fetal gene therapy, 61.1% of all respondents were likely to enroll, 28.7% were unlikely, and 10.2% were neither likely nor unlikely. When comparing those with different SMA types, 73.3% of those affected by types 0 and 1 would be likely to enroll compared to 56.4% of those affected by types 2 and 3 (p = 0.13) (Figure 4). Increasing respondent age was significantly associated with a higher likelihood of enrolling in this type of fetal trial, while being a patient (as opposed to a parent) was significantly associated with a decreased likelihood of wanting to enroll in a fetal gene trial.

When asked about a hypothetical approved fetal gene therapy, 87% of all respondents would choose such a treatment option while 6.5% were unlikely and 6.5% felt neutral about such a therapy. In the subanalysis, 93.3% of those affected by types 0 and 1 compared to 84.6% of those affected by types 2 and 3 would choose an approved fetal gene therapy (p = 0.34) (Figure 5). On univariate analysis, no variables were associated with an increased likelihood of choosing such a therapy.

4 | DISCUSSION

It is important as we consider the pathway to a first in-human clinical trial to engage the patient community and understand their perspectives. In our survey of families in the United States affected by SMA, most parents subjectively felt there was a moderate or excessive delay in diagnosis, with a higher percentage reporting excessive delay for patients with less severe SMA phenotypes. When developing fetal therapies, it is also necessary to improve access to and development of early screening in parallel to ensure the timely identification of patients who would qualify for and benefit from these trials and therapies. Currently, 46/50 states screen for SMA in newborns, and SMA is still being incorporated into standard newborn screening panels in other countries. Prenatal SMA testing is voluntary in the United States but leads to an earlier diagnosis and initiation of therapy.[27,28] In addition to standard fetal testing with CVS and amniocentesis, techniques for noninvasive prenatal diagnosis of SMA have also been piloted,[29] but the widespread adoption of fetal screening is not yet present. In other surveys, respondents have supported early testing for SMA due to its ability to prepare parents for caring for a disabled child and reduce the potential emotional impact of the disease.[30] It is important to note that this survey was distributed prior to all the

states adopting routine screening for SMA, although prenatal testing for SMA has rapidly expanded since SMA was added to the federal Recommended Uni-form Screening Panel (RUSP) for newborn screening in 2018.[31]

Most of our respondents were strongly supportive of prenatal testing for SMA; this percentage was higher among respondents affected by more severe SMA phenotypes. This subset of respondents may have felt that, based on their experiences, there was more to gain from an earlier diagnosis. Our findings are consistent with previous surveys that found that most patients/families affected by SMA support pre-conception and prenatal SMA screening, with some discrepancies between patients with type 2 SMA and other subtypes.[32,33] Respondents believed prenatal screening can raise awareness of SMA and enable reproductive choice, with pre-conception screening reducing SMA-related terminations.[22] Patients with SMA who argued against screening raised concerns about stigmatization and social engineering.[34,35] We were unable to elicit the rationale for the choices endorsed in our survey, but the fear of SMA-related terminations or stigma may also contribute to the differences regarding prenatal testing noted in our survey.

In our survey, respondents were more likely to pursue any approved therapy compared to enrolling in any clinical trial. There is a lot of ethical complexity in early phase trials for severe pediatric diseases, such as the limited treatment options, uncertain risks and benefits, and the fact that patient communities are often highly motivated to shape and/or fund experimental research.[36] These factors may have contributed to our findings regarding attitudes toward clinical trials. Within approved therapies, respondents were more likely to pursue gene therapy compared to ASO therapy, a preference repeated for theoretical phase one clinical trials. This was consistent with the existing literature, where patients with SMA in a discrete choice experiment indicated preference for a one-time IV infusion or an oral agent over serial intrathecal infusions.[37]

Respondents affected by type 1 SMA were more likely than respondents affected by a less severe (types two-thirds) phenotype to enroll in a fetal clinical trial or choose an approved fetal therapy. Previously, patients with more severe forms of SMA and lower function status have reported lower health-related quality of life, more activity impairment, and increased need for a caretaker.[38–40] Patients with a greater disease severity indicated a preference for improvement of symptoms over stabilization.[41,42] Therefore, based on their experiences, patients and caregivers affected by a more severe form of SMA in our survey may have felt that future generations would have more to gain from prenatal therapy, tipping the scale so that the benefits of prenatal therapy outweighed the risks in our theoretical scenarios.

Additionally, respondents were less likely to choose both established and a clinical trial for fetal ASO/small molecule therapy if the patient had received postnatal gene therapy. As several postnatal therapies now exist for children with SMA that improve motor function particularly when delivered early,[14,43–46] we speculate that these patients may already have reduced disease severity and feel that future generations would have less to gain from prenatal therapy. It’s possible that some families and patients may have received a postnatal therapy that did not meet their therapeutic expectations, and thus these respondents did not see the value in similar therapies being delivered in utero.

Parents and patients also differed in their opinions regarding fetal gene therapy; patients were less likely to enroll in a trial for fetal gene therapy than a parent enrolling their affected child. Previous studies suggest that parents of children with chronic diseases, including SMA, are more likely than the patients themselves to view the disease negatively.[41,47–50] Moreover, parents of affected patients are more likely to view patients as being more dependent than patients themselves.[47] This may be partially explained by the fact that parents who respond to these surveys tend to be caregivers for younger children with more severe phenotypes, versus patients who have survived to adulthood; additionally, parents answering on behalf of younger patients may have had less time to adjust to the diagnosis. Parents likely feel an increased sense of responsibility to secure the best possible outcome for their child.[47,51]

Finally, a subset of patients with SMA may display hesitancy toward gene therapy from a disability identity perspective, as some patients consider SMA to be an integral part of their identity.[32,52] Some patients with SMA are concerned that portraying SMA as a disease to be “eradicated” with novel drugs may engender negative views toward SMA and disability, or that drug development may come at a cost for everyday interventions (such as vans or wheelchairs) that significantly impact adult patients.[52] While adults with late-onset SMA do struggle with physical impairments and access to a diverse array of healthcare needs, many patients lead meaningful and productive lives[53,54] and the benefits of prenatal gene therapy may not appear to outweigh the risks. Ultimately, patients’ decision-making regarding prenatal therapy will be affected by the same factors regarding postnatal treatment, such as cost, risk factors, available information, side effects, insurance coverage, time constraints, access to clinical sites, functional status, and disability identity.[52]

This study has several limitations. Although SMA is a pan-ethnic disease, respondents to our survey were mostly white and highly educated, with 70% possessing a bachelor’s degree or higher. This is not unusual for a survey distributed via Cure SMA, but our voluntary sample group is not representative of all members of the SMA community. A study of carrier testing of >72,400 specimens revealed a carrier frequency ranging from 1/47 in the Caucasian population to 1/72 in the African American population.[55] The majority of our respondents (63%) had already elected to receive ASO and a significant minority (15% and 28%, respectively) had received small molecule and gene therapy, which suggests that the respondents may be more receptive toward receiving novel therapies. Additionally, subjects who are more interested in research and novel therapies may have been more likely to respond to our survey.

We grouped patients with type 1 and type 0 in our analysis to protect the privacy of the single respondent family affected by type 0. This may have led to possible bias. However, the responses of that single family affected by type 0 fell within the majority opinion of type 1 respondents. Furthermore, we think it is important to include the perspectives of both the type 0 and type I patients in our analysis as both these patient groups are potential candidates for fetal therapy. It is important to consider that in general, SMA clinical severity is a continuum rather than truly presenting as distinct types.[56] We divide SMA into types (based on disease onset and motor milestone achieved) for practical clinical care and clinical trial reasons, but there is no major underlying biological difference between a baby that

shows weakness at birth (type 0) versus one that shows weakness within days of birth (severe type I). We believe there is clinical and scientific rationale to group patients with types 0 and 1. Moreover, it is appropriate to group these patients given that these are the two subtypes that could be enrolled in future gene therapy trials.

Our survey was not previously validated, and we were unable to ask for respondents' rationale behind survey responses. It would be interesting to repeat this survey as prenatal screening for SMA becomes more widespread. A prenatal or neonatal diagnosis might significantly affect the outcome of these results and as an SMA diagnosis becomes more common, a follow-up survey would be instructive. Moreover, qualitative studies could offer insight into the nuanced opinions and experiences of members in the SMA community as they pertain to prenatal therapy. However, people's responses to hypothetical situations on a survey do not necessarily translate to their actions in real life,[57,58] and as fetal therapies are still in the preclinical phase, our survey responses are based on theoretical questions. There is a need for future studies to investigate how social factors such as socioeconomic status, health literacy, and cultural and religious views impact attitudes toward fetal trials and therapies. Moreover, it will be important to strive to include a more diverse group of respondents to capture all types of families affected by SMA.

A strength of our study is the large number of responses we received from a rare disease community, including from respondents affected by more severe phenotypes. The SMA community has been very active in contributing their voices to research and providing perspectives for guiding drug and policy development,[30,41,47,59] and partnerships with an advocacy group such as Cure SMA have previously allowed widespread outreach to affected families.[60] We encourage all researchers to partner with patient advocacy groups to amplify the voices of those most affected by the disease and to seek solutions that recognize their priorities.

5 | CONCLUSION

This is the first stakeholder survey conducted for fetal therapies for patients with SMA and offers meaningful insights into patient and parent attitudes toward emerging fetal therapies. Although great advances have been made for the treatment of spinal muscular atrophy, it remains a devastating disease for which innovative therapies need to be developed. These survey results will guide discussions with FDA and other partners as we explore the feasibility of a phase I clinical trial for in utero therapies for SMA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Key points

What's already know about this topic?

- Optimal therapeutic outcome in many SMA patients is limited by motor neuron pathology that begins prenatally and is incompletely reversed by treatment delivered postnatally. In a preclinical model, in utero delivered therapeutics have successfully ameliorated the SMA phenotype. Involving the patient and caregiver community is crucial as we consider the pathway to a first in-human clinical fetal therapy trial for rare diseases, such as SMA.

What does this study add?

- This is the first stakeholder survey of parents and patients with SMA and offers insights into attitudes toward prenatal diagnosis, emerging fetal therapies, and clinical trials. Fetal therapies are viewed positively by the SMA community and prenatal gene therapy is the favored modality. More than half of the respondents would enroll in a phase I trial for fetal therapy (ASO or small molecule or gene therapy).

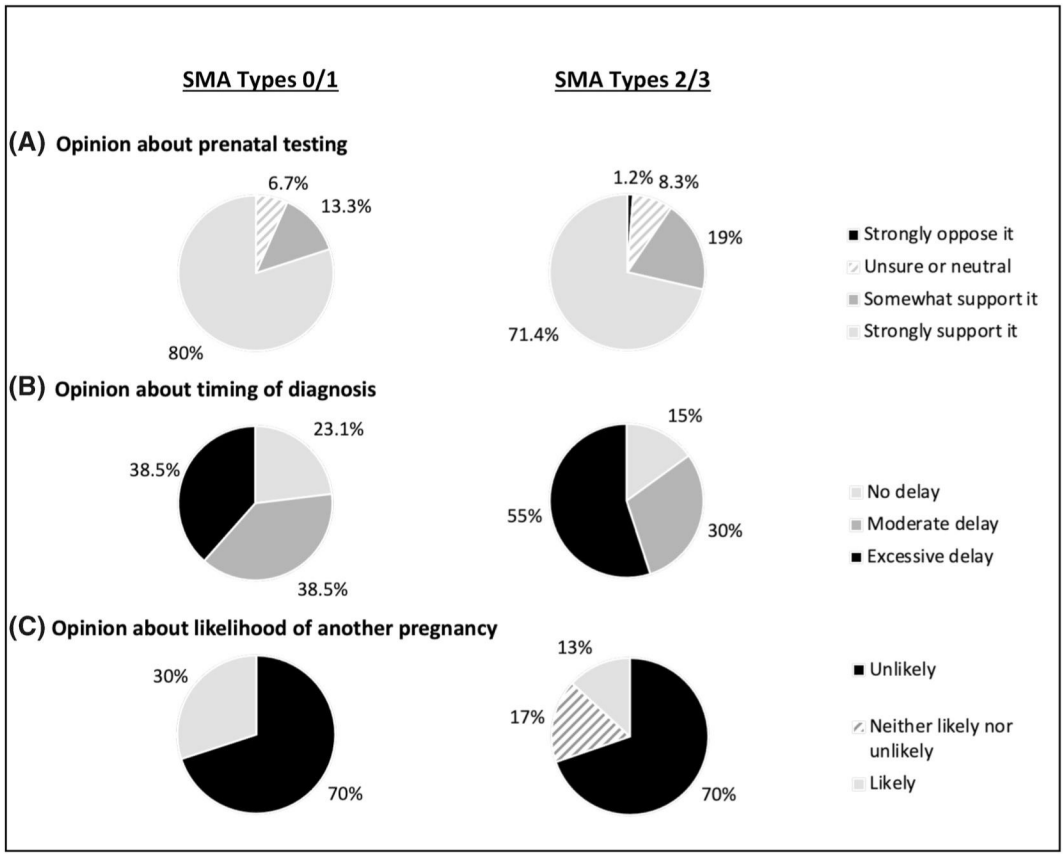
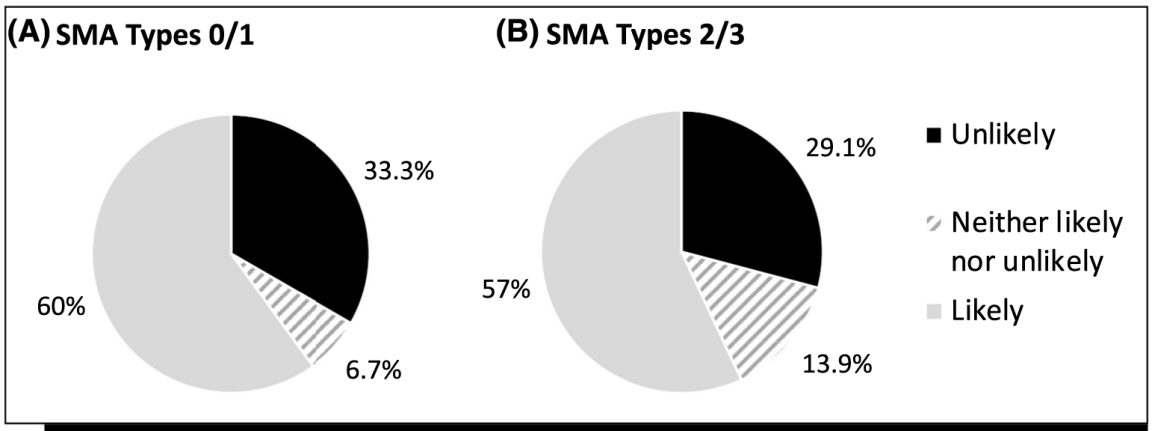


FIGURE 1.

Attitudes toward a diagnosis of Spinal muscular atrophy (SMA) and future pregnancy. The left panel corresponds to respondents affected by SMA types 0 and 1, while the right panel corresponds to respondents affected by types 2 and 3. (A), Respondents were asked "How do you feel about prenatal testing for SMA?"; $n = 30$ for types 0/1, $n = 84$ for types two-thirds. (B), Respondents were asked "What is your opinion about the time it took for your child to receive a diagnosis of SMA?"; $n = 26$ for types 0/1, $n = 20$ for types two-thirds. (C), Respondents were asked "How likely are you or your partner to have another pregnancy?"; $n = 30$ for types 0/1, $n = 76$ for types two-thirds

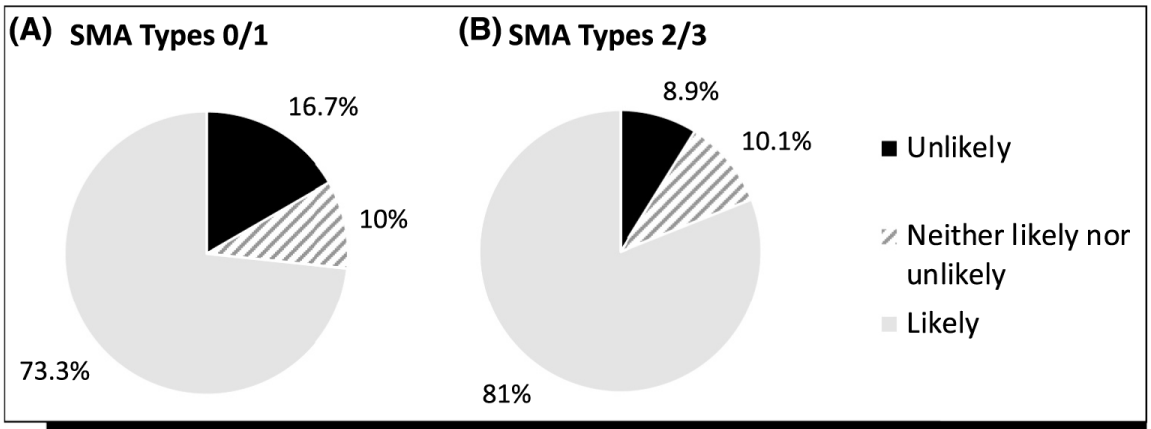


(C)

Variable	OR	95% CI	P-value
Respondent age	1.04	1-1.08	0.036
Opinion of excessive delay for diagnosis	7.38	1.44-37.77	0.016
Received gene therapy	0.2	0.05-0.75	0.017

FIGURE 2.

Attitudes toward enrolling in a phase I trial for fetal antisense oligonucleotide (ASO) therapy. Respondents were asked the question "If you or your partner were to become pregnant and the fetus was diagnosed with Spinal muscular atrophy (SMA), how likely would you be to enroll in a phase I clinical trial (to determine drug safety) for fetal ASO therapy?" (A) Respondents affected by Types 0 and 1 ($n = 30$), (B) respondents affected by Types 2 and 3 ($n = 76$), $p = 0.83$, Chi-squared test, and (C) variables associated on univariate regression

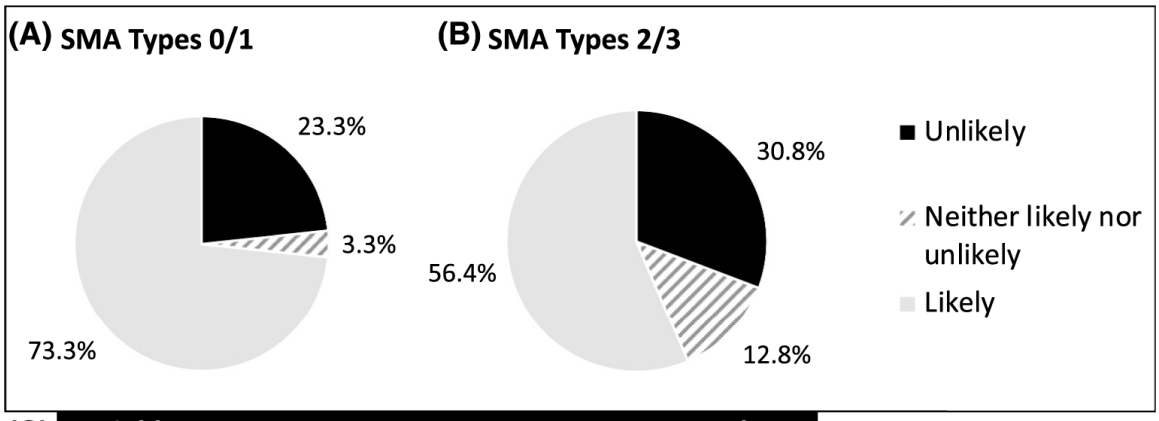


(C)

Variable	OR	95% CI	P-value
Opinion of moderate delay for diagnosis	7.42	1.1-50.17	0.04
Opinion of excessive delay for diagnosis	4.47	0.88-22.64	0.07
Received gene therapy	0.13	0.03-0.57	0.007

FIGURE 3.

Attitudes toward a hypothetical approved fetal antisense oligonucleotide (ASO) or small molecule therapy. Respondents were asked the question "If fetal ASO or small molecule therapy became an FDA-approved therapy, how likely would you be to choose this treatment for a future pregnancy affected by Spinal muscular atrophy (SMA)?" (A) respondents affected by Types 0 and 1 ($n = 30$), (B) respondents affected by Types 2 and 3 ($n = 76$), $p = 0.43$, Chi-squared test, and (C) variables associated on univariate regression



(C)

Variable	OR	95% CI	P-value
Respondent age	1.04	1-1.09	0.029
Patient	0.31	0.13-0.7	0.005

FIGURE 4.

Attitudes toward a phase I trial for fetal gene therapy. Respondents were asked the question "If you or your partner were to become pregnant and the fetus was diagnosed with Spinal muscular atrophy (SMA), how likely would you be to enroll in a phase I clinical trial (to determine drug safety) for fetal gene therapy?" (A) Respondents affected by Types 0 and 1 ($n = 30$), (B) respondents affected by Types 2 and 3 ($n = 76$), $p = 0.13$, Chi-squared test, and (C) variables associated on univariate regression

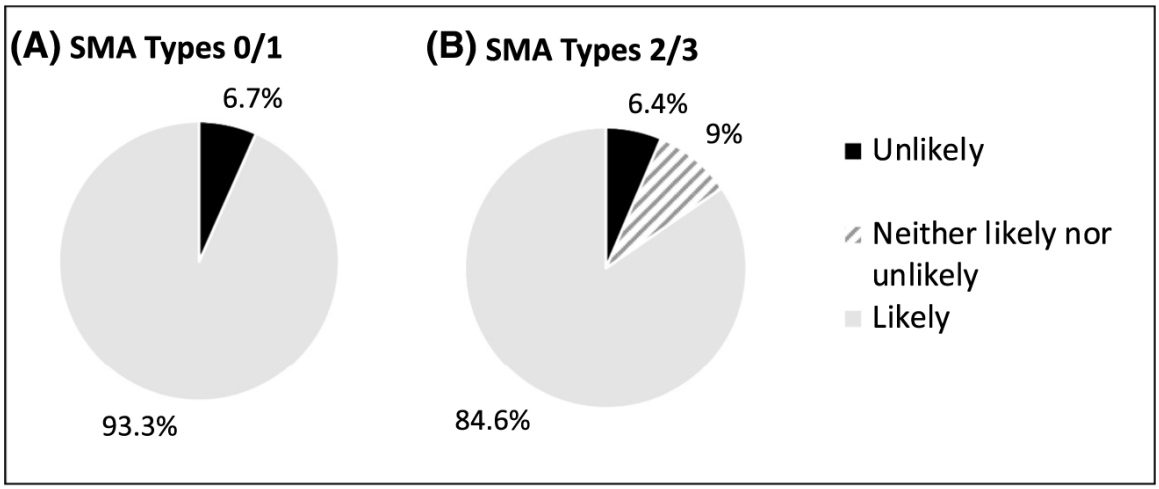


FIGURE 5.

Attitudes toward a hypothetical approved fetal gene therapy. Respondents were asked the question "If fetal gene therapy became an FDA-approved therapy, how likely would you be to choose this treatment for a future pregnancy affected by Spinal muscular atrophy (SMA)?" (A) Respondents affected by Types 0 and 1 ($n = 30$) and (B) respondents affected by Types 2 and 3 ($n = 76$), $p = 0.34$, Chi-squared test

TABLE 1

Demographic characteristics of survey respondents (n = 114)

Variables (number of respondents)	n (%) or median (range)
Patient (n = 114)	68 (59.6%)
Female (n = 109)	92 (84.4%)
Caucasian ethnicity (n = 109)	96 (88.1%)
Highest level of education (n = 109)	
High or middle school	7 (6.4%)
Some college	23 (21.1%)
Bachelor's degree	38 (34.9%)
Graduate studies	41 (37.6%)
Respondent age (n = 114)	37 (19–68)
Single affected child (n = 46)	42 (91.3%)
SMA Type (n = 114)	
Type 0	1 (0.9%)
Parent	1
Patient	0
Type 1	29 (25.4%)
Parent	25
Patient	4
Type 2	50 (43.9%)
Parent	16
Patient	34
Type 3	34 (29.8%)
Parent	4
Patient	30
Prenatal diagnosis (n = 108)	2 (1.9%)
Age (months) at postnatal diagnosis (n = 106)	
Type 1	5 (0–18)
Type 2	15 (6–48)
Type 3	53 (1–420)
Received ASO (n = 109)	69 (63.3%)
Received small molecule therapy (n = 109)	16 (14.7%)
Received gene therapy (n = 46)	13 (28.3%)

Note: Not all respondents completely answered every question, thus the n is indicated for each variable.

Abbreviations: ASO, antisense oligonucleotide; SMA, spinal muscular atrophy.