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ORIGINAL ARTICLE

Evolving approaches to prenatal genetic counseling for Spinal Muscular Atrophy in the new treatment era

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disease characterized by muscle weakness and atrophy with usually typical cognition. The first disease-modifying therapy for SMA, nusinersen, was approved by the United States Food and Drug Administration (FDA) in 2016 and leads to improved outcomes, especially when administered presymptomatically. Population-wide carrier screening and newborn screening (NBS) are now recommended by several professional organizations to promote reproductive autonomy, early diagnosis, and treatment. Prenatal genetic counselors (GCs) are important providers of the SMA screening and diagnosis process, but the possible impact of nusinersen on their practice has not been explored. A survey of 182 prenatal GCs in the United States (US) assessed baseline knowledge of nusinersen and likelihood of discussing this option with prospective parents. The majority of GCs (94.5%) were aware of this drug, and almost all (87.3%) felt that this information would affect pregnancy management decisions. However, less than half of GCs (49.2%) felt confident discussing nusinersen, 45.1% were unaware if this treatment was available in their practice setting, and one in five (19.3%) did not know where to find information about SMA treatments. Participants were more confident and knowledgeable about NBS for SMA, and several indicated that NBS would reduce their emphasis on carrier screening and diagnostic testing, not recognizing that an early prenatal diagnosis can enable preparations for complex, time-sensitive treatment. Only 5.0% of participants felt that a prenatal GC should discuss nusinersen with prospective parents. However, encouragingly, nearly all GCs who felt confident discussing this treatment option (86.4%) reported using this information weekly in their real-world practice. These data highlight an opportunity to provide up-to-date education about SMA treatments, as well as the significant impacts of early diagnosis. Additionally, interdisciplinary communication and care may be appropriate to clarify healthcare resources available and support a variety of patient needs. Increasing awareness and confidence about available options can help prenatal GCs empower patient autonomy and shared decision-making in the new era of disease-modifying treatment for SMA.

KEYWORDS
carrier testing, genetic counseling, neurogenetics, newborn screening, spinal muscular atrophy, treatment

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is one of the most common autosomal recessive genetic diseases, with a pan-ethnic carrier frequency of approximately 1/54 and an incidence of 1/11,000 live births (Sugarman et al., 2012). The SMA phenotype is characterized by muscle weakness and atrophy with usually typical cognition (Kolb & Kissel, 2015). The molecular etiology of SMA is biallelic pathogenic variants in the survival motor neuron (*SMN1*) gene (Lefebvre et al., 1995). Phenotype severity shows a strong but not absolute inverse correlation with the copy number of *SMN2*, a nearly identical paralog that produces approximately 10% functional protein due to alternative splicing (Calucho et al., 2018; Lefebvre et al., 1997). Historically, the majority of individuals with 2 copies of *SMN2* develop SMA type I, which is the most common disease subtype (Calucho et al., 2018). Children with this severe phenotype show symptoms in their first six months of life, never sit unassisted, and often do not survive beyond 2 years of age (Kolb & Kissel, 2015). Individuals with 3 copies of *SMN2* may develop type I disease (15%), but are more likely to display type II or type III phenotypes (Calucho et al., 2018). SMA type II presents between 6 and 18 months of age; these children are able to sit unassisted but never walk (Calucho et al., 2018). Patients with 4 copies of *SMN2* are most likely to develop SMA type III, which develops in childhood after ambulation but eventually requires the use of a wheelchair (Calucho et al., 2018).

Given the severity of this disorder and relatively high pan-ethnic carrier frequency, the American College of Medical Genetics (ACMG) has recommended SMA carrier screening for all reproductive couples since 2008 (Prior, 2008). More recently, the American College of Obstetricians and Gynecologists (ACOG) also updated their practice guidelines to include SMA carrier screening for the general population (ACOG, 2017). Genetic counseling has been an important component of the SMA genetic testing and diagnosis process for many years (Ogino & Wilson, 2002). The Accreditation Council for Genetic Counseling (ACGC) reviews and certifies training programs in the United States and Canada and provides practice-based competencies (PBCs) that entry-level GCs are expected to meet. According to these PBCs, a trained GC should be aware of all current management options to facilitate informed decision-making (ACGC, 2019). This responsibility is especially relevant today, because recent therapeutic advances are changing the progression and prognosis of SMA, a historically life-limiting condition (Messina et al., 2021).

Nusinersen is the first drug ever shown to modify disease course and improve outcomes for patients with SMA. This drug is an antisense oligonucleotide that increases production of full-length protein from the *SMN2* transcript by binding to an intronic splicing silencer and promoting inclusion of exon 7 (Hua et al., 2010). In 2016, nusinersen was reviewed by the US Food and Drug Administration (FDA), a US governmental agency that evaluates the safety and effectiveness of new drugs before allowing them to be prescribed to patients. The FDA approved nusinersen for treatment of any patient with SMA, encompassing all ages and phenotypes (Office of Drug Evaluation, 2016). This treatment does not cure the underlying genetic cause of disease, and so requires delivery to the cerebrospinal fluid via intrathecal injection every 4 months for life (Messina et al., 2021). Additionally, the drug is expensive at US$125,000 (United States dollar) per dose, summing to US$750,000 in the first year and US$375,000 each subsequent year (Messina et al., 2021). However, SMA was an expensive disease to treat before nusinersen, with the 3-year healthcare utilization costs of children with tracheostomies estimated at US$952,885 per patient (Lee et al., 2018). Though nusinersen is costly and requires ongoing administration, the FDA described it as an 'unprecedented advance' in clinical treatment for this serious genetic disease (ODE, 2016).

Nusinersen has the most significant benefit when initiated prior to irreversible motor neuron loss, so affected children have the greatest chance to benefit when diagnosed presymptomatically (De Vivo et al., 2019; Finkel et al., 2017). In the open-label NURTURE study, 25 infants with a genetic diagnosis of SMA (2 or 3 copies of *SMN2*) received nusinersen presymptomatically (median age of 22 days at first dose). Interim analysis was performed following a median of 12 doses over 33.9 months of treatment and all children were living, none required tracheostomy or permanent ventilation, 100% could sit independently, and 88% could walk independently (De Vivo et al., 2019). These motor milestones were achieved for the majority of children within typical developmental periods, which is a much improved clinical course from untreated SMA (De Vivo et al., 2019). In comparison, 73 children in the randomized controlled ENDEAR study who began treatment after symptom onset (2 copies of *SMN2*, mean age of 163 days at first dose) had positive but less dramatic outcomes: after 6 doses of nusinersen over 10 months, 8% achieved independent sitting and just 1% were able to stand (Finkel et al., 2017).

With the availability of effective treatment, SMA has been added to the Recommended Uniform Screening Panel (RUSP), a suggested list of conditions for US states to include in their

What is known about this topic?

SMA is a serious genetic condition with population carrier screening recommended in the prenatal setting. A disease-modifying therapy, nusinersen, has been approved and should be administered in the early newborn period for maximum benefit.

What this paper adds to the topic?

Prenatal genetic counselors are aware of nusinersen and feel that discussing this treatment with patients would affect pregnancy management decisions. However, there is a need for increased education and interdisciplinary communication to empower provider confidence applying the information in practice.

newborn screening (NBS) programs (US Department of Health & Human Services, 2018). At the time of this writing, 38/50 states have implemented or are piloting NBS for SMA, with 85% of newborns in the United States screened at birth (CureSMA, 2021). A treatment algorithm for infants diagnosed through this pipeline has also been developed, with the strong recommendation that all infants with 2–4 copies of *SMN2* begin receiving treatment immediately (Glascock et al., 2018, 2020). This recommendation has not been endorsed worldwide, in part due to the risk/benefit profile of initiating treatment in an asymptomatic infant who may not develop signs of SMA type III for years (Cuscó et al., 2020; Müller-Felber et al., 2020). In rare cases of congenital 'type 0' SMA with only 1 copy of *SMN2* present, treatment can be initiated according to physician discretion but has shown limited benefit in case reports (Glascock et al., 2018; Matesanz et al., 2020; Tiberi et al., 2020). However, for infants with 2–3 copies of *SMN2*, representing the most common and severe potential phenotypes, it is generally accepted that early diagnosis and treatment should be prioritized to maximize potential benefits for the affected individual.

While nusinersen is the first effective treatment for SMA, the landscape continues to evolve with more options and increased complexity. A one-time infusion gene replacement therapy was approved by the FDA in May 2019 for patients with SMA under 2 years of age, and an oral *SMN2* mRNA splicing modulator was approved in August 2020 for patients with SMA older than 2 months (US FDA, 2019, 2020). SMA is also the rare disease with the most potential treatment options in the clinical pipeline (Serra-Juhe & Tizzano, 2019). These public health policy changes and treatment options are important for prenatal GCs to be aware of during conversations about carrier screening and prenatal testing. Traditionally, options for an affected pregnancy included termination versus continuing the pregnancy and preparing for an affected child. Novel SMA treatment options present a third alternative, and so the purpose of this study was to explore how prenatal GCs have incorporated discussion of nusinersen into clinical practice. This research provides the first data on how a significantly improved disease course affects attitudes and genetic counseling in the prenatal setting.

2 | METHODS

2.1 | Participants

Participants were American Board of Genetic Counselors (ABGC) board-certified or board-eligible GCs currently providing prenatal or preconception counseling to patients in the United States, either in-person or remotely. Recruitment notices were distributed by the National Society of Genetic Counselors (NSGC) and ABGC professional societies. Data collection took place from October to December 2018, approximately 2 years after nusinersen was FDA-approved.

2.2 | Instrumentation

An anonymous online survey was utilized, and the study was determined to be exempt from full review and approved by the Brandeis University Institutional Review Board (IRB). All participants provided informed consent by initiating the survey and answering 'yes' to the first question. The survey consisted of 25 items including multiple choice, Likert scale, and open-ended questions. A copy of the survey is provided in the supplementary materials. Several questions were modified from an instrument that had previously been administered to prenatal GCs regarding novel treatment for cystic fibrosis (CF; Elsas et al., 2017). Other elements were based on a review of the literature and clinical experience of the investigators, with the survey divided into four sections:

1. Demographics: Participants were asked to provide their state of practice, work environment, years of prenatal experience, cases per week, service delivery methods used, and patient insurance coverage.
2. Background knowledge: Questions were asked regarding participants' previous experience with neurogenetics/SMA, their knowledge of nusinersen, the availability of the drug in their healthcare setting, and the resources they typically used to learn about new treatments for SMA. Baseline knowledge of the drug was assessed in this section using a previously designed self-reported metric (Elsas et al., 2017).

The first 8 survey questions did not mention SMA or nusinersen in order to minimize ascertainment bias. Between sections 2 and 3, educational information was presented about nusinersen including the molecular basis, risks and benefits, dosing and administration, cost, and updates to NBS for SMA.

3. Clinical Scenario: A prenatal case was presented in a stepwise fashion, and participants were asked to report their likelihood of discussing topics about SMA and treatment options at each step. The steps of the clinical scenario included (a) a carrier screening visit for a pregnant patient with no family history of SMA, (b) one parent identified as a carrier of SMA, (c) both parents identified as carriers of SMA, and (d) a positive prenatal diagnosis of SMA.
4. Clinical Frequency and Comments: Participants were asked to estimate how frequently they encountered scenarios related to SMA/nusinersen in practice and had the option to provide open-ended comments.

2.3 | Data analysis

Quantitative data were analyzed using IBM SPSS Statistics software, version 25. Categorical variables were compared using chi-squared test, or Fisher's exact test when >20% of cells had expected counts

TABLE 1 Demographics and background knowledge

	University Hospital	*Private hospital/ Medical facility*	*Public Hospital/ Medical Facility*	*Physician's Private Practice*	*Diagnostic Laboratory*	*Telegenetics Company*	*Other*
Work environment	31.9%	25.3%	22.0%	12.6%	4.3%	2.2%	1.6%
	<1 year	*1-4 years*	*5-9 years*	*10-14 years*	*15-19 years*	*20-25 years*	*25+ years*
Prenatal experience	18.1%	37.4%	21.4%	9.3%	6.6%	3.3%	3.8%
			Private Insurance	*Public insurance*	*Not sure*	*No insurance*	*Other*
Insurance Coverage of Patient Population			52.4%	38.3%	5.5%	2.7%	1.1%
			Never heard of it	*Heard of it but not sure exactly what it is*		*Know a little bit about it*	*Know quite a bit about it*
Familiarity with nusinersen			5.5%	20.9%		53.8%	19.8%
			Not at all important	*Slightly important*	*Moderately important*	*Very important*	*Extremely important*
Importance of prenatal GCs knowing about treatment options for SMA			*0.0%*	*6.0%*	*20.9%*	*44.0%*	*29.1%*
			Never	*Very rarely*	*Yearly*	*Monthly*	*Weekly*
Frequency of discussing nusinersen in practice			*42.2%*	*16.7%*	*20.1%*	*8.9%*	*12.2%*
				No	*Not sure*		*Yes*
Specialized training in neurogenetics or SMA				83.4%	N/A		16.6%
SMA specialists/treatment centers available near practice				4.9%	41.2%		53.8%
Nusinersen offered as a treatment option in health care setting				35.2%	45.1%		19.8%
	Lectures and Conferences	*Colleagues*	*Scientific Journal Articles*	*Professional Practice Guidelines*	*Patients & Advocacy Organizations*	*Media*	*Drug Manufacturers*	*FDA*
Educational resources used	88.5%	72.5%	64.3%	62.6%	31.8%	28.5%	14.3%	2.7%
	Neurologist	*Geneticist*	*Pediatric GC*	*Other*	*Pediatrician*	*Prenatal GC*	*MFM*	*OB-GYN*
Provider to discuss nusinersen	40.1%	29.1%	10.4%	7.7%	5.0%	5.0%	2.2%	0.6%

This table displays baseline characteristics of the study population, including professional demographics, attitudes and familiarity with nusinersen, and resources available. Values are listed in the order that responses were presented if relevant (i.e., scales), or otherwise with the highest response first. The highest response for each question is indicated with a border.

less than 5. Paired-sample *t* tests were used to compare mean responses on an ordinal scale.

Several response categories were collapsed for analysis, with the resulting categories used consistently for all statistical tests. The likelihood of discussing nusinersen throughout the clinical scenario was collapsed from 5 Likert scale options to 3 categories.

1. 'Extremely likely' or 'Somewhat likely' (noted as 'likely' in subsequent text for conciseness).
2. 'Neither likely nor unlikely'.
3. 'Extremely unlikely' or 'Somewhat unlikely' (noted as 'unlikely' in subsequent text for conciseness).

Agree and disagree Likert scale questions were also collapsed from 5 to 3 categories, resulting in:

1. 'Strongly agree' or 'Somewhat agree'.
2. 'Neither agree nor disagree'.
3. 'Strongly disagree' or 'Somewhat disagree'.

These responses were similar enough in context to be combined post hoc to facilitate analysis according to response trends. Of note, the full 5-category Likert scale breakdown was included in Figures 2-4 for interest. The frequency of discussion in practice was also simplified from 6 responses to 4:

1. 'Very frequently, several times per week' combined with 'Frequently, at least once per week' (noted as 'weekly' in subsequent text for conciseness).
2. 'Occasionally, at least once per month' (noted as 'monthly' in subsequent text for conciseness).
3. 'Rarely, a few times per year' combined with 'Very rarely, at least once in the past'.
4. 'Never'.

Finally, length of prenatal experience was simplified into three ranges: less than 5 years, 5 – 15 years, or more than 15 years. Practice frequency and length of experience responses were both combined into these broader ranges due to lack of response for certain choices. Open-ended responses were analyzed for themes.

3 | RESULTS

182 complete responses were used in the final study analysis, corresponding to approximately 12% of US-based prenatal/preconception

GCs (NSGC, 2018). Demographic information is shown in Table 1. There were no significant relationships between the insurance coverage of the patient population served and any GC demographics or reported treatment availability.

Table 1 shows that the majority of participants had no specific training in neurogenetics or SMA, and limited baseline knowledge of nusinersen, but felt it was important for prenatal GCs to know about SMA treatment options. Demographic factors related to higher baseline knowledge of the drug are illustrated in Figure 1. Participants who rated this knowledge as 'extremely important' were significantly more likely to practice near SMA specialists/treatment centers ($p < .001$ *by Fisher's exact test*), and/or work in a setting where nusinersen was offered ($p = .002$ *by Fisher's exact test*). Only 5.0% of respondents felt that a prenatal GC was the most appropriate provider to discuss nusinersen with patients. Instead, participants indicated a neurologist or geneticist should provide this information.

The next portion of the survey asked GCs to imagine a clinical scenario involving SMA screening and to rate which topics they would discuss at each point in the process. This section was administered after providing information about nusinersen as described in the Methods section. Throughout the first three steps of the clinical scenario, the majority of participants were likely to discuss the risk of SMA in the current pregnancy, possible symptoms of SMA, and prenatal diagnostic testing for SMA. The likelihood of discussing nusinersen increased significantly throughout every step of the clinical scenario, with responses summarized in Figure 2.

The likelihood of discussing nusinersen throughout the scenario was significantly related to baseline knowledge of the drug ($p < .001$ *by Fisher's exact test at all 4 steps*) and perceived importance of treatment knowledge ($p < .001$ *by Fisher's exact test at all 4 steps*). Participants who worked in a setting where nusinersen was offered were likely to begin this discussion earlier in the clinical scenario than GCs who worked in a setting without nusinersen available (*initial visit:* $p = .036$ *by Fisher's exact test*, *one carrier parent:* $p = .014$ *by Fisher's exact test*). Local availability of the drug was not significantly related to the likelihood of discussing nusinersen with two carrier parents or a positive prenatal diagnosis.

Figure 3 shows the information about nusinersen that participants were likely to share with parents after a prenatal diagnosis of SMA. Of note, the survey did not ask about pregnancy termination throughout the clinical scenario. However, 10 respondents commented that they would discuss this option in the case of a prenatal diagnosis. Other write-in topics to discuss during a prenatal diagnosis disclosure included referral to gene therapy research study, and referral to specialists, including a maternal–fetal medicine physician (MFM) to discuss delivery plan and neonatology to discuss postnatal care.

Participants were then asked the extent to which they agreed or disagreed with various statements about SMA and nusinersen. Responses are illustrated in Figure 4. Participants were significantly more likely to feel confident discussing newborn screening than they were discussing nusinersen ($p < .001$, $t = 8.337$, $df = 180$) and significantly more likely to know where to find information about newborn screening than information about nusinersen ($p < .001$, $t = 4.211$, $df = 180$).

As seen in Figure 4, GCs were least likely to report feeling confident discussing nusinersen with patients. Participants who did feel confident were significantly more likely to have higher baseline knowledge of the drug ($p < .001$ *by Fisher's exact test*), practice near SMA treatment centers ($p < .001$ *by Fisher's exact test*), work in a setting where nusinersen was offered ($p < .001$ *by Fisher's exact test*), and/or perceive this knowledge as important for prenatal GCs ($p < .001$ *by Fisher's exact test*). There were no significant relationships between educational resources used and confidence discussing nusinersen with patients. Respondents who felt most confident

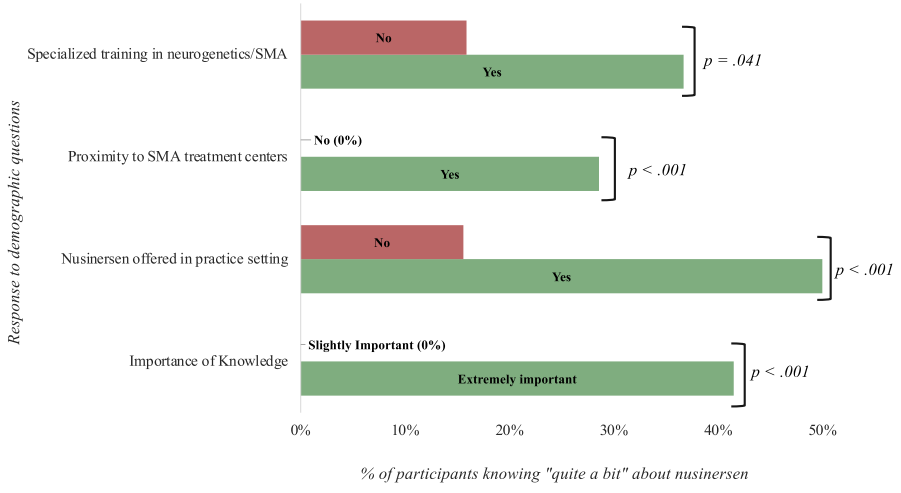

FIGURE 1 Demographic factors significantly influencing baseline knowledge of nusinersen. This figure illustrates the demographic factors significantly related to participants' baseline knowledge of nusinersen. The y-axis lists the four significant factors that were identified. There are 2 bars per factor, representing the 'positive' and 'negative' responses to that demographic question. The length of each bar represents the percentage of participants who selected that response and also reported knowing 'quite a bit' about nusinersen. $n = 182$

were significantly more likely to mention this treatment option during every step of the hypothetical clinical scenario ($p < .001$ *by Fisher's exact test for initial carrier screening, one carrier parent, and 2 carrier parents; $p = .029$ by Fisher's exact test for positive prenatal diagnosis*). Additionally, 86.4% of GCs who felt most confident discussing nusinersen reported using this knowledge at least once per week in their real-world practice, a significantly higher frequency than colleagues who were less confident ($p < .001$, $\chi^2 = 49.501$, $df = 6$).

As seen in Figure 4, participants were generally comfortable explaining NBS for SMA, knew where to find information on this topic, and felt confident discussing NBS with patients. GCs were significantly less likely to think that information about NBS would affect pregnancy management decisions compared with information about nusinersen (61.9% versus 87.3%, $p < .001$, $t = 6.212$, $df = 180$). However, participants were significantly more likely to discuss NBS for SMA than they were to discuss nusinersen for SMA treatment during the first 2 steps of the clinical scenario (*initial carrier screening* $p < .001$, $t = 4.728$, $df = 178$; *one carrier parent* $p = .003$, $t = 3.003$, $df = 178$).

Participants were next asked to estimate how frequently they encountered the previous scenarios in their own clinical practice. The majority of participants counseled for SMA carrier screening at least weekly (79%), encountered positive screening monthly (54.7%), and had managed at least one positive prenatal diagnosis (58.6%). The frequency of discussing nusinersen in practice is shown in Table 1. Participants who discussed nusinersen weekly in practice were more likely to work near SMA specialists/treatment centers ($p < .001$ *by Fisher's exact test*), practice in a setting where nusinersen was offered ($p < .001$, $\chi^2 = 32.615$, $df = 6$), and/or know where to find information about treatment options ($p = .004$ *by Fisher's exact test*).

The final question of the survey was a free-text opportunity for participants to provide additional comments regarding their experience discussing nusinersen in practice. Several participants described having limited experience or knowledge of this drug, saying '*I had not heard of [nusinersen] until now as the situation has not arisen*', '*I would like more information to provide to patients*', and '*I would like to know more about SMA treatments in the pipeline but don't really know the best places to look*'. One respondent suggested a novel educational resource, '*There should be a frequent prenatal GC webinar about emerging treatments/ clinical trials*'. A second participant described a useful learning opportunity, saying, *'when [nusinersen] became available, our facility set up a meeting with the neuro rehabilitation physician and genetic counselors at [local children's hospital] to review outcomes of the drug and how it will change our counseling…hearing it from providers that actually use the drug was most beneficial*'. The relationship between carrier screening and NBS was mentioned by several participants, saying '*After SMA was added to the newborn screen, I've had fewer patients opt for carrier screening*', '*decrease in interest regarding carrier screening for SMA since it has been added to NBS in my state*', *'couples may choose to defer screening knowing that baby will be tested at birth regardless'*, and '*If my state already had SMA on the newborn panel, I don't think I would emphasize carrier screening as thoroughly as I currently do, as it would not impact the care or outcomes for the newborn involved*'. Another common theme was the prenatal GC's role and scope of practice. One participant explained, '*I see a prenatal [genetic] counselor's responsibility in this scenario to be informing the couple of the existence of new treatments such as [nusinersen] and referring to experts…*' Another stated, '*I feel comfortable giving my patient a light overview to say that there is a new therapy…given turnaround time for testing and time-limits for termination, the initial goal is to help a patient decide if they even want to pursue genetic testing and amniocentesis*'. Some GCs shared stories of patients who had pursued prenatal diagnosis of SMA since the availability of nusinersen, saying '*they really weighed the potential benefit of [nusinersen] in debating whether to continue this pregnancy now that a treatment is available…*' and *'[nusinersen] is influencing pregnancy management decisions'*.

4 | DISCUSSION

To our knowledge, this is the first study that explores how disease-modifying treatment has impacted the views and attitudes of GCs providing prenatal genetic counseling for SMA. Our data suggest that while some GCs feel prepared to discuss this option with patients, there is a need for further education and communication about nusinersen and other emerging treatments for SMA. This presents an opportunity to improve patient care and ensure that prospective parent screening for SMA receive accurate information about all options available.

SMA is a traditionally devastating genetic disease with established recommendations for population-wide screening. The main goal of carrier screening programs is to increase autonomy, options, and informed decision-making (Aharoni et al., 2020). There are several time points when this screening can be implemented, with decreasing options available at each stage. The earliest opportunity is preconception carrier screening, which is recommended by professional practice guidelines in order to maximize autonomy of prospective parents (ACOG, 2017; Gregg et al., 2021). If carrier status is known before conception, two carrier parents may access preimplantation genetic testing (PGT) with the goal of establishing a pregnancy with an unaffected fetus. This technology has been successfully used with families at risk for SMA for over 20 years (Dreesen et al., 1998). Parents may also choose to build their family using an alternate method than genetic material from both parents, or to conceive a pregnancy spontaneously with or without prenatal diagnosis (Gregg et al., 2021). While this does maximize options, approximately 45% of pregnancies in the United States are unplanned and therefore the timing of preconception screening may not be realistic in practice (Finer & Zolna, 2016).

Our current study examined attitudes toward screening for SMA and discussing treatment prenatally during an ongoing pregnancy. Professional guidelines recommend that if screening is done during pregnancy, partners should be screened concurrently with diagnostic testing offered if both are carriers (Gregg et al., 2021). If an SMA diagnosis is made at this time point, parental autonomy is decreased

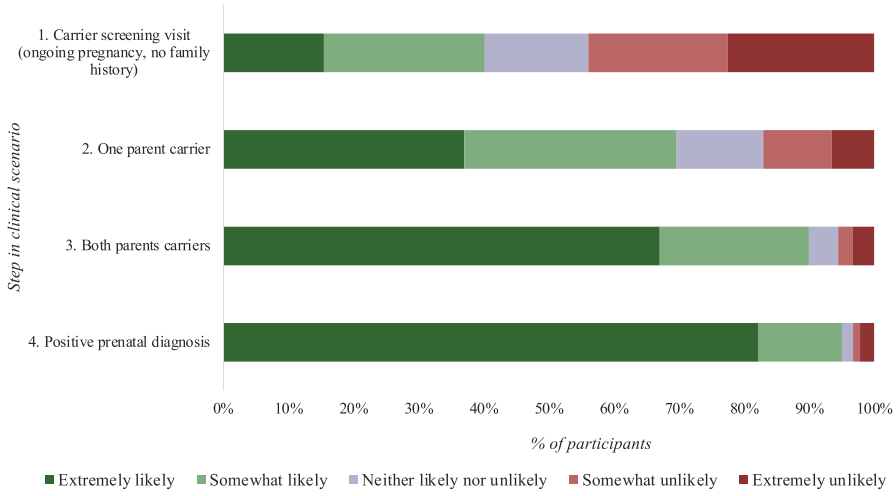

FIGURE 2 Likelihood of discussing nusinersen throughout clinical scenario. This figure shows participants' likelihood of discussing nusinersen throughout the clinical scenario, after receiving information about the drug. The four scenario steps are shown on the y-axis. At each step, participants were asked how likely they were to discuss nusinersen for SMA treatment on a 5-point Likert scale. The x-axis shows the percentage of participants choosing each response. $n = 182$

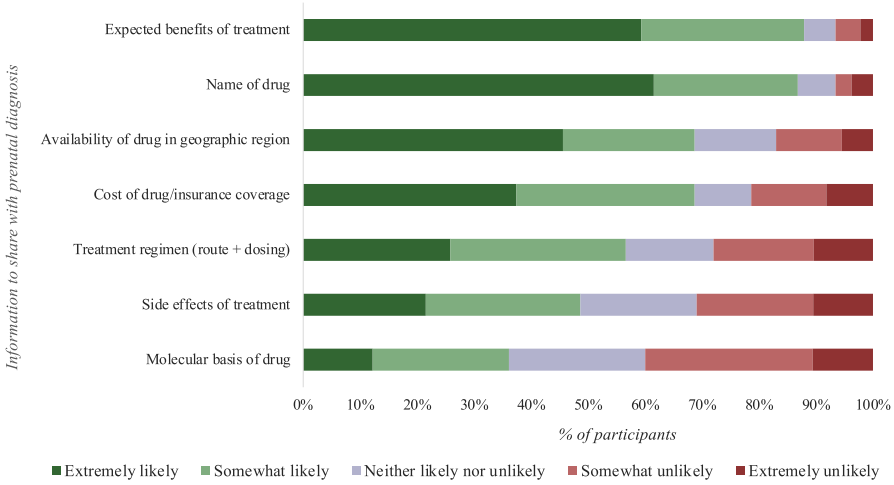

FIGURE 3 Information to share about nusinersen after prenatal diagnosis of SMA. This figure shows participants' likelihood of discussing information about nusinersen after a positive prenatal diagnosis of SMA. The y-axis lists the various topics that were queried. Participants were asked their likelihood of discussing each topic on a 5-point Likert scale. The x-axis shows the percentage of participants choosing each response. Responses are listed in descending order of likelihood (combining 'extremely likely' and 'somewhat likely' to determine order, for consistency with statistical analysis). $n = 182$

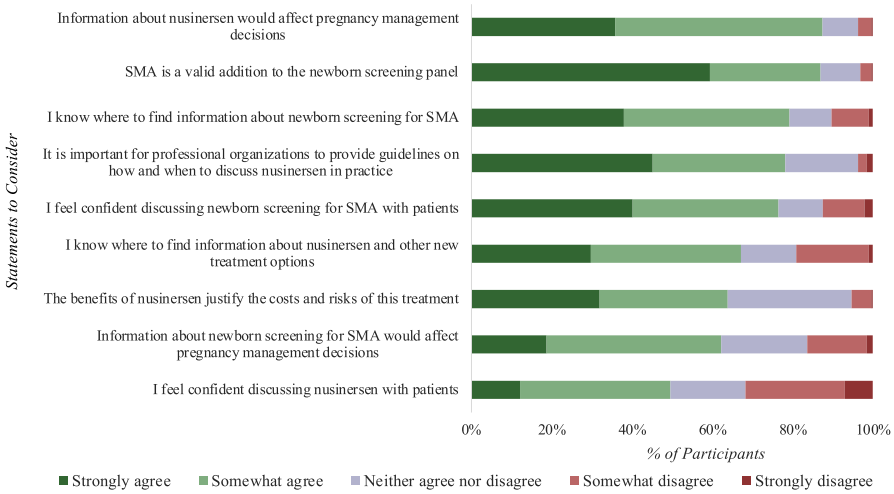

FIGURE 4 Agree versus. Disagree. This figure shows participants' agreement with various statements about SMA and nusinersen. The y-axis lists the various statements that were presented. Participants were asked their agreement with each statement on a 5-point Likert scale. The x-axis shows the percentage of participants choosing each response. Responses are listed in descending order of agreement (combining 'strongly agree' and 'somewhat agree' to determine order, for consistency with statistical analysis). $n = 182$

compared to preconception screening. Options have traditionally been limited to continuing the pregnancy and preparing for an affected child, or stopping the pregnancy, which often has a strict time limit based on gestational age. Even with treatment, SMA is a high-burden chronic condition for the patient, family, and healthcare system (Aharoni et al., 2020). In this current study, 10 participants provided free-text comments that they would discuss termination after a prenatal diagnosis. This highlights the serious decisions that prospective parents are faced with, and the importance of being well-informed about all available options.

With the availability of nusinersen and other disease-modifying treatments, a novel pregnancy management option has emerged: Parents can elect to continue the pregnancy and prepare to treat the affected child shortly after birth. In order to provide balanced information on all available options and support parental autonomy, prenatal GCs should have a working knowledge of both the natural history of SMA and potential treated phenotypes. The current results show that nearly all prenatal GCs felt information about nusinersen would affect decision-making. Even if parents are not considering termination, a prenatal diagnosis provides an opportunity to discuss early presymptomatic treatment, which offers the greatest potential benefits to the child.

The importance of early intervention for SMA has been well-established. SMA pathogenesis appears to begin in utero, and the disease is known to be biologically active prior to symptom onset (De Vivo et al., 2019; Kong et al., 2021). Fetal treatment is being explored in animal studies, with the hypothesis that prenatal intervention could provide maximum long-term benefit for severely affected individuals (Kong et al., 2021). The loss of motor neurons and motor function is irreversible, but can be prevented with earlier initiation of treatment (Glascock et al., 2020). Prenatal GCs should be aware of this time-sensitive window for maximal therapeutic benefit and of potential treatment delays associated with a postnatal diagnosis via NBS. In the Australian NBS program, 44% of newborns (4/9) identified with SMA developed symptoms in the first few weeks of life before treatment could be coordinated (Kariyawasam et al., 2020). In the first year of universal NBS in New York state, 50% of affected infants (3/6) had delayed treatment due to insurance authorization requirements (Kay et al., 2020). The German NBS program has also resulted in delayed treatment after symptoms develop, due to lengthy insurance approvals and a 'watchful waiting' approach for infants with 4 copies of *SMN2* (Müller-Felber et al., 2020). NBS is an important and relatively equitable public health program, but prenatal screening provides more time to coordinate presymptomatic therapy for maximum long-term benefit. Additionally, it is important to note that NBS is quite dependent on regional policies and only 2% of newborns worldwide are currently screened for SMA, including just 24% of infants in countries where treatment is available (Dangouloff et al., 2021).

In this study, participants were more confident finding information and discussing NBS than SMA treatment and more likely to introduce this concept early in counseling. Several GCs suggested that NBS availability would decrease rates of carrier screening and prenatal diagnosis in their patient populations, and even that they would personally de-emphasize carrier screening due to its apparent lack of impact with NBS in place. It is possible that this counseling may discourage parents from pursuing carrier screening or diagnostic testing, perceiving that a postnatal diagnosis provides the same outcomes as prenatal. However, even with NBS and treatments available, there is certainly still justification to offer carrier screening and early diagnosis during pregnancy (Aharoni et al., 2020).

Treatment for SMA is far more complex than management of conditions initially included on NBS, that is, phenylketonuria necessitating a phenylalanine-free diet. All approved drugs are prohibitively expensive, ranging from US$340,000 annually to US$2,125,000 for a one-time dose (Messina et al., 2021). The insurance approval process can be lengthy, with 35% of caregivers for patients with Type 1 SMA reporting a 1–6 month delay or longer (Chen et al., 2021). There are now multiple approved drugs available, each with a specific risk/benefit profile and potential long-term side effects, and parents need time to learn about different options (Waldrop & Elsheikh, 2020). Administration can be burdensome and is only offered at certain hospitals throughout the country, with caregivers of pediatric patients with SMA reporting an average 4.9 hr drive to a treatment center and 11.32 hr associated with administration (Chen et al., 2021). Finally, nusinersen treatment is recommended as soon as possible within the first few weeks of life, and making these major decisions while adjusting to a newborn with a serious diagnosis may be quite stressful. Prenatal GCs should be aware that a prenatal diagnosis enables preparations for prenatal care, delivery management, psychosocial support, and logistics once the child is born.

The maximal impact of SMA treatments depends not only on early diagnosis, but also a multidisciplinary standard of care (Mercuri, Finkel, et al., 2018; Messina et al., 2021). In the prenatal period, this may include MFM to discuss delivery, neonatology to discuss postnatal care, and neurology to facilitate treatment administration, as indicated by participants in the current study. A prenatal GC has an important role on this team to enable clear communication, shared decision-making, and psychosocial support, which are all critical for families to cope with the impact of diagnosis (Mercuri, Finkel, et al., 2018; Serra-Juhe & Tizzano, 2019). GCs also have specialized knowledge regarding the molecular basis of disease, which can be quite complicated given *SMN2* and other phenotype modifiers, 'silent' carriers with normal *SMN1* gene dosage (2 copies on one chromosome +0 copies on the other), germline mosaicism, and de novo mutations which contribute to 2% of cases (Prior, 2008; Serra-Juhe & Tizzano, 2019; Wirth et al., 1997). In many healthcare settings, GCs help coordinate prenatal testing and follow-up and can serve as a resource for the family regarding recurrence risk, cascade screening, and future pregnancies (Serra-Juhe & Tizzano, 2019).

Despite this unique role, almost half of GCs in the current study had never mentioned SMA treatment options to their patients, and

nearly all felt that a provider other than a prenatal GC should share information about nusinersen. These findings are in line with results of a previous study analyzing how treatment for CF impacted prenatal counseling for this condition, when 81.5% of prenatal GCs felt that information about the new drug should be presented by a specialist (Elsas et al., 2017). Those authors cautioned that if a patient does not receive information about potential treatments during a GC session, they might make pregnancy management decisions without ever consulting a specialist or learning all available options (Elsas et al., 2017). The authors called for GCs to incorporate some discussion of treatment options in the prenatal setting, and for the community to consider the responsibilities and relationship between GCs and specialists in prenatal care (Elsas et al., 2017). We reinforce this recommendation and encourage prenatal GCs to incorporate up-to-date information about SMA treatments into their practice. In a previous study of experiences with genetic counseling for SMA, parents of affected children described needing more information on early diagnosis and proactive treatment interventions, with clear explanations of options (Meldrum et al., 2007). Parents also wanted more compassion during diagnosis, and increased respect for their decisions from healthcare providers (Meldrum et al., 2007). These perspectives indicate an important role for GCs to function within a multidisciplinary team. GCs can make prospective parents aware of early diagnosis and treatment options for decision-making, compassionately support any choice they make, and if appropriate facilitate care with other specialists for continued management.

In order for GCs to function effectively in this role, they must have sufficient baseline knowledge of available treatment options, and know where to find additional information for specific cases. Our results are encouraging in that 73.6% of GCs were at least somewhat familiar with nusinersen for SMA treatment, compared with just 20.2% of GCs in a previous study of novel drugs for CF (Elsas et al., 2017). However, our data suggest that a subset of GCs are not currently acquiring knowledge about novel SMA treatments from existing sources. The free-text comments endorsed this gap and also recommended accessible, timely materials such as webinars and online materials. Additionally, GCs must understand the healthcare resources available to their patients. In this study, almost half of GCs were unsure if SMA specialists were available in their area (41.2%) or if nusinersen was offered (45.1%). One suggestion to address this knowledge gap is increasing interdisciplinary communication, as one responder emphasized that meeting with the local children's hospital was most helpful to understand available resources and inform their practice.

Encouragingly, in this study, the majority of respondents felt that it was important for prenatal GCs to know about SMA treatment options, and those who were most confident discussing nusinersen were able to apply this knowledge regularly in their real-world practice. GCs have long held an important role in the screening and diagnosis of SMA, which has entered an exciting new era of transformative treatments. With the unique skill set of genetics expertise, patient advocacy, and psychosocial support, GCs can empower parents with all options available to turn a devastating diagnosis into a manageable situation.

4.1 | Study limitations

This was a small study, with a response rate of approximately 12% of prenatal GCs. The demographics of respondents (work environment and region of practice) were representative of the greater NSGC membership ascertained in the 2018 Professional Status Survey, but the study may have limited generalizability due to sample size. Results may not be applicable to other healthcare settings with differences in access to genetic counseling, SMA screening, or treatment. Additionally, the survey instrument used was not validated, though some questions were based on an instrument previously administered to prenatal GCs (Elsas et al., 2017). The data were self-reported and therefore may not reflect what GCs would actually discuss in a counseling session. GCs responded from 34 different states at many different stages of implementing newborn screening for SMA. Finally, as this was a voluntary study, ascertainment bias may affect the validity of the findings. The recruitment notices and first 8 survey questions specifically did not mention SMA or nusinersen, in order to reduce self-selection of participants with detailed knowledge of these topics.

4.2 | Practice implications

The current analysis suggests a need for prenatal GCs to learn about the quickly evolving field of SMA treatments in a timely, accessible manner. Resources to consider include reliable information presented through webinars and other electronic formats. Individual practices should consider increased communication about local resources available and the roles of various providers on a multidisciplinary care team. GCs should advocate for the profession as a unique and important support role for families at risk for SMA.

4.3 | Research recommendations

As disease-modifying treatments for SMA become more widely available, further data should be collected on how these options affect family planning and pregnancy management decisions. It is clear that these drugs impact clinical practice and outcomes, but currently limited data on whether this has changed decision-making for those at risk of having an affected child.

It is important to conduct research with families affected by SMA, to consider their perspectives regarding this complex ethical situation and the information necessary for informed decision-making in a prenatal scenario. Additionally, to facilitate multidisciplinary care, it is important to explore the attitudes, understanding, and informational needs of other healthcare providers to optimize patient care and empowerment.

5 | CONCLUSIONS

SMA has entered a new era of therapeutic management and population-wide screening. Prenatal GCs have an important role in this evolving landscape, as more patients are offered SMA carrier screening during pregnancy and increasing numbers of cases will be identified during this time-sensitive window. An informed, compassionate, and competent GC must present all available options to their patients, including the option to continue an affected pregnancy and treat the child shortly after birth. To facilitate effective GC practice in this complex landscape, continuing education opportunities and multidisciplinary relationships should be prioritized throughout the workforce, including novel ways to communicate information quickly.

SMA is the first genetic condition with effective and time-dependent treatment leading to population-wide screening recommendations, but it will not be the last. Antisense oligonucleotides, gene therapies, and other small molecule treatments are modifiable technologies being developed for many other genetic conditions that were previously lethal in childhood. GCs will increasingly have a unique and important role in population genetic screening programs designed to enhance reproductive autonomy and maximize the benefits of treatment for individuals.

AUTHOR CONTRIBUTIONS

Bethany Zettler provided substantial contributions to the conception or design of the work; the acquisition, analysis, and interpretation of data for the work; and drafting the work. She confirms that she had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Elicia Estrella provided substantial contributions to the conception or design of the work; revising it critically for important intellectual content; and final approval of the version to be published. Khalida Liaquat provided substantial contributions to the conception or design of the work; revising it critically for important intellectual content; and final approval of the version to be published. Lauren Lichten provided substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work; revising it critically for important intellectual content; and final approval of the version to be published. All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST

Bethany Zettler received an advisory board honorarium from Novartis Gene Therapies. Khalida Liaquat is a full time, salaried employee of Quest Diagnostics and received an advisory board honorarium from Novartis Gene Therapies. Elicia Estrella and Lauren Lichten declare that they have no conflict of interest.

HUMAN STUDIES AND INFORMED CONSENT

This study was determined to be exempt from full review and approved by the Brandeis University Institutional Review Board (IRB). The study conforms to recognized standards including the Declaration of Helsinki and US Federal Policy for the Protection of Human Subjects.

ANIMAL STUDIES

No non-human animal studies were carried out by the authors for this article.

DATA SHARING AND DATA ACCESSIBILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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