SMA Community Risk Tolerance Update: Comparison of 2022 and 2017 SMA Risk/Benefit Survey Data

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EXECUTIVE SUMMARY

INTRODUCTION

In 2022, Cure SMA commissioned Silicon Valley Research Group to conduct a United States-based risk/benefit survey of individuals with spinal muscular atrophy (SMA) and their caregivers. The aim of the 2022 SMA Risk/Benefit Survey was to determine if risk tolerance had evolved in the wake of U.S. Food and Drug Administration (FDA) approval of three disease modifying therapies (DMTs) for SMA. To achieve this aim, results of the 2022 survey were compared to a similar survey conducted by Cure SMA and Silicon Valley Research Group in 2017. [1]

Spinal Muscular Atrophy (SMA)

Until recent advances in treatment, SMA was the leading genetic cause of infant mortality in the U.S. and worldwide. [1-3] SMA is an autosomal recessive disease, and approximately 1 in 40-50 (6 million) people living in the U.S. are genetic carriers. The current birth prevalence of SMA in the U.S. is approximately 1 in 14,694. [4] An estimated 9,000-9,500 individuals currently live with SMA. [5] In 95% of cases, SMA occurs when biallelic deletion of the *SMN1* gene leads to insufficient levels of the survival motor neuron (SMN) protein. [6-8] SMN is a ubiquitously expressed protein that performs critical cellular functions. [9-12] Reduced expression of SMN is particularly devastating in the nervous system, where low levels of the SMN protein cause motor neuron death, disrupted communication at the neuromuscular junction, and subsequent muscle wasting. [13, 14] The *SMN2* modifier gene also encodes the SMN protein. Although *SMN2* only produces a small amount of fully functional SMN protein, it can compensate to some degree for the loss of *SMN1* in individuals with SMA. As such, *SMN2* copy number inversely correlates with disease severity. [15, 16]

Historically, SMA disease severity has been classified as Type 0-4, in order of decreasing severity, depending on clinical factors such as age of symptom onset and maximum motor function achieved. (Table 1) [16-19]

Table 1. SMA type classification prior to FDA-approved disease modifying therapies

TYPE	AGE AT SYMPTOM ONSET	INCIDENCE	PREVALENCE	MAXIMUM MOTOR FUNCTION ACHIEVED	SMN2 COPY NUMBER	LIFE EXPECTANCY
0	IN UTERO	<1%	<1%	NONE; DECREASED FETAL MOVEMENT; CONTRACTURES AT BIRTH	**1**	Days-Weeks
1	<6 MONTHS	60%	15%	NEVER SITS INDEPENDENTLY	1,**2**,3	<2 Years
2	6-18 MONTHS	25%	70%	SITS INDEPENDENTLY	2,**3**,4	20-40 Years
3	1.5-10 YEARS	15%	15%	WALKS, THEN REGRESSION	**3**,**4**,5	Normal
4	>35 YEARS	<1%	<1%	SLOW DECLINE	**4**,**5**	Normal

Bold numerals indicate the most common *SMN2* copy number for each type.
Table was adapted from the 2016 SMA Europe and TREAT-NMD briefing document to the Clinical Trial Readiness in Spinal Muscular Atrophy Meeting (SMA) SMA Europe, TREAT-NMD, European Medicines Agency meeting: https://www.ema.europa.eu/en/documents/other/briefing-document-clinical-trial-readiness-spinal-muscular-atrophy-sma-sma-europe-treat-nmd-and-european-medicines-agency-meeting_en.pdf

However, approval by FDA of three DMTs has dramatically altered the natural history of SMA. The question of how to reclassify the diversifying range of disease phenotypes is under active discussion among SMA researchers and clinicians. [20-23]

Living with SMA

In all SMA types, degeneration of the alpha motor neurons of the spinal cord results in progressive proximal muscle weakness, atrophy, and loss of function. Without DMT, infants with the more severe forms of SMA may develop respiratory and/or nutritional complications, fail to achieve developmental motor milestones, and be at risk for premature death. [24] Untreated individuals with less severe forms of SMA may achieve developmental milestones in early childhood only to lose muscle function gradually over the remainder of their lives. [25, 26] In addition to progressive disability, teens and adults with SMA may experience fatigue, pain, psychological stress, and eventual dependence on caregivers. [27] Caring for an individual of any age with SMA may have substantial impacts on quality of life for the caregiver. [28, 29]

Disease Modifying Therapies and Unmet Treatment Needs

Beginning in 2016, FDA has approved three DMTs for SMA, each of which protects motor neurons and preserves muscle function by restoring levels of SMN protein through a unique mechanism. (Table 2)

Table 2. FDA-approved disease modifying therapies for SMA

Treatment	FDA Approval	Mechanism of Action
Nusinersen (Spinraza®)	Approved in 2016 for use in children and adults. [30]	Antisense oligonucleotide
Onasemnogene abeparvovec (Zolgensma®)	Approved in 2019 for children under two years of age. [31]	Gene therapy
Risdiplam (Evrysdi®)	Approved in 2020 for patients older than 2 months and in 2022 for patients of any age. [32]	RNA splicing modifier

Each of these DMTs may slow disease progression and dramatically improve survival rates, particularly when treatment is administered immediately after birth. [33] Yet responses to these therapies vary depending on factors like age of treatment administration, disease severity, and *SMN2* copy number. Individuals with SMA who receive treatment later in disease progression may experience a halting or slowing of disease progression but are unlikely to regain motor function. [34-36] Furthermore, real world data has revealed that some infants living with severe SMA who were treated soon after birth continue to experience deficits in nutritional and respiratory function [37] and/or scoliosis [38].

Therefore, unmet treatment needs remain for many individuals living with SMA in the U.S. including, but not limited to:

- Children with severe forms of SMA who did not receive emergent DMT immediately after birth.
- Teens and adults with SMA for whom treatment was not available until later in disease progression.
- Individuals of any age for whom DMT is less effective due to known or unknown factors.

The SMA drug development pipeline is currently burgeoning with new therapies designed to address the unmet treatment needs of individuals of all ages living with SMA. [39] One of Cure SMA's top priorities is to relay the SMA community's treatment experiences and preferences to FDA in support of patient-centered decisions about new SMA drugs. As novel SMA treatments are poised to advance into clinical trials, this report is intended to share an update on the risk/benefit profile of the U.S. SMA community.

2022 SMA Risk/Benefit Survey Methodology

The 2022 and 2017 SMA Risk/Benefit surveys were conducted using Best/Worst Scaling (BWS). In this method of questioning, respondents chose best and worst attributes rather than using a numeric scale to indicate strength of preference, minimizing response bias. Respondents were asked how willing they were to live with each of 11 different SMA treatment risks in exchange for 12 potential treatment benefits. (Table 3) Data were combined and analyzed for trends in risk tolerance in the general population of respondents (Overall Sample), as well as in three sub-samples organized according to the reported SMA type of the affected individual (SMA Type Samples).

Table 3. Potential risks and treatment benefits test in the survey

Risks	Treatment Benefits
Common side effects	Increased overall muscle strength
Side effect of dizziness	Consistent muscle performance/strength
General anesthesia to administer treatment	Improvement in ability to swallow
Invasive means to administer treatment	Improvement in ability to speak/communicate
1/100,000 risk of organ SEs requiring immediate MA	Improvement in breathing function
Increased risks of respiratory or other infections	Improved proximal mobility/ functionality
1 /100,000 risk of SEs resulting in organ failure	Increased core strength
1/1,000 risk of organ SEs requiring immediate MA	Increased upper limb strength
Life-threatening allergic reactions	Decreased fatigue
1/1,000 risk of SEs resulting in organ failure	Lessening of symptoms' severity
Worsening in quality of life	Prolonging lifespan
	Slowing or stopping of disease progression

Descriptions of risks and benefits are simplified here. Complete descriptions can be found on page X of the full-length report.
MA = medical attention; SEs = side effects.

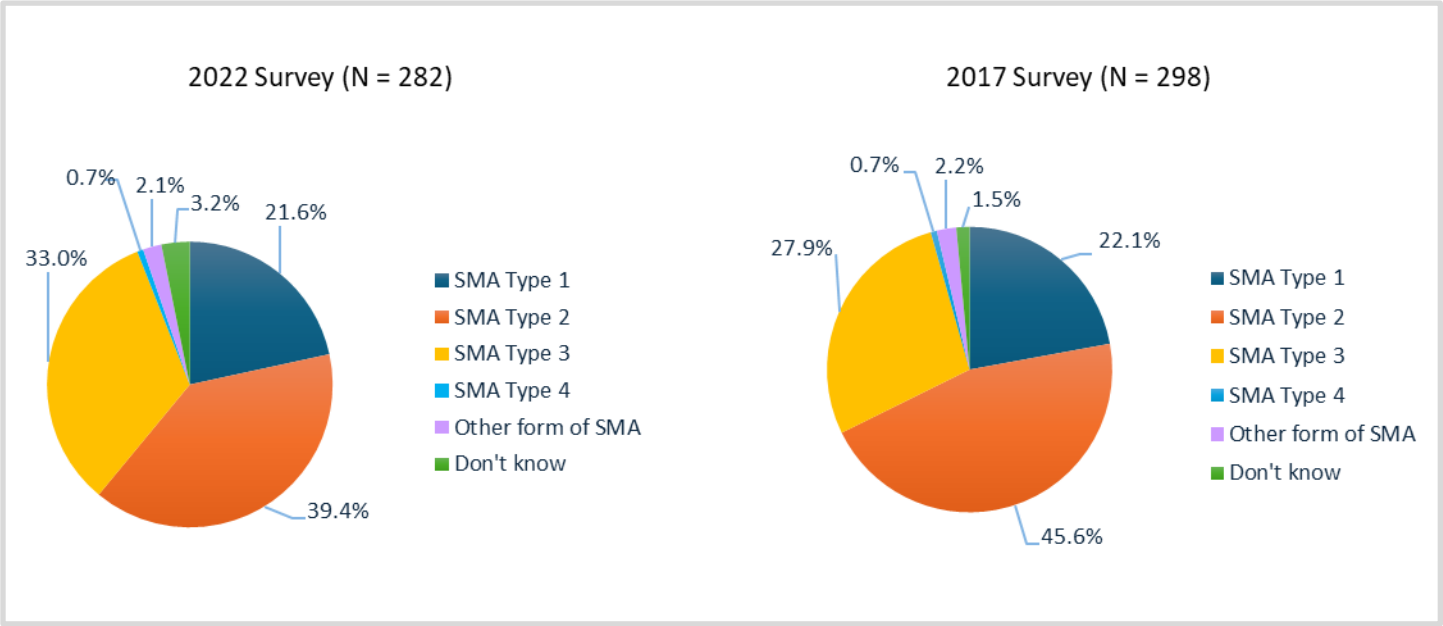
2022 SMA Risk/Benefit Survey Results

Respondent Demographics

The 2022 and 2017 survey respondent sample demographics were **similar**, with a few differences:

- The 2022 Overall Sample was slightly smaller (N=282) than the 2017 Overall Sample (N=298). For both the 2022 and 2017 surveys, respondents were at least 18 years old and resided within the U.S. Caregivers responded for individuals younger than 18 years of age.
- A greater percentage of 2022 respondents were individuals with SMA compared to 2017 (49% vs. 28%, respectively).
- Conversely, a smaller percentage of the 2022 Overall Sample were caregivers of people with SMA compared to the 2017 Overall Sample (51% vs. 72%, respectively.)
- In both surveys, the majority of respondents who identified as caregivers were parents of individuals with SMA (92.4% in 2022 and 94.2% in 2017).
- In both surveys, affected individuals were most likely to report having Type 2, followed by Type 3, and then Type 1 SMA; the percentage of each varied slightly between studies. (Figure 2)

Figure 2. SMA type of affected individuals responding to or represented in surveys



Risk/Benefit Results

The 2022 SMA Risk/Benefit Survey results were **very similar** to the 2017 survey results. For all 12 possible treatment benefits, both the 2022 and 2017 Overall Samples consistently ranked the same four risks among the *most tolerable* and the same four risks among the *least tolerable*. (Table 4)

However, the 2022 rank order of the four *most tolerable* risks was inverted compared to the 2017 rank order. (Table 4)

For example:

- The 2022 Overall Sample most frequently ranked "common side effects" as the first *most tolerable* risk across treatment benefits, whereas the 2017 Overall Sample most frequently ranked "invasive means to administer treatment" as first *most tolerable*.

- Conversely, the 2022 Overall Sample most frequently ranked the risk of "invasive means to administer treatment" as fourth *most tolerable* across treatment benefits, whereas the 2017 Overall Sample most frequently ranked "common side effects" as fourth *most tolerable*.

Table 4. Risks most frequently ranked among *most tolerable* or *least tolerable* across all treatment benefits

Most Tolerable Risks

2022 Overall Sample (N = 282)	Rank	2017 Overall Sample (N = 298)
Common side effects	1	Invasive means to administer treatment
Dizziness	2	General anesthesia
General anesthesia	3	Dizziness
Invasive means to administer treatment	4	Common side effects

Least Tolerable Risks

2022 Overall Sample (N = 282)	Rank	2017 Overall Sample (N = 298)
Worsening in quality of life	1	Worsening in quality of life
1/1,000 risk of SEs resulting in organ failure	2	1/1,000 risk of SEs resulting in organ failure
Life-threatening allergic reactions	3	Life-threatening allergic reactions
1/1,000 risk of organ SEs requiring immediate MA	4	1/1,000 risk of organ SEs requiring immediate MA

Risk labels are abbreviations of complete descriptions on page 12 of the full report.
SEs = side effects; MA = medical attention.

Survey results from 2022 and 2017 SMA Type Samples were also **very similar**, with some minor exceptions, for example:

- Across the 12 tested potential treatment benefits, the 2022 SMA Type 1 sample most frequently ranked "dizziness" and the first *most tolerable* risk, whereas the 2017 SMA Type 1 Sample most frequently ranked "invasive means to administer treatment" as first *most tolerable*.

- The 2022 SMA Types 2 and 3 Samples most frequently ranked "common side effects" as first *most tolerable* across all treatment benefits, whereas the 2017 SMA Types 2 and 3 Samples most frequently ranked "invasive means to administer treatment" as first *most tolerable*.

- All SMA Type Samples from both the 2022 and 2017 surveys most frequently ranked "worsening in quality of life" as the first *least tolerable* risk across all treatment benefits.

Conclusion

The strong similarities between the 2022 and 2017 SMA Risk/Benefit Survey results suggest that people with SMA and their caregivers are still willing to live with many different treatment risks in exchange for a variety of possible treatment benefits. These findings likely reflect that important unmet treatment needs remain in the SMA community, despite the currently available DMTs. This information may be utilized to support future patient-centered decision making around SMA drug development and approval.

SMA COMMUNITY RISK TOLERANCE UPDATE: COMPARISON OF 2022 AND 2017 SMA RISK/BENEFIT SURVEY DATA

INTRODUCTION

In 2017, Cure SMA conducted the first-of-its-kind SMA Risk/Benefit Survey to learn how willing people with spinal muscular atrophy (SMA) and their caregivers were to live with certain possible treatment risks in exchange for a variety of potential treatment benefits. [40] The study was conducted just after the first disease modifying therapy (DMT) for SMA was approved by the United States Food and Drug Administration (FDA). [30] Results of the 2017 survey indicated that the community was tolerant of a wide range of risks in exchange for a range of possible treatment benefits, and that risk tolerance did not vary notably by the type of SMA an affected individual had.

Since the 2017 survey, two additional DMTs for SMA have been approved by FDA [31, 32], and today, an estimated 70% of people living in the U.S. with SMA have been treated with at least one DMT. [41] In light of the rapid and dramatic transformation of the treatment landscape, Cure SMA conducted a second SMA Risk/Benefit Survey in 2022 to determine if risk tolerance in the SMA community had evolved as the treatment landscape has shifted.

The aims of the 2022 SMA Risk/Benefit Survey were:

- To determine if the risk/benefit preferences of the general population of respondents (Overall Sample) differed from those of 2017.
- To determine if the risk/benefit preferences of individuals with a given SMA Type (SMA Type Sample) differed from those of their 2017 counterparts.

Spinal Muscular Atrophy

SMA is a genetic neuromuscular disease characterized by progressive muscle weakness and atrophy that often leads to substantial disability, including paralysis and risk of premature death. [42] Prior to the recent FDA approval of three DMTs for SMA in the U.S. [43], SMA was the leading genetic cause of infant mortality nationally and worldwide. [1-3] Approximately 1 in 40-50 (6 million) individuals living in the U.S. are genetic carriers, where the current birth prevalence of SMA is approximately 1 in 14,694 [4]. An estimated 9,000-9,500 individuals currently live with SMA in the U.S. [5]

Molecular Mechanism of Disease

SMA is caused in 95% of cases by biallelic deletion of the *SMN1* gene [6-8]. Deletion of *SMN1* leads to insufficient production of the survival motor neuron (SMN) protein [44]. This protein is critical to the health and survival of alpha motor neurons in the spinal cord, the nerve cells responsible for proper muscle function and strength. The SMN protein is also encoded by the *SMN2* gene, which produces a small amount of functional SMN and partially compensates for the loss of *SMN1* in individuals with SMA. As such, *SMN2* copy number and disease severity are inversely correlated. [15, 16] (Table 1)

Natural History of SMA

In SMA, insufficient levels of the SMN protein result in the deterioration and death of alpha motor neurons in the spinal cord, causing a degradation in neuromuscular communication and progressive loss of muscle strength and function. [45] In addition, because the SMN protein is required for essential cellular functions throughout the body, SMA is increasingly considered to be a multi-system disease that impacts many organs including skeletal muscle, bone and connective tissue, the heart, the liver, the pancreas, and the spleen and immune system. [46-50]

Without emergent treatment, infants with severe SMA develop respiratory and/or nutritional complications [25], scoliosis [26], and contractures [26]; fail to achieve developmental motor milestones [16]; and are at high risk for death before the age of two years [24]. Untreated individuals with less severe forms of SMA may begin to lose muscle function during their teens or adulthood [25, 26, 51] and may also develop fatigue, pain, sleep disorders, depression and/or anxiety, and dependence upon caregivers. [16, 19, 52, 53] Caring for an individual of any age with SMA may substantially impact quality of life for the caregiver. [28, 29]

Historically, SMA disease severity has been classified as Type 0-4, with Type 0 being the most severe and Type 4 being the least severe. (SMA Type 0 is very rare and usually results in either fetal demise or death shortly after birth.) Under the historic classification system, SMA Type is determined by clinical factors such as age of onset and maximum motor function achieved. [16-19] (Table 1)

Table 1. SMA Type classification prior to FDA-approved disease modifying therapies

TYPE	AGE AT SYMPTOM ONSET	INCIDENCE	PREVALENCE	MAXIMUM MOTOR FUNCTION ACHIEVED	SMN2 COPY NUMBER	LIFE EXPECTANCY
0	IN UTERO	<1%	<1%	NONE; DECREASED FETAL MOVEMENT; CONTRACTURES AT BIRTH	**1**	Days-Weeks
1	<6 MONTHS	60%	15%	NEVER SITS INDEPENDENTLY	1,**2**,3	<2 Years
2	6-18 MONTHS	25%	70%	SITS INDEPENDENTLY	2,**3**,4	20-40 Years
3	1.5-10 YEARS	15%	15%	WALKS, THEN REGRESSION	**3**,**4**,5	Normal
4	>35 YEARS	<1%	<1%	SLOW DECLINE	**4,5**	Normal

Bold numerals indicate the most common *SMN2* copy number for each type.
Table was adapted from the 2016 SMA Europe and TREAT-NMD briefing document to the Clinical Trial Readiness in Spinal Muscular Atrophy Meeting (SMA) SMA Europe, TREAT-NMD, European Medicines Agency meeting: https://www.ema.europa.eu/en/documents/other/briefing-document-clinical-trial-readiness-spinal-muscular-atrophy-sma-sma-europe-treat-nmd-and-european-medicines-agency-meeting_en.pdf

However, with the FDA approval of three DMTs, SMA disease phenotypes have rapidly evolved and diversified, particularly in individuals who receive early treatment. [23, 54] SMA researchers and clinicians are actively discussing the question of how to reclassify the broadening range of novel disease phenotypes in the new treatment era. [20-23]

Disease Modifying Therapies

FDA has approved three DMTs for SMA, each of which protects motor neurons and preserves muscle function by restoring levels of SMN protein through a unique mechanism. (Table 2) First, FDA approved the antisense oligonucleotide, nusinersen, in 2016 for use in children and adults with SMA. [30] Next, the gene therapy, onasemnogene abeparvovec, was approved in 2019 for use in children under the age of two. [31] Finally, the RNA splicing modifier, risdiplam, was approved in 2020 for patients older than 2 months and the label was expanded in 2022 for patients of any age. [32]

Table 2. FDA-approved disease modifying therapies for SMA

Treatment	FDA Approval	Mechanism of Action
Nusinersen (Spinraza®)	Approved in 2016 for use in children and adults. [30]	Antisense oligonucleotide
Onasemnogene abeparvovec (Zolgensma®)	Approved in 2019 for children under two years of age. [31]	Gene therapy
Risdiplam (Evrysdi®)	Approved in 2020 for patients older than 2 months and in 2022 for patients of any age. [32]	RNA splicing modifier

Unmet Treatment Needs

Research has shown that each of these "SMN-dependent" DMTs slows disease progression and improves survival rates, but treatment response can vary due to known and unknown factors. [33, 55] For example, real world data has demonstrated that some children with severe SMA who receive emergent treatment in infancy may still develop deficits in nutritional and respiratory function [37] and/or scoliosis [38].

"If you compare my three children, you will see a huge improvement of motor function. However, each of them could still benefit from another drug or dual drugs to fully increase the ability for them to be comparable to 'typical children' . . . there is still so much that can be done to make simple every-day tasks more manageable. My six-year-old should not be able to vocalize that his smile is broken or that he has almost died two times."

– Mother of three children with SMA, each of whom received DMT at a different stage in disease progression [56]

Furthermore, in some older individuals with SMA who do not receive treatment until later in disease progression, DMTs may halt or slow disease progression but may not restore lost function or strength. [34-36]

"Treatment has allowed me not to lose more of my abilities. I can now brush my own hair, lift a plate, and help with cooking. I can now sit over the edge of my bed on my own and write for multiple minutes straight . . . These are major improvements that have given me independence in high school . . . However, I often have to choose between taking a shower and doing homework because I don't have the energy to do both."

– Teen living with SMA [56]

Therefore, unmet treatment needs remain for many individuals living with SMA in the U.S. including, but not limited to:

- Children with severe forms of SMA who did not receive emergent DMT immediately after birth.
- Teens and adults with SMA for whom treatment was not available until later in disease progression.
- Individuals of any age for whom DMT is less effective due to known or unknown factors.

Understanding The Risk Tolerance of the SMA Community

Although several studies have captured the treatment priorities of individuals with SMA and their caregivers [57-59], the 2017 SMA Risk/Benefit Survey was the first U.S. study aimed at understanding which treatment risks members of the SMA community were most and least willing to live with in exchange for a variety of treatment benefits. [40] The 2017 survey yielded a risk/tolerance profile of the SMA community on the cusp of widespread availability of DMTs in the U.S. In 2022, Cure SMA wanted to repeat the survey to determine if the profile had evolved as more treatment options became available to people with SMA. In this report, a comparative analysis of the results from these two risk/benefit studies is presented, with the goal of highlighting any changes in risk tolerance that may have occurred.

2022 SMA Risk/Benefit Survey Methodology

In the fall of 2022, Cure SMA invited members of the SMA community to participate in the second SMA Risk/Benefit Survey. Inclusion criteria were as follows: 1) Individuals with a confirmed diagnosis of SMA who have reached the age of majority. (Note: In the U.S., the age of majority is 19 in Alabama and Nebraska, 21 in Puerto Rico, and 18 in all other states.) 2) Parents of children with SMA aged 0-18 years. 3) Parents of adults with SMA who may be too limited in mobility to respond independently. The survey was IRB-approved and compliant prior to dissemination. No personally identifiable information (PII) was collected from survey respondents to enable community members to share their opinions confidentially. Responses were collected, tallied, and analyzed by Silicon Valley Research Group.

Best/Worst Scaling (BWS), also known as Maximum Differential Scaling discrete choice modeling, was selected as the survey methodology. Unlike simple rating and ranking questions, BWS questions facilitate preference ranking of the tested attributes. Because respondents choose best and worst attributes rather than indicate strength of preference using a numeric scale, response bias is minimized. BWS has been utilized previously in many patient preference studies. [60, 61]

In the present survey, respondents were asked how willing they were to live with each of 11 different possible SMA treatment risks in exchange for 12 potential treatment benefits. (Table 3) Risks and treatment benefits tested in the 2022 survey were identical to those tested in the 2017 study. The process by which risks and benefits were selected for the 2017 survey is described in Cruz et al. (2019). [40] Briefly, data from Cure SMA focus groups and published studies were used to develop initial lists of risks and treatment benefits, which were in turn evaluated by an internal working group that included researchers, physicians, Cure SMA staff, and a core team from the Silicon Valley Research Group. Cure SMA then interviewed one parent caring for someone with each SMA type, and one adult living with each SMA type, and incorporated their feedback into the final lists of tested risks and benefits.

Table 3. Treatment risks and benefits tested in the 2022 and 2017 surveys

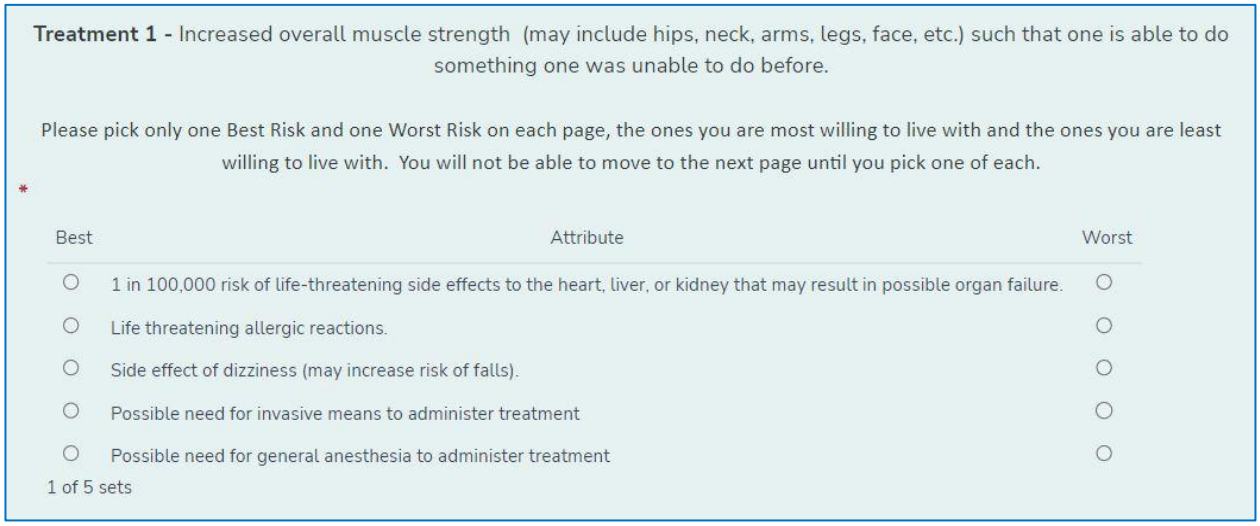
Risks
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.
Side effect of dizziness (may increase risk of falls)
Possible need for general anesthesia to administer treatment
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.)
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention
Increased risks of respiratory or other infections as a result of medication
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention
Life-threatening allergic reactions
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure
Worsening in "quality of life" (possibly due to drug's side effects, worsening condition, etc.)

	Treatment Benefits
1.	Increased overall muscle strength (may include hips, neck, arms, legs, face, etc.) such that one is able to do something one was unable to do before
2.	Consistent muscle performance/strength (i.e., muscles work relatively the same throughout the day; muscle strength does not vary greatly from day to day)
3.	Improvement in ability to swallow
4.	Improvement in ability to speak/communicate
5.	Improvement in breathing function (may include, less infections, less time on BiPAP or vent; stronger cough, decrease in belly breathing)
6.	Improved proximal mobility/ functionality (getting up, balancing when sitting or standing, walking, jumping, running, climbing stairs, fewer falls)
7.	Increased core strength (to allow for greater and longer stability when sitting, better rolling while sleeping, etc.)
8.	Increased upper limb (arm) strength allowing the ability to perform basic personal tasks (such as brushing teeth, washing face, writing with a pen, etc.)
9.	Decreased fatigue, increased energy and ability to do more in a day
10.	Lessening of symptoms' severity (decrease in, tremors, muscle weakness, etc.) or experiencing less symptoms than before treatment was introduced
11.	Prolonging lifespan (Increasing length of life)
12.	Slowing or stopping of disease progression

BiPAP = bilevel positive airway pressure

Respondents were queried about each treatment benefit five times. Each question asked the respondent to select the best and worst risks---the risks they were *most* and *least* willing to live with---from five risks selected at random. (Figure 1)

Figure 1. Sample survey question



The risk results for each possible treatment benefit were then combined, and the final score for each risk was calculated by subtracting the number of times a risk was chosen as worst from the times it was chosen as best, and dividing this number by the total number of times a risk appeared as an option. (An example is shown in Table 4) The higher the score, the more willing respondents were to live with that risk. The scores are vectors and represent both magnitude and direction; i.e., if the score of one item is two times bigger than that of another item within the data set, it can be interpreted as being twice as attractive.

Table 4. Calculation of 2022 Overall Sample risk scores for potential "increased overall muscle strength"

Risk	Rank	Best	Worst	Not Chosen	Score
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	1	50	4.75	45.25	0.45
Side effect of dizziness (may increase risk of falls).	2	47.15	2.47	50.38	0.45
Possible need for general anesthesia to administer treatment	3	43.38	4.57	52.05	0.39
Possible need for invasive means to administer treatment	4	28.59	6.72	64.69	0.22
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may interfere with normal organ functioning and therefore require immediate medical attention	5	19.33	6.66	74.01	0.13
Increased risks of respiratory or other infections as a result of medication.	6	13.32	10.59	76.09	0.03
1 in 100,000 risk of life-threatening side effects to the heart, liver, or kidney that may result in possible organ failure.	7	9.5	18.22	72.28	-0.09
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may interfere with normal organ functioning and therefore require immediate medical attention	8	4.32	25	70.68	-0.21
Life threatening allergic reactions.	9	1.82	26.48	71.7	-0.25
1 in 1,000 risk of life-threatening side effects to the heart, liver, or kidney that may result in possible organ failure.	10	1.24	47.05	51.71	-0.46
Worsening in "quality of life" (possibly due to drug's side effects, worsening condition, etc.).	11	0.96	68.05	30.99	-0.67

Each risk's rank is based on the risk score in the far-right column. A positive score means that the risk was selected as *best* more often than *worst*. The closer the score is to 1, the *more willing* respondents were to live with a risk. The closer a score is to -1, the *less willing* respondents were to live with the risk.

Data were analyzed for trends in risk tolerance in the general population of respondents (Overall Sample), as well as in three sub-samples organized according to reported SMA type of the affected individual (SMA Type Samples). Risk scores and risk ranking from the 2022 and 2017 surveys were compared to identify differences in risk tolerance at the different survey timepoints.

RESULTS

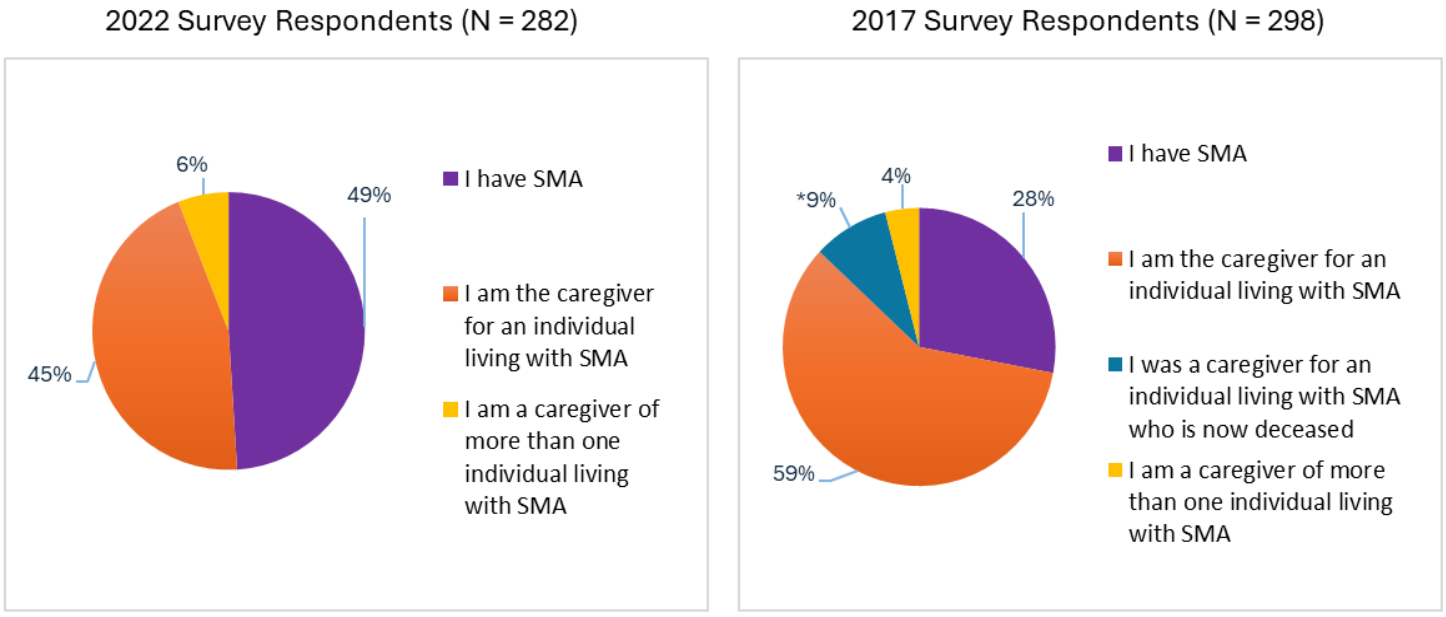
Demographic Characteristics of Survey Respondents

The general respondent population (Overall Sample) for the 2022 SMA Risk-Benefit Surveys was **similar** to that of 2017. (Figure 2) The Overall Sample size of the 2022 survey was 282 respondents, and that of the 2017 survey was 298 respondents.[1]

However, there were a few differences between the 2022 and 2017 Overall Samples:

- A greater percentage of 2022 respondents were individuals with SMA compared to 2017 (49% vs. 28%, respectively).
- Conversely, a smaller percentage of the 2022 Overall Sample were caregivers of people with SMA compared to the 2017 Overall Sample (51% vs. 72%, respectively.)

Figure 2. Relationship of survey respondents to individuals with SMA

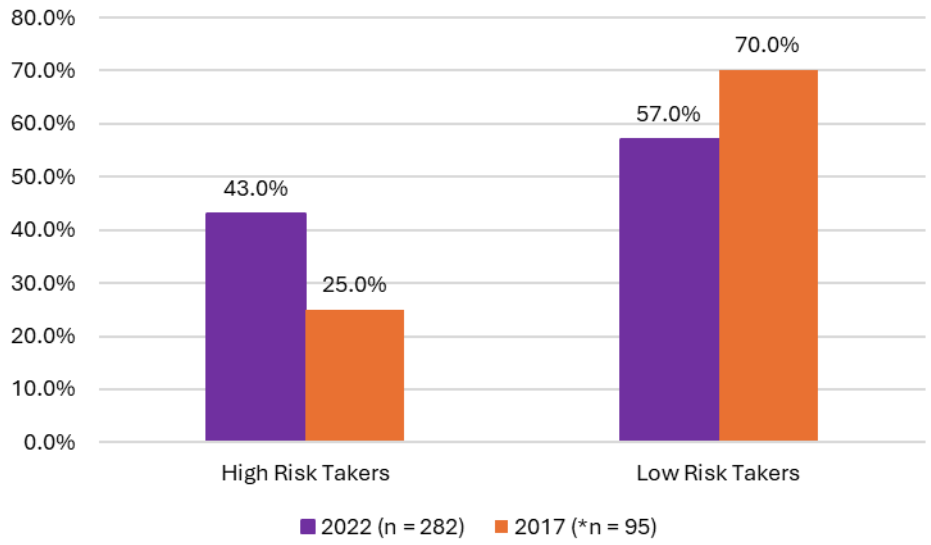


Caregivers of deceased individuals were not eligible to participate in the 2022 survey.
The majority of caregiver respondents in both surveys were a parent of the individual with SMA (92.4% in 2022 and 94.2% in 2017) .

[1] For both surveys, respondents were at least 18 years old and resided within the U.S. Caregivers were able to respond on behalf of persons with SMA aged 0-18 years of age, as well as on behalf of adults living with SMA.

- Risk-taking profiles (Figure 3)
  - In both the 2022 and 2017 surveys, more respondents reported being low than high risk takers (57% and 70%, respectively).
  - However, in 2022, a notably greater percentage reported being high risk takers (43.0% versus 25.0%, respectively) than in 2017.

Figure 3. Risk-taking profiles of respondents



*Respondents could opt out of demographic questions in 2017 but not in 2022.

Demographic Characteristics of Individuals with SMA

The demographic characteristics of the individuals with SMA who responded to, or were represented in, the 2022 survey were **similar** to those in the 2017 survey.[2] (Table 5) For example, in both 2022 and 2017, most individuals with SMA were single (77.0% and 84.0%, respectively) and white (84.8% and 81.6%, respectively).

However, there were a few differences between the two populations.

- Age
  - In 2022, a greater percentage of individuals with SMA were teens and adults than in 2017 (60.2% versus 52.5%, respectively.)
  - Conversely, a smaller percentage of individuals with SMA were infants and children in 2022 compared to 2017 (39.8% versus 47.5%, respectively).

[2] Additional demographic information is available in Appendix A.

- Gender
  - In 2022, notably more females than males with SMA were represented in the survey (62.0% versus 37.0%).
  - In 2017, the percentages of females and males represented in the study were somewhat similar (54.0% versus 46.0%).

Table 5. Demographic characteristics of individuals with SMA**

Age	**2022** (n=282)	**2017** (n=272)
1 or younger	8.5%	5.5%
> 1 year and < 2 years	5.7%	2.2%
> 2 years and < 3 years	4.3%	8.1%
3 to 6 years	13.1%	17.3%
7 to 12 years	8.2%	14.3%
13 to 17 years	1.8%	11.0%
18 to 34 years	26.2%	22.8%
35 to 49 years	16.3%	11.4%
50 to 65 years	12.4%	5.5%
Older than 65 years	3.5%	1.8%
Gender	**2022** (n=282)	**2017** (n=272)
Female	62.0%	54.0%
Male	37.0%	46.0%
Prefer not to answer	1.0%	N/A*
Marital Status	**2022** (n=282)	**2017** (n=272)
Single (never married)	77.0%	84.0%
Married, civil union, or domestic partnership	18.0%	14.0%
Divorce	5.0%	2.0%

Racial Identity*	**2022** (n=282)	N/A*
White	84.8%	*
Two or more races	5.7%	*
Prefer not to answer	3.2%	*
Black or African American	2.8%	*
Asian	1.8%	*
American Indian or Alaska native	1.1%	*
Native Hawaiian or other Pacific Islander	0.7%	*
Racial Identity*	N/A*	**2017** (n=272)
White	*	81.6%
Asian or Pacific Islander	*	8.8%
Hispanic or Latino	*	7.4%
Black or African American	*	1.5%
Native American or American Indian	*	0.7%

*Categories varied between the two surveys.
**For more demographic data, see Appendix A.
Note: Respondents could opt out of answering demographic questions in 2017 but not in 2022.

- SMA Type (Figure 4)
  - In both surveys, respondents were most likely to report having/caring for someone who had SMA Type 2, followed by Type 3, and then Type 1.
  - However, in 2022, slightly fewer respondents reported having/caring for someone who had SMA Type 2 (39.4% and 45.6%, respectively), and slightly more 2022 respondents reported having/caring for someone who had SMA Type 3 (33.0% versus 27.9%, respectively).

Figure 4. SMA Type of affected individuals in 2022 and 2017 surveys

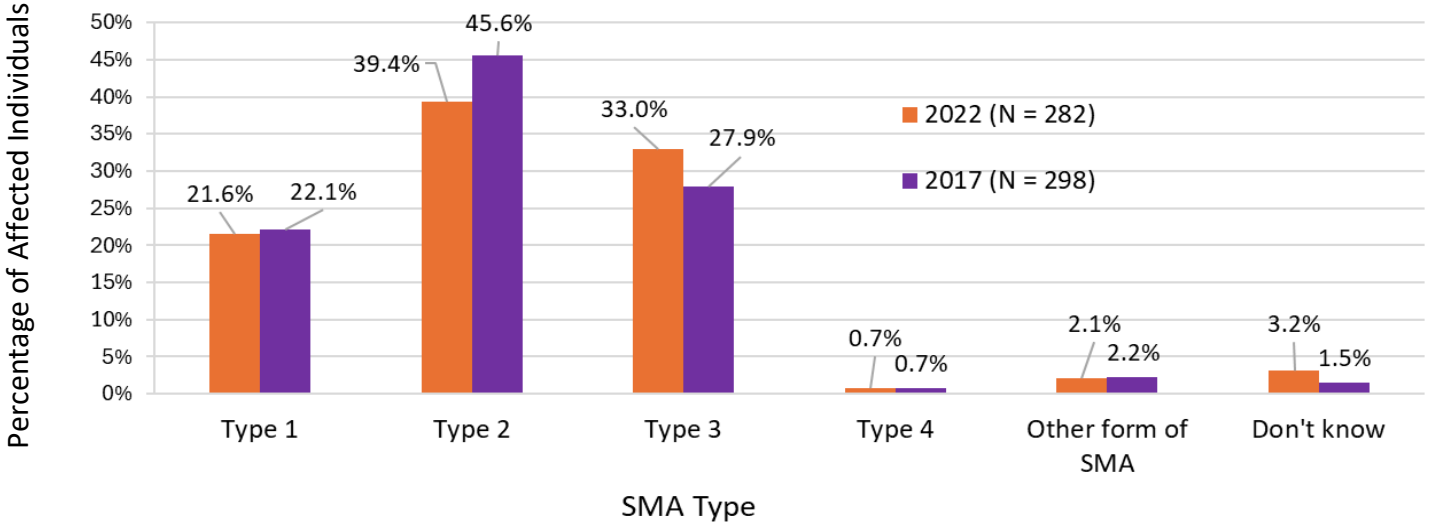
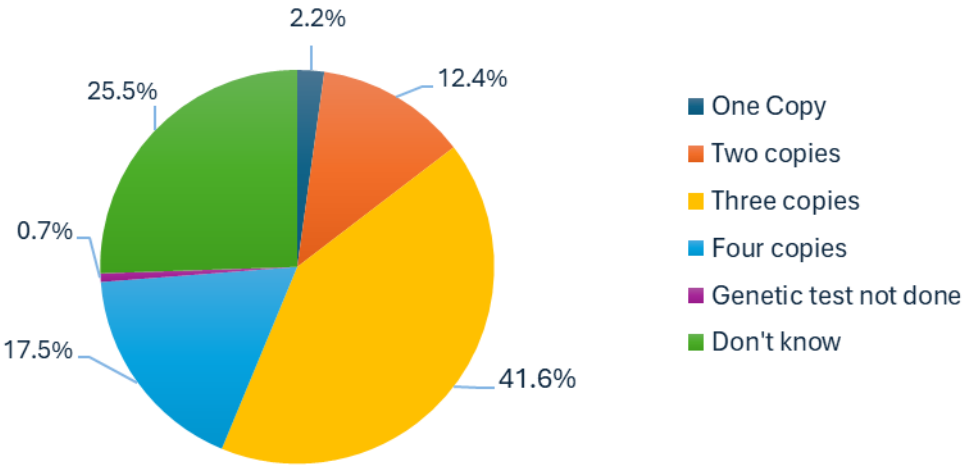


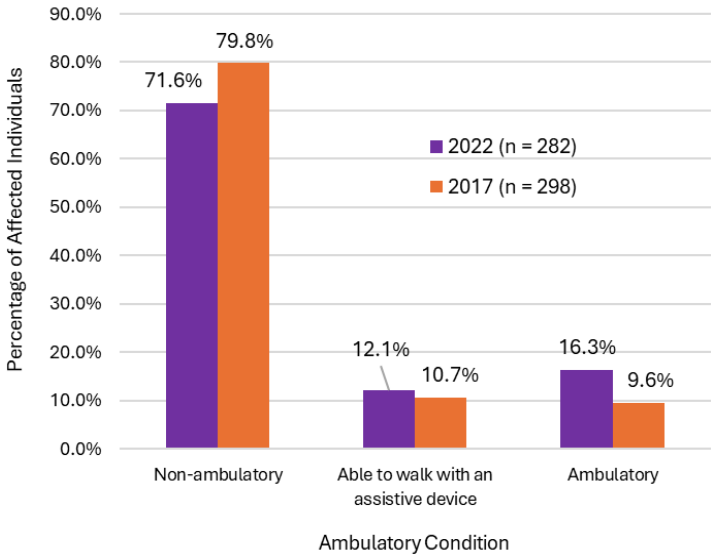
Figure 5. *SMN2* copy number of individuals with SMA in 2022*



*Respondents were queried about *SMN2* copy number in 2022 (n = 282) but not 2017. As DMTs have become more widely available, SMA phenotypes have broadened and evolved, causing a shift from classification according to clinical criteria to classification that takes into account *SMN2* copy number and other factors.

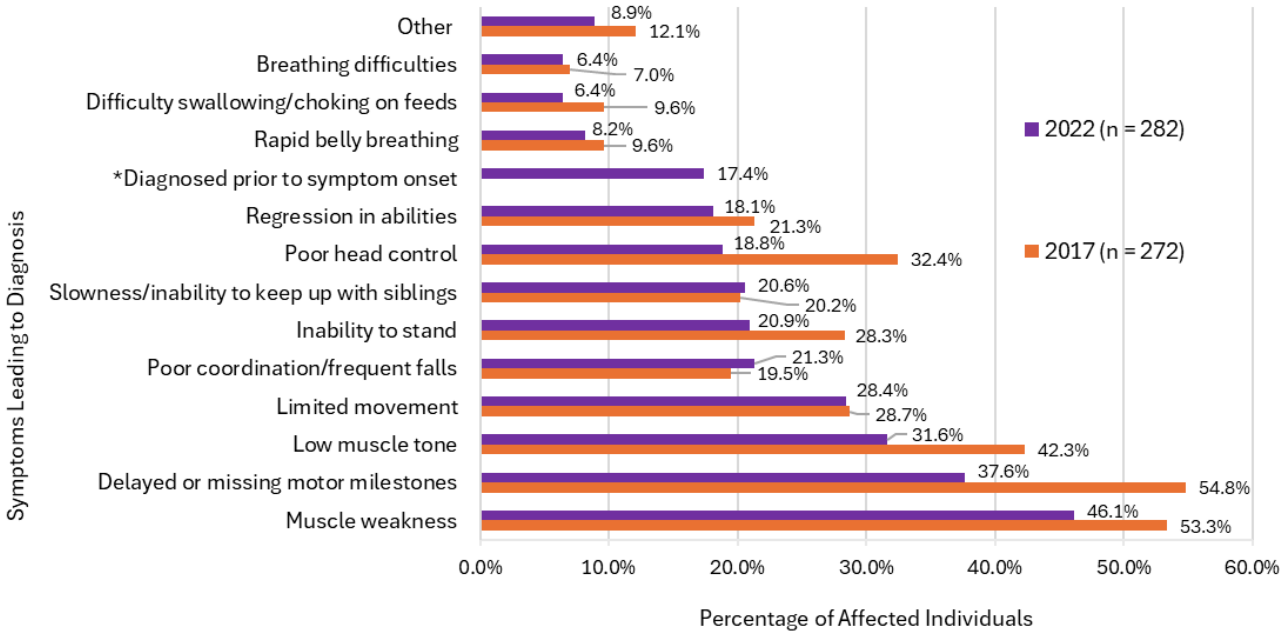
- SMA copy number (Figure 5)
  - In 2022,* the greatest percentage of respondents reported that they or the person in their care had three copies of *SMN2* (41.6%), followed by four copies (17.5%), and then two copies (12.4%).
- Ambulatory condition (Figure 6)
  - Slightly fewer persons reported that they or the person in their care were/was non-ambulatory in 2022 compared to 2017 (71.6% versus 79.8 %, respectively).
  - Slightly more people reported that they or the person in their care were/was able to walk with an assistive device (12.1% versus 10.7%, respectively), or were/was ambulatory (16.3% versus 9.6%, respectively), in 2022 compared to 2017.

Figure 6. Ambulatory condition of individuals with SMA



- Symptoms leading to a diagnosis of SMA (Figure 7)
  - In both 2022 and 2017, respondents reported that a range of symptoms lead to a diagnosis of SMA.
  - The most frequently reported symptoms for both the 2022 and 2017 surveys were low muscle tone (31.6% and 42.3%, respectively), delayed or missing motor milestones (37.6% and 54.8%, respectively), and muscle weakness (46.1% and 53.3%, respectively).

Figure 7. Symptoms leading to diagnosis of SMA



*This category was not included in the 2017 survey. Note: When queried about time since diagnosis, 69.1% of 2022 respondents and 67.3% of 2017 respondents indicated they had been diagnosed five or more years prior to the survey.

- Quality of life (Table 6)
  - 2022 and 2017 respondents similarly ranked abilities that would enhance quality of life if improved from treatment.
  - There were slight differences between the order in which 2022 and 2017 respondents ranked their top five priorities for improvement.

Table 6. Ranking of abilities that would enhance quality of life if improved from treatment

Item	2022 Rank	2017 Rank
Go to restroom by oneself	1	1
Attend to personal hygiene independently	2	4
Chew and swallow food	3	5
Spend time alone/be independent	4	2
Engage in social activities and build relationships	5	3
Sit up (assisted or independently) without the need for frequent suctioning	6	6
Attend work or school	7	7
Dress oneself	8	8
Hug my loved ones or for my loved one to hug me	9	9
Engage in physical activities (playing sports, going to the gym)	10	10
Sleep by myself (in my own room)	11	11

Red numerals indicate where 2017 rank differs from 2022 rank.
For 2022, n = 282; for 2017, n = 272.

- Activities of daily living (Table 7)
  - 2022 and 2017 respondents similarly ranked activities of daily living with respect to which they would most like to experience improvements in from treatment.
  - There were slight differences between the rank order of the lower priority activities of daily living.

Table 7. Ranking of activities of daily living in which respondents would like to experience improvement

Item	2022 Rank	2017 Rank
Increased independence in mobility	1	1
Going to the restroom by self/Toileting self	2	2
Feeding self	3	3
Ability to spend time alone/be independent	4	4
Dressing self	5	6
Turning in bed	6	5
Transferring from wheelchair to bed unaided	7	7
Brushing teeth	8	10
Using a keyboard	9	8
Writing with a pen	10	9
Brushing hair	11	11

Red numerals indicate where 2017 rank differs from 2022 rank. For 2022, n = 282; for 2017, n = 272.

Risk Scores by Treatment Benefit

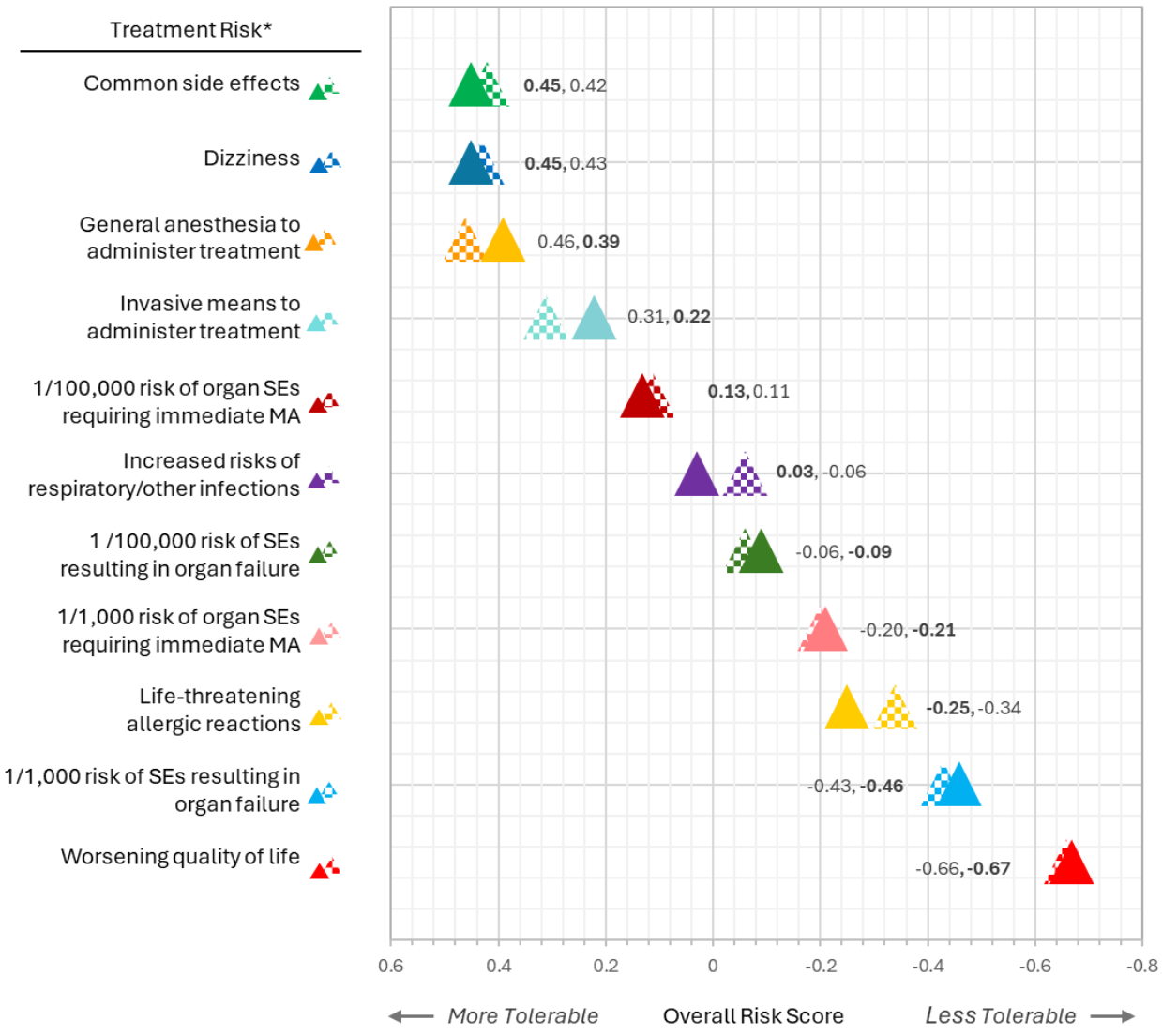
When analyzed by treatment benefit, Overall Sample risk scores from the 2022 and 2017 Risk/Benefit Surveys were generally **very similar** to each other and are presented in Figures 8 through 19.

SMA Type Sample risk scores that contributed to notable disparities between Overall Sample Scores are presented in Tables 8 through 18.

Treatment Benefit 1: Increased overall muscle strength

- The 2022 and 2017 Overall Sample risk scores for Treatment Benefit 1 were **very similar**. No notable disparities between risk scores were identified for this benefit. (Figure 8)

Figure 8. Overall Sample risk scores for Treatment Benefit 1: Increased overall muscle strength

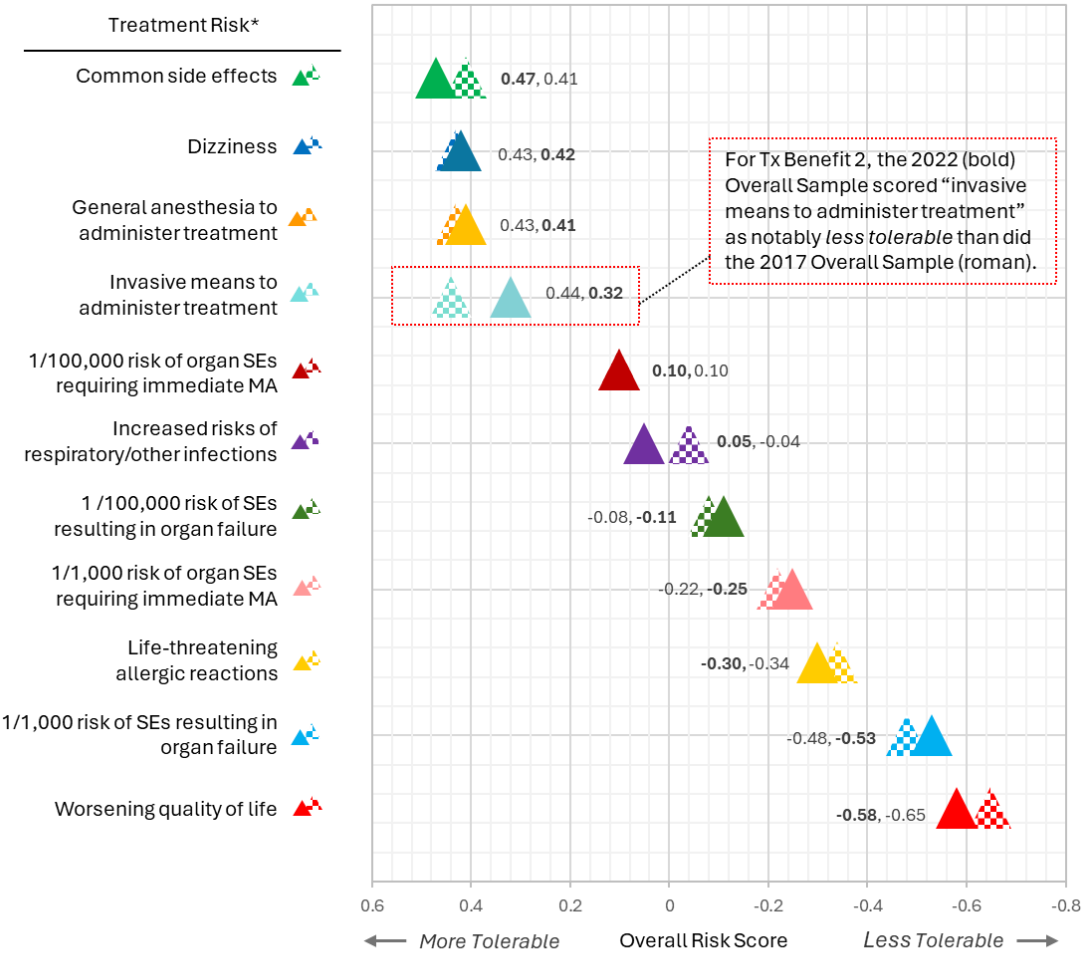


*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, N = 282; 2017 scores are roman, N = 298; Tx = treatment; SEs = side effects; MA = medical attention.

Treatment Benefit 2: Consistent muscle performance and strength

- The 2022 and 2017 Overall Sample risk scores for Treatment Benefit 2 were **very similar**, with one exception. (Figure 9; boxed in red)

Figure 9. Overall Sample risk scores for Treatment Benefit 2: Consistent muscle performance/strength



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, N = 282; 2017 scores are roman, N = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- SMA Type Sample risk scores indicated that respondents in the 2022 Type 1 and Type 3 Samples were notably *less tolerant* of the risk of "invasive means to administer treatment" in exchange for Treatment Benefit 2 than were their 2017 counterparts. (Table 8; shaded in aqua)

Table 8. SMA Type Sample risk scores for Treatment Benefit 2

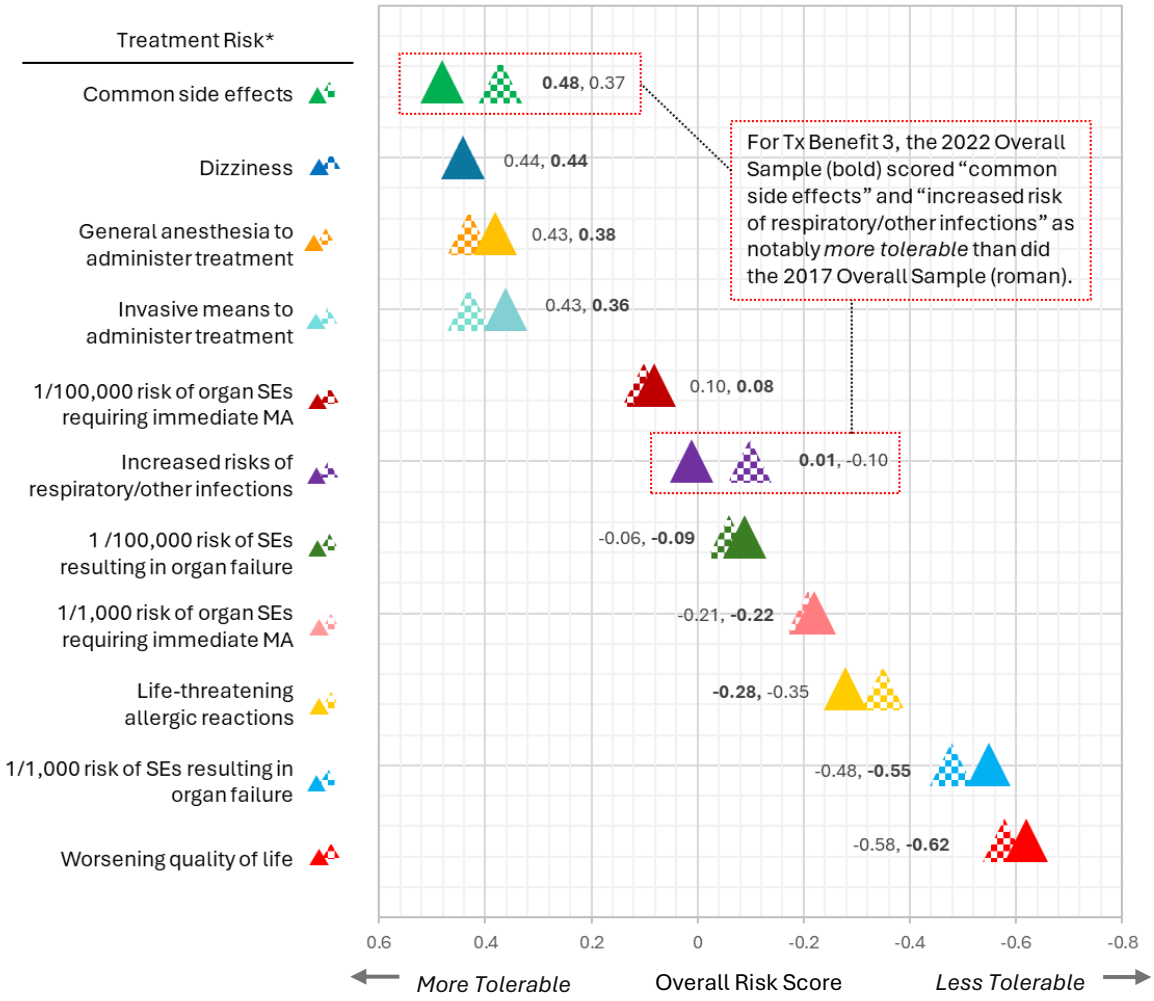
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Invasive means	0.75, **0.28**	0.46, **0.40**	0.49, **0.26**

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Treatment Benefit 3: Improvement in ability to swallow

- 2022 and 2017 Overall Sample risk scores for Treatment Benefit 3 were **very similar**, with two exceptions. (Figure 10; boxed in red)

Figure 10. Overall Sample risk scores for Treatment Benefit 3: Improvement in ability to swallow



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- The 2022 SMA Type 2 and 3 Samples scored "common side effects" as notably *more tolerable* for Treatment Benefit 3 than did their 2017 counterparts. (Table 9; shaded in green)
- The 2022 SMA Type 2 Sample also scored "increase risks of respiratory/other infections" as notably *more tolerable* than did its 2017 counterpart. (Table 9; shaded in purple)

Table 9. SMA Type Sample risk scores for Treatment Benefit 3

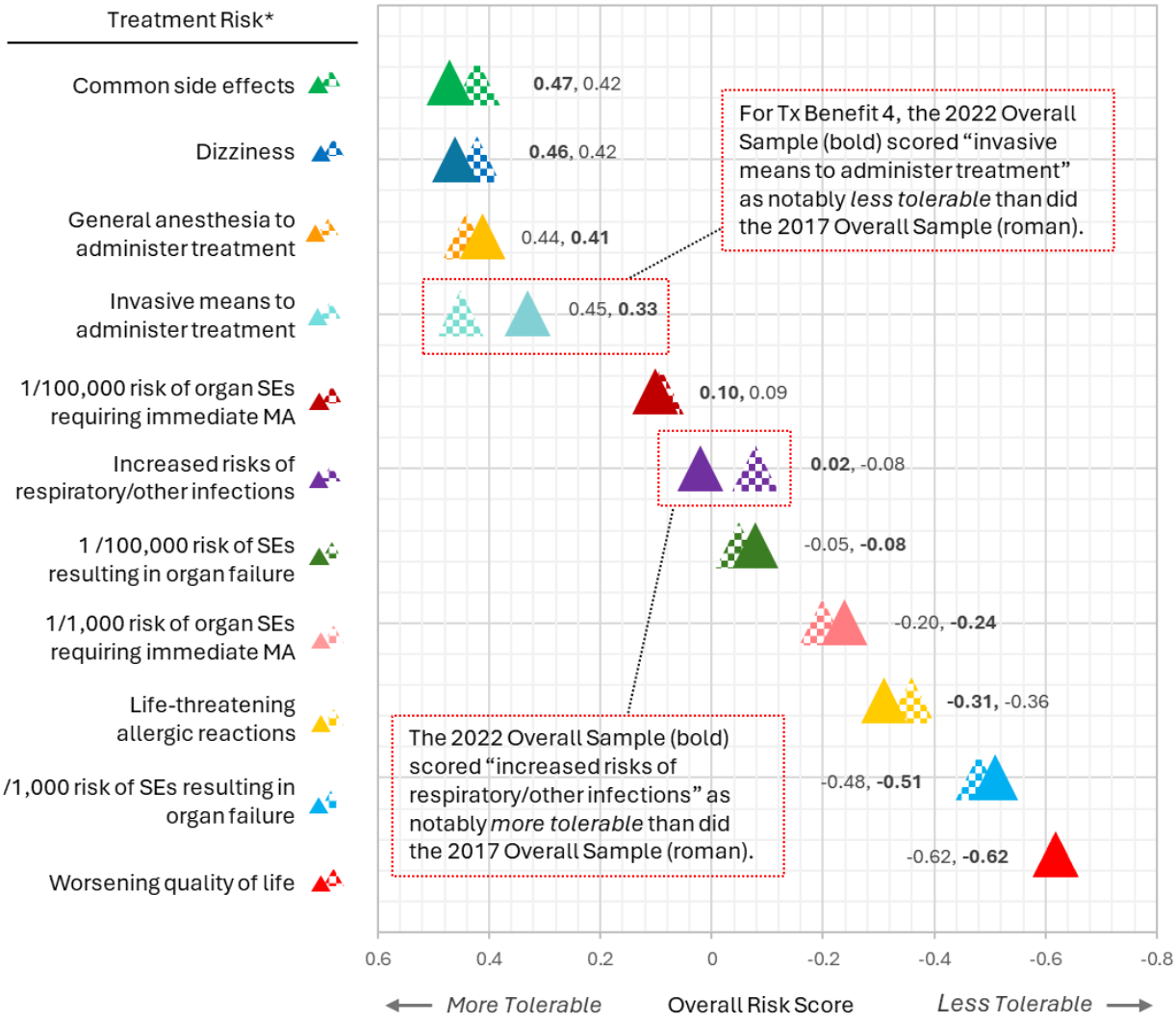
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Common SEs	0.80, **0.49**	**0.51**, 0.50	**0.46**, 0.37
Increased infections	0.00, **-0.01**	**-0.02**, -0.25	0.12, **0.06**

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Treatment Benefit 4: Improvement in ability to communicate

- For Treatment Benefit 4, 2022 and 2017 Overall Sample risk scores were **very similar**, with two exceptions. (Figure 11; boxed in red)

Figure 11. Overall Sample risk scores for Treatment Benefit 4: Improvement in ability to communicate



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- All three 2022 SMA Type Samples scored "invasive means" as notably *less tolerable* for Treatment Benefit 4 than their 2017 counterparts. (Table 10; shaded in aqua)
- The 2022 SMA Type 2 Sample scored "increased risks of respiratory/other infections" as notably *more tolerable* than did its 2017 counterpart. (Table 10; shaded in purple)

Table 10. SMA Type Sample risk scores for Treatment Benefit 4

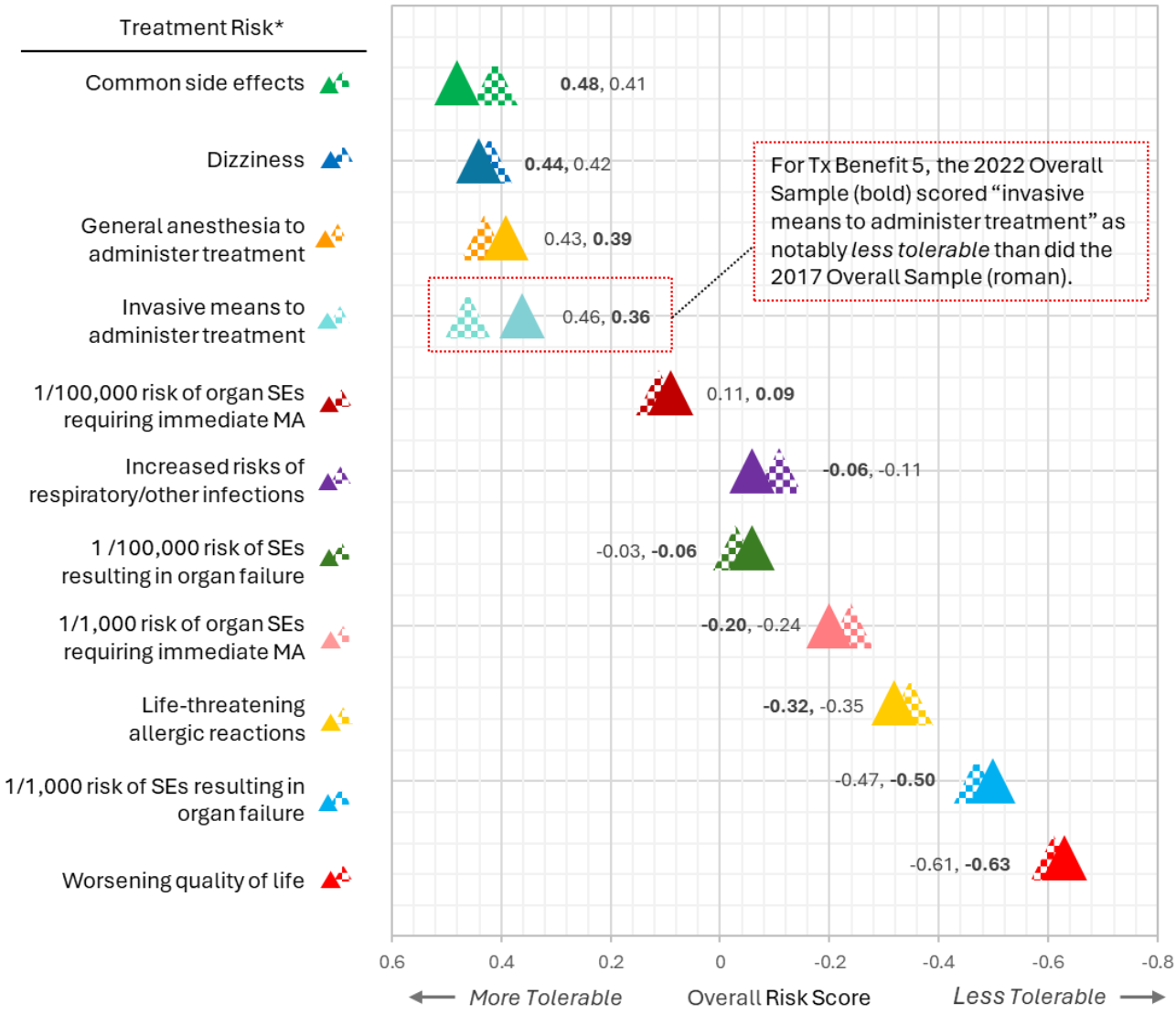
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Invasive means	0.50, **0.31**	0.53, **0.36**	0.57, **0.32**
Increased infections	0.00, **-0.03**	**-0.06**, -0.22	0.07, **0.13**

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Treatment Benefit 5: Improvement in respiratory function

- The 2022 and 2017 Overall Sample risk scores for Treatment Benefit 5 were **very similar**, with one exception. (Figure 12; boxed in red)

Figure 12. Overall Sample risk scores for Treatment Benefit 5: Improvement in respiratory function



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- All 2022 Type Sample risk scores indicated that respondents were notably *less tolerant* of the risk of "invasive means to administer treatment" in exchange for Treatment Benefit 5 than were their 2017 counterparts. (Table 11; shaded in aqua)

Table 11. SMA Type Sample risk scores for Treatment Benefit 5

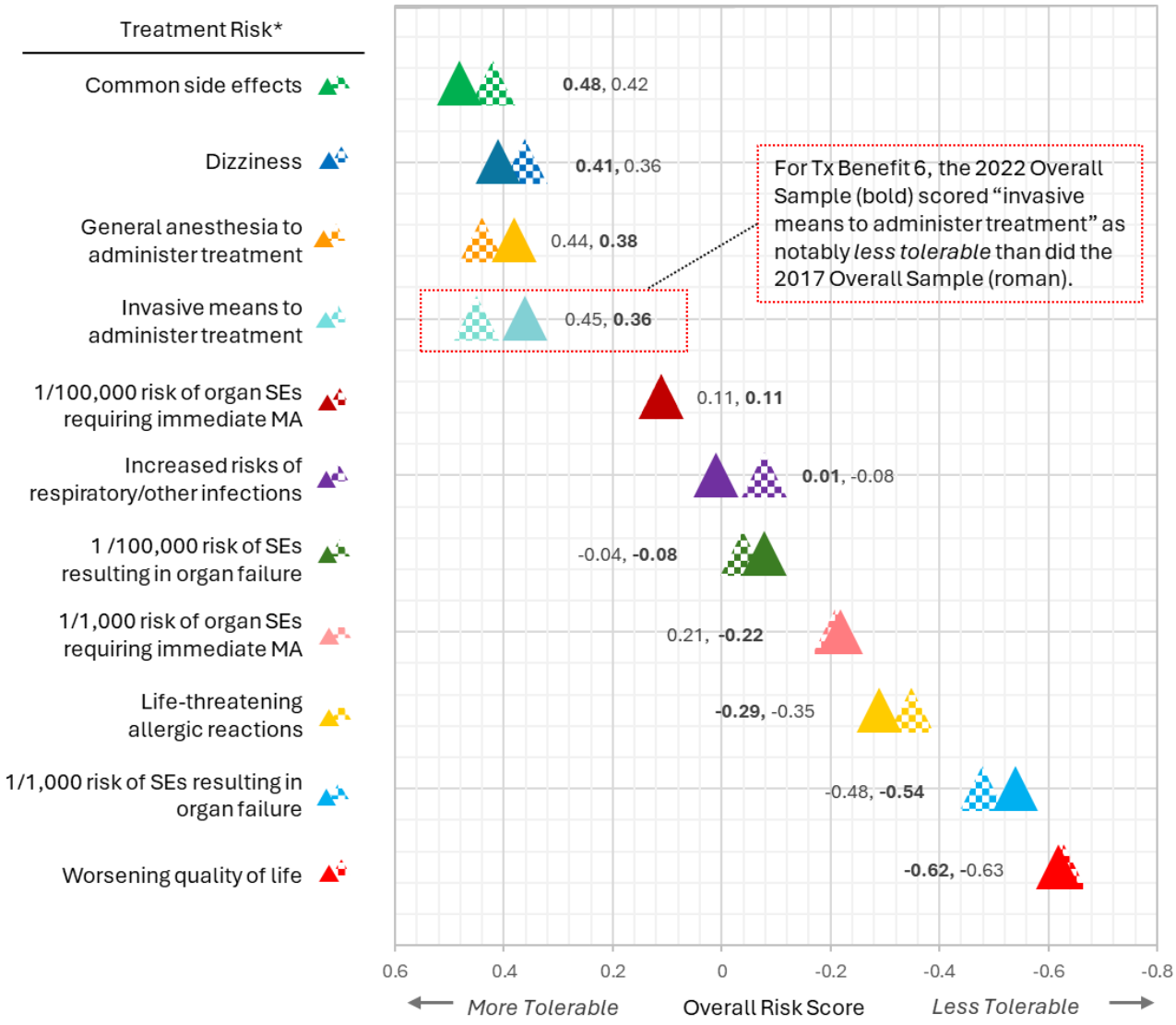
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Invasive means	0.50, **0.28**	0.45, **0.42**	0.48, **0.36**

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Treatment Benefit 6: Improvement in proximal mobility and function

- The 2022 and 2017 Overall Sample risk scores for Treatment Benefit 6 were **very similar**, with one exception. (Figure 13; boxed in red)

Figure 13. Overall Sample risk scores for Treatment Benefit 6: Improvement in proximal mobility and function



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- Risk scores from all three 2022 Type Samples suggested that respondents regarded "invasive means to administer treatment" as notably *less tolerable* in exchange for Treatment Benefit 6 than did their 2017 counterparts. (Table 12; shaded in aqua)

Table 12. SMA Type Sample risk scores for Treatment Benefit 6

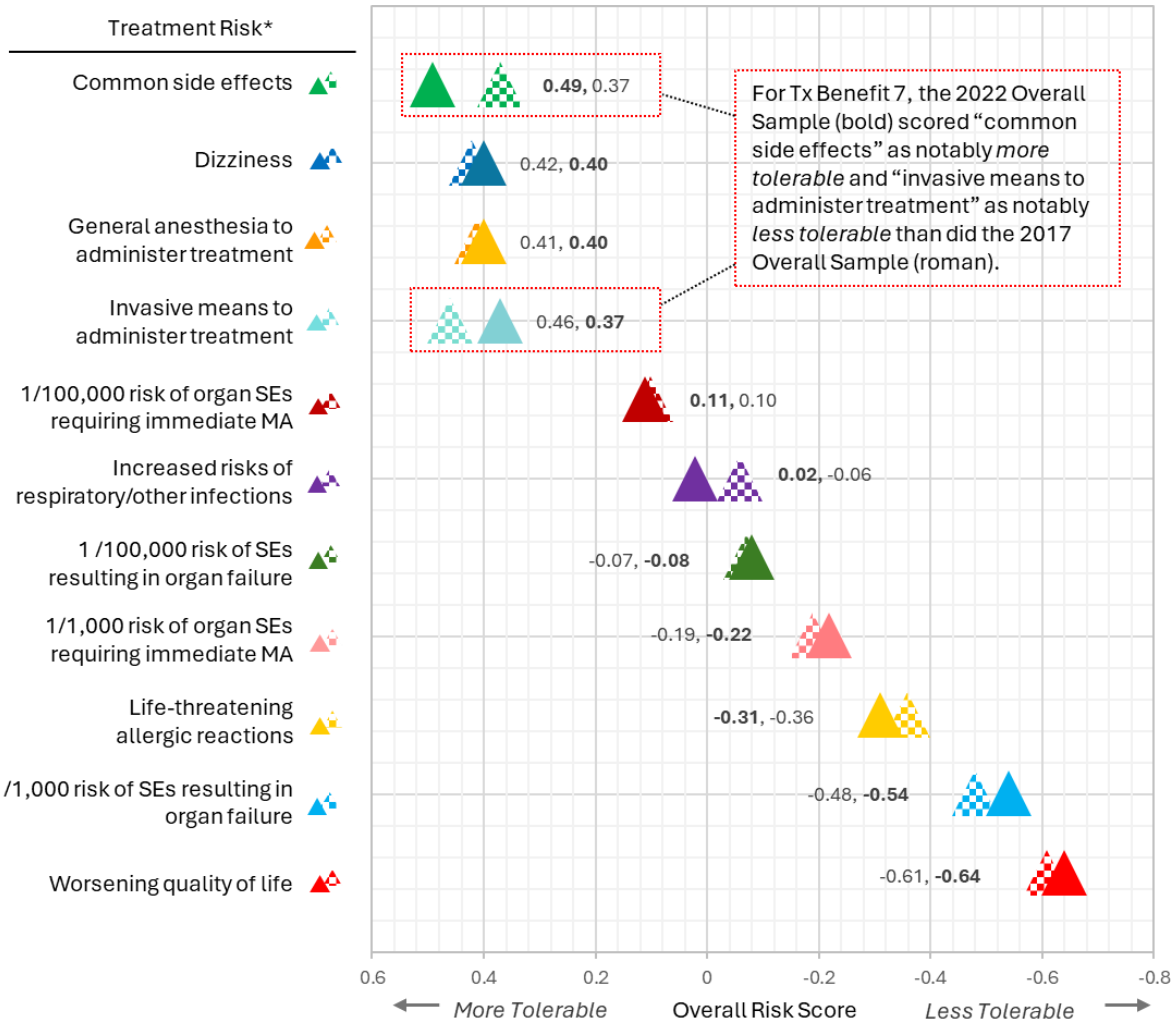
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Invasive means	0.75, **0.36**	0.52, **0.40**	0.55, **0.45**

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Treatment Benefit 7: Increased core strength

- The 2022 and 2017 Overall Sample risk scores for Treatment Benefit 7 were **very similar**, with two exceptions. (Figure 14; boxed in red)

Figure 14. Overall Sample risk scores for Treatment Benefit 7: Increased core strength



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- The 2022 Type 2 and 3 Samples scored "common side effects" as notably *more tolerable* for Treatment Benefit 7 than did their 2017 counterparts. (Table 13; shaded in green)
- The 2022 Type 1 and 3 Samples scored "invasive means to administer treatment" as notably *less tolerable* than did their 2017 counterparts. (Table 13; shaded in aqua)

Table 13. SMA Type Sample risk scores for Treatment Benefit 7

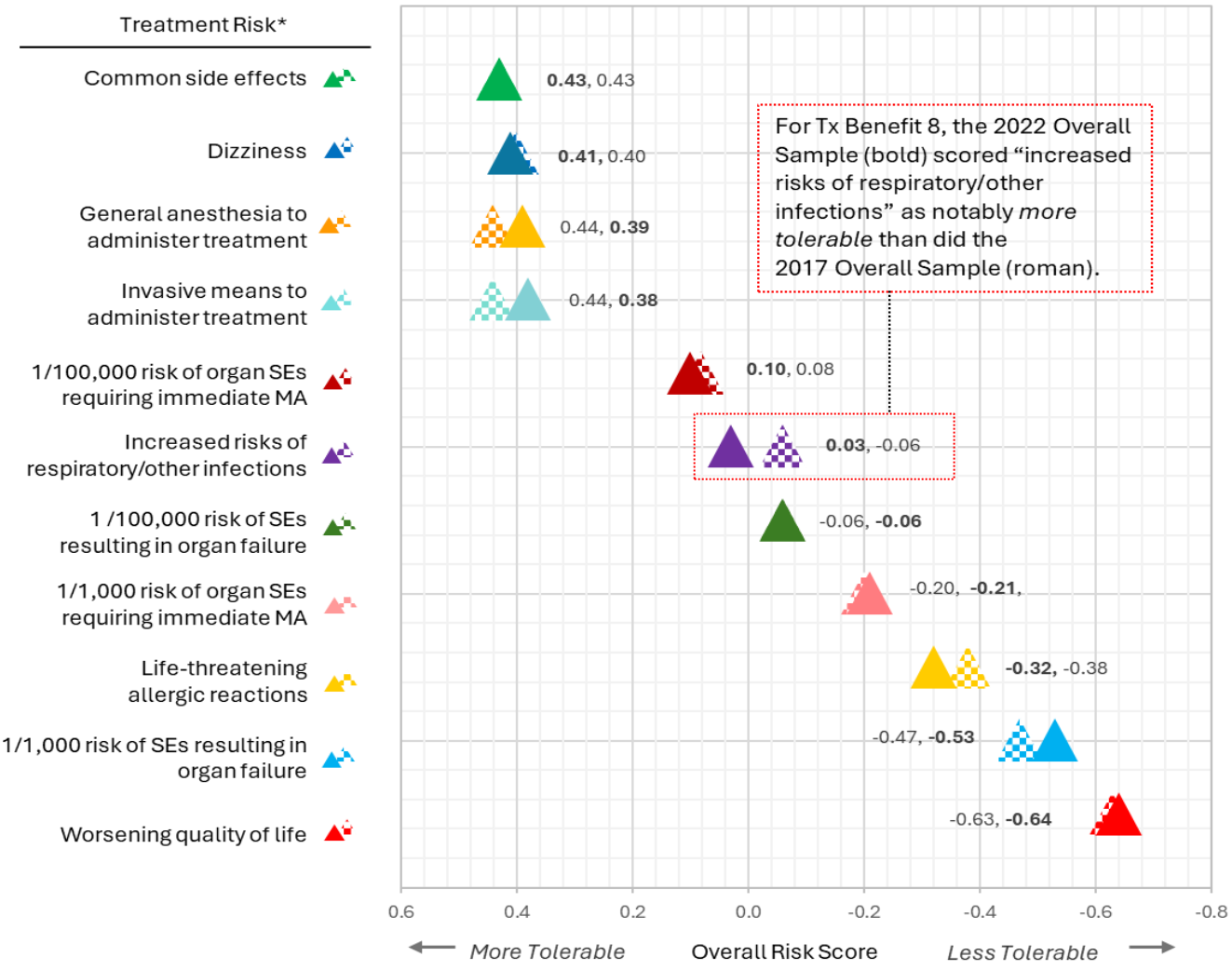
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Common SEs	**0.54**, 0.50	**0.53,** 0.33	**0.44**, 0.34
Invasive means	1.0, **0.32**	**0.45,** 0.39	0.60, **0.41**

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Treatment Benefit 8: Increased upper limb strength

- The 2022 and 2017 Overall Sample risk scores for Treatment Benefit 8 were **very similar**, with one exception. (Figure 15; boxed in red)

Figure 15. Overall Sample risk scores for Treatment Benefit 8: Increased upper limb strength



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- The 2022 Type 2 Sample risk scores indicated that these respondents regarded "increased risk of respiratory/other infections" as notably *more tolerable* in exchange for Treatment Benefit 8 than did their 2017 counterparts. (Table 14; shaded in purple)

Table 14. SMA Type Sample risk scores for Treatment Benefit 8

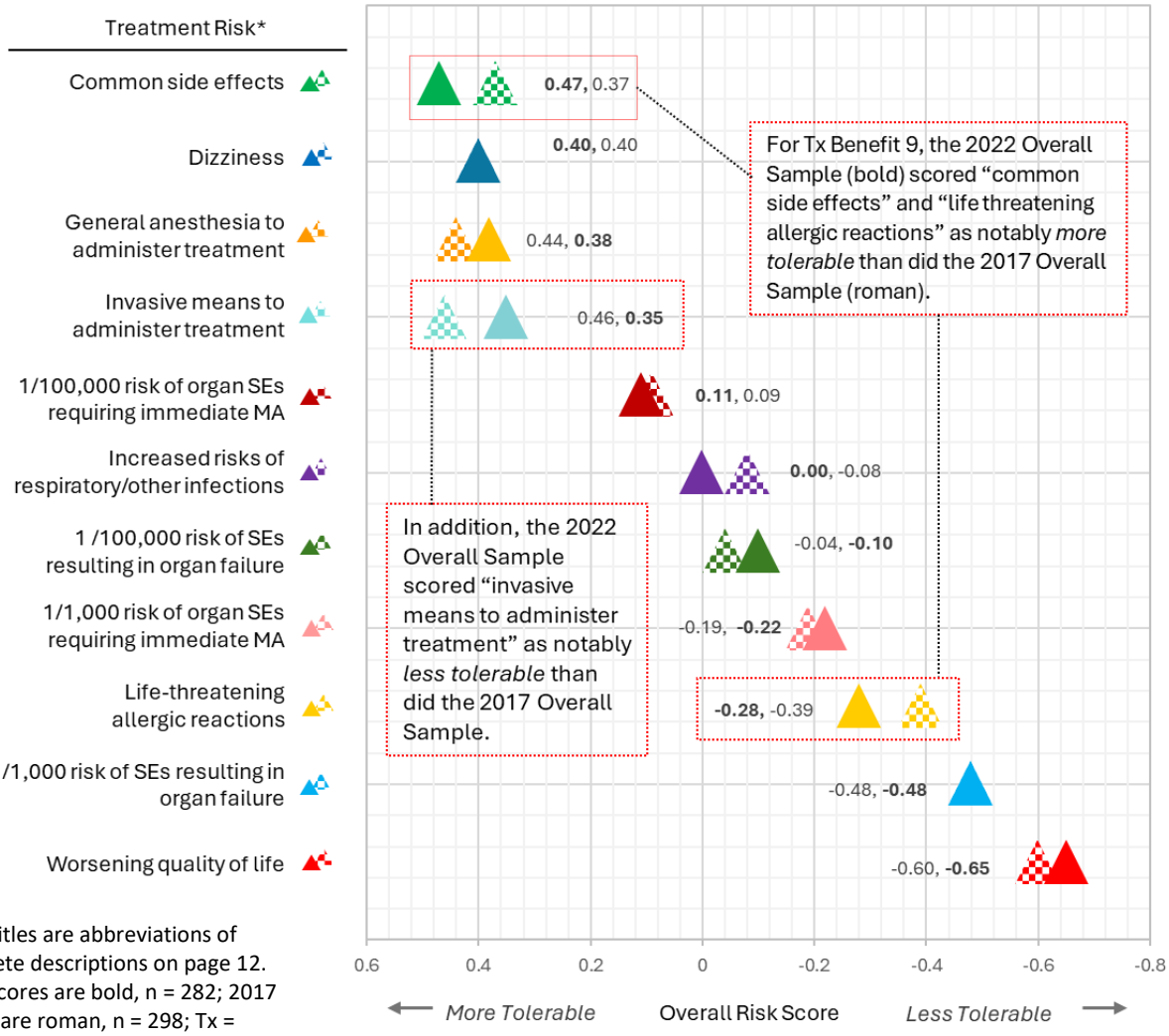
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Increased infections	**0.01**, 0.00	**0.00**, -0.23	**0.08**, 0.07

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74 .

Treatment Benefit 9: Decreased fatigue

- The 2022 and 2017 Overall Sample risk scores for Treatment Benefit 9 were **very similar**, with three exceptions. (Figure 16; boxed in red)

Figure 16. Overall Sample risk scores for Treatment Benefit 9: Decreased fatigue



*Risk titles are abbreviations of complete descriptions on page 12. 2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- The 2022 Type 1 and 2 Samples scored "common side effects" as notably *more tolerable* for Treatment Benefit 9 than did their 2017 counterparts. (Table 15; shaded in green)

- All 2022 SMA Type Samples scored "invasive means to administer

Table 15. SMA Type Sample risk scores for Treatment Benefit 9

	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Common SEs	**0.49**, 0.00	**0.47**, 0.34	**0.47**, 0.41
Invasive means	1.00, **0.35**	0.47, **0.39**	0.55, **0.34**
Allergic reactions	0.00, **-0.29**	**-0.23**, -0.42	**-0.30**, -0.45

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

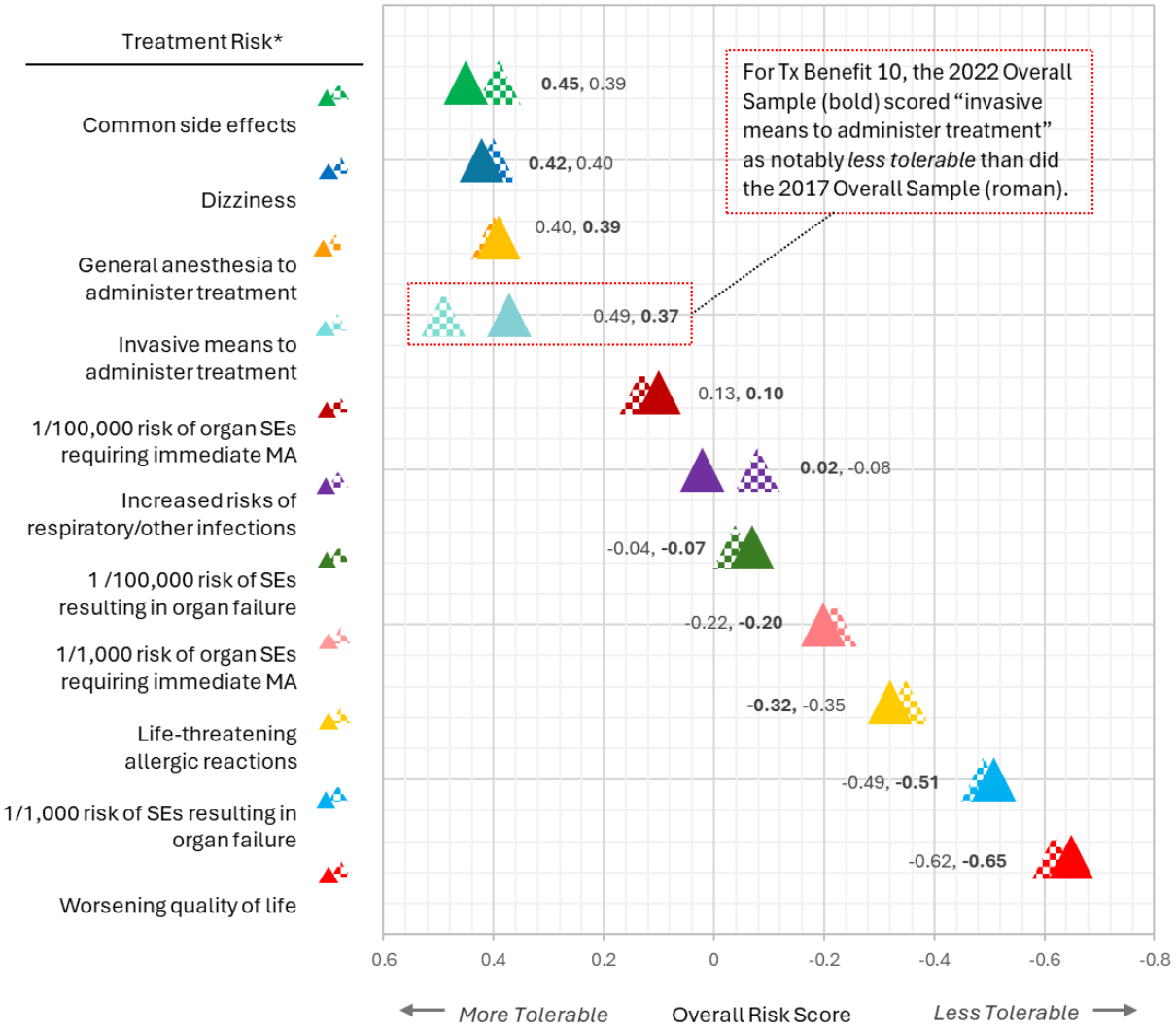
treatment" as notably *less tolerable* for Treatment Benefit 9 than did their 2017 counterparts. (Table 15; shaded in aqua)

- Finally, the 2022 Type 2 and Type 3 Samples scored "allergic reactions" as notably *more tolerable* for Treatment Benefit 9 than did their 2017 counterparts. (Table 15; shaded in yellow)

Treatment Benefit 10 : Lessening of symptoms' severity/less symptoms

- The 2022 and 2017 Overall Sample risk scores for Treatment Benefit 10 were **very similar**, with one exception. (Figure 17; boxed in red)

Figure 17. Overall Sample risk scores for Treatment Benefit 10: Lessening of symptoms' severity/less symptoms



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- All 2022 SMA Type Samples scored "invasive means to administer treatment" as notably *less tolerable* in exchange for Treatment Benefit 10 than did their 2017 counterparts. (Table 16; shaded in aqua)

Table 16. SMA Type Sample risk scores for Treatment Benefit 10

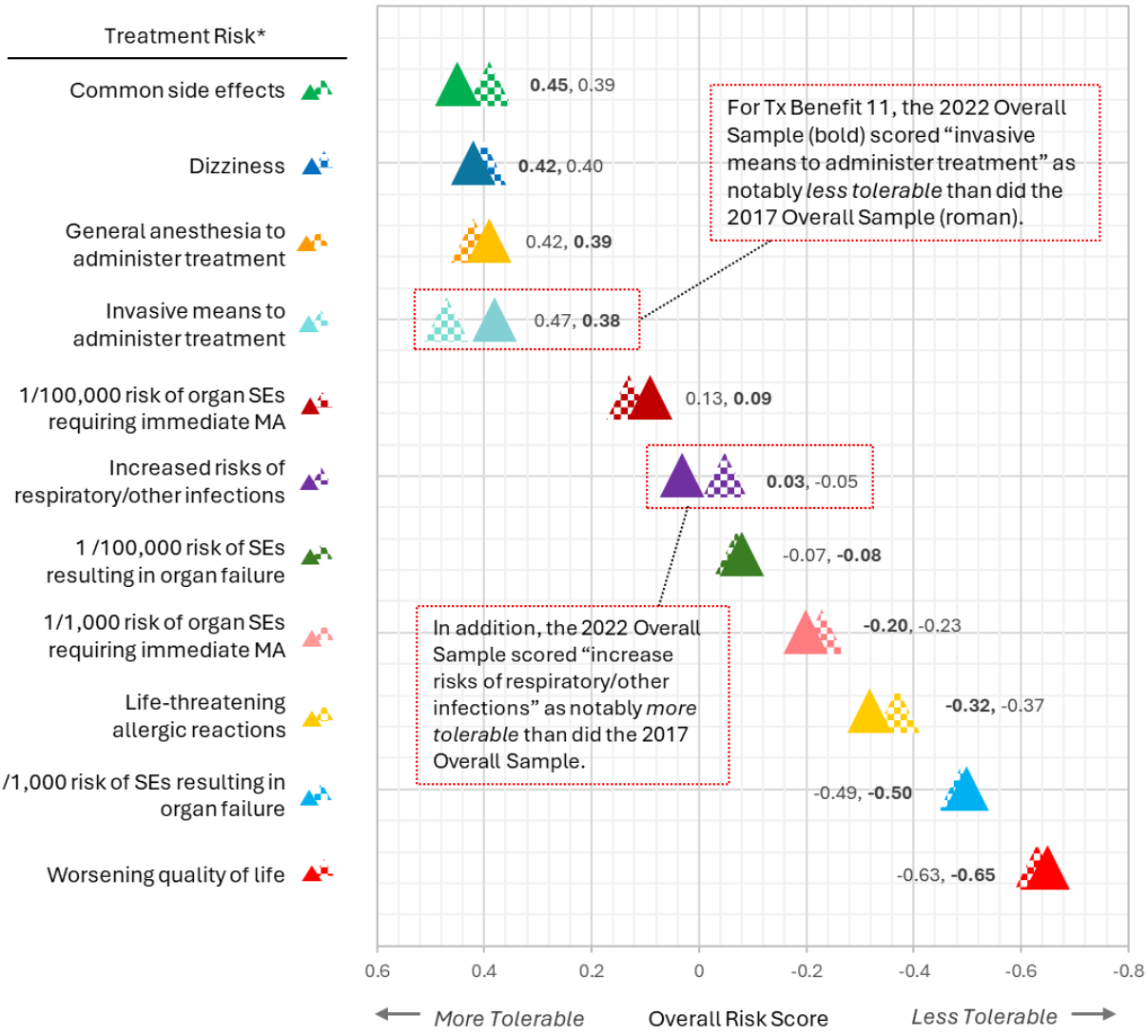
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Invasive means	0.80, **0.37**	0.54, **0.44**	0.60, **0.45**

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Treatment Benefit 11: Prolonging lifespan

- 2022 and 2017 Overall Sample risk scores for Treatment Benefit 11 were **very similar**, with two exceptions. (Figure 18; boxed in red)

Figure 18. Overall Sample risk scores for Treatment Benefit 11: Prolonging life span



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- The 2022 Type 1 and Type 3 Samples scored "invasive means to administer treatment" as notably *less tolerable* for Treatment Benefit 11 than did their 2017 counterparts. (Table 17; shaded in aqua)
- The 2022 Type 2 Sample scored "increased risk of respiratory/other infections" as notably *more tolerable* than did its 2017 counterpart. (Table 17; shaded in purple)

Table 17. SMA Type Sample risk scores for Treatment Benefit 11

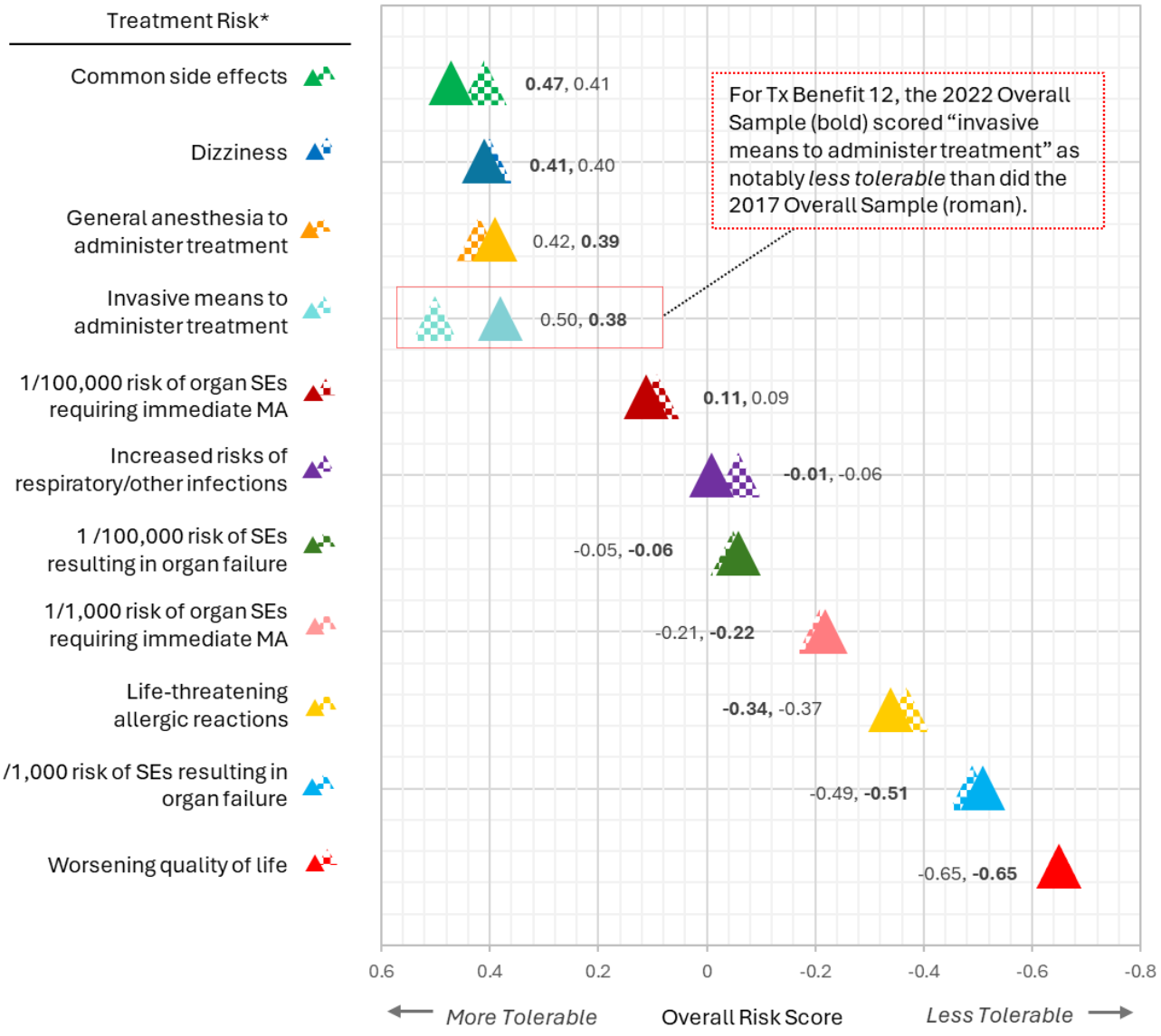
	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Invasive means	1.00, **0.33**	0.43, **0.42**	0.52, **0.43**
Increased infections	0.00, **-0.01**	**-0.02**, -0.23	**0.11**, 0.08

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Treatment Benefit 12: Slowing down or stopping disease progression

- 2022 and 2017 Overall Sample risk scores for Treatment Benefit 12 were **very similar**, with one exception. (Figure 19; boxed in red)

Figure 19. Overall Sample risk scores for Treatment Benefit 12: Slow down or stopping of disease progression



*Risk titles are abbreviations of complete descriptions on page 12.
2022 scores are bold, n = 282; 2017 scores are roman, n = 298; Tx = treatment; SEs = side effects; MA = medical attention.

- The 2022 Type 1 and Type 3 Samples scored "invasive means to administer treatment" as notably *less tolerable* for Treatment Benefit 12 than did their 2017 counterparts. (Table 18; shaded in aqua)

Table 18. SMA Type Sample risk scores for Treatment Benefit 12

	Sample*		
Risk	SMA Type 1	SMA Type 2	SMA Type 3
Invasive means	1.00, **0.40**	0.53, **0.49**	0.60, **0.38**

2022 scores are bold; 2017 scores are roman. *2022 Type 1 Sample n = 61; Type 2 Sample n = 111; and Type 3 Sample n = 93. 2017 Type 1 Sample n = 60; Type 2 Sample n = 124; and Type 3 Sample n = 74.

Key Takeaways from Risk Score Data

- 2022 and 2017 Overall Sample risk scores were **very similar** across treatment benefits, with a few notable recurring disparities.

- For 9 out of 12 potential treatment benefits, risk scores indicated that the 2022 Overall Sample was notably *less tolerant* of the risk of "invasive means to administer treatment" than the 2017 Overall Sample.

    - For all 9 of these treatment benefits, the 2022 SMA Type 1 Sample scored the risk of "invasive means to administer treatment" as notably *less tolerable* than did its 2017 counterpart.

    - For 4 of 9 of these treatment benefits, the 2022 SMA Type 2 Sample scored the risk of "invasive means to administer treatment" as notably *less tolerable* than did its 2017 counterpart.

    - For 8 of 9 of these treatment benefits, the 2022 SMA Type 3 Sample scored the risk of "invasive means to administer treatment" as notably *less tolerable* than did its 2017 counterpart.

- For 4 out of 12 potential treatment benefits, risk scores indicated that the 2022 Overall Sample was notably *more tolerant* of "increased risks of respiratory or other infections" than the 2017 Overall Sample.

    - For all 4 of these treatment benefits, only the 2022 SMA Type 2 Sample scored "increased risk of respiratory or other infections" as notably *more tolerable* than did its 2017 counterpart.

Risk Ranking by Treatment Benefit

To compare which risks the 2022 and 2017 Overall Samples considered *most* and *least tolerable*, risks were assigned a rank according to their risk score. (Table 19) The more positive a risk's score was for a given benefit, the more tolerable it was considered, and the higher its rank was on a scale of 1 to 11 (from most to least tolerable).

In general, the 2022 risk rankings for each treatment benefit were **very similar** to those from the 2017 survey, with some slight differences. (Table 19)

- Most tolerable risks
  - Both the 2022 and the 2017 Overall Samples consistently ranked "commons side effects," "dizziness," "general anesthesia to administer treatment," and "invasive means to administer treatment" among the four *most tolerable* risks,
  - However, rank order of these four risks varied between treatment benefits and between the 2022 and 2017 Overall Samples
- Least tolerable risks
  - Both the 2022 and 2017 Overall Samples consistently ranked the following four risks *least tolerable,* in the following order: "worsening quality of life," "1/1000 risk of side effects results in organ failure," "life-threatening allergic reactions," and "1/1000 risk of organ side effects requiring immediate medical attention," respectively.
  - Rank order of these four risks did *not* vary with treatment benefit or between surveys.
- Other notable disparities
  - For 9 out of 12 potential treatment benefits, the 2022 Overall Sample ranked "increased risks of respiratory and other infections" as *more tolerable* than did the 2017 Overall Sample (rank 6 versus 7, respectively).
  - For 9 out of 12 potential treatment benefits, the 2022 Overall Sample ranked "1/100,000 risk of side effects resulting in organ failure" as *less tolerable* than did the 2017 Overall Sample (rank 7 versus 6, respectively).

Table 19. Risk rankings for each treatment benefit: 2022 Overall Sample vs. 2017 Overall Sample

Treatment Risk*	Treatment Benefit**: 1. Increased overall muscle strength	2. Consistent muscle performance/strength	3. Improvement in ability to swallow	4. Improvement in ability to speak/communicate	5. Improvement in respiratory function	6. Improved proximal mobility and function	7. Increased core strength	8. Increased upper limb strength	9. Decreased fatigue	10. Less severe/fewer symptoms	11. Prolonging lifespan	12. Slowing/stopping of disease progression
Common side effects	**1** (3)	**1** (4)	**1** (4)	**1** (4)	**1** (4)	**1** (3)	**1** (4)	**1** (3)	**1** (4)	**1** (4)	**1** (4)	**1** (3)
Dizziness	**2** (2)	**3** (3)	**2** (1)	**2** (3)	**2** (3)	**4** (4)	**3** (2)	**3** (4)	**2** (3)	**3** (2)	**2** (3)	**3** (4)
General anesthesia to administer treatment	**3** (1)	**2** (2)	**3** (2)	**3** (2)	**3** (2)	**3** (2)	**4** (3)	**4** (2)	**3** (2)	**4** (3)	**4** (2)	**4** (2)
Invasive means to administer treatment	**4** (4)	**4** (1)	**4** (3)	**4** (1)	**4** (1)	**2** (1)	**2** (1)	**2** (1)	**4** (1)	**2** (1)	**3** (1)	**2** (1)
1/100,000 risk of organ SEs requiring immediate MA	**5** (5)	**5** (5)	**5** (5)	**5** (5)	**5** (5)	**5** (5)	**5** (5)	**5** (5)	**5** (5)	**5** (5)	**5** (5)	**5** (5)
Increased risks of respiratory/other infections	**6** (7)	**6** (6)	**6** (7)	**6** (7)	**6** (7)	**6** (7)	**6** (6)	**6** (7)	**6** (7)	**6** (7)	**6** (6)	**6** (7)
1 /100,000 risk of SEs resulting in organ failure	**7** (6)	**7** (7)	**7** (6)	**7** (6)	**7** (6)	**7** (6)	**7** (7)	**7** (6)	**7** (6)	**7** (6)	**7** (7)	**7** (6)
1/1,000 risk of organ SEs requiring immediate MA	**8** (8)	**8** (8)	**8** (8)	**8** (8)	**8** (8)	**8** (8)	**8** (8)	**8** (8)	**8** (8)	**8** (8)	**8** (8)	**8** (8)
Life-threatening allergic reactions	**9** (9)	**9** (9)	**9** (9)	**9** (9)	**9** (9)	**9** (9)	**9** (9)	**9** (9)	**9** (9)	**9** (9)	**9** (9)	**9** (9)
1/1,000 risk of SEs resulting in organ failure	**10** (10)	**10** (10)	**10** (10)	**10** (10)	**10** (10)	**10** (10)	**10** (10)	**10** (10)	**10** (10)	**10** (10)	**10** (10)	**10** (10)
Worsening quality of life	**11** (11)	**11** (11)	**11** (11)	**11** (11)	**11** (11)	**11** (11)	**11** (11)	**11** (11)	**11** (11)	**11** (11)	**11** (11)	**11** (11)

2022 scores are bold, N = 282; 2017 scores are roman, N = 298. Where 2022 and 2017 rank differs, 2022 rank appears in red.
*Risk labels are abbreviations of complete descriptions on page 12.
**Benefit labels are abbreviations of complete descriptions on page 12.
Tx = treatment; SEs = side effects; MA = medical attention.

Cumulative Risk Rankings

To identify which risks were most likely to be ranked *most* and *least tolerable*, rankings for each risk were averaged across treatment benefits within each sample, which yielded a cumulative risk ranking for each risk.

- Overall Sample (Table 20)
  - Most tolerable risks
    - Both the 2022 and 2017 Overall Samples were most likely to rank "common side effects," "dizziness," "general anesthesia," and "invasive means to administer treatment" among the four *most tolerable* risks. However, the 2022 rank order of these risks was inverted compared to that of 2017.
    - Notably, the 2022 Overall Sample was most likely to rank "common side effects" as first *most tolerable*, whereas the 2017 Overall Sample was most likely to rank "invasive means to administer treatment" as the first *most tolerable* risk.
  - Least tolerable risks
    - Both the 2022 and the 2017 Overall Samples were most likely to rank as *least tolerable* "worsening in quality of life," "1/1,000 risk of side effects resulting in organ failure," "life threatening allergic reactions," and "1/1,000 risk of organ side effects requiring immediate medical attention," in that order.

Table 20. Cumulative most and least tolerable risk rankings: 2022 Overall Sample vs. 2017 Overall Sample

Most Tolerable Risks

2022 Overall Sample (N = 282)	Rank	2017 Overall Sample (N = 298)
Common side effects	1	Invasive means to administer treatment
Dizziness	2	General anesthesia
General anesthesia	3	Dizziness
Invasive means to administer treatment	4	Common side effects

Least Tolerable Risks

2022 Overall Sample (N = 282)	Rank	2017 Overall Sample (N = 298)
Worsening in quality of life	1	Worsening in quality of life
1/1,000 risk of SEs resulting in organ failure	2	1/1,000 risk of SEs resulting in organ failure
Life-threatening allergic reactions	3	Life-threatening allergic reactions
1/1,000 risk of organ SEs requiring immediate MA	4	1/1,000 risk of organ SEs requiring immediate MA

Risk labels are abbreviations of complete descriptions on page 12.
SEs = side effects; MA = medical attention.

- SMA Type 1 Sample (Table 21)
  - Most tolerable risks
    - Whereas the 2022 Type 1 Sample was most likely to rank "dizziness" at the first *most tolerable* risk, the 2017 Type 1 did not rank this risk among the four *most tolerable*.
    - The 2017 Type 1 Sample was most likely to rank "invasive means to administer treatment" as the first *most tolerable* risk, whereas the 2022 Type 1 Sample was most likely to rank it as fourth *most tolerable*.
  - Least tolerable risks
    - Both the 2022 and the 2017 SMA Type 1 Samples were most likely to rank "worsening in quality of life" and "1/1,000 risk of side effects resulting in organ failure" as the first and second *least tolerable* risks, respectively.
    - The 2017 SMA Type 1 Sample was most likely to rank "1/100,000 risk of side effects resulting in organ failure" as fourth *least tolerable*, whereas the 2022 Type 1 Sample did not rank this risk among the four *least tolerable*.

Table 21. Cumulative most and least tolerable risks: 2022 SMA Type 1 Sample vs. 2017 SMA Type 1 Sample

Most Tolerable Risks

2022 SMA Type 1 Sample (n = 60)	Rank	2017 SMA Type 1 Sample (n = 61)
Dizziness	1	Invasive means to administer treatment
Common side effects	2	Common side effects
General anesthesia	3	General anesthesia
Invasive means to administer treatment	4	1/100,000 risk of organ SEs requiring immediate MA

Least Tolerable Risks

2022 SMA Type 1 Sample (n = 60)	Rank	2017 SMA Type 1 Sample (n = 61)
Worsening in quality of life	1	Worsening in quality of life
1/1,000 risk of SEs resulting in organ failure	2	1/1,000 risk of SEs resulting in organ failure
Life-threatening allergic reactions	3	1/1,000 risk of organ SEs requiring immediate MA
1/1,000 risk of organ SEs requiring immediate MA	4	1/100,000 risk of SEs resulting in organ failure

Risk labels are abbreviations of complete descriptions on page 12.
SEs = side effects; MA = medical attention.

SMA Type 2 Sample (Table 22)

- Most tolerable risks

  - The SMA Type 2 Samples from both the 2022 and 2017 surveys were most likely to rank ranked "common side effects," "dizziness," "invasive means to administer treatment," and "general anesthesia" among the four *most tolerable* risks.

  - However, the 2022 Type 2 Sample was most likely to rank "common side effects" and "invasive means to administer treatment" as first and third most tolerable, respectively; whereas the 2017 Type 2 Sample was most likely to rank the two risks inversely.

- Least tolerable risks

  - Both the 2022 and the 2017 Type 2 Samples were most likely to rank "worsening in quality of life," "1/1,000 risk of side effects resulting in organ failure," and "life-threatening allergic reactions" as the first, second, and third *least tolerable* risks, respectively.

  - However, the 2022 Type 2 Sample was most likely to rank "1/1,000 risk of organ side effects requiring immediate medical attention" as the fourth *least tolerable* risk, whereas the 2017 Type 2 Sample was most likely to rank "increased risk of respiratory and other infections" as fourth *least tolerable*.

Table 22. Cumulative most and least tolerable risks: 2022 SMA Type 2 Sample vs. 2017 SMA Type 2 Sample

Most Tolerable Risks

2022 SMA Type 2 Sample (n = 111)	Rank	2017 SMA Type 2 Sample (n = 124)
Common side effects	1	Invasive means to administer treatment
Dizziness	2	Dizziness
Invasive means to administer treatment	3	Common side effects
General anesthesia	4	General anesthesia

Least Tolerable Risks

2022 SMA Type 2 Sample (n = 111)	Rank	2017 SMA Type 2 Sample (n = 124)
Worsening in quality of life	1	Worsening in quality of life
1/1,000 risk of SEs resulting in organ failure	2	1/1,000 risk of SEs resulting in organ failure
Life-threatening allergic reactions	3	Life-threatening allergic reactions
1/1,000 risk of organ SEs requiring immediate MA	4	Increased risk of respiratory and other infections

Risk labels are abbreviations of complete descriptions on page 12.
SEs = side effects; MA = medical attention.

- SMA Type 3 Sample (Table 23)
  - Most tolerable risks
    - Both the 2022 and 2017 SMA Type 3 Samples were most likely to rank "common side effects," "dizziness," "invasive means to administer treatment," and "general anesthesia" among the four *most tolerable* risks; however, rank order varied between samples for all risks except "dizziness," which was ranked as fourth *most tolerable* by both samples.
    - Notably, the 2017 Type 3 Sample was most likely to rank most "invasive means to administer treatment" as the first *most tolerable* risk, whereas the 2022 Type 3 Sample was most likely to rank it as third *most tolerable*.
  - Least tolerable risks
    - Both the 2022 and the 2017 Type 3 Samples were most likely to rank "worsening in quality of life," "1/1,000 risk of side effects resulting in organ failure," "life-threatening allergic reactions," and "1/1,000 risk of organ side effects requiring immediate medical attention" as the fourth least tolerable risks, in that order.

Table 23. Cumulative most and least tolerable risks: 2022 Type 3 Sample vs. 2017 Type 3 Sample

Most Tolerable Risks

2022 SMA Type 3 Sample (n = 93)	Rank	2017 SMA Type 3 Sample (n = 74)
Common side effects	1	Invasive means to administer treatment
General anesthesia	2	Common side effects
Invasive means to administer treatment	3	General anesthesia
Dizziness	4	Dizziness

Least Tolerable Risks

2022 SMA Type 3 Sample (n = 93)	Rank	2017 SMA Type 3 Sample (n = 74)
Worsening in quality of life	1	1/1,000 risk of SEs resulting in organ failure
1/1,000 risk of SEs resulting in organ failure	2	Worsening in quality of life
Life-threatening allergic reactions	3	Life-threatening allergic reactions
1/1,000 risk of organ SEs requiring immediate MA	4	1/1,000 risk of organ SEs requiring immediate MA

Risk labels are abbreviations of complete descriptions on page 12.
SEs = side effects; MA = medical attention.

Key Takeaways from Cumulative Risk Ranking Results

- The 2022 and 2017 Overall Sample cumulative risk rankings were **similar**, with a few notable disparities.
  - Most tolerable risks
    - Both the 2022 and 2017 Overall Samples were most likely to rank "common side effects," "dizziness," "general anesthesia," and "invasive means to administer treatment" among the four *most tolerable*, although the rank order of these risks was inverted in 2022 compared to 2017.
    - Notably, the 2022 Overall Sample was most likely to rank "common side effects" as first *most tolerable*, whereas the 2017 Overall Sample was most likely to rank "invasive means to administer treatment" as first *most tolerable*.
  - Least tolerable risks
    - The 2022 and the 2017 Overall Samples were most likely to rank the same four risks as *least tolerable*: "worsening in quality of life," "1/1,000" risk of side effects resulting in organ failure," "life threatening allergic reactions," and "1/1,000 risk of organ side effects requiring immediate medical attention," in that order.
- The cumulative risk rankings of the 2022 and 2017 SMA Type 1-3 Samples were **similar**, with a few notable disparities.
  - Most tolerable risks
    - The 2022 SMA Type 1 Sample was most likely to rank "dizziness" and the first *most tolerable* risk, whereas the 2017 SMA Type 1 Sample was most likely to rank "invasive means to administer treatment" as first *most tolerable*.
    - The 2022 SMA Types 2 and 3 Samples were most likely to rank "common side effects" as first *most tolerable* across all treatment benefits, whereas the 2017 SMA Types 2 and 3 Samples were most likely to rank "invasive means to administer treatment" as first *most tolerable*.
  - Least tolerable risks
    - All SMA Type Samples from both the 2022 and 2017 surveys most frequently ranked "worsening in quality of life" as the first *least tolerable* risk.
    - There was some variability between the risks that the 2022 and 2017 SMA Type Samples were most likely to rank among the third and fourth *least tolerable*.

Conclusion

Overall, the 2022 SMA Risk/Benefit Survey results were very similar to those from the 2017 survey. Results from both surveys indicated that respondents would tolerate a wide range of possible risks in exchange for a variety of potential treatment benefits.

The most notable disparity between 2022 and 2017 survey results was that 2022 respondents, especially those with SMA Types 1 and 3, were less tolerant of the risk of "invasive means to administer treatment" in exchange for most surveyed potential treatment benefits. This shift may reflect the increased availability of different treatment options between 2017 and 2022.

The fact that risk tolerance has remained high despite the increased availability of DMTs is reflective of the unmet needs remaining for people living with SMA. DMTs are known to produce the most robust effects when given early. As such, individuals for whom early treatment was not available tend to have high unmet needs. However, even for individuals treated early in life, prior to symptom onset, the available therapies are not curative and unmet needs remain. Continued therapeutic development is required to meet these needs, and the results of this survey indicate that the SMA community is willing to tolerate considerable risk for further treatment benefit.

One of Cure SMA's key aims is to facilitate the incorporation of patient perspectives into the drug development and approval process. This report is intended to update FDA on the current risk/benefit profile of the SMA community as new SMA treatments designed to address current unmet needs advance through the clinical trial pipeline.

References

[1] Bach JR, Baird JS, Plosky D, Navado J, Weaver B. Spinal muscular atrophy type 1: Management and outcomes. Pediatr Pulmonol. 2002;34(1):16-22.
[2] Borkowska J, Rudnik-Schoneborn S, Hausmanowa-Petrusewicz I, Zerres K. Early infantile form of spinal muscular atrophy (Werdnig-Hoffmann disease) with prolonged survival. Folia Neuropathol. 2002;40(1):19-26.
[3] Chung BH, Wong VC, Ip P. Spinal muscular atrophy: Survival pattern and functional status. Pediatrics. 2004;114(5):e548-53.
[4] Belter L, Taylor JL, Jorgensen E, et al. Newborn screening and birth prevalence for spinal muscular atrophy in the US. JAMA pediatrics. 2024.
[5] Belter L, Whitmire, S., Welsh, E., Schroth, M. State of SMA 2023. 2024.
[6] Milligan JN, Blasco-Perez L, Costa-Roger M, Codina-Sola M, Tizzano EF. Recommendations for interpreting and reporting silent carrier and disease-modifying variants in SMA testing workflows. Genes (Basel). 2022;13(9).
[7] Keinath MC, Prior DE, Prior TW. Spinal muscular atrophy: Mutations, testing, and clinical relevance. Appl Clin Genet. 2021;14:11-25.
[8] Wirth B, Karakaya M, Kye MJ, Mendoza-Ferreira N. Twenty-five years of spinal muscular atrophy research: From phenotype to genotype to therapy, and what comes next. Annu Rev Genomics Hum Genet. 2020;21:231-61.
[9] Chaytow H, Huang YT, Gillingwater TH, Faller KME. The role of survival motor neuron protein (SMN) in protein homeostasis. Cell Mol Life Sci. 2018;75(21):3877-94.
[10] Singh RN, Howell MD, Ottesen EW, Singh NN. Diverse role of survival motor neuron protein. Biochim Biophys Acta Gene Regul Mech. 2017;1860(3):299-315.
[11] Coovert DD, Le TT, McAndrew PE, et al. The survival motor neuron protein in spinal muscular atrophy. Hum Mol Genet. 1997;6(8):1205-14.
[12] Li DK, Tisdale S, Lotti F, Pellizzoni L. SMN control of rnp assembly: From post-transcriptional gene regulation to motor neuron disease. Semin Cell Dev Biol. 2014;32:22-9.

[13] Nagano S, Araki T. Axonal transport and local translation of mRNA in neurodegenerative diseases. Frontiers in Molecular Neuroscience. 2021;14:697973.
[14] Cuartas J, Gangwani L. R-loop mediated DNA damage and impaired DNA repair in spinal muscular atrophy. Frontiers in Cellular Neuroscience. 2022;16:826608.
[15] Ogino S, Leonard DG, Rennert H, Ewens WJ, Wilson RB. Genetic risk assessment in carrier testing for spinal muscular atrophy. Am J Med Genet. 2002;110(4):301-7.
[16] Wadman RI, Stam M, Gijzen M, et al. Association of motor milestones, *SMN2* copy and outcome in spinal muscular atrophy types 0-4. J Neurol Neurosurg Psychiatry. 2017;88(4):365-7.
[17] Zerres K, Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. Arch Neurol. 1995;52(5):518-23.
[18] Russman BS. Spinal muscular atrophy: Clinical classification and disease heterogeneity. J Child Neurol. 2007;22(8):946-51.
[19] Piepers S, van den Berg LH, Brugman F, et al. A natural history study of late onset spinal muscular atrophy types 3b and 4. J Neurol. 2008;255(9):1400-4.
[20] Ravi B, Chan-Cortes MH, Sumner CJ. Gene-targeting therapeutics for neurological disease: Lessons learned from spinal muscular atrophy. Annu Rev Med. 2021;72:1-14.
[21] Aslesh T, Yokota T. Restoring SMN expression: An overview of the therapeutic developments for the treatment of spinal muscular atrophy. Cells. 2022;11(3).
[22] Mercuri E, Pera MC, Scoto M, Finkel R, Muntoni F. Spinal muscular atrophy - Insights and challenges in the treatment era. Nat Rev Neurol. 2020;16(12):706-15.
[23] Schroth M, Deans J, Arya K, et al. Spinal muscular atrophy update in best practices: Recommendations for diagnosis considerations. Neurol Clin Pract. 2024;14(4):e200310.
[24] Cances C, Vlodavets D, Comi GP, et al. Natural history of type 1 spinal muscular atrophy: A retrospective, global, multicenter study. Orphanet J Rare Dis. 2022;17(1):300.
[25] Martí Y, Aponte Ribero V, Batson S, et al. A systematic literature review of the natural history of respiratory, swallowing, feeding, and speech functions in spinal muscular atrophy (SMA). J Neuromuscul Dis. 2024.
[26] Aponte Ribero V, Martí Y, Batson S, et al. Systematic literature review of the natural history of spinal muscular atrophy: Motor function, scoliosis, and contractures. Neurology. 2023;101(21):e2103-e13.
[27] de Lemus M, Cattinari MG, Pascual SI, et al. Identification of the most relevant aspects of spinal muscular atrophy (SMA) with impact on the quality of life of SMA patients and their caregivers: The profuture project, a qualitative study. Journal of patient-reported outcomes. 2024;8(1):78.
[28] Brown L, Hoffman K, Corbo-Galli C, et al. Use of the assessment of caregiver experience with neuromuscular disease (ACEND) in spinal muscular atrophy. Journal of Clinical Medicine. 2024;13(4).
[29] Brandt M, Johannsen L, Inhestern L, Bergelt C. Parents as informal caregivers of children and adolescents with spinal muscular atrophy: A systematic review of quantitative and qualitative data on the psychosocial situation, caregiver burden, and family needs. Orphanet J Rare Dis. 2022;17(1):274.
[30] Spinraza prescribing information. Cambridge: Biogen; 2016 [cited 20 Feb 2025]. Available from: https://www.spinraza.com/content/dam/commercial/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf.
[31] Zolgensma prescribing information Bannockburn: AveXis Inc.; 2019 [cited 20 Feb 2025]. Available from: https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf.
[32] Evrysdi prescribing information San Francisco: Genentech; 2020 [cited 20 Feb 2025]. Available from: https://www.gene.com/download/pdf/evrysdi_prescribing.pdf.
[33] Lee BH, Waldrop MA, Connolly AM, Ciafaloni E. Time is muscle: A recommendation for early treatment for preterm infants with spinal muscular atrophy. Muscle Nerve. 2021;64(2):153-5.
[34] Finkel RS, Ryan MM, Pascual Pascual SI, et al. Scientific rationale for a higher dose of nusinersen. Annals of Clinical and Translational Neurology. 2022;9(6):819-29.
[35] Hagenacker T, Wurster CD, Günther R, et al. Nusinersen in adults with 5q spinal muscular atrophy: A non-interventional, multicentre, observational cohort study. The Lancet Neurology. 2020;19(4):317-25.
[36] Osmanovic A, Schreiber-Katz O, Petri S. Nusinersen wearing-off in adult 5q-spinal muscular atrophy patients. Brain Sci. 2021;11(3).
[37] Giess D, Erdos J, Wild C. An updated systematic review on spinal muscular atrophy patients treated with nusinersen,

onasemnogene abeparvovec (at least 24 months), risdiplam (at least 12 months) or combination therapies. Eur J Paediatr Neurol. 2024;51:84-92.
[38] Ruythooren F, Moens P. Spinal muscular atrophy scoliosis in the era of background therapies-A review of the literature. Journal of Clinical Medicine. 2024;13(12).
[39] Cure SMA. SMA Drug Pipeline. 2025 [cited 20 Feb 2025]. Available from: https://www.curesma.org/sma-drug-pipeline/.
[40] Cruz R, Belter L, Wasnock M, Nazarelli A, Jarecki J. Evaluating benefit-risk decision-making in spinal muscular atrophy: A first-ever study to assess risk tolerance in the SMA patient community. Clinical Therapeutics. 2019;41(5):943-60 e4.
[41] Belter L, Whitmire, S., Welsh, E., Schroth, M. State of SMA: 2023 report. 2024 May 6, 2024.
[42] Mercuri E, Sumner CJ, Muntoni F, Darras BT, Finkel RS. Spinal muscular atrophy. Nature Reviews Disease Primers. 2022;8(1):52.
[43] Cure SMA. Newborn Screening for SMA. 2022 [cited 20 Feb 2025]. Available from: https://www.curesma.org/newborn-screening-for-sma/
[44] Lefebvre S, Burlet P, Liu Q, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. Nat Genet. 1997;16(3):265-9.
[45] Torri F, Mancuso M, Siciliano G, Ricci G. Beyond motor neurons in spinal muscular atrophy: A focus on neuromuscular junction. Int J Mol Sci. 2024;25(13).
[46] Nash LA, Burns JK, Chardon JW, Kothary R, Parks RJ. Spinal muscular atrophy: More than a disease of motor neurons? Curr Mol Med. 2016;16(9):779-92.
[47] Yeo CJJ, Tizzano EF, Darras BT. Challenges and opportunities in spinal muscular atrophy therapeutics. The Lancet Neurology. 2024;23(2):205-18.
[48] Hamilton G, Gillingwater TH. Spinal muscular atrophy: Going beyond the motor neuron. Trends Mol Med. 2013;19(1):40-50.
[49] Detering NT, Zambon A, Hensel N, et al. 264th ENMC international workshop: Multi-system involvement in spinal muscular atrophy hoofddorp, the netherlands, November 19th - 21st 2021. Neuromuscul Disord. 2022;32(8):697-705.
[50] Jha NN, Kim JK, Her YR, Monani UR. Muscle: An independent contributor to the neuromuscular spinal muscular atrophy disease phenotype. JCI Insight. 2023;8(18).
[51] Wadman RI, Wijngaarde CA, Stam M, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol. 2018;25(3):512-8.
[52] Ricci M, Cicala G, Capasso A, et al. Clinical phenotype of pediatric and adult patients with spinal muscular atrophy with four *SMN2* copies: Are they really all stable? Ann Neurol. 2023;94(6):1126-35.
[53] Lusakowska A, Jedrzejowska M, Kaminska A, et al. Observation of the natural course of type 3 spinal muscular atrophy: Data from the Polish registry of spinal muscular atrophy. Orphanet J Rare Dis. 2021;16(1):150.
[54] Schorling DC, Pechmann A, Kirschner J. Advances in treatment of spinal muscular atrophy - new phenotypes, new challenges, new implications for care. J Neuromuscul Dis. 2020;7(1):1-13.
[55] Cooper K, Nalbant G, Sutton A, et al. Systematic review of presymptomatic treatment for spinal muscular atrophy. Int J Neonatal Screen. 2024;10(3).
[56] Cure SMA. FDA patient-led listening session. 2022 [cited 2025 Februray 10]. Available from: https://www.fda.gov/media/162961/download?attachment.
[57] Patel A, Toro W, Bourke S, et al. Treatment preferences in spinal muscular atrophy: A swing weighting study for caregivers of patients with SMA types 1 and 2. PLoS One. 2024;19(10):e0309666.
[58] Cruz R, Lenz M, Belter L, Hobby K, Jarecki J, Smart T. Cure SMA Voice of the Patient Report. 2018 [cited 20 Feb 2025]. Available from: https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf.
[59] Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh WS. Understanding the experiences and needs of individuals with spinal muscular atrophy and their parents: A qualitative study. BMC Neurol. 2015;15:217.
[60] Cheung KL, Wijnen BF, Hollin IL, et al. Using best-worst scaling to investigate preferences in health care. Pharmacoeconomics. 2016;34(12):1195-209.
[61] Hollin IL, Paskett J, Schuster ALR, Crossnohere NL, Bridges JFP. Best-worst scaling and the prioritization of objects in health: A systematic review. Pharmacoeconomics. 2022;40(9):883-99.

APPENDIX A

Table A1. Additional demographic characteristics of individuals with SMA

Education	**2022** (n = 282)	**2017** (n = 272)
No schooling to eighth grade	39.0%	49.1%
Some high school, no diploma	1.8%	13.6%
High school graduate, diploma, or equivalent (eg., GED)	9.9%	2.8%
Some college credit, no degree	9.6%	7%
Trade/technical/ vocational training	1.1%	1.5%
Associate degree (for example: AA, AS)	6.7%	1.8%
Bachelor's degree (for example: BA, BS)	15.2%	14.0%
Master's degree (for example: MA, MS)	13.8%	7.7%
Professional degree	N/A*	1.1%
Doctorate degree (for example: PhD, EdD, MD, DDS)	2.8%	1.1%

*Category was not included in 2022

Employment Status	**2022** (n = 282)	**2017** (n = 272)
Not currently employed	31.2%	25.4%
Full-time student	20.2%	38.6%
Employed full-time (working 30 hours or more a week)	16.3%	12.5%
Employed part-time (working less than 30 hours a week)	11.0%	6.6%
Retired	6.7%	6.3%
Part-time student	2.8%	10.7%
Other	11.7%	N/A**

**Category was not included in 2022