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ORIGINAL RESEARCH

Understanding Caregivers' Experiences of Rett Syndrome: A Multinational Study of Symptoms and Meaningful Outcomes of Potential Treatments

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ABSTRACT

Introduction: Caregivers have first-hand experience of facing the daily challenges of Rett syndrome (RTT). The aim of this study was to understand caregivers' experiences of RTT, including challenging symptoms that caregivers hope novel therapies will address.

Methods: This non-interventional, qualitative and quantitative market research study engaged caregivers of individuals with RTT in the USA, the UK, Canada, and Israel, through an online survey comprising both closed- and open-ended items. Survey domains included age of symptom onset, symptom severity and impact on quality of life, the most challenging symptoms, and caregiver perspectives on meaningful improvement.

Results: A total of 323 caregivers completed the survey. Symptoms with the most severe and lasting impact on patients' quality of life typically presented by 6 years of age. These symptoms included loss of speech, loss of purposeful use of hands, and gait disturbances. Caregivers reported a dynamic and lifelong burden associated with impairments in activities of daily living and expressed a desire for improvement across these functional domains following gene therapy treatment.

Conclusion: Despite RTT's clinical heterogeneity, similarities emerged in caregivers' daily experiences and their hopes regarding gene therapy treatment. Caregivers believe meaningful improvements for people with RTT would be improved function and enhanced autonomy

Prior Presentation: Part of this work was presented at the International Rett Syndrome Foundation (IRSF) Annual Meeting on June 5–7, 2023, Nashville, TN, USA. Poster 64: Emily McGinnis, Benit Maru, Chelsea Karbocus, John Ashkenas, Kristin LaBounty Phillips. Caregivers' Understanding of Gene Therapy Clinical Trials: Knowledge Gaps and Opportunities for Education. Data were also previously presented, in part, at IRSF Annual Meeting in on April 26–27, 2022, Nashville, TN, USA. Poster 38: Kristin LaBounty Phillips, Emily McGinnis, Kome Okposo, Fatemeh Tavakkoli, Suyash Prasad. Leveraging insights about the Rett syndrome patient experience to inform development of clinical trials. Poster 39: Kristin LaBounty Phillips, Emily McGinnis, Kome Okposo, Suyash Prasad. Rett syndrome in adulthood: the caregiver perspective.

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related to fine and gross motor abilities, and improved ability to communicate needs.

Keywords: Activities of daily living; Caregiver survey; Gene therapy; Meaningful improvements; MECP2; Neurodevelopmental disorder; Quality of life; Rett syndrome; Symptom burden

Key Summary Points

Why carry out this study?

There is broad heterogeneity in the symptoms and severity of Rett syndrome (RTT); therefore, it is important to understand which symptoms have the greatest impact on patients, their families, and caregivers to ensure their perspectives and priorities are considered when designing gene therapy trials

Understanding the lived experience of caregivers of patients with RTT will help align study outcome measures with caregivers' needs and concerns

To aid the development of an investigational gene therapy for RTT this study sought caregiver input on the most challenging symptoms affecting patients with RTT, and what improvements to these symptoms caregivers would consider to be meaningful

What was learned from the study?

Symptoms with the most severe and lasting impact on patients' quality of life, including loss of speech, loss of purposeful use of hands, and gait disturbances. typically presented by 6 years of age

Despite variability in symptoms, caregivers judged improvements to be meaningful if they enhanced patient autonomy, allowed for communication of needs and preferences, or reduced caregiving demands

Caregivers expressed interest in participating in a gene therapy trial and were generally motivated by the hope of improved quality of life

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INTRODUCTION

Rett syndrome (RTT) is a progressive neurodevelopmental disorder primarily affecting female individuals, usually associated with loss-of-function mutations in the X-linked *MECP2* gene. *MECP2* encodes methyl-CpG-binding protein 2, a key regulator of neuronal and synaptic function in the brain [1–3]. Global incidence is thought to be 1 per 10,000–20,000 female births [4], although clinical heterogeneity may lead to mis- and underdiagnosis.

Typically, patients experience an initial period of normal development (ages 6–18 months), followed by motor skill regression, loss of spoken language and purposeful hand use, onset of hand stereotypies, gastrointestinal (GI) issues, abnormal gait, and growth failure [4–7]. Notably, patients with RTT typically display a lack of acquisition of new skills beyond 6 years of age [8]. Common neurologic features of RTT, including autonomic and breathing dysregulation, seizures, and swallowing and speech disorders, also emerge at this time [3–5, 9,10]. After approximately age 10, individuals with RTT may experience further motor impairment, muscle weakness, scoliosis, joint contractures, spasticity, dystonia, and worsening breathing patterns [2–6]. Individuals affected by RTT can survive beyond their fifth decade of life [11,12]. The severity of their functional impairments necessitates long-term, continuous care and results in an extremely high caregiver burden [10–15].

While trofinetide has recently been approved for management of RTT symptoms in children ≥ 2 years of age in the USA and Canada [16–18], the current standard of care in much of the world remains as supportive symptomatic treatment [5, 9, 16–19]. Given the unmet need for therapies addressing RTT's genetic cause, disease-modifying therapies such as gene therapy (GT) offer a promising hope to ameliorate, or potentially reverse, the debilitating effects of RTT [20,21].

Given the heterogeneity of symptoms, the lived experience of caregivers of patients with RTT represents an important resource for developers of new therapeutics, to ensure that caregivers' perspectives and priorities are considered in trial design and regulatory review [22–25]. During the development of the investigational GT for RTT, Taysha Gene Therapies, Inc. sought caregiver input to help align study outcome measures with caregivers' needs and concerns.

This large multinational study sought to understand caregivers' views of the most challenging symptoms affecting patients with RTT, and what improvements to these symptoms caregivers would consider to be meaningful, in addition to exploring the caregiver perspective on GT clinical trials.

METHODS

Study Design

This was a non-interventional qualitative and quantitative study consisting of online surveys with caregivers of patients with RTT. In the development of the survey, a USA workgroup ($n = 20$) was invited via partnership with the International Rett Syndrome Foundation (IRSF) and Rett Syndrome Research Trust (RSRT) to participate in an online survey followed by a 2-hour video focus group centered on the experience of caring for patients with RTT and caregiver views of meaningful improvement following the administration of a hypothetical GT.

The insights gathered in the workgroup were utilized to develop the online survey described here, which was completed by caregivers of patients with RTT who were identified in partnership with patient advocacy groups (PAGs; USA: IRSF and RSRT; Canada: Ontario Rett Syndrome Association [ORSA]; UK: Reverse Rett; Israel: Israel Rett Syndrome Association [IRSA]). The survey was administered to all caregivers with email addresses in the PAGs' databases for IRSF, ORSA, Reverse Rett, and IRSA. RSRT used social media (Facebook) and sent personal emails to a targeted group of caregivers of patients ≥ 18 years of age with RTT. IRSA targeted female individuals only. To avoid overlap between databases, response was requested from only one respondent per household and Internet Protocol (IP) addresses were used to prevent duplicative responses.

The survey was written in English and translated to Hebrew and French for participants from Israel and Francophone Canada. The survey consisted of open-ended and multiple-choice questions that explored symptom onset and evolution; the most challenging symptoms of RTT and symptoms having the greatest impact; meaningful improvements across communication, gross motor, and fine motor developmental milestones; and respondents' interest in and receptivity to enrolling in GT clinical trials.

Ethical Approval

Ethics committee approval was not required for this study, as it was determined to be minimal risk to participants. Nonetheless, strict ethical procedures were followed in accordance with the Declaration of Helsinki 1964 and its later amendments. Participation was entirely voluntary and privacy protections included anonymous data collection (i.e., no personally identifiable information was collected) and secure, access-restricted data storage consistent with relevant data protection regulations (e.g., General Data Protection Regulation and applicable USA privacy standards). The survey was conducted according to the ethical principles for market research as outlined by the American Marketing Association. Data were anonymized by third-party vendors.

Caregivers were presented with a brief study overview that included the research objectives and the name of the study sponsor prior to participation. Consent to participate was implied by the caregivers' initiation of the online survey by clicking "Agree to continue." As the survey was conducted anonymously, separate consent for publication of individual data was not obtained. Results are reported only in aggregate form, and no information that could reasonably identify participants is included in the manuscript.

Up to a pre-established quota (total $n=112$), participants in the USA, Canada, and the UK received $25 compensation; all subsequent participants chose to proceed without compensation. As a result of regional legislation, compensation was not available to Israeli participants; in lieu of compensation, a comparable donation was made toward IRSA.

Data Analysis

Survey data were analyzed and summarized in a structured manner after duplicate entries had been removed. Descriptive analyses were used to generate frequency distributions and summary statistics to identify trends, patterns, and variations in the data.

Survey questions requiring open-ended responses were qualitatively analyzed using the Framework method, as described previously [26]. This multistage approach allows for systematic analysis of qualitative data, an iterative process allowing for several points of alignment within the research team, and for the ongoing re-examination of codes and categories. Details of the code themes used in this analysis are provided in the Supplementary Material (Tables S1, S2).

Statistical Analysis

Descriptive statistics are used throughout. For claims related to improvements that caregivers judged as meaningful, the denominator refers to the subset of survey respondents who identified the functional impairment (e.g., difficulties with communication, hand use, or ambulation/gross motor) as challenging for themselves and/or the patient for whom they care.

RESULTS

Participants

In total, 323 caregivers from the USA ($n=85$), the UK ($n=115$), Canada ($n=45$), and Israel ($n=78$) participated. Of these, four respondents were caregivers of male individuals with RTT. The proportion of caregivers of adult patients was greater in the USA group (79%) than the other countries (range 24–47%) (Table 1).

Table 1 Caregiver and patient characteristics

Caregivers per country, *n* (%)	Total	USA	Canada	Israel	UK
Patient age group, years of age	***N*** **= 323**[a]	***n*** **= 85**	***n*** **= 45**	***n*** **= 78**	***n*** **= 115**
0–6	80 (25)	12 (14)	9 (20)	30 (38)	29 (25)
7–12	66 (20)	2 (2)	9 (20)	21 (27)	34 (30)
13–17	35 (11)	4 (5)	6 (13)	8 (10)	17 (15)
≥ 18	142 (44)	67 (79)	21 (47)	19 (24)	35 (30)

[a]Four respondents were caregivers of male individuals with Rett syndrome

Symptom Onset Reported by Caregivers

Although age at onset varied across symptoms, patients typically experienced a majority of symptoms by 6 years of age (Fig. 1). The most commonly reported symptoms showed an earlier age onset (<6 years of age). These included symptoms such as involuntary hand movements (93%, *n* = 300), loss of speech (93%, *n* = 300), loss of purposeful hand use (89%, *n* = 287), and gait disturbances (82%, *n* = 265). Scoliosis or kyphosis (69%, *n* = 224), seizures or Rett "episodes" (81%, *n* = 262), rigidity, spasticity (66%, *n* = 214), anxiety or other mood disorders (73%, *n* = 236), hypertonia (49%, *n* = 159), and loss of ability to walk independently (67%, *n* = 217) tended to show later onset. Age of onset for symptoms was generally consistent regardless of country (Fig. S1).

The occurrence of new symptoms throughout the patients' life became more apparent upon thematic analysis of the age-at-onset data. Over three-quarters of respondents (76%, *n* = 245) indicated that ≥ 1 new or newly challenging symptom had emerged in the 2 years prior to

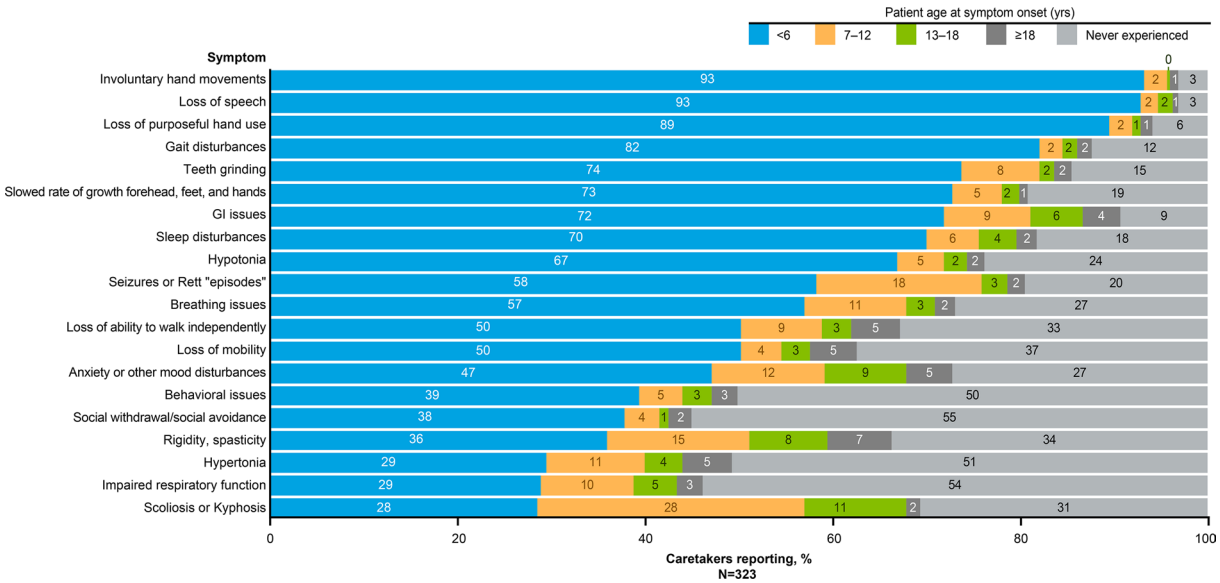

Fig. 1 Age of symptom onset reported by caregivers of patients with Rett syndrome. Question: What symptoms of Rett syndrome has your loved one experienced and about what age did the symptoms begin? Answer format—choose one category: > 12 months, 3–6 yrs, 7–12 yrs, 13–17 yrs, 18–26 yrs, 27–37 yrs, ≥ 38 yrs. *Note*: Some categories were combined for analysis. GI, gastrointestinal; yrs, years

the survey, the most common of which was the loss of mobility, reported by 63% of caregivers.

Symptoms of Rett Syndrome with the Greatest Impact on Quality of Life

Symptoms that were most commonly reported as having a severe impact on quality of life (QoL) included loss of speech (81%, $n=261$), loss of purposeful hand use (80%, $n=259$), loss of independent walking (61%, $n=198$), loss of mobility (59%, $n=189$), and involuntary hand movements (57%, $n=184$). Caregivers also reported gait disturbances (54%, $n=175$), gastrointestinal (GI) issues/constipation (38%, $n=124$), hypotonia (38%, $n=123$), and seizures (36%, $n=117$) as having severe QoL impact (Fig. 2). Symptoms considered to have the greatest impact on QoL were largely similar regardless of country (Fig. S2).

The "Top 5" most challenging symptoms according to caregivers were loss of speech (83%, $n=269$), loss of purposeful hand use (70%, $n=226$), seizures or "Rett episodes" (45%, $n=146$), loss of independent walking (42%, $n=135$), and GI issues (33%, $n=105$) (Fig. 3a). As to why caregivers considered certain symptoms more challenging than others, thematic analysis of responses identified that impactful symptoms were associated by caregivers with loss of autonomy (89%, $n=289$), difficulty communicating physical needs (84%, $n=271$), and physical and mental impact on the patient (81%, $n=263$) (Fig. 3b; see Fig. S3 for stratification by country). Additionally, caregivers noted the impact of RTT symptoms on themselves (73%, $n=237$) and other family members (33%, $n=105$), as well as stress and strain on the family overall (52%, $n=167$).

Meaningful Improvements in Symptoms of Rett Syndrome

Caregivers offered free-form responses that together elucidated key themes in what would be considered meaningful improvements in their patients' lived-in experiences that would make a hypothetical gene therapy worthwhile. Selected open-ended responses collated on communication, hand use, gross motor function, seizures, and GI complications are highlighted in Table 2.

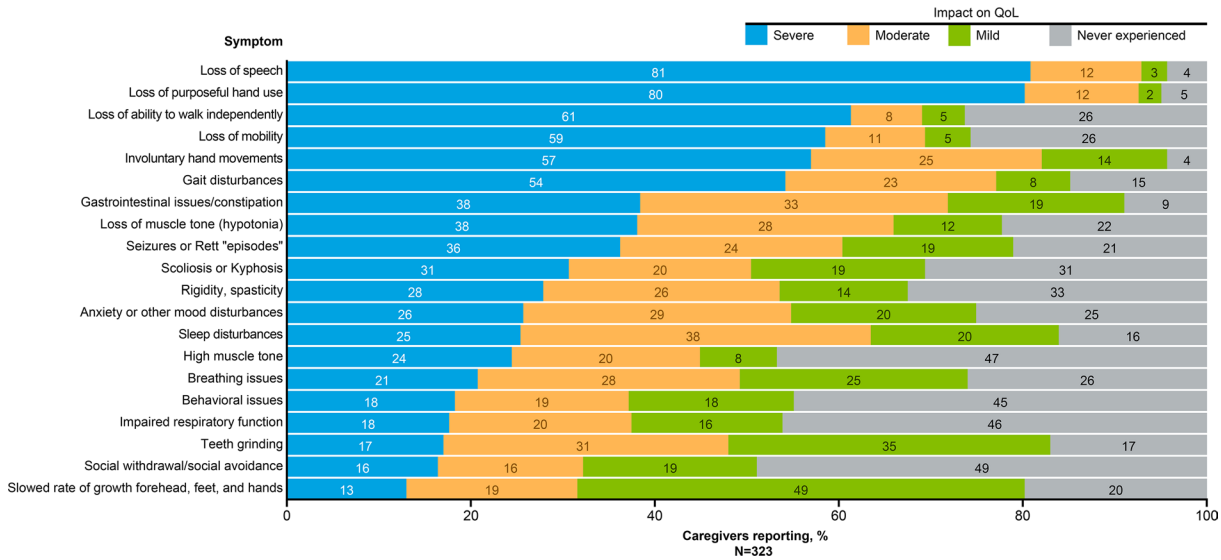

Fig. 2 Impact of symptom severity on patients' QoL, as reported by caregivers. Question: How much have the following symptoms impacted your loved one's QoL? Answer format—choose one category: Severe impact on QoL, moderate impact on QoL, mild impact on QoL, never experienced. QoL, quality of life

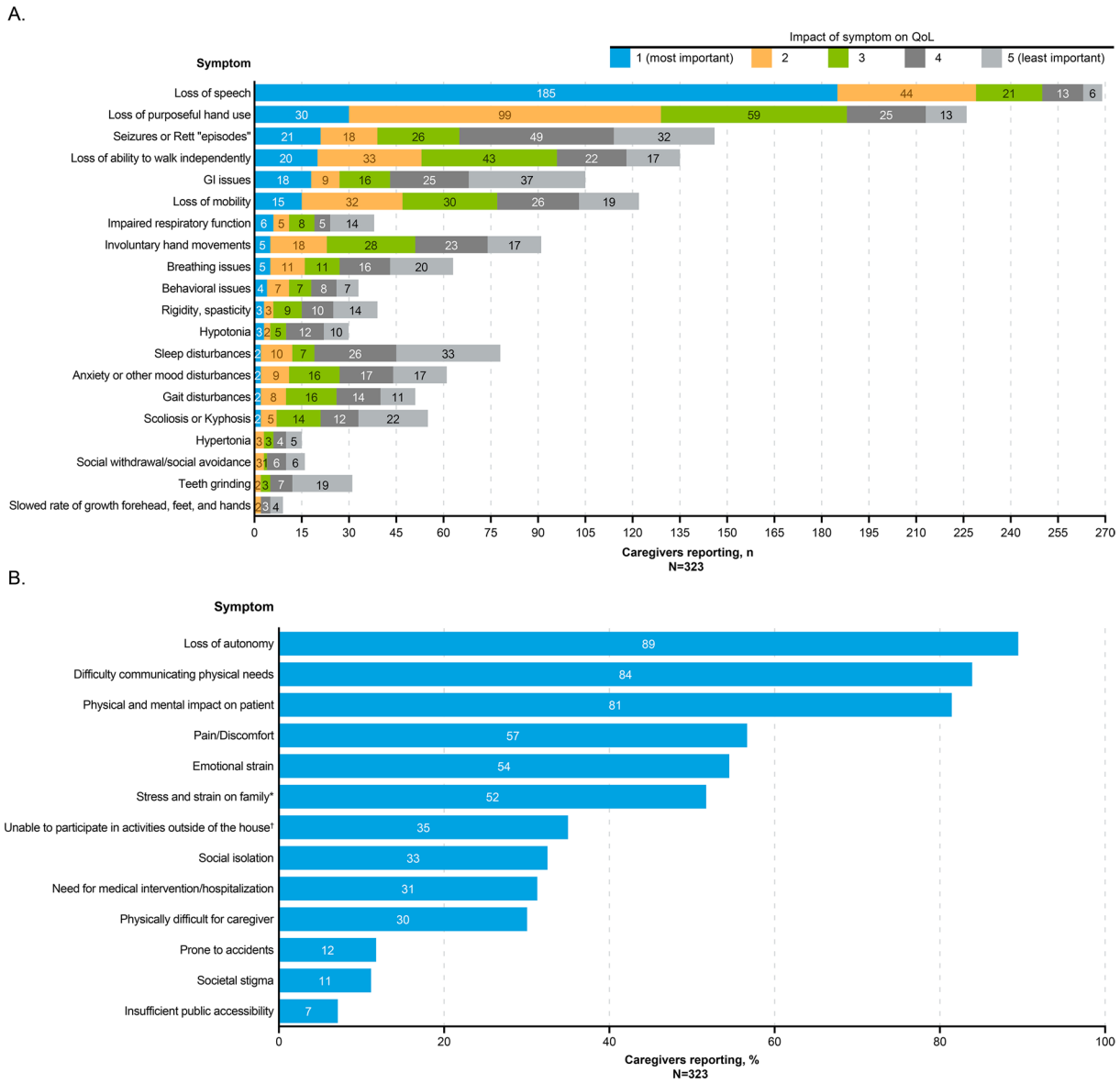

Fig. 3 Symptoms that caregivers consider the most impactful on patients' QoL. **a** Symptoms ranked by impact of QoL. **b** Thematic analysis of rationale as to why "Top 5" symptoms were considered to be the most challenging. Question: **a** Which symptoms of Rett have the greatest impact on your loved one's QoL? Answer format—please select and rank the top 5 most challenging symptoms, with 1 being the most impactful. **b** For each of the five symptoms you've selected above, please tell us why you've ranked them this way. Explain how each impacts the QoL for you, your family, and your loved one. Answer format—open ended. *Including financial strain, family dynamics, logistics of care, etc. †Including education, recreation, etc. GI, gastrointestinal; QoL, quality of life; yrs, years

Communication

Of the 323 caregivers who participated in the survey, 98.8% ($n=319$) reported that patients' inability to communicate was among the most challenging symptoms of RTT. As they rely on patients' subtle eye movements, facial expressions, and vocalizations, caregivers are not always confident that they can understand and respond to the needs (e.g., pain alleviation,

Table 2 Selected open-ended responses given by caregivers of patients with Rett syndrome

Topic	Country	Patient age (years)	Caregiver testimonial
Communication	Israel	0–6	"She used to say some words quite easily. Like Dad, and bath, and tomato. She lost these words."
	Canada	≥ 18	"Inability to verbally express her needs and wants and communicate thoughts and feelings (this refers to loss of speech and poor language skills) is the hardest to handle… impacts her social interactions, ability to make friends, and sustain relationships."
Hand use	USA	0–6	"She is not able to protect herself/catch herself if she falls, feed herself, or use her hands to explore the world/toys. These are all critical to development and activities of daily living."
	USA	7–12	"If she had purposeful use of hands, she would be more independent in various daily living tasks. She could feed herself, dress herself, use a walker, use an electric wheelchair, use a touch screen device to communicate."
Ambulation/mobility	UK	0–6	"My daughter loves to walk around. She was always unsteady and had falls but was able to manage on a flat surface. She has completely lost the ability to walk on her own now and this frustrates her more now."
	USA	≥ 18	"Since she doesn't walk, we have to carry and move her. As we get older and older, that will get harder and harder. If she could walk some steps and/or stand that would be much easier."
Seizures	UK	0–6	"Episodes/seizures are now more frequent throughout the day and becoming longer and more 'jerky.' Her body then goes limp which can be dangerous depending how securely she is sitting."
	USA	≥ 18	"Seizures have taken away normalcy as well as the health effects they have on the body. It makes it more difficult to find caregivers [and] many [day] programs are less willing to allow her to fully participate."
Gastrointestinal	Canada	7–12	"Her GI issues cause her so much pain and discomfort. She does not struggle with constipation but [air swallowing]."
	USA	≥ 18	"Tummy aches happen daily regardless of diet and we've tried many. It's very frustrating to see your child in such distress and be able to do nothing to stop it."

Quotes from caregivers may have been shortened for clarity and revised to correct typographical errors

GI gastrointestinal

hunger, thirst, or toileting) and desires of the patient. Over half of respondents (53%) indicated that communication devices are used in some capacity.

Regarding improvements in verbal or nonverbal communication that would be most meaningful, caregivers cited the patients' ability to express their needs (73%, $n = 232$),

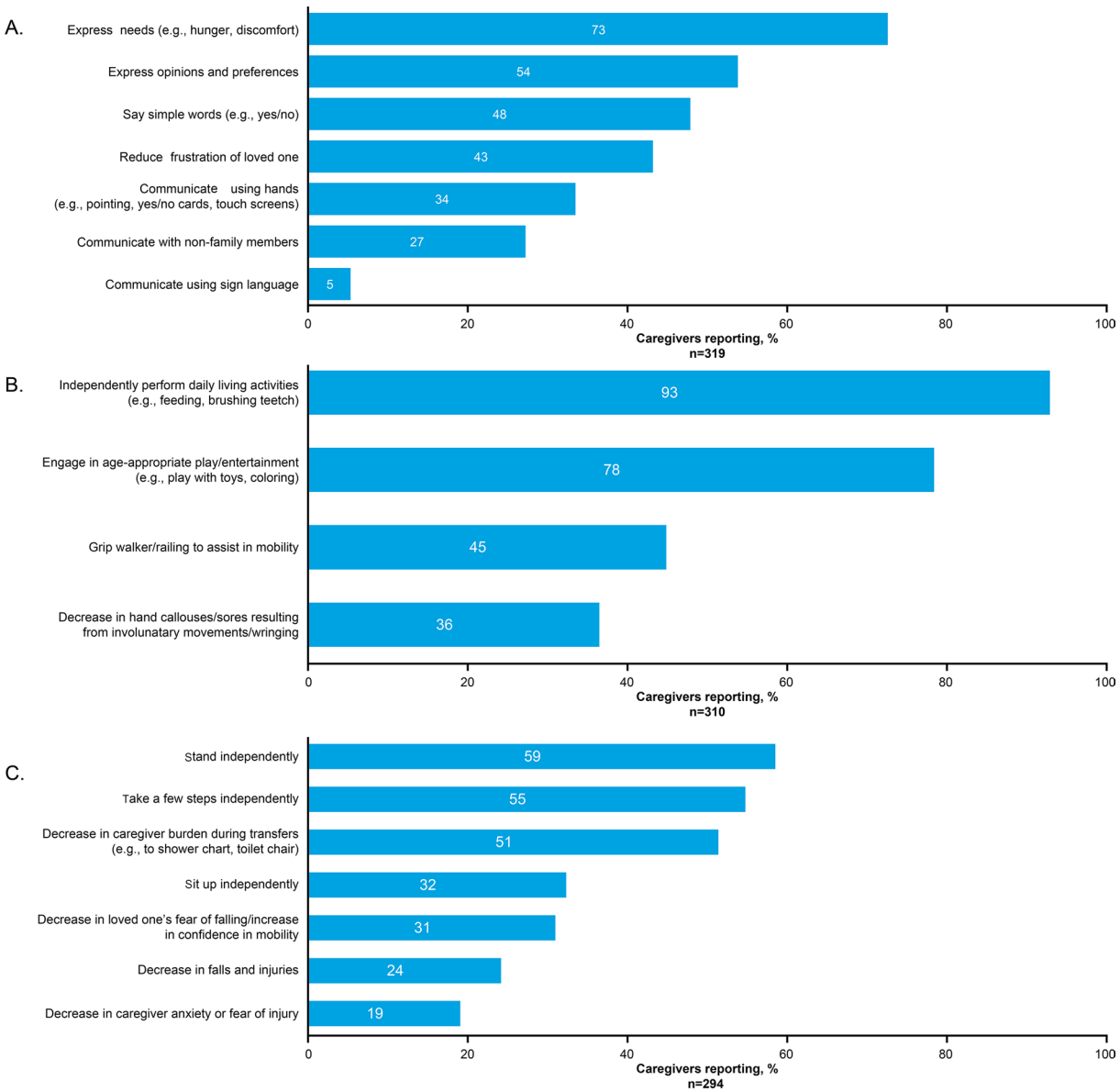

Fig. 4 Most desired improvements reported by caregivers of patients with Rett syndrome who experience: **a** Communication issues; **b** Hand-use issues; **c** Mobility issues. Question: When it comes to [communication/hand-use/mobility] issues, which of the following are most important? Answer format—respondents could select ≤ 3 improvements for each category

followed by the ability to express opinions and preferences (54%, $n = 172$), say simple words (48%, $n = 153$), and reduce frustration of loved one (43%, $n = 138$) (Fig. 4a).

Fine Motor Function (Purposeful Hand Use and Involuntary Movement)

Loss of hand function significantly limits

autonomy in RTT, affecting the ability to perform basic activities of daily living and reducing opportunities for independent engagement [27]. Caregivers emphasized that improvements in hand function would be a meaningful therapeutic outcome, with 34% ($n = 107$) specifically identifying enhanced hand use as an important benefit. Caregivers ($n = 310$) described specific hand-use challenges that restrict daily functioning and improvements that would be particularly meaningful included greater ability to perform self-care tasks such as eating and grooming (93%, $n = 288$), participate in play or other engaging activities (78%, $n = 243$), and support mobility or transfers (45%, $n = 139$; Fig. 4b).

Gross Motor Function

Caregivers reported wide variability in patients' current level of mobility, leading to distinct concerns for ambulatory versus non-ambulatory individuals (Fig. 1). For those who were ambulatory (33%, $n = 106/323$), gait and balance difficulties raised fears of falls and injury. Caregivers—particularly those of older age—also noted that limited mobility created increasing physical challenges for transfers and toileting as patients grew larger and heavier. As such, most caregivers (51%, $n = 151/294$) indicated that improved mobility (e.g., ability to help with transfers) would meaningfully decrease caregivers' physical burden. A similar number identified the ability to stand independently (59%, $n = 172/294$) or take a few steps independently (55%, $n = 161/294$) as the most desired improvements (Fig. 4c).

Disease Management

Participants described the multidisciplinary care required to manage RTT, with the patient's care team expanding as the patient grows older and their needs become more complex. Approaches to symptom management varied with patient age and across the countries represented (Table S3). Physical therapy was common, with ≥ 72% of caregivers in each country reporting its use in patients under 18 years of age. Speech/language therapy and occupational therapy were also widely used, especially among patients under 18 years of age. Among medications, antiseizure drugs were also common, with ≥ 57% of adult patients requiring their use. Scoliosis surgery and feeding tube use were notably more common in USA patients than in other countries, especially among adult patients. Across countries, most supportive therapies appear to be used less commonly for adult patients, perhaps reflecting decreased access.

Expectations for Gene Therapy and Clinical Trials

Caregivers generally expressed interest in participating in a potential GT clinical trial for RTT, with 290/311 (93%) of participants stating they were interested or may be interested (Fig. 5). Among caregivers answering "Yes", 112/194 (58%) indicated that they sought to improve patient QoL. There was a general correlation between higher interest and younger age; interest was highest among caregivers of younger patients, with 31/44 (70%) of caregivers of patients ≤ 4 years of age and 63/82 (77%) of those 5–11 years of age answering "Yes". Still,

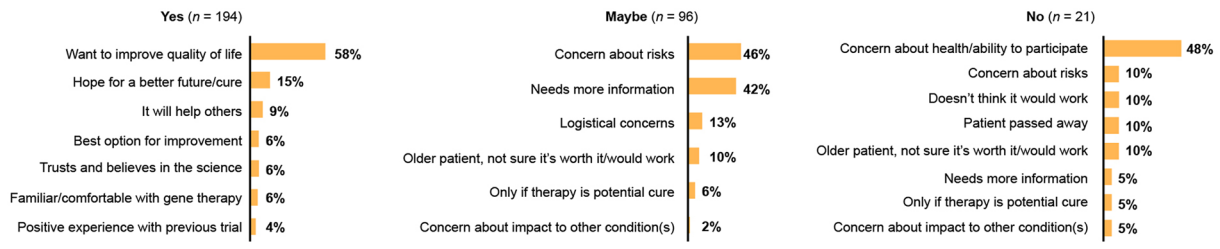

Fig. 5 Reasons cited for level of caregiver interest in a potential gene therapy clinical trial for Rett syndrome. $N = 311$

there is a high level of overall interest in GT trials among caregivers of patients ≥18 years of age. Most (135/142; 95%) were interested in participating or learning more about participating in a clinical trial, and only 5% ($n=7$) would be unwilling to participate at all. The caregiver of a child aged 13–17 years from the UK stated: "Yes. GT seems to represent the best possible hope for a significant change in her condition" (Table S4).

Some differences in priorities emerged between respondents answering "Yes" (62%, $n=194/311$) versus "Maybe" (31%, $n=96/311$). Those answering "Maybe" were driven by concerns about risks (46%, 44/96) and a general need for more information (42%, $n=40/96$). Caregivers not willing to participate in GT clinical trials expressed concerns about the patients' age (being too old) or overall health status, as they were perceived to be too fragile for treatment (Table S4). For example, the caregiver of a female aged ≥ 18 years, from the USA stated: "No—my daughter already has so many comorbid health conditions, this would not be feasible" (Table S4).

DISCUSSION

Clinical presentation in RTT is highly individualized, with varying severity of physical, mental, and behavioral symptoms. This variability, plus the absence of surrogate biomarkers, greatly complicates assessment of disease improvement on a unitary scale [4, 28]. In practice, clinicians focus on symptoms that can be quantitatively measured, such as seizures, autonomic dysfunction, and orthopedic needs. The challenge of assessing the condition of patients with RTT takes on greater importance given the prospect of novel therapeutics, such as GT [20, 28]. To ensure that trials report outcomes that are clinically meaningful, developers should attend to the lived experience and priorities of RTT caregivers [23, 28].

This study explored caregivers' perspectives on the daily burdens of RTT, what improvements would be considered meaningful, and their attitudes toward trial participation.

Despite the heterogeneous nature of RTT symptoms, caregivers across regions and age groups consistently identified loss of fine motor skills, including purposeful hand use, and loss of verbal communication, followed by loss of mobility, as having the greatest impact on QoL. These symptoms were generally reported to begin before 6 years of age.

The survey reported here was designed to interrogate meaningful improvement in the hallmark RTT symptoms (i.e., communication, fine motor function, gross motor function). In other studies, caregivers have highlighted the high burden associated with seizures [1]. In our population, 80% of caregivers ($n=260$) reported that their loved ones experience seizures, and seizures were identified as third among the "Top 5" most challenging symptoms. The fact that a smaller number of respondents ($n=116$; 36%) identified seizures as having a severe effect on QoL may reflect the effectiveness of anti-seizure medication; for individuals experiencing satisfactory seizure control, the burden of seizures may be lessened.

These findings are generally aligned with previous studies that identified caregivers' greatest concerns as communication difficulties, seizures, lack of hand use, difficulties associated with walking, and difficulties with verbal self-expression and self-care among the most prevalent problems for patients with RTT [1, 7]. The current analysis also underlines the dynamic nature of RTT, in which symptoms arise de novo over time and/or become newly problematic, requiring caregivers to remain flexible in their patterns of care. This feature of the disease may represent an important burden for caregivers and may help developers address the most crucial symptoms for patients and their caregivers.

Access to various forms of RTT care clearly differs across the countries represented, likely reflecting different levels of support for patients with RTT in some of the countries, rather than distinct clinical needs in the different jurisdictions; for instance, scoliosis surgery is likely less commonly performed outside the USA. In all four countries, it appears that previously common supportive therapies (e.g., physical therapy and occupational therapy) are used less often in adults than patients under 18 (Table S3). This

pattern may be ascribed to a drop-off in available services as patients age and perhaps are no longer of school age; further investigation is warranted.

Caregivers in the current study identified treatment responses that might correspond to meaningful functional improvement. These included enhanced communication abilities, even to the extent of expressing simple responses such as "yes" or "no", as well as increased hand function to facilitate activities such as self-feeding. Regarding mobility, the capacity to stand or take a few independent steps would not only enhance patient autonomy but also alleviate physical demands on caregivers. Interestingly, on the basis of semi-structured interviews and thematic analysis with 40 RTT caregivers, McGraw et al. [29] came to broadly similar conclusions regarding improved communication and motor function as potentially meaningful benefits that would affect patients' social, psychological, and physical well-being.

Meaningful responses will necessarily vary depending on each individual's disease severity and challenging symptoms; they may also shift with disease progression in a given patient. Nevertheless, our thematic analysis identified three common features of RTT that appear to account for many of the potential treatment responses that caregivers found meaningful. Namely, meaningful improvements seem to be those that enhance patient autonomy, allow for communication of needs and preferences, and reduce physical and mental impacts of RTT.

Finally, the survey results demonstrated that while there is generally enthusiasm among caregivers for taking part in RTT GT clinical trials, there is also a need for useful and understandable education. Ensuring that caregivers are well informed about GT clinical trials must be a priority for all stakeholders—from industry to advocacy—in the RTT community.

Limitations and Strengths

This study was fielded prior to the commercial approval of trofinetide in the USA and Canada, so the impact of this new treatment option was not assessed.

Geographic limitations include that recruitment in the USA was focused on patients ≥ 18 years of age and recruitment in Canada was mostly focused on patients from Ontario, a small cohort that may not represent the full patient population and the experience in other Canadian provinces. The survey was translated into Hebrew and French; no back-translation was performed.

Additionally, as findings were based on caregiver recollection, neither the patients' clinical diagnoses (e.g., typical versus atypical RTT; presence or absence of a confirmed *MECP2* mutation; formal RTT diagnosis) nor their treatment histories were validated by clinical records. Background information was not captured regarding social determinants of health, including economic considerations and access to specialized care. These may have a geographic component that was not evaluated (e.g., heterogeneity of access to care and services within or among the various countries represented).

Other limitations may include the wording of some questions as survey questions focused on the loss and gain of milestones but did not assess if a milestone had never been reached, for example if a patient had never acquired speech. Although this may be considered a gap in the assessment of patient experience, as it would not have been possible for a patient to have lost a skill they had never acquired, loss and gain are considered appropriate measures of a patient's experience. A recent publication described the trajectory of skill acquisition, loss and regain in females with RTT and concluded that both loss and gain can be clearly tracked in trajectories [8].

Notably, the findings described here were designed as market research in the development of a clinical trial assessing the GT TSHA-102, now being investigated in the REVEAL studies (NCT05606614 [30], NCT06152237 [31]). The nature of market research may have introduced subtle biases in the participant population. For instance, participants engaged with advocacy groups might have greater knowledge of GT, and potentially higher interest in it, relative to other caregivers. Furthermore, response relied on caregivers engaging with email and/or social media (RSRT) which may have introduced bias;

response rates are not available as there was no data to confirm whether an email was opened, or for how many people viewed the Facebook page.

Conversely, strengths of the present study include its multipart approach and inclusion of thematic analysis of open-ended responses to survey questions, enabling in-depth evaluation of caregiver perspectives and experiences. Furthermore, despite the rarity of RTT, a large sample size of 323 caregivers with individuals from the USA, UK, Canada, and Israel participated in this survey. The large sample size enabled age stratification, and although granularity of data may have been useful in those < 6 years of age, the data were intentionally analyzed to align with the developmental plateau at ≥ 6 years of age, where most skill gain, loss, and regain in RTT has stabilized [8]. Beyond 6 years of age, data focused on patients aged 7–12 years to enable an understanding of patient experiences in the early development plateau, while stratification at 13–18 years of age allows a focus on adolescence during which a change in symptoms may be observed, such as scoliosis [32], worsening motor skills [33], and an increase in sedentary behavior [34]. Finally, stratification of adult patients > 18 years of age is important to characterize the experience of adults with RTT, which is frequently overlooked in RTT studies.

CONCLUSIONS

RTT is a progressive and highly heterogeneous disease that requires caregivers to manage a diverse and changing array of challenges. Despite this variability, caregivers in this study consistently judged improvements to be meaningful if they enhanced patient autonomy, allowed for communication of needs and preferences, or reduced caregiving demands. Caregivers also expressed interest in GT trial participation, generally motivated by the hope of improved QoL. Ongoing research seeks to further investigate caregiver perspectives on meaningful improvements in RTT, especially concerning the achievement or recovery of developmental milestones in communication and in fine and gross motor skills.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available as the research participants consented that their responses would only be used in communicating the research findings to Taysha Gene Therapies, Inc. and Avalere Health.

Declarations

Conflict of Interest. Bruria Ben-Zeev reports no conflicting interests. Elsa Rossignol is a paid consultant for Acadia Pharmaceuticals and Taysha Gene Therapies, Inc. and is an investigator for the ongoing REVEAL gene therapy trials by Taysha Gene Therapies, Inc. Daniel E. Lumsden is a paid consultant to Neurogene and has received unrestricted educational grants from Medtronic to support attendance at scientific meetings. Deborah A. Bilder is a paid consultant for Taysha Gene Therapies, Inc. Chelsea Karbocus, Emily McGinnis, and Kristin LaBounty Phillips are employees and shareholders of Taysha Gene Therapies, Inc., which is developing an investigational gene therapy for Rett syndrome and sponsored the research presented in this publication. Natalie Guido-Estrada, Monica Coenraads, Sigal Hertz Tirosh, Paige Nues, Sabrina Millson, Rachael Stevenson, and John Ashkenas report no conflicts of interest.

Ethical Approval. Ethics committee approval was not required for this study, as it was determined to be minimal risk to participants. Nonetheless, strict ethical procedures were followed in accordance with the Declaration of Helsinki 1964 and its later amendments. Participation was entirely voluntary and privacy protections included anonymous data collection (i.e., no personally identifiable information was collected) and secure, access-restricted data storage consistent with relevant data protection regulations (e.g., General Data Protection Regulation and applicable USA privacy standards). The survey was conducted according to the ethical principles for market research as outlined by the American Marketing Association. Data were anonymized by third-party vendors. Caregivers were presented with a brief study overview that included the research objectives and the name of the study sponsor prior to participation. Consent to participate was implied by the caregivers' initiation of the online survey by clicking "Agree to continue." As the survey was conducted anonymously, separate consent for publication of individual data was not obtained. Results are reported only in aggregate form, and no information that could reasonably identify participants is included in the manuscript. Up to a pre-established quota (total n=112), participants in the USA, Canada, and the UK received $25 compensation; all subsequent participants chose to proceed without compensation. Due to regional legislation, compensation was not available to Israeli participants; in lieu of compensation, a comparable donation was made toward the IRSA.

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