rett syndrome research trust

International Rett Syndrome Foundation

VOICE OF THE PATIENT REPORT

Rett Syndrome Externally-Led Patient-Focused Drug Development Meeting

Meeting Date: March 11, 2022

Meeting hosted by: The International Rett Syndrome Foundation (IRSF) and the Rett Syndrome Research Trust (RSRT)

Submitted to: The U.S. Food and Drug Administration (FDA)

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VOICE OF THE PATIENT REPORT: *LIVING WITH RETT SYNDROME*

This Voice of the Patient report was prepared by the International Rett Syndrome Foundation (IRSF) and the Rett Syndrome Research Trust (RSRT) as a summary of the input shared by people and families living with Rett syndrome during an Externally-Led Patient Focused Drug Development Meeting (EL-PFDD). This meeting was hosted virtually on March 11, 2022.

Authors and Collaborators: This report was prepared and submitted on behalf of the Rett Syndrome Research Trust (RSRT) and the International Rett Syndrome Foundation (IRSF) by: Monica Coenraads, CEO, RSRT; Jana Von Hehn, PhD, Chief Scientific Officer, RSRT; Tim Frank, Chief Marketing and Development Officer, IRSF; Melissa Kennedy, CEO, IRSF; Dominique C. Pichard, MD, Chief Science Officer, IRSF; Chrystal Palaty, PhD, medical writer.

Consulting Partners include James Valentine, Esq. and Larry Bauer, RN, MA, from Hyman, Phelps & McNamara, P.C.

RSRT and IRSF contracted with Chrystal Palaty, PhD., from Metaphase Health Research Consulting Inc. for assistance in writing this report.

Disclosures: IRSF is a tax-exempt, charitable organization and is eligible to receive tax- deductible contributions under the IRS Code 501(c)(3). IRSF receives funding from pharmaceutical companies in the form of unrestricted grants and sponsorship of programs and events.

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James Valentine, Esq. and Larry Bauer, RN, MA are employed by Hyman, Phelps & McNamara, P.C., a law firm that represents patient advocacy organizations and companies that are developing therapeutics and technologies to advance health.

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Report Version Date: August 9, 2022

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VOICE OF THE PATIENT REPORT: *LIVING WITH RETT SYNDROME*

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Acknowledgements:

This report is dedicated to those living with Rett syndrome, their caregivers, and their loved ones.

IRSF and RSRT sincerely thank the families and caregivers who attended the March 11, 2022 EL-PFDD meeting or contributed post-meeting comments and shared their personal insights and experiences of living with Rett syndrome in order to help us all better understand the disorder and its consequences. It is our hope that the positive impact of this meeting will be felt for years to come.

Thank you to the FDA for giving us permission to hold this meeting and to the FDA staff who attended or viewed the meeting. A special thanks to Will Lewallen from the FDA's patient-focused drug development program staff who guided us through the meeting development process.

Thank you to Dr. Wilson Bryan from the Center for Biologics Evaluation and Research at FDA for offering his perspectives on the patient-focused drug development meeting. Thank you to Dr. Eric Marsh, Associate Professor of Neurology in Pediatrics at the Children's Hospital of Philadelphia in the University of Pennsylvania and Director of the Rett Syndrome Center of Excellence at the Children's Hospital of Philadelphia, for providing a comprehensive clinical overview of Rett syndrome.

Thank you to Dudley Digital Works media team. We thank James Valentine, Larry Bauer, and the other planning committee members, including staff from IRSF and RSRT, who worked hard to organize this meeting.

Thank you to our supporters, especially our gold sponsor, Shape Therapeutics, our silver sponsors, Acadia Pharmaceuticals, Anavex Life Sciences, Novartis Gene Therapies, Taysha Gene Therapies, and Vyant Bio, and our bronze sponsors, Alcyone Therapeutics, DepYmed, Herophilus, and Neuren Pharmaceuticals.

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EXECUTIVE SUMMARY AND KEY MEETING INSIGHTS

The International Rett Syndrome Foundation (IRSF) and the Rett Syndrome Research Trust (RSRT) co-hosted a virtual Rett Syndrome Externally-Led PFDD (EL-PFDD) meeting on March 11, 2022. This meeting was held to provide patient and caregiver perspectives of the symptoms and burdens associated with Rett syndrome in daily life, as well as the massive unmet treatment needs experienced by patients.

This EL-PFDD meeting was modeled after the work of the FDA's Patient-Focused Drug Development (PFDD) initiative aimed to more systematically gather patient perspectives on their condition and on available treatments. The Voice of the Patient report represents a high-level summary of the perspectives generously shared by the families and caregivers of individuals living with Rett syndrome during the EL-PFDD meeting. The report also includes selected quotes from an abundance of comments that were submitted through an online portal during the EL-PFDD meeting and for thirty days after the event.

It is the hope of RSRT and IRSF that the Voice of the Patient report will be used to guide therapeutic development and inform the FDA's benefit-risk evaluations when assessing therapies to address Rett syndrome. One goal of this report is to aid therapeutic developers to catalyze better treatments and ultimately a cure for those living with Rett syndrome.

IRSF and the RSRT have provided this report to the FDA on behalf of the Rett syndrome community, and it is publicly available for the many stakeholders in the Rett syndrome community including other federal agencies, clinicians, advocacy and professional organizations, biopharmaceutical companies, and universities from across the world. The input received from the March 11, 2022, EL-PFDD meeting reflects a wide range of Rett syndrome experiences, however not all symptoms and impacts may be captured in this report.

This report is a reflection of what was shared by patients and caregivers at the meeting and is no way an endorsement for any specific treatment modality. Both sponsor organizations endorse treatment planning for people living with Rett syndrome to occur in conjunction with their treating medical team.

The final report, the meeting transcript, a document containing the comments submitted through an online portal, and a recording of the meeting can be found at: https://rettpfdd.org. According to YouTube statistics, the meeting has been streamed over 2052 times as of August 9, 2022.

Key meeting themes and insights:

1. **Rett syndrome is characterized by a long and diverse list of symptoms and most families deal with eight or more symptoms at any one time.** Although symptoms manifest differently in each individual, the inability to communicate is the top area of concern. Rett syndrome symptoms are interrelated or contribute to one another, and are constantly changing, forcing individuals and their families to adapt. Individuals living with Rett syndrome experience dramatic regressions and unexpected setbacks throughout their lives.

2. **Individuals living with Rett syndrome are cognitively aware yet are unable to effectively act on their desire to communicate or participate in conversations, and are often misunderstood.** Many go through great efforts to communicate with their caregivers. Many caregivers reported that their loved ones are aware of their limitations and often seemed sad.

3. **Rett syndrome interferes with virtually all activities of daily life, including one's ability to feed, toilet and care for themselves.** As a result, individuals with Rett syndrome need help with every aspect of daily life, and require 24/7 care throughout their entire lives. Caregivers worry about their loved one's future care when they are no longer able to be the primary care providers, they worry about how disease progression will affect their loved one, and they worry about premature immortality or sudden death.

4. **A cure for Rett syndrome and treatments to specifically address Rett syndrome are urgently needed and not currently available.** There are no FDA approved or disease-modifying medications or treatments for individuals living with Rett syndrome. Each individual living with Rett syndrome requires many different types of medication, many different therapies, and many types of supports and equipment to address each of their symptoms, yet these only help somewhat or very little. Caregivers are desperate for new therapies and are willing to try anything to lessen the suffering for their loved ones, including investigational medications, off-label drugs and any other approaches that could support improvement.

5. **The burden of both Rett syndrome and the therapies required to address symptoms is tremendous, not only for individuals living with Rett syndrome, but on their caregivers and families.** Therapies are absolutely essential for maintaining skills, and without constant effort in each area, individuals living with Rett syndrome will regress. Taking their loved ones to appointments with various specialists, maintaining therapies, and providing daily care requires much effort and is very time-consuming and exhausting for caregivers and families.

6. **Functional improvements in communication/speech and hand use are the aspects of Rett syndrome ranked as most important for a possible new therapeutic.** Caregivers emphasized that even minor functional improvements -- saying a few words, the ability to grasp or touch an object, initiation of movement -- will contribute to greater autonomy and massively improve the quality of life for people with Rett syndrome.

7. **Additional areas of unmet therapeutic need** include clinical trials and therapies for males, therapies that result in functional improvements, and more meaningful endpoints for clinical trials.

INTRODUCTION AND MEETING OVERVIEW

Clinical overview of Rett Syndrome[1]

Rett syndrome is a serious neurodevelopmental disorder first described in 1966 by Andreas Rett. Clinical features were described in 1983 by Dr. Bengt Hagberg and subsequently clinical diagnostic criteria were developed and later updated in 2010 by Dr. Jeff Neul and colleagues. In 1999, variants in the *MECP2* gene were identified as the genetic origin of Rett syndrome, and mutations in *MECP2* are found in greater than 95% of cases. The *MECP2* gene encodes methyl-CpG binding protein 2, an abundant DNA binding protein that modulates expression of many genes.

Rett syndrome, the most common genetic cause of severe disability in females, occurs with an incidence of one in 10,000-15,000 live female births and less commonly in males. Different *MECP2* gene variations are associated with different levels of disease severity. Expanded genetic testing has led to the discovery of *MECP2* variants in males with Rett syndrome and in females who do not exhibit the classic Rett syndrome presentation.

Though the gene responsible for Rett syndrome has been identified, Rett syndrome is a clinical diagnosis. In addition to the presence of regression, the four major criteria are (1) partial or complete loss of acquired purposeful hand movement; (2) partial or complete loss of acquired spoken language; (3) gait abnormalities which range from dyspraxic gait to an absence of ability; and (4) development of stereotypic hand movement.[2] Exclusion criteria include brain injury, such as trauma or hypoxic ischemic encephalopathy, or grossly abnormal psychomotor development in the first six months of life. Rett syndrome also includes eleven supportive criteria, most of which are described in the paragraphs below.

In classic or typical Rett syndrome, individuals experience normal post-natal development followed by a period of developmental delay between six and 18 months of age. Between the ages of one and four years, individuals demonstrate a clear regression in speech and purposeful hand movements, begin to have mobility challenges, and display stereotypic hand movements. Individuals then experience a stationary or plateau phase, often with recovery or stabilization of cognitive and nonverbal communication skills. A proportion of individuals living with Rett syndrome will experience a secondary loss of motor skills in their early teens, including rigidity or spasticity, often with some Parkinsonian features.

Rett syndrome is characterized by neurological issues, developmental issues, severe disability, low tone, gait abnormalities, lack of hand use, and an absence of fine motor skills. Individuals living with Rett syndrome often develop movement disorders, including dystonia, or hyperkinetic movements. Between 80% to 90% of individuals living with Rett syndrome experience epilepsy, and behavioral issues can emerge as well.

Other prevalent symptoms include GI issues, including bowel dysmotility, constipation, and reflux. Feeding issues are common often requiring a feeding tube. Many individuals experience failure to thrive. Individuals often experience dysautonomia, including cold hands and feet, disordered breathing, and prolonged QT syndrome. Almost all individuals with Rett syndrome develop scoliosis with many having to undergo surgery. Other musculoskeletal issues may also arise including hip issues and contractures. Lung issues often occurring from aspiration and frequent pneumonias may occur.

[1]This information was provided by Dr. Eric Marsh. MD, PhD, during his presentation on March 11, 2022. Dr March is an Associate Professor of Neurology in Pediatrics at the Children's Hospital of Philadelphia in the University of Pennsylvania and Director of the Rett syndrome Center of Excellence at the Children's Hospital of Philadelphia.

[2]Neul JL, Kaufmann WE, Glaze DG, et al: Rett syndrome: Revised diagnostic criteria and nomenclature. Annals of Neurology 68:944-950, 2010

There are no FDA approved specific Rett syndrome treatments, although many FDA approved drugs are used to try to manage individual symptoms due to Rett syndrome. The long list of medications and therapies required for individuals living with Rett syndrome are described more fully in this report. Primary care guidelines are published to screen for the many medical issues that arise.[3]

Rett syndrome is not considered a fatal condition. However, complications from a variety of symptoms, most commonly seizures, autonomic dysfunction, pneumonia, and GI issues, often lead to premature death.

MEETING SUMMARY

Introduction & Format

The Rett Syndrome Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting was held virtually on March 11, 2022. Online polling, live discussion with panelists and callers, as well as discussion of comments written in and for up to 30 days after the meeting provided the content summarized in this report.

Meeting Co-Sponsors	Rett Syndrome Research Trust & International Rett Syndrome Foundation	
Meeting Moderator	James Valentine, JD, MHS	Hyman, Phelps & McNamara
Meeting co-moderator	Dominique Pichard, MD	IRSF
Welcome	Monica Coenraads, MBA	RSRT
Opening Remarks	Wilson Bryan, MD	FDA
Clinical Overview	Eric Marsh, MD, PhD	Children's Hospital of Philadelphia

Attendance

Online polling recorded the demographics of the meeting attendees showing that approximately 86% were from the US, 94% represented females with Rett syndrome, 68% represented pediatric individuals, and 99% had a variant in the MECP2 gene. Full results are presented in **Appendix 1**.

The following table summarizes the meeting attendance:

Attendee	n
Individuals with Rett syndrome	100
Caregivers	303
Family members (siblings/grandparents)	50
Friends	79
FDA	24
Industry	97
Scientists	35
Healthcare providers	19
Non-profit	25
Other (investors, educators, others)	23
Total	**755**

[3]Fu C, Armstrong D, Marsh E, Lieberman D, Motil K, Witt R, et al. Consensus guidelines on managing Rett syndrome across the lifespan. BMJ Paediatrics Open. 2020;4(1):e000717. DOI: 10.1136/bmjpo-2020-000717

Meeting Session Summaries

The meeting agenda is in **Appendix 2**, and the questions provided for meeting discussion are in **Appendix 3**. The Rett Syndrome EL-PFDD meeting was organized into two sessions. The morning session was, *Rett Syndrome Patient Voices: Symptoms and Daily Impacts*, and the afternoon session was *Rett Syndrome Patient Voices: Current and Future Treatments*.

The morning session, focused on symptoms and daily impacts, continued with five pre-recorded caregivers who represented a range of experiences of living with and caring for an individual with Rett syndrome. James Valentine moderated a discussion between several people who served on a live Zoom panel as well as people who dialed in by phone. Caregivers shared stories about their children's regressions, the perplexing emergence of symptoms and challenges in obtaining a diagnosis. They described how hard their loved ones struggled, how much they suffered, and the incredible joy that their children sometimes expressed. Caregivers described the heartbreaking impacts that the disease has had on their loved ones living with Rett syndrome and their entire families. Several described how Rett syndrome had stolen their children from them. A selection of relevant comments entered through the online submission portal were read by Dr. Pichard. The names of all panelists and callers are listed in **Appendix 4**.

The afternoon session designated to focus on current and future treatments opened with a pre-recorded panel of five caregivers who described different medical therapies and other treatments they use to address Rett syndrome symptoms. Meeting attendees participated in online polling, and called in and submitted written comments. Their voices were added to the moderated discussion by James Valentine and Dr. Pichard. Caregivers described the extensive medications, therapies, equipment, and hard work that was required for their loved ones to just retain their abilities. They described significant therapy setbacks imposed by COVID-19. They talked about how medications have offered very little relief to their loved ones, they described profound unmet needs, and the extreme lengths that they went to try to find solutions. Finally, caregivers shared their hopes for what new therapies could offer to their loved ones.

The online polling results from sessions 1 and 2 are included in **Appendices 5 and 6**, respectively.

Meeting Conclusion & Post-Meeting Participation

To conclude, Larry Bauer, RN, MA, provided a reflective summary of the key messages heard throughout the meeting and Dr. Pichard closed the meeting by thanking all the participants and attendees.

To include as many voices as possible, the online comment submission portal was open for four weeks after the meeting. Selected comments are included in the body of this report, and all submitted comments are included in an accompanying PDF, which is available at https://rettpfdd.org.

SESSION 1. RETT SYNDROME PATIENT VOICES: SYMPTOMS AND DAILY IMPACTS

Key Themes from Session 1

Key themes are the points that were emphasized throughout the meeting by many parents and caregivers. These are listed below in bold, and illustrated with just a few of the many, many quotes and comments provided. Unless otherwise indicated, all quotes and comments are from the caregivers and parents of individuals living with Rett syndrome.

Rett syndrome is a diverse disease which manifests with a different constellation of symptoms for each individual.

"Imagine losing your ability to speak. Imagine losing the ability to walk, to use your hands, and to eat or drink on your own. Imagine having uncontrollable seizures. Now, if you can, imagine having all of those things happen to you. That is the nightmare that my 7-year-old daughter lives with." ~ Stephanie, parent of a 7-year-old daughter living with Rett syndrome

"It's hard to pinpoint the top 1-3 concerns, as our child has about ten major issues that change in ranking based on the day, week, month, from pervasive gross and fine motor impairment, non-verbal, hypotonia, uncontrolled epilepsy, dysphagia, dystonia, osteopenia, sleep issues, underactive and withdrawn affect, sensory processing delays, incontinence ... and more." ~ Paige N., comment submitted online

SADIE

Rett syndrome symptoms are often interrelated or contribute to one another.

"Of all the symptoms of Rett Syndrome, I think that apraxia, by far, is the most challenging and frustrating for us all. It controls every part of her body, as apraxia is the inability to make and deliver correct movement instructions to the body. It results in difficulty with skilled movements even when a person has the ability and desire to do them. My daughter's body works. Her brain works. But something gets in the way of the message being sent from one to the other and she sometimes does the opposite." ~ Alexa D., comment submitted online

"Her mood, breathing, seizure activity, sleep disturbances and everything ultimately affect the way she communicates." ~ Mari B., comment submitted online

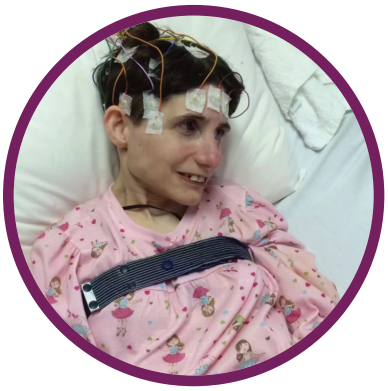
Rett syndrome symptoms are constantly changing, even from one day to the next.

"The symptoms are so all encompassing, and they are ever rotating... It's just one thing leads to the next, and then a symptom might pop out that's just suddenly completely debilitating or destabilizing in some way and requires complete reorganization of everything." ~ Sarah C., parent of a 14-year-old daughter with Rett syndrome

"I feel like some days, we really are focused on the GI issues and the reflux and that's the most important thing and other days, it's the wheelchair and the cramps she's getting in her legs." ~ Patty, parent of a 15-year-old daughter living with Rett syndrome

MAYA

Many caregivers described dramatic regressions and unexpected setbacks in their loved ones' abilities.


ANN

"[Our daughter] developed normally until 24 months doing what every child would do at that age, then Rett began to present itself. It was as if someone pulled the plug on everything. Over the next several months, she stopped playing with toys and sat with a blank stare on her face. It was as if she could no longer hear. We were very scared and didn't know what to do. What was wrong with our beautiful healthy daughter? Did we do something to cause this? … Within six months, uncontrollable hand ringing, continual biting of her fingers and severe hyper-ventilating began… Our path to seeking professional help began, yet no one could provide a definite diagnosis."
~ Jack, parent of a 52-year-old daughter living with Rett syndrome

"For the first 20 months of his life, he met all of his developmental milestones with the exception of speech. … But then he suffered a dramatic regression stage in which he was pulled inside himself, for lack of a better way to put it. After years of struggling to get an accurate diagnosis, we found out he had Rett syndrome at the age of six." ~ Kate, caregiver of a 14-year-old son living with Rett syndrome

"Her most trying time was around age two going through regression, when she would cry and scream endlessly, miserable, unable to be consoled, sleep, fighting to eat then spitting up everything, for months on end as we watched her lose all hand use, speech, and the little gross motor skills she had developed …. That was a nightmarish time for her and heartbreaking for us that fortunately slowly settled down by age 3-1/2 but then epilepsy and GI symptoms began, and we had new worries to confront." ~ Paige N, comment submitted online

"The most frustrating thing about Rett syndrome is that no matter how hard our daughter works, Rett seems to continuously cause setbacks. She worked so hard to crawl and now cannot. She seemed about to walk with a walker, but regression took that dream away." ~ Jillian M., comment submitted online

Individuals living with Rett syndrome are trapped inside their bodies without the ability to communicate and yet are often aware of how Rett syndrome limits them.

"Perhaps the hardest thing about Rett syndrome is that [our daughter] understands everything. She follows every conversation. She laughs at every joke. She also understands what she can't do, and she's devastated by her disabilities. We often see her crying when she's looking at other kids at the park or in the neighborhood who are playing because she can't join them." ~ Stephanie, parent of a 7-year-old daughter living with Rett syndrome


MAGNOLIA

"My daughter may not be able to play, walk, talk, but she's in there and she's aware of her disability. My heart breaks for her every second of the day that she can't do something as simple as hold a fork." ~ Shauna T., comment submitted online

"She works incredibly hard for simple things we take for granted each day. She perseveres but it leaves her exhausted. She is fully aware of her limitations and the implication it has on her life." ~ JT, comment submitted online

Individuals living with Rett syndrome have enormous care requirements each day and throughout their entire lives.


MAYA

"Rett affects all aspects of daily living for [our daughter]. She's unable to feed, toilet or dress herself. She needs constant supervision due to her epilepsy. Her sensory seeking needs make it dangerous for her to do a lot of activities. Sometimes she'll put things in her mouth or reach out for things that she just shouldn't touch." ~ Alex, parent of a 3- year-old daughter living with Rett syndrome

"She is unable to communicate and tells us what she needs or wants. She needs supervision 24/7 to allow her to be able to eat, drink, play, anything that she may need or want." ~ Amanda F., comment submitted online

The inability to communicate is the most frequently AND most concerning Rett Syndrome-related health concern.

Caregivers in attendance at the EL-PFDD meeting used online polling to first select all of the Rett syndrome-related manifestations that their loved ones experienced. They were then asked to select their top three most troublesome. The poll results are presented in **Appendix 5, Q1 & Q2** and described and with few exceptions, the results of Q1/Q2 were similar. Communication was the top ranked health concern in both polls, followed by impaired hand use or repetitive hand movements, gastrointestinal issues, mobility and balance issues, seizures, and breathing irregularities. Each health concern is described with patient quotes, below.

Communication/Speech impairment

Communication/speech impairment was the overwhelming first choice of caregivers. Communication/speech impairment is experienced by 96% of individuals living with Rett syndrome and was selected by 79% of caregivers as their most troublesome symptom.

"[Our daughter] can't speak. She does communicate somewhat through an alternative device. [We] invested huge effort in her being able to communicate, but it's only allowed her to communicate so much. Sometimes she cries because she cannot be understood, especially in more social situations. And so, communication has always been number one for us and for [our daughter]." ~ Dmitri, parent of a 12-year-old daughter living with Rett syndrome

"We are yet unable to see any obvious signs of repeatable and expressive language. We've come to terms with the fact she could not say mama or dada, which is heartbreaking, but hope she'll be able to in time by other means, tell us even the simplest things such as she's thirsty or tired. Despite at that, we can see that she loves us, and she loves being loved by us." ~ Sebastian, parent of a 3-year-old daughter living with Rett syndrome

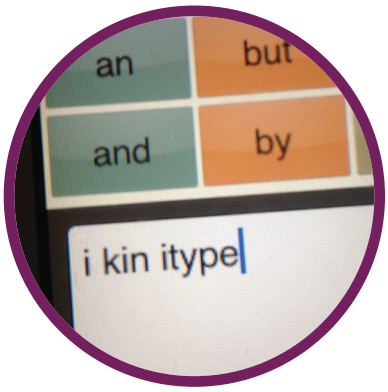
Challenges with communication can be related to speech impairment and also to limitations in hand or eye movements.

"Communication is number one and at the hub of the inability to do so many other things… That and hand use, I feel like if you had one or the other, then you'd be a whole lot better off because either they could do something for themselves or ask you to do it for them. When you don't have either, that's when the frustration starts." ~ Ben, parent of a 3-year-old daughter living with Rett syndrome

Despite their challenges, many individuals living with Rett syndrome find ways to communicate with their caregivers.

"On our best days, our daughter is mobile and able to communicate with us and others with gestures, pointing, eye-gaze, and sometimes even through verbal language. The days where she feels understood and heard are her happiest." ~ Lillian W., comment submitted online

"She'll communicate with us by directly looking at us, babbling 'words' to us, and reaching out to touch things, pushing things away, slapping at us to hurry, and laughing at the silly things we ask her." ~ Julie N., comment submitted online



The inability to communicate is often life-threatening.

"It's so frightening that she has no way to let us know when something is going terribly wrong with her body." David described his daughter's large Hodgkin's lymphoma tumor. *"We were totally unaware of it until it got so large (fist-sized) that it started to restrict the blood flow back to her heart (aka Superior Vena Cava Syndrome), causing her head and neck to swell and for the veins in her chest to bulge. She had probably been suffering for months (or years) and we had no way of knowing until she swelled up. She nearly died."* ~ David K., comment submitted online

After being misdiagnosed with a stomach virus, a massive infection from Tonya's daughter's gall bladder led to a massive heart attack. *"They said she would not survive. Thankfully she did and she is 20 now. But how different that outcome could have been had she been able to communicate that her stomach hurt, and where at, that her chest hurt, etc. More details from her could have helped them diagnosis her properly and treat her, versus just saying it's a stomach virus."* ~ Tonya H., comment submitted online

Impaired hand use or repetitive hand movements

Impaired hand use or repetitive hand movements is the second most frequently experienced symptom of Rett syndrome, selected by 84% of caregivers and one of the top three most troublesome by 34% of caregivers. Caregivers described activities such as clasping, wringing and finger flicking.

"The lack of hand use is the most significant of Rett on my daughter and our family. … That lack of hand use makes her completely dependent on others for all care. She cannot feed herself, operate a wheelchair, point to a want or a need, type or write, hold onto a walker, play with a toy, pull up a blanket if she's cold at night, turn the page of a book." ~ Lena C., comment submitted online

"My daughter has many repetitive hand movements that are outside of her control. These movements cause her discomfort and distraction, and she is much happier when her arms are braced. ...She also is still able to walk but her arm movements make her balance unsteady." ~ Kristy H., comment submitted online

Gastrointestinal issues (acid reflux, bloating, constipation, air swallowing)

Gastrointestinal issues were the third most frequent symptom, experienced by 80% of the individuals living with Rett syndrome represented. These were selected by 31% of caregivers as one of their top three most troublesome.

GI-related issues cause pain and discomfort for many individuals living with Rett syndrome

"GI issues plague [our daughter] on a daily basis, whether constipation, gassiness or reflux. [She] seems to be in discomfort for a good number of hours throughout the day." ~ Sebastian, parent of a 3-year-old daughter living with Rett syndrome

"Our daughter has chronic constipation and bad tummy aches daily, sometimes screaming in pain because she's so backed up and bloated. This of course hinders quality of life." ~ Alysson W., comment submitted online

"Severe trapped wind and gas can cause screaming episodes. Keeps her awake all night and affects my health too." ~ Juliet G., comment submitted online

MAYA

Lower GI issues can be severe enough to lead to death.

"She ended up with just horrible bowel constipation and obstructions ... and ended up spending six months, inpatient, in the hospital. And after that, ... cardiac arrest. We were successfully able to bring her back from that." ~ Wendy, parent of a 21-year-old daughter living with Rett syndrome

"Our child died in 2020 due to sepsis triggered by a bowel rupture. At that time, she was exclusively J-tube fed and already suffered repeated bowel obstructions." ~ Heather D[1]., comment submitted online

Mobility or balance difficulties (walking, crawling, weight bearing for transfers)

Mobility or balance difficulties were the fourth most frequently experienced symptom of Rett syndrome selected by 74% of caregivers. They were selected by 34% of caregivers as one of their top three most troublesome. Caregivers described how different Rett syndrome-related symptoms including apraxia, scoliosis or spine conditions, movement disturbances or muscle tone abnormalities can impair movement and balance. The lack of exercise and movement all contribute to a deterioration in health.

"The biggest disabling feature of Rett syndrome for [our daughter], is apraxia and motor planning. Because of her apraxia, [she] is unable to perform many motor functions and body movements. She is unable to talk. The impaired motor planning makes her unable to organize, plan and carry out a task." ~ Jennifer, parent of a 15-year-old daughter living with Rett syndrome

[1]This information was provided by Dr. Eric Marsh. MD, PhD, during his presentation on March 11, 2022. Dr March is an Associate Professor of Neurology in Pediatrics at the Children's Hospital of Philadelphia in the University of Pennsylvania and Director of the Rett syndrome Center of Excellence at the Children's Hospital of Philadelphia.

"He is a wheelchair user and his orthopedic impairments are getting worse as he ages. He is nine years old now and weighs 55lbs. He cannot bear weight anymore." ~ Joanne R., comment submitted online

"She is still able to walk with assistance and walk without assistance to some extent in our home, but we find that when we're transitioning between getting out of bed or after she's been sitting on the couch for a period of time, those transitions are really unstable. … She can't change her position without our assistance." ~ Sarah C. parent of a 14-year-old daughter living with Rett syndrome

BROOKE

Seizures

Seizures were selected by 36% of caregivers as the second most troublesome and the seventh most frequently experienced Rett syndrome symptom, selected by 63% of caregivers.

"At age seven, seizures began. Despite being on seizure meds, at one point, she experienced non-stop seizures for a day and was hospitalized. She recovered from that and has been on seizure meds since. [Our daughter] has suffered these seizures for nearly 50 years and they continue to this day, witnessing them and not knowing if she'll survive is excruciating. Managing her seizure meds to minimize frequency and duration has been a struggle, but nothing compared to what she endures." ~ Jack, parent of a 52-year-old daughter living with Rett syndrome

"Since August, [our daughter] has endured 57 seizures. Last week alone, [she] had 20 seizures. Her body is being pummeled by seizures and there's nothing that we can do. I can't tell you how many times we've ridden in an ambulance or sat in the emergency room, crying, begging her to hold on, to tough it out, and to be brave while swarms of doctors are coming into and out of the room to try to give her help and make the seizures stop." ~ Stephanie, parent of a 7-year-old daughter living with Rett syndrome

"She had as many as 10 seizures per day with breath holding and vomiting, often causing bacterial pneumonia and hospitalizations. … Now with two medications and the VNS, she may have only two or three seizures a day, usually shorter duration than before." ~ Leslie G., parent of a 43-year-old daughter living with Rett syndrome

HEATHER

Several parents described "Rett episodes", which can be detected on an EEG, but are still not well defined.

"There is a term in the community called Rett episodes, which seems to be a catchall term for poorly managed, non-seizure, neurologic movement episodes. This is the thing, for us at least, that we are least able to manage. Traditional seizures are under control, but these neurologic episodes have not been able to be addressed. Doctors, even Rett syndrome specialists don't seem to have any additional ideas for what to try to manage these episodes." ~ Brian W., comment submitted online

"When my daughter hyperventilate-like breathes, I know she is about to have a 'Rett spell'." *These are so strong that Carmen's daughter crumples to the ground.* ~ Carmen L., comment submitted online

Eating or swallowing difficulties

Eating or swallowing difficulties were the sixth most frequently experienced symptom of Rett syndrome, selected by 65% of caregivers. Eating or swallowing difficulties were selected by 18% of caregivers as one of their loved ones' top three most troublesome and included challenges such as vomiting, choking, and aspiration.

"Her low tone affects her swallow, so she has a feeding tube and can only safely have small tastes that must be suctioned back out. She often chokes on her saliva, bad enough to turn purple, which causes people to keep their distance. We have to always be nearby on alert because those coughs have caused her to aspirate, throw up and develop pneumonia in the past." ~ Brian, caregiver of a 14-year-old daughter living with Rett syndrome

GI issues impact nutrition and growth and can create other problems.

"[Our daughter] has a hard time mechanically eating her foods. One of us needs to be with her at all times to make sure she chews properly, monitor how much she's eating and to feed her. In turn, her behavior becomes more difficult and she is resistant to wanting to eat. Getting a variety of foods and enough food into her has been challenging." ~ Sebastian, parent to 3-year-old daughter living with Rett syndrome

"She does not have the great appetite she used to and lost almost 10 pounds in the last two years, in spite of the additional nutrition."
~ Leslie G., parent of a 43-year-old daughter living with Rett syndrome.

MADDEN

Eating and swallowing challenges combined with respiratory and GI issues have resulted in the installation of nasogastric (NG), gastric (G) or jejunostomy (J) tubes.

"The very natural, autonomic skill to nurse or drink a bottle was exhausting for him as an infant and became the initial reason for his first hospital stay of many due to failure to thrive. After an extensive stay in medical workup, [our son] came home with an NG tube to protect him from aspiration.
This was a symptom to a larger problem, but no expert could figure it out. [His] ability to have a relatively coordinated swallow did not improve. The risk of aspirational pneumonia became greater, which then led to a G-Tube." ~ Jenna, parent of a 7-year-old son who died from complications of Rett syndrome

"We have difficulties with feeding as she aspirates thin liquids. She received a G-tube at 21 years old and still has GI issues." ~ Sonya D., comment submitted online

Vomiting can be extreme for people living with Rett syndrome.

"There have been mornings where we've gone to get her and seen bile stains marking her bedsheets. One frightful morning in particular, we went in to find her in gray pallor and covered in coffee ground-like vomit." ~ Sebastian, parent of a 3-year-old daughter living with Rett syndrome

Stephanie described how g-tube related reflux causes extreme vomiting for her daughter. "Two weeks ago, [our daughter] vomited 16 times. There was nothing left in her stomach to come out. Her insides were completely raw and her throat burned and she gasped for breath. I thought she might die and by the look on her face, I think she did too. I will be haunted for the rest of my life by that panic look in her eye and tears streaming down her little cheeks." ~ Stephanie, parent of a 7-year-old daughter living with Rett syndrome

Sleep disturbances

Sleep disturbances were reported by 46% of caregivers and were selected by 13% of caregivers as one of their top three most troublesome Rett syndrome-related health concerns. All family members are impacted by sleep disturbances, and additional quotes are described in later sections of the report.

> *"My daughter has insomnia every night of her life despite many interventions. The daytime is a nightmare with all of the symptoms discussed. Nighttime, for many, is even worse."* ~ Stephanie B., comment submitted online

Emotional/behavioral problems

Emotional and behavioral problems are experienced by 45% of individuals living with Rett syndrome represented but were selected by 11% of caregivers as one of their top three most troublesome. Caregivers and parents described screaming, anxiety and separation issues, deep sadness, aggression and self harming experienced by those living with Rett syndrome.

> *"Screaming for hours at a time over decades has led to a severely limited social life for all", including siblings and parents.* ~ Melinda L., comment submitted online

> Stephanie described how her daughter living with Rett syndrome, *"Wakes up in the middle of the night screaming."* Her older sibling, *"Sometimes sleeps with a pillow over her head to drown out the sounds."* The older daughter often hears her sister screaming when they are not together. *"We've called these phantom screams."* ~ Stephanie, parent of a 7-year-old daughter living with Rett syndrome

Many individuals living with Rett syndrome experience sadness which intensifies as they become older. Some caregivers felt that this is related to an awareness of their limitations.

> *"She was joyful as a child and teenager. As she has gotten into her mid twenties... I worry more about her everyday. She has a general sadness and anxiety that is only occasionally replaced with happiness and laughter. She cries more. Our family does not know if it is pain, frustration, or anxiety."* ~ Karen F., comment submitted online

> *"She cries sometimes when she's alone. And when we ask why she just says, 'Rett syndrome'. She cheered during her sister's dance recital, but not before crying because as she told us, she wanted so badly to dance like that herself."* ~ Brian, parent of a 14-year-old daughter living with Rett syndrome

BECCA

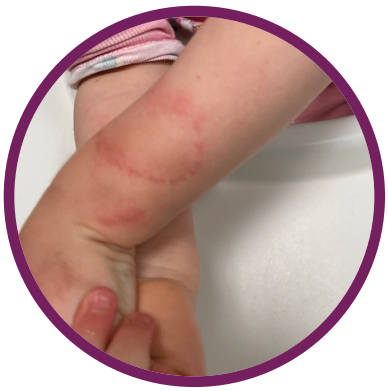
Aggressive behaviors can be an outlet for frustration, pain and discomfort and sensory overstimulation.

> *"My daughter has always had severe behavioral issues, and that goes from screaming, to aggression, to self-injurious behaviors. ... They range from biting me, scratching me, headbutting me when she was little. ... She throws things that she doesn't want. She does have some language, but when she is unable to make her point, she'll just pick whatever is nearby and throw it."* Melinda added that caregivers are often reluctant to discuss the aggressive behaviors. *"People are afraid to talk about this aspect. They think they're doing something wrong, or they're embarrassed, or they're ashamed that their child beats them up. And I think it's an under- spoken-about aspect of Rett syndrome."* ~ Melinda, parent of a 28-year-old daughter living with Rett syndrome

Self-harm requires constant oversight and puts parents in a stressful high-alert state.

"She was constantly biting everything and everyone. She would bite her arms so hard out of frustration and anger. Her forearms were covered in blood, and we'd have to bandage them." ~ Alex, parent of a 3-year-old daughter living with Rett syndrome

"Self-injurious behavior, which is probably the number one stressor for my family … because we just love him so much and to see him do that is indescribable, to be honest. We all move quickly to try to prevent it at all times and we all live of sort of in a hyper alert state because of it. … That has really altered everything in our family's life, and most importantly, his life." ~ Kate, parent of a 14-year-old son living with Rett syndrome



MAYA

Breathing difficulties (hyperventilation, apnea/breath holding)

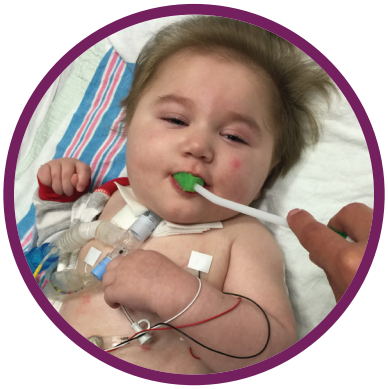
Breathing difficulties were the fifth most frequently experienced symptom of Rett syndrome, selected by 73% of caregivers, and were selected by 18% of caregivers as one of their top three most troublesome. Several caregivers emphasized their concern with the term "breath holding" as this implies that it is intentional but is not.

For many caregivers, breathing issues are their loved ones' most extreme symptom.

"[She] has severe respiratory issues, hyperventilating or not breathing. She will turn purple. … Never a regulated respiration. She is either hyperventilating or breath holding." ~ Wendy P., comment submitted online

"Her breath holding episodes are so dangerous (she crumples to the ground and hits her head on things) that until we found the proper medication, we could not take her anywhere. Even now, the episodes can still occur at any time--just not as often." ~ Claire M., comment submitted online

"She alternates hyperventilating and holding her breath." Sarah's daughter experiences 5-6 episodes an hour, and they lead to falls, impacting her mobility. *"With the onset of these breathing abnormalities, she was no longer able to bear weight when she's hyperventilating due to being very lightheaded and unable to control her body in those moments. … She became wheelchair bound a good bit of the day, because these breathing abnormality episodes would start randomly."* ~ Sarah M., parent of a 9-year-old daughter living with Rett syndrome



MADDEN

Breathing difficulties are related to other symptoms including choking, constipation, seizures, and infections.

"If her body is uncomfortable or anxious, [our daughter] can't swallow and her upper airway fills with secretions. She gasps and has to lay on her side until she can relax. Constipation makes this worse, and she's diapered and requires daily enemas for airway safety. … [Our daughter] has central and obstructive apnea with borderline dangerous CO2 levels. She has preliminary indications of pulmonary hypertension, but she can't tolerate a CPAP mask on her face, or she stops swallowing and chokes repeatedly multiple times." ~ Brian, parent of a 14-year-old daughter living with Rett syndrome

"Our daughter swallows so much air it causes trapped gas which turns to pain episodes that then lead to seizures. This causes us to watch her intently at all times and feel much guilt for not being able to see this occurring as there is nothing to help alleviate this symptom." ~ Samantha B., comment submitted online

Spine conditions (scoliosis, kyphosis)

Spine conditions including scoliosis and kyphosis are experienced by 39% of individuals living with Rett syndrome represented, and 10% of caregivers selected this as one of their top three most troublesome Rett syndrome-related health conditions. This health concern often emerges during the early teen years and progresses to the point that many individuals living with Rett syndrome require a spinal fusion.

"[Scoliosis] has taken over our lives as we try to help stabilize her spine and keep her organs from getting bunched up and causing other problems." ~ Matthew, parent of a 14-year-old daughter living with Rett syndrome

HEATHER

"She is unable to hold her head up even on her good days and leans dramatically to the left even when in her wheelchair or asleep. She has progressive scoliosis which we are told will soon require a total hip replacement and a spinal fusion." ~ Megan N., comment submitted online

"Scoliosis progressed and added to the struggle to keep her balance. An uncomfortable back brace didn't help and by age 14, spinal fusion surgery was in her future. She was not strong enough for surgery at the time and a G-tube was placed for extra nutrition. A year later, when surgery was finally done, they were not able to correct it all the way and she still remains quite curved." ~ Leslie G., parent of a 43-year-old daughter living with Rett syndrome

Movement disturbances (tremors, spasms, abnormal eye movements)

Movement disturbances are experienced by 49% of individuals living with Rett syndrome represented and selected by 6% of caregivers as one of their top three most troublesome health concerns. In addition to tremors, spasms and abnormal eye movements, caregivers described dystonia, a repetitive and involuntary contracting of muscles which can affect one or more parts of the body as well as dyskinesias which are involuntary, erratic, writhing movements of the face, arms, legs or trunk.

"My body shakes when I don't want it to. Sometimes I think about how I wish I could do more during the day. … My body doesn't listen very well, so someone holds my hand when I want to stir, pour or chop." ~ Becca W., a young woman living with Rett syndrome, and EL-PFDD meeting participant

In addition to seizures, Kristy's daughter experiences, *"Periods of dystonia where her mouth freezes open and her muscles tense. For those who are less familiar with her, these can be confused with seizure activity, and that complicates treatment even though she is still conscious during the dystonia, though she is not during her seizures. Her dystonia can make her sore, while her seizures can make her tired. Both are a safety concern and impact her daily life."* ~ Kristy H., comment submitted online

"His movement disorders classified as oral dyskinesia, became one of the hardest things to endure in the last year of life. The facial oral episodes were so frequent and so intense. [Our son] pushed out four baby teeth and severed part of his tongue, a football mouth guard was his only protection." ~ Jenna, parent of a 7-year-old son who died from complications of Rett syndrome

Dental issues (teeth grinding, dental procedures)

Dental issues are experienced by 38% of individuals living with Rett syndrome and selected by 5% of caregivers as one of their top three most troublesome health effect. As Jenna described above, dental issues can occur as a result of movement disturbances. Other caregivers described the dental damage caused by teeth grinding and falls.

For Alexa's daughter, tooth grinding, *"Causes such pain and irritability. Her teeth have been ground down to next to nothing and no one has been able to provide us with any sort of solution. I see where her teeth used to be and just sob. The tension in her body must be so great."* ~ Alexa D., comment submitted online

"She has even sharpened her teeth now with that bruxism all day." ~ Radhika D., comment submitted online

"She has had some terrible falls at her program. She now has three anterior teeth implants and two root canals, she had 13 stitches over her left eye." ~ Karen F., comment submitted online

HANNAH

Muscle tone abnormalities (high tone/rigidity)

Muscle tone abnormalities are experienced by 63% of individuals living with Rett syndrome and were selected by 4% of caregivers as one of their top three most troublesome. Some caregivers described how the muscle rigidity leads to pain and stiffness, creates challenges with activities of daily living including changing, sitting and transportation.

"As she has aged and after her scoliosis treatment her rigidity has become so difficult. … We have a tough time with even day to day care. Changing her is very difficult as her legs are always extremely tight. Her neck muscles have become extremely rigid, and she actually looks to the sky most of the day which makes it difficult to be part of everyday interactions." ~ Karen W., comment submitted online

Kate described that her daughter, *"May not be able to get in or out the car if her body can't reduce rigidity to even go in the sit position to make it to a doctor appointment or therapy."* ~ Kate B., comment submitted online

Heart issues (long QT)

Heart issues are experienced by 7% of individuals living with Rett syndrome, were selected by 5% of caregivers as one of their top three most troublesome. Heart issues can be severe.

"At only four years old she already has borderline left ventricular hypertrophy and borderline Long QT [syndrome], and scoliosis." ~ Melissa B., comment submitted online

Rett syndrome-related heart issues killed Jenna's 7-year-old son. *"In the last year, [our son's] heart quickly came to the forefront of the hardships and symptoms of his Rett syndrome. His prolonged QTc coupled with his progressively critically low heart rate was too much for his fragile body to endure on its own."*

MADDEN

Low bone density and fractures (osteoporosis, osteopenia)

Low bone density and fractures are experienced by 18% of individuals living with Rett syndrome represented and were selected by 1% of caregivers as one of their top three most troublesome but were not described during the meeting nor in any of the comments submitted online.

Other issues

Other issues are experienced by 11% of individuals living with Rett syndrome represented and were selected by 1% of caregivers as one of their top three most troublesome. Caregivers described pain, suffering and discomfort, immune system issues and infections, and multiple hospitalizations, described below. They also described cortical visual impairment, food allergies and sensitivities, skin issues including eczema and psoriasis, and incontinence.

Pain, suffering and discomfort. Throughout the meeting, caregivers described pain and discomfort from gastric issues, scoliosis and muscle tone abnormalities. They described headaches and injuries from seizures and falls. Some described how helpless they often felt.

ALEX

> *"Her headaches were so bad. She would slam her head into the hardwood floor or the walls to try and relieve the pain."* ~ Alex, parent of a 3 -year-old daughter living with Rett syndrome

> Sonya's daughter, *"Has pain from her GI issues. She constantly has tremors and moves her body non-stop when in pain."* ~ Sonya D., comment submitted online

> *"I couldn't express the hell I have gone through watching my daughter have drop seizures. Her little face slams into cement, hardwood flooring or any other dangerous landing because I didn't/don't have enough time to run and catch her before her face hit the ground. To hear the loud scream and not be able to help ease her pain after such dangerous falls and then you have the aftermath. Watching your child have black and blue face reminding you of the disastrous fall."* ~ Shirin E., comment submitted online

Immune issues and infections. Many individuals living with Rett syndrome are susceptible to respiratory infections, especially bacterial pneumonia from aspiration, and urinary tract infections from constant diapering. These can lead to lengthy hospitalizations.

> *"Any little infection, whether it be RSV, rhinovirus, or even when she had COVID-19, it's an immediate long term stay in the hospital. … We're in the hospital once every three months. … Usually that timeframe between August and March are our biggest worry areas, where you have that infection season. … Last March she came up with an exotic, rare virus. … And it put her in a coma for six days, kept her in a severe state of epilepticus. Upon coming out of the coma, it immediately threw her into a second regression, reversing all progress that was made after the first regression."* Bill also described, *"Having to combat frequent urinary tract infection due to the permanent diapering, because she is not ambulatory."* ~ Bill, parent of a 4-year-old daughter living with Rett syndrome

Rett syndrome obstructs every area of life and all activities of daily living.

Caregivers used online polling to select their top three activities of daily life that are most important to them, that their loved one is not able to do or struggles with due to Rett syndrome. Communication was the top impact, followed by socializing with peers/siblings and activities involving the use of their hands. Poll results are presented in **Appendix 5, Q3** and illustrated with caregiver comments below.

"In all honesty, it would be easier to list the ways that Rett syndrome does not affect my daughter's life. On our best days she is happy and smiling and never sheds a tear. On most days there's at least one occasion where she's crying without the ability to tell us what is wrong." ~ Jenna G., comment submitted online

"Julia is trapped in a body she can't make work. … I try to make sure she has enjoyable life experiences, but I wish she could 'participate' in life like her siblings and not just be a spectator. … Have friends, socialize, be invited places, enjoy food, communicate. Rett Syndrome is a lonely place to reside for my daughter." ~ Virginia F., comment submitted online

SADIE

Communication

Communication was the specific activity of daily life most impacted by Rett syndrome, selected by 91% of caregivers. Communication impacts everything. This was emphasized by a key meeting theme: without the ability to communicate, individuals living with Rett syndrome are trapped inside their bodies.

"I feel that communication is the top barrier to a quality life for my daughter. Without communication it is, and will continue to be, nearly impossible for my daughter to form meaningful relationships with people outside her immediate family and most significantly with her peers. What is life with no meaningful relationships? Imagine your life with no friends or without the ability to tell your loved ones how you feel. It's very sad." ~ Christy D., comment submitted online

"She gets so frustrated when she can't tell us what she wants to eat or drink or what TV show she wants to watch. All of these decisions are left to other people to make for her. …. She's lost her independence completely." ~ Stephanie, parent of a 7-year-old daughter living with Rett syndrome

"Although she has very expressive eyes, she cannot verbalize or communicate wants, needs, emotions and feelings. It is often a lot of guesswork." ~ Jack, parent of a 52-year-old daughter living with Rett syndrome

Activities involving use of their hands

Activities involving use of their hands was selected by 59% of caregivers as a top activity of daily life impacted by Rett syndrome. As previously described, impaired hand activities impact both communication and independence.

"If she had her hands, she would be able to communicate using ASL/pointing/pushing buttons on a device, feed herself, tie her shoes, etc. If she had her hand function, she would be able to be independent." ~ Sarah A., comment submitted online

Alysson described the impact of apraxia. *"My girl can't play with most of the toys that are out there for her age range, let alone simply pick up and hold anything."* ~ Alysson W., comment submitted online

Socializing with peers/siblings

Socializing with peers and siblings was selected by 59% of caregivers as a top activity of daily life impacted by Rett syndrome and generated many, many comments.

"She values her friendships in spite of how her body limits them. Most of the time, she can't respond fast enough to participate in a conversation. … Each day is hard to predict, so Becca struggles to socialize often enough to make meaningful connections. She likes to send text messages, but with everything going on, it can take a long time to craft even a short message. Additionally, because she gets sick every few months for a month or longer, it's hard to commit to plans in advance. So, she often doesn't get invited in the first place." ~ Brian, parent of a 14-year-old daughter living with Rett syndrome.

"When I ask if she would like to have friends and play with other children, she tells me 'yes'. But she cannot communicate in many meaningful ways, so other children never know quite how to talk to her." ~ Claire M., comment submitted online

The lack of independence play makes socializing hard. Individuals living with Rett syndrome are often ignored or rejected by peers.

"She loves hearing and seeing other kids, but they often see her as different and avoid her. It's honestly heartbreaking to see her so excited by them when they don't want anything to do with her." ~ Alex, parent of a 3-year-old daughter living with Rett syndrome

"She has the same interests and desires as her peers but is largely rejected by her peer group due to her limitations in speech and motor skills." ~ JT, comment submitted online

"Because of Rett syndrome, children won't approach her and people don't see [her] for who she is. They see a little girl in a wheelchair who is slow to respond, seemingly expressionless, and they ignore her or uncomfortably move on for fear they might get roped into our problems." ~ Julie N., comment submitted online

BECCA

Activities on feet (walking/ambulating) and participating in and enjoying recreational activities and events

Activities on feet, including walking and ambulating were selected by 33% of caregivers as a top activity of daily life impacted by Rett syndrome. Participating in and enjoying recreational activities and events were selected by 26% of caregivers as a top activity of daily life impacted by Rett syndrome. Caregivers described multiple barriers including mobility, behaviors (screaming), environmental sensitivities, requirements for specialized equipment, appropriate/discrete location for changes, and extra assistance.

"Everything we do takes a lot of planning and equipment. Even a trip to the beach requires us to obtain a beach wheelchair. Our daughter cannot run around with her brother or friends, swim on her own, or do most of the things that a 7-year-old girl would do without a great deal of assistance." ~ Deanna A., comment submitted online

"Activities that we enjoy but cannot fully do are, in short: all of them. Our daughter loves the outdoors more than anything. But, depending on how well her day is going, the most she can usually do is sit in her wheelchair outside. We ski, and she has to use a Mountainman bucket instead of the skis she once used. We once used a carrier to take her on hikes, but she has gotten too big for it and cannot enjoy the trails. She loves to swim, but has to be held by another person at all times. She loves camping but that is no longer an option. It is impossible to live life as she would like." ~ Molly F., comment submitted online


MAGNOLIA

"Every activity requires assistance and so many activities are closed off or limited due to Rett. ...Sensory issues also limit activities--wind, sun, temperature, noise all present challenges." Lena described how, "People's reaction to her yelling and moaning, or constant teeth grinding, or making raspberry sounds with her mouth, that limit our participation at many community events." ~ Lena C., comment submitted online

Travel and vacationing, sleeping, eating by mouth, attending school or having a job.

These impacts were each selected by less than 10% of caregivers as top activities of daily life impacted by Rett syndrome. Travel and vacationing and sleeping were each selected by 9% of caregivers, eating by mouth was selected by 6% of caregivers and attending school and having a job were selected by 5% of caregivers respectively as a top activity impacted by Rett syndrome. Many described a range of education challenges for their loved ones with Rett syndrome including boredom, visual impairment, high care requirements, finding a school environment where their child could thrive.

Other impacts: Rett syndrome profoundly impacts families and caregivers

Although none of the poll respondents selected any "other" as a response option, this was likely because the poll only permitted caregivers to select three responses. One impact of Rett syndrome described throughout the meeting was the impact on caregivers and families. Families are often faced with difficult choices. All family relationships are impacted. Caregivers described the burden that they experience as well as their grief and trauma.

"As you are hearing today there are so many different versions of Rett syndrome, but the common thread is that we are all struggling." ~ Lena C., comment submitted online

Rett syndrome profoundly impacts all family members and family activities.

"She cannot leave the house for school, social events, therapies, appointments and we, her parents and siblings, cancel all activities or trade off so one can go to work or helps other kids while the other stands on edge to give her care and medical support from home or be ready to run to the hospital if she needs more care than we can administer from home." ~ Paige N., comment submitted online

"Rett syndrome certainly controls our lifestyle to the max. ... We do not go out and about into many public settings because the fear of her behaviors and from several past experiences. We feel so secluded and lonely because our family can't go out together like 'Normal Families'. We have other children besides [our daughter with Rett syndrome] that we'd like to both be there for and feel we have to choose which parent is going to participate." ~ Jessica A., comment submitted online

Rett syndrome profoundly impacts all relationships and dynamics, not only with the individual living with Rett syndrome. Marriages are affected.


HANNAH

"Due to Rett syndrome I didn't just miss the opportunity to see my sister enjoying a 'normal' life, I'm losing a little bit of my mother every day who has her whole life on hold in order to take care of my sister." ~ Márcia A., sibling of an individual with Rett syndrome, comment submitted online

"Not only the caregivers but the siblings also have to take a step back with the attention we can provide as parents to them to take care of our loved one struggling with Rett syndrome." ~ Karen W., comment submitted online

"Rett affects all relationships no matter if they are direct, distant, new relationships etc. ...To find help to care for her and to be able to go out on a date with my own hubs has become a challenge in itself. My friends have dwindled down too, as she became more complex and effects our daily socialization times with others. Even immediate family members started to shy away." ~ Maggie. W., comment submitted online

"We have daily therapists, and nurses in and out of the home all day. It makes it impossible to really have a life outside of just care giving and work. My wife and I have not been out together for recreation in over five years." ~ Bill L., comment submitted online

"Due to her behaviors, over the years I've become isolated. It's impossible to make plans on a regular basis and it takes a team to come together just for me to take one night out on a rare occasion." ~ Melinda L., comment submitted online

Siblings are particularly impacted.

Shirin described how Rett syndrome impacts a sibling. *"She has stopped going to eat out with us since she is always worried that [her sister] will have a seizure or 10 and if it will be massive, scary or take away all of my attention on her. All fair points ... she is still a child and needs her mom and her mom is emotionally, physically and mentally drained and heartbroken."* ~ Shirin E., comment submitted online

Caregiving is extremely demanding mentally, emotionally and physically.


MAGNOLIA

"Caring for her is exhausting as we (my husband and I) get older. I got breast cancer three years ago and am currently still under therapy. Let me tell you something: not easy. She needs us for everything, and when I say everything, I mean every single thing you could think of." ~ Orietta M., comment submitted online

"There's just so much pain and wear and tear on our joints as we're trying to scooch and move. ... How can we continue to do this? And one of the difficulties in finding anyone who can take care of [our daughter] that's not us, who can or will do those types of things. It is a big wear and tear on your body. And for her of course." ~ Sarah C., parent of a 14-year-old daughter with Rett syndrome

Caregivers worry about who will care for their loved one when they are no longer able to.

Caregivers were asked to select their top three worries about their loved one's condition in the future. In addition to worrying about who would care for their loved one when they are no longer able to, caregivers also worried about the stress of not knowing how Rett syndrome will progress and premature mortality, including sudden unexpected death. Results are in **Appendix 5, Q4** and illustrated below with relevant quotes.

Who will care for my child when I am no longer able to?

This top worry was selected by 88% of caregivers and described in detail throughout the meeting. Many were afraid their loved one will be institutionalized because of the high burden of care.

"I balance a fear of institutional care … with a fear of the burden the care of my 11-year-old daughter could eventually place on her siblings or another family member if something happened to us or as we age. This is a full-time job for a parent. How would my other kids care for her needs if they had children of their own to also care for?" ~ Melinda G., comment submitted online

HEATHER

"Both my wife and I are about 50, and we are thinking, 'How are we going to be able to handle it in 10 years?'… I don't know if it's an option for me to live until 150, but definitely, hopefully, the cure can be discovered before that issue needs to be solved." ~ Dmitri, parent of a 12-year-old daughter with Rett syndrome

Julie described her fears of institutional care when she can no longer care for her daughter, *"We're terrified of putting her into an institution. We're terrified of the stories of abuse and neglect. No one will care for her as well as her parents — although this is what we ideally want, we are realistic about this and just want someone who will care and love her and advocate for her."* ~ Julie N., comment submitted online

Fears are reinforced by past experiences.

"We have care/support workers who give us breaks, but anytime she stays with them for any length of time, we are right back to the motility troubles, leaving us with weeks of getting back on track. No one knows her as well as we do. We know the beginning signs of reflux and can prevent her from aspirating at night. When left with someone else, they miss it, and we end up three weeks in hospital with pneumonia. We know when an impaction is starting in her bowels, and we know to get on top of it in a timely manner. When we let someone else care for her for a couple of weeks, we are back to having an intense regimen once she gets home, and we are back to several urgent care and/or ER visits." ~ Kandy H., comment submitted online

The stress of not knowing how Rett syndrome will progress

The stress of not knowing how Rett syndrome will progress was a top three worry, selected by 45% of caregivers. Other worries selected by caregivers as one of their top three included: worsening mobility, movement and balance problems (30%); vulnerability (23%); having uncontrolled seizures/status epilepticus (13%); long-term effects of seizures and medications (10%); chronic infections including pneumonia, urinary tract infections (8%); regular colds and viruses frequently leading to hospitalizations (5%); worsening nutrition issues (4%). There were very few comments related to these worries that were not already included in other sections of the report.

> *"We are certainly worried that she's now entering puberty and that's when further regressions are possible. We are pretty worried that all of her symptoms will become worse."* ~ Dmitri, parent of a 12-year-old daughter with Rett syndrome

> *"She feels so much pain only at the age of five, I'm terrified as symptoms worsen because I've seen them happen over time and what she's going to experience down the road."* ~ Usree, parent of a 6-year-old daughter living with Rett syndrome

Premature mortality including sudden unexpected death

Premature mortality, including sudden unexpected death, was a top three worry selected by 44% of caregivers.

> *"Imagine going to bed each night wondering if your child will still be breathing when you go to them in the morning. Every single night. Its debilitating and I wish it on no one."* ~ Christy D., parent of a 12-year-old daughter living with Rett syndrome,

> Leslie M. unexpectedly lost her 5-year-old daughter from Rett syndrome complications. *"We were always afraid that she would go to sleep and never wake up. Then, … the unimaginable action happened. She was exhausted from yet another round of seizures, so she took a nap. When we went to wake her up, we couldn't. …Rett syndrome stole [our daughter] from us in the middle of her second semester of kindergarten. Rett took away Halloween, her favorite holiday, birthdays, and a longer relationship with her 18-month-old sister."*

BROOKE

Other worries

Other top three worries selected by caregivers included vulnerability (23%); financial stability for my family or loved one (15%), and other worries (6%). These mostly included worries about the physical and emotional wellbeing and comfort of their children, especially with regards to pain.

SESSION 2: RETT SYNDROME PATIENT VOICES: CURRENT AND FUTURE TREATMENTS

Key Themes from Session 2

There are no FDA approved Rett syndrome therapies or disease-modifying therapeutics for individuals living with Rett syndrome. All individuals living with Rett syndrome require many medications, surgical interventions therapies and equipment to address their symptoms, however these approaches are not developed specifically for Rett syndrome and they work poorly.

> *"Rett syndrome is one of the absolute most debilitating and tragic syndromes that exists. Not only because it starts in childhood but because there's not one single effective medical treatment or medication to even reduce the symptoms of the actual syndrome. Sure, there's treatments for the complications of Rett syndrome like, epilepsy, scoliosis, muscle rigidity, etc. but there's no treatment for the syndrome itself. We need a cure. We need help. My daughter deserves a better life."* ~ Jenna G., comment submitted online

> *"Our daughter is 9-years-old and has Rett Syndrome. Over the last six month her seizures have increased drastically. She even was taken by ambulance from school because she seized and stopped breathing. She is in pain daily because of her constipation, GI issues, and severe scoliosis. I worry about her every second and she still manages to smile and change our perspective on life. I would do anything for her to have a medicine or treatment to make her life better."* ~ Denay H., comment submitted online

SADIE

> *"We've modified her diet [and] added a new medication almost every six months of her life to combat her reflux, her GI, her seizure/dystonia episodes, her anxiety and sadness as her body takes more away from her. We have fought for continued OT, PT, augmentative communication, massage therapy and her right to be in the classroom."* ~ Kate B., comment submitted online

> *"We dream every single day about what her life would be like, what she would be able to accomplish, if she didn't have Rett syndrome. It's why we have explored every medicine and treatment we could possibly find to help her lead her best life."* ~ AJ, parent of an 11-year-old girl living with Rett syndrome

Rett syndrome symptoms as well as the medications and therapies impose a tremendous burden on those living with Rett syndrome.

> *"My daughter was five years old when she passed away last year from Rett syndrome complications. In her short five years, she bravely endured numerous treatments, procedures and therapies. … Though the surgeries, studies and hospitalizations aided her quality of life, they were not without cost. … Although we were extremely grateful for the therapies, we also know how much they required of her."* ~ Leslie M., parent of a 5-year-old daughter who died from complications of Rett syndrome

Individuals living with Rett syndrome have tried many available medications and medical treatments.

Caregivers of individuals living with Rett syndrome used online polling to select all medications and medical treatments that they had tried, and each poll respondent selected an average of 8.2 different medications. Poll results are presented in **Appendix 6, Q1** and described with patient quotes, below.

Supplements, medications, or diet for gastrointestinal health

Supplements, medications, or diet for gastrointestinal health were the top medical treatment option, selected by 80% of caregivers. Caregivers described a range of medications: Omeprazole, Nexium and Pepcid for gastric reflux; fish oil, magnesium and MiraLAX for constipation. Many described complex diet and nutrition modifications. Not all approaches worked for everyone.

"For some time, we'd been treating her chronic constipation with fish oil, magnesium, and stool softener, as needed. But now her stomach was becoming increasingly bloated. I took her to a GI doctor, was told that since she had Rett, it must be from swallowing air. I took her to several other doctors who ...said to give her MiraLAX. That only made her more bloated. They had no other suggestions for me." ~ Heidi, parent of a 16-year-old living with Rett syndrome

"The gluten-free casein-free diet has been a game-changer! Her neurologist prescribed it, so staff at her residence had to make it. It soon became apparent that the diet must be adhered to strictly and absolutely - this took a while to achieve." ~ Jill J., comment submitted online

Paige described her daughter's best days. "All of her equipment and formulas [are] mixed and ready for 5 g-tube special formula meals and hydration throughout the day plus one orally fed special blended pureed meal spoon-fed orally by caregiver because she enjoys the sensory taste texture and social aspect of eating, all of which are portioned, timed and equally spaced to respect her reflux and slow gastric emptying." ~ Paige N., comment submitted online

Anti-seizure medications

Anti-seizure medications were used by 67% of caregivers for seizures and for breath-holding.

Her seizures have gone from frequent tonic-clonic seizures to the rare partial seizure with the help of a cocktail of anti-epileptic drugs." ~ Jennifer, parent of a 15-year-old daughter living with Rett syndrome

"She has intractable epilepsy for which she has tried at least ten seizure meds- currently she is on four medicines twice a day and still experiences tonic-clonic seizures multiple times each day." ~ Megan N., comment submitted online

"We've seen huge improvements with our 4-year-old's breath holding episodes since we put her on Zonisamide. Before putting her on this medication, she would have 60-70 episodes per day, sometimes as many as one per minute. She couldn't do therapy and we couldn't go anywhere. She was very unsafe because she would crumple to the ground, jerk her limbs, and hit her head on things. Now, she can go hours with only 2-3 episodes." ~ Claire M., comment submitted online

MAYA

Seizure medications have side effects and didn't work for all.

"At age five, she was prescribed a number of different seizure medications to address her sudden increase in seizure activity. Each powerful anti-convulsant came with its own side effects. None of them stopped her seizures for long. … we would've tried anything to give her some relief because she was incapable of attending school safely. She had to be close to her rescue medication at all times." ~ AJ, parent of an 11-year-old girl living with Rett syndrome

"The seizure medications made her sleepy during the day and restless at night. And despite the medications, the seizures became worse. She had as many as 10 seizures per day with breath holding and vomiting, often causing bacterial pneumonia and hospitalizations. Several medications and combinations were tried. Most either made her sleepy or agitated or she would develop a rash, but none eliminated the seizures." ~ Leslie G., parent of a 43-year-old daughter living with Rett syndrome

"The seizure medication absolutely squashes her personality and her ability to enjoy life." ~ Mickey, parent of a 24-year-old daughter living with Rett syndrome

HEATHER

Medications or supplements to help with sleep

Medications or supplements to help with sleep were selected by 62% of caregivers.

"She needs her sleep aid every night, which was prescribed by a physician to help her sleep seizures. I and my husband, we do not remember the last time we have slept continuously for eight hours." ~ Nida Z., comment submitted online

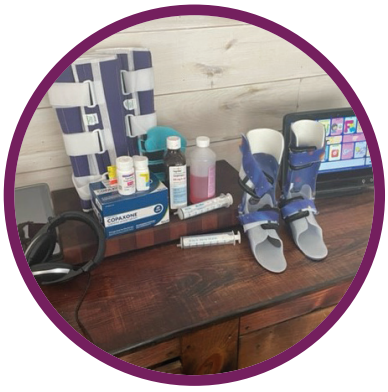
"Trazodone (with a little Baclofen) greatly helps with sleeping issues." ~ David K., comment submitted online

Supplements to improve growth and nutrition

Supplements to improve growth and nutrition was selected by 45% of caregivers.

"We discovered Trienza made by Houston Pharmaceuticals — enzymes that complete the digestion of the breakdown products of gluten and casein in people with autism, and clearly also with [our daughter]." ~ Jill J., comment submitted online

Patty described success at moving from formula to providing a nutritious diet of home blends. "*She hasn't had formula or any packaged food in about four years. We've seen her feeling better at times and we've been able to control when she is sick. We can adjust what we're feeding her, going back to just chicken noodle soup when you don't feel well. That has been powerful for us as a family."* ~ Patty, parent of a 15-year-old daughter living with Rett syndrome



Surgery (g-tube, hip dysplasia, VNS, spinal fusion, lap Nissen)

Surgery was selected by 44% of caregivers who described how their loved ones had each experienced many types of surgeries, many for medical equipment insertions: g-tube insertion, cecostomy tubes, VNS, spinal fusion, pacemakers, tracheostomy, ear tubes.

> Patty described her daughter's G-tube as a life saver for reducing aspiration and pneumonia, providing seizure medications, and for adequate hydration. *"I think right now, her gastric tube (G tube) has been the saving grace of a lot of our issues. For us, the feeding tube simplified she could get her seizure meds accurately. … As much as it hurt us as parents and we felt like failures, we also felt like a relief within about a week that life just got easier."* ~ Patty, parent of a 15-year-old daughter living with Rett syndrome

Some described how difficult surgeries were for their loved ones.

"[Our daughter] endured spinal correction surgery, which was grueling, both in the actual surgery as well as during her recovery. This surgery not only strengthened her spine, but stopped her from suffering from daily reflux." ~ Jennifer, parent of a 15-year-old daughter living with Rett syndrome

"Her scoliosis surgery was an extremely difficult time in her life. She was in the hospital for 21 days and most of that time was in ICU due to infections". ~ Karen W., comment submitted online

"When [scoliosis] surgery was finally done, they were not able to correct it all the way and she still remains quite curved. … After the surgery, she was able to walk short distances with assistance, but slowly began to lose strength and couldn't stand anymore." ~ Leslie G., parent of a 43-year-old daughter living with Rett syndrome

HEATHER

Cannabidiol or CBD (Epidiolex) or other cannabis supplements

Cannabidiol or CBD (Epidiolex) or other cannabis supplements was selected by 43% of caregivers.

"Marinol (which is a synthetic THC) helps immensely. It helps her with pain, anxiety, seizures, sleeping as well as appetite boosting amongst other things." ~ Jessica K., parent of a 7-year-old daughter with Rett syndrome.

"CBD oil will help calm her body; she does not pace as much (since she still has her ability to walk). It helps her mood the most it, keeps her happy." ~ Kendra I., comment submitted online

"She is now only on a cannabis prescription pill. … She seems much more calm, less anxiety, is able to look directly at people speaking." ~ Jaette C., comment submitted online

Treatment for infections

Medications to treat infections was selected by 35% of caregivers who described the different types of infections their loved ones experienced: repeated aspiration-pneumonia, urinary tract infections, sepsis, and even small intestinal bacterial overgrowth, or SIBO.

Heidi suspected that her daughter had SIBO. *"I asked [her physician] to treat her for it empirically and she agreed. … Afterwards, she was a new person. The bloating disappeared and she was happy."* She treats her daughter with antibiotics every six months to keep the SIBO at bay. ~ Heidi, parent of a 16-year-old living with Rett syndrome

"Our grandson had multiple respiratory infections at an early age (18 months of age) He was tested and found to be immunocompromised. He started on monthly infusions of IGG [immunoglobulin G]. He has not had a problem with infections since." ~ Cynthia F., comment submitted online

Anxiety or depression medications

Anxiety or depression medications were selected by 31% of caregivers, who described selective serotonin reuptake inhibitors (SSRIs) such as escitalopram (Cipralex or Lexapro), ketamine, risperidone/Risperdal, Haloperidol/Haldol. Some caregivers were reluctant to use these medications, some experienced success, while others reported side effects and failure, often with the same medications.

"At age nine, we put [our daughter] on Lexapro. We tried to avoid it, because I didn't want to her to have any kind of mood-altering medication… but the doctors told us it would help, and it really has." ~ AJ, parent of an 11-year-old girl living with Rett syndrome

Heidi's daughter tried Risperdal for her anxiety and aggression. "It was horrible. [Our daughter] was confused, dizzy and began to drool, but still agitated. We had discontinued it after two weeks. The side effects vanished, except for the drooling, which lasted two years." ~ Heidi, parent of a 16-year-old living with Rett syndrome

"We finally found a medication, Haldol, that helped and eliminated the finger flicking and some other behaviors. Nine-months after starting Haldol, [our daughter] is experiencing Parkinsonism and dyskinesia as the side effects of Haldol. So now we are withdrawing her from it and will most likely see her damaging behaviors returns." ~ Wendy P., comment submitted online

"We have put [our daughter] on anti anxiety medications that don't seem to have an effect at a low dose and we worry about the ones recommended due to side effects … It's heartbreaking to see her filled with anxiety and sadness or pain and not know how to comfort her or how to treat her to alleviate what she is experiencing." ~ Karen F., comment submitted online

HANNAH

Other medications or medical treatments

Other medications were selected by 27% of caregivers and included statins, dextromethorphan, and off-label medications. Lack of improvement and side effects were reported

"When [our daughter] was eight, we tried statins. We saw a noticeable improvement. Unfortunately, her blood test revealed that the statins were causing her liver issues, so we had to stop after just a month." ~ Heidi, parent of a 16-year-old living with Rett syndrome

"We had heard that Dextromethorphan, a key ingredient in cough syrup, was being tested in Rett syndrome… as it was an over-the-counter and safe drug, we decided to try it. We were desperate as we were watching in horror as our daughter, also terrified, was rapidly losing skills. After several months of no improvement, we decided to discontinue." ~ Heidi, parent of a 16-year-old living with Rett syndrome

"At age eight, we put her on off- label medication for mountain climbers in hopes that it would give her some relief from her constant struggles to breathe. She still wakes up gasping for air every single morning and struggles to catch her breath most of the day, but she doesn't turn blue or black from lack of oxygen anymore." ~ AJ, parent of an 11-year-old girl living with Rett syndrome

MAGNOLIA

Investigational medication in a clinical trial

Investigational medications in a clinical trial were selected by 26% of caregivers, and many described how they would go to great lengths to access treatment.

"We literally moved to Texas for 7-8 weeks from Virginia so that she could participate [in a clinical trial]." ~ Geraldine W., comment submitted online

"Although we would not know if [our daughter] would receive the drug or placebo, we also knew that if she completed the trial, she would have the opportunity to enter the open label phase. We weighed possible benefit versus risk and came to the conclusion that if it could help our daughter, we needed to try it. Within a couple of weeks of starting the trial, we began to see positive changes. Although we could not be certain that [our daughter] was getting the drug, we felt confident she was due to the extraordinary improvements. … She began to use her EyeGaze computer not only more accurately, but much faster to be able to communicate and to type." Jennifer also described improvements in her daughter's fine motor coordination, improvements in her muscle tone and gains in her ability to ambulate, and an improved ability to initiate activity such as walking and sitting. ~ Jennifer, parent of a 15-year old daughter living with Rett syndrome

"We were part of an Epidiolex trial… My daughter was on it for about a month before the trial had to end early because of COVID, but it helped with her hand use and it helped her with gaining control of her hands." Heather's daughter could now control her hands to touch and make choices, and to activate easy toys. "She responds so much more quickly than she used to and appropriately. She'll laugh. Before, it used to be that she might laugh 20 seconds after something funny happened. But now, she'll do it in the moment, which has been huge for her being part of our family and being interactive with her brother and sister. …Her quality of life is so much higher because of this research and medications." ~ Heather, parent of a 5-year-old daughter living with Rett syndrome

ANN

"During trials, we saw significant improvement in her behavior, including alertness, stopped seizures, stopped salivating, stopped hand ringing. When the trial ended, her behavior reverted, seizures also reverted. So were filled with great hope of a quick approval." ~ Jack, parent of a 52-year-old daughter living with Rett syndrome

"After seeing minimal improvements, we began to see horrible behavior changes. She started having more frequent screaming outbursts. Her aggression started becoming more prominent. The GI issues became more unmanageable. The diarrhea, that was the number one side effect, had been well managed for the first 3-4 months, became uncontrollable."
~ Paige B., comment submitted online

Medications or surgery for tense muscles (hypertonia or rigidity)

Medications or surgery for tense muscles (hypertonia or rigidity) were selected by 20% of caregivers. Caregivers mentioned baclofen (a muscle relaxant and antispasmodic agent) as well as Botulinum toxin (botox), therapies which appear to decrease in effectiveness with time.


BECCA

"We deal with spasticity, which is challenging, trying to find the right combination of medications, Botox, and therapies. … Although the botox treatments have made an enormous improvement in her rigidity, we hope that this remains this way as her doctor has informed us that unfortunately this may not work as well as she continues this treatment. … Increasing the Baclofen is not an option as she is on the highest dose possible."
~ Karen W., comments submitted online

Medications for breathing abnormalities

Medications for breathing abnormalities were selected by 20% of caregivers.


MADDEN

As a result of central apnea, Heather D[1]'s daughter, *"She would just stop breathing, no pre-signs, no underlying illness. Sometimes it was tied to seizures, but often not. She was on continuous oxygen and then adding a seizure medication, Topiramate, to the mix significantly reduced that frequency."* ~ Heather D[1]., comment submitted online

"Prior to being in the trial she had a rebreathing mask (think CPAP mask, vents closed but with a metre length of elephant tubing off the mask) which she had to use for six hours a day every day. Severe hyperventilating caused dangerously low CO2 levels. … After being on sarizotan she was able to stop using the rebreathing mask." ~ Becky J., comment submitted online

Bone density treatments, ketogenic diets or modified Atkins diets and no medications.

Bone density treatments were selected by 12% of caregivers, ketogenic diet or modified Atkins diet were selected by 11% of caregivers, and 6% of caregivers selected that they are not using medications to help manage symptoms of Rett syndrome. There were no comments made during the meeting or submitted online for any of these specific treatment options.

Individuals living with Rett syndrome require extensive functional therapies, communication devices, as well as other therapies and equipment to help manage the symptoms of Rett syndrome.

Caregivers of individuals living with Rett syndrome used online polling to select all approaches besides medications and medical treatments that they had tried, including more holistic or non-traditional treatment approaches. Caregivers selected an average of 6.7 different approaches that each of their loved ones had tried. Poll results are presented in **Appendix 6, Q2** and described with patient quotes, below.

Physical therapy and/or occupational therapy and Speech therapy

Physical therapy and/or occupational therapy and speech therapy were the two top response options, selected by 94% and 84% of caregivers, respectively. Caregivers described the extensive amounts of therapy their loved ones require in order to just retain their abilities, and the enormous effort, time and expense associated with all this therapy. Many reported success with these therapies.

EMMA

"Life for [our daughter] includes daily physical, occupational and communication therapy at school and at home. In the past, we have traveled to Toronto, which is a six-hour, one way drive for [her] to participate in intensive physical therapy. Twice a day for a block of two weeks, every three months, [she] worked through exercises that would provoke her brain in the hopes that new motor pathways would be made. We did see some success in her core strength and her ability to stand." ~ Jennifer, parent of a 15-year-old daughter living with Rett syndrome

"My daughter, 6 years old, has been seeing occupational and physical therapists twice a week for more than three years. I cannot overstate how grateful we are for their work. These therapies have helped her to engage in other activities: going to day camp, focused reading, completing arts and crafts projects, playing board games, and more. When I look at where she was at the time of her diagnosis to how she is able to play using her hands today, makes me hopeful." ~ Jonathan H., parent of a 6-year-old daughter living with Rett syndrome

"Our current regimen: Last year we had 120 home ABA sessions (includes elements of PT, OT, speech, music, etc.), 95 other therapies, plus whatever PT/OT/speech sessions happen during school hours. It is overwhelming, to say the least. … -- but the relentless nature of Rett requires constant/continual vigilance." ~ Matthew H.'s, comment submitted online. (Note that Matthew's description of his daughter's current regimen filled almost a full page.)

Communication aids/devices

Communication aids and devices, including flashcards, eyegaze devices also known as AAC (Augmentative and Alternative communication devices) such as Tobii, spelling boards and iPads, were the third most selected response option, chosen by 82% of caregivers. These were frequently mentioned during the meeting and in the online comments.

"There was one piece of equipment that unlocked a new world for her, the Tobii EyeGaze device. ...But it wasn't easy. We had trainings to learn how to use the Tobii device. It tired her out at times. It was slow and that frustrated her." Leslie's daughter used her device to express her preferences, her likes and dislikes." ~ Leslie M., parent of a child who passed away at the age of five from Rett syndrome complications

"The communication device that she's using is Tobii. It uses eye-gaze technology, ... [and] she can select either letters or words and conceptually she can build sentences from words. This is not an easy exercise by any means, because even if I sit down and try to build a sentence out of the words on the screen, it will take some time." ~ Dmitri, parent of a 12-year-old daughter living with Rett syndrome

BROOKE

Although communication devices are an asset for many individuals living with Rett syndrome, just as many are unable to use them successfully due to apraxia, lack of training or lack of access including not having a device in their language.

"When it works, it works great. But when your daughter or son is going through just a moment, and those moments are actually pretty extended at times, where control of their body, control of their eyes, all of it isn't aligned, communication takes a real crater." ~ Allen, parent of a 5-year-old daughter living with Rett syndrome

"She used to use a Tobii eye gaze. She doesn't use that anymore as much as she used to. She has adopted this blinking, yes, no, because when she's in the hospital and out on all of the medications, the Tobii is so difficult for her to be able to focus on and talk to us through." ~ Wendy, parent of a 21-year-old daughter living with Rett syndrome.

Mobility and walking aids

Mobility and walking aids were selected by 75% of caregivers. These included a wide range of equipment and technologies including braces, standers, walkers, strollers or wheelchairs as well as gait trainers, and ankle foot orthotics (AFOs).

"The Rett diagnosis never felt more real than when the equipment rolled into our lives. There was the stander, her five point harness, specialized high chair, and her walker with wheels that gave her the momentary sensation of walking." ~ Leslie M., parent of a child who passed away at the age of five from Rett syndrome complications.

"She has equipment including ankle foot orthoses, a ultraflex braces to help with a knee flexion contracture and mild bilateral plantarflexion contractures, a gait trainer, a dynamic stander, a wheelchair, Rifton activity chair, ... an electrical stimulation unit to engage her abdominal musculature and improve her posture." ~ Deanna A., comment submitted online

HEATHER

Incontinence supplies

Incontinence supplies were selected by over two-thirds, or 67% of caregivers. In addition to diapers, caregivers described the requirement for adult changing tables and toileting/ showering chairs.

Home and auto modifications

Home and auto modifications were selected by 58% of caregivers as something that they are using to manage symptoms of Rett syndrome. They described hospital beds, ramps, ramp vans, ceiling lifts and wall padding to prevent injury. Some described extensive renovations and accessible homes.

"A specially modified wheelchair, a hospital bed, … a ramp to our house and we purchased a ramp van for transportation. Lifting was difficult, so a ceiling lift was installed over her bed." ~ Leslie G., parent of a 43-year-old daughter living with Rett syndrome.

"We decided to build a new home that is handicap accessible with wide doorways, a walk-in shower, and a lower sink, with her bedroom on the first floor. We will likely need a ceiling track lift eventually, and plan to get a wheelchair van at some point. As of now, we use portable ramps to get her chair into and out of our minivan." ~ Deanna A., comment submitted online

EMMA

Hand use or repetitive hand movement aids

Hand use or repetitive hand movement aids such as splints or gloves were selected by 58% of caregivers.

"She would always have her hands in her mouth, so we had to use bamboo splint to keeping her hands out of her mouth. I'd feel guilty at first thinking I'm restraining my child in a way, but she was relieved by that too. She didn't want to mouth her hands. - Heather, parent of a 5-year-old daughter living with Rett syndrome

"She has to wear arm braces to help reduce the hand biting and hitting against her teeth. We take them off when she sleeps and give her breaks sometimes when she eats. We have tried many different hand protectors, arm straps/brace, and had custom braces made. This presents challenges daily, and a lot of effort to put on, take off, and continuously wash/clean." ~ Nick G., comment submitted online

Alternative or homeopathic approaches

Alternative or homeopathic approaches were selected by 55% of caregivers. During the meeting parents described many approaches including homeopathy, aqua therapy, Rolfing, cranial-sacral massage, yoga, vibration platforms, anti-gravity boards, adapted skiing, hippotherapy.

"At age four, she met with a homeopathic doctor who prescribed her a litany of vitamins and supplements costing hundreds of dollars a month, in order to help maybe ease her GI issues, address her anxiety, or just keep her bones strong." ~ AJ, parent of an 11-year-old girl living with Rett syndrome

"Another thing that we have done that is one of the best therapies, is aqua therapy. Around here it's not easy to find. We did end up getting a really large hot tub, that is like a swim spa hot tub, to do the aqua therapy with her in there." ~ Wendy, parent of a 21-year-old daughter living with Rett syndrome

"Some therapies bring her joy--like skiing, hippotherapy, and music therapy, suggesting emotional needs that we sometimes forget in our anxiousness to address the challenges of her body." ~ Matthew H., comment submitted online

MAGNOLIA

Sleep or seizure monitoring devices

Sleep or seizure monitoring devices were selected by 27% of caregivers.

> Due to, *"Central and obstructive apnea with borderline dangerous CO2 levels, she wears a pulse oximeter every night."* ~ Brian, parent of a 14-year-old daughter living with Rett syndrome.

Breathing support aids

Breathing support devices were each selected by 27% of caregivers. Caregivers described supplemental oxygen, suction, vibration vests, cough assist machine, BiPap positive pressure ventilators, asthma inhalers, and nebulizers.


BECCA

> *"Bipap machine for severe obstructive sleep apnea (despite tonsillectomy), … and inhalers as needed for asthma."* ~ Deanna A., comment submitted online

> *"Nebulizer, suction machine, cough assist device, and percussive vest, all of which are used twice a day when she's healthy and every four hours when sick."* ~ Megan N., comment submitted online

Other approaches

Other approaches were selected by 16% of caregivers. Parents described the different infection control and bowel regimens, specialized equipment including body braces and prism glasses, and other strategies including education consultants, and even moving their families across the country to access care and better living conditions for their loved ones living with Rett syndrome.


EMMA

> *"She wears AFOs and a Boston TLSO brace (which we call her suit of armor) to approximate normal posture."* ~ Megan N., comment submitted online

> *"[Our daughter] works remotely with an assistive technology consultant in California, as well as with her special education teacher and occupational and speech therapist."* ~ Jennifer, parent of a 15-year-old daughter living with Rett syndrome

> *"We moved from Maryland to Missouri cross country, so that she could get a chance … to learn in a school which accepted her with open arms."* ~ Nida, parent of an 18-year-old daughter living with Rett syndrome

Treatments used the least often, including no treatments.

Feeding therapy was selected by 27% of caregivers, seizure dogs were selected by 2% of caregivers, and 1% of caregivers are currently not doing anything to help manage symptoms. These treatment options did not generate any comments.

Current medication and treatment regimens only control Rett syndrome symptoms "somewhat" or "very little".

Caregivers used online polling to report their level of satisfaction with their current regimen in terms of controlling symptoms. Most reported that their current regimen controls their loved one's disease either "somewhat" (45%) or "very little" (45%). Only 1% of respondents reported that the current regimen controls their loved one's disease "not at all", and 6% reported that it controls disease "to a great extent". A total of 2% reported that this question was "not applicable because we are not using anything". Poll results are presented in **Appendix 6, Q3**.

Current approaches and therapies for the symptoms of Rett syndrome only treat some and not all of the symptoms, are not very effective at treating target symptoms, and cause side effects.

Caregivers of individuals living with Rett syndrome used online polling to select their top three drawbacks of current treatment approaches. Poll results are presented in **Appendix 6, Q4**. Many of these drawbacks were already described in the previous two sections, on medications and therapies; further patient quotes are included below.

Only treats some, not all, symptoms and not very effective at treating target symptoms

These were the top two downsides selected by caregivers. "Only treats some, not all, symptoms", was selected by 73% of caregivers. "Not very effective at treating target symptoms", was selected by 63% of caregivers which was entirely consistent with the results of the previous poll question (Q3).

> *"Medications have thus far seemed to do very little and in no way stave off continuous regression and the medical challenges she faces. It seems that each year brings new complications and crushes our hopes for her."* ~ Jillian M., comment submitted online

> *"All of these treatments are helpful to some degree or provide some relief, but they only address a fraction of the issues or keep them somewhat at bay. All of these treatments and equipment are cumbersome and time consuming, and take away from other, more enjoyable things that we could be doing as a family (although we do them with adaptations as much as possible)."* ~ Deanna A., comment submitted online

> *"Does treatment help? Somewhat. Procedures are controlled. Her spine was fixed with surgery. She sleeps with medication. However, it doesn't change the fact that she still has Rett syndrome. She still can't talk, use her hands, take care of herself. Given that she has Rett, she's in a fairly good place, but compared to the rest of the world, she's severely disabled."* ~ Donna G., comment submitted online

Side effects

Side effects was selected by 45% of caregivers as a top treatment drawback. Many of the medication side effects were described in previous sections of this report.

High cost or co-pay, not covered by insurance

This downside was selected by 29% of caregivers. Throughout the meeting, caregivers emphasized that therapy and treatments are essential for their loved ones to maintain their abilities, yet many insurance companies will not cover these therapies as they don't show measurable improvement.

> *"It's been difficult because insurance does not want to pay for the PT and OT visits because they aren't seeing progress. Although we feel with Rett syndrome maintaining skills, and preventing regression is progress."* ~ Kristy H., comment submitted online

> Lisa described the difficulties she had in getting a new seizure medication approved for her daughter. *"It took four appeals from our neurologist over the course over five months to finally get dosing approved to see if this would be an effective drug for treating [our daughter's] seizures."* ~ Lisa E., comment submitted online

Requires too much effort and/or time commitment.

This downside was selected by 21% of caregivers, who discussed the tremendous efforts required to treat their loved ones and difficulties in achieving balance for their families.

> *"Instead of sports, dancing, and auditioning for the school play, [our daughter's] schedule's full of therapy appointments; physical therapy, occupational therapy, and communication therapy to help [her] relearn how to communicate using an eye gaze computer called a Tobii."* ~ Stephanie, parent of a 7-year-old daughter living with Rett syndrome

> *"We had 95 additional visits that are scoliosis-related, and most of them are about a 60-mile drive from where we live. So...gas, vehicles, tag-teaming with employment, and ... that takes [my daughter] out of school ... too."* ~ Matthew, parent of a 14-year-old daughter living with Rett syndrome

MAYA

Limited availability or accessibility

Limited availability or accessibility was selected by 17% of caregivers. Caregivers described funding challenges, limitations due to geography and time as well as limitations because of COVID-19.

> *"Therapy needs to be aggressive and consistent. Without the finances and dependent on what is provided by her program, therapy is very minimal and frustrating. The sad thing is that she is happiest when she is getting an aggressive amount of therapy. Her will to push herself to do better is remarkable ... I hear people talking about the therapy that they have access to but as with everything, without finances, you are limited."* ~ Karen F., comment submitted online

Route of administration and other drawbacks

Route of administration was selected by 11% of caregivers and highlighted throughout the meeting as a challenge. Other drawbacks were selected by 6% caregivers, but specific examples were not mentioned.

> *"Probably the biggest problem we have is giving her the medication, because she does not have a G-tube. ... But so many of the medicines, she doesn't like taking. And even the few that she can take -- sprinkled on ice cream or mixed in food -- has ruined that whole food group for her."* ~ Colleen, parent of a 24-year-old daughter living with Rett syndrome

"We pay extra for our pharmacy to add flavorings to her medications so she doesn't resent us for giving it to her. However, figuring out the best medications for [our daughter] who is 6 years old, has taken us a long time. We've had to adjust medications, doses, frequency, etc." ~ Paige B., comment submitted online

Therapies that result in even minor improvements in function would result in enormous quality of life benefits for individuals living with Rett syndrome.

Caregivers used online polling to select the top three aspects of Rett syndrome that they would choose as most important for a possible new therapeutic to improve. Poll results are presented in **Appendix 6, Q5**. Caregivers selected communication/speech impairment and impaired hand use or repetitive hand movements as the top two selections.

Communication/Speech impairment

Communication/speech impairment was the aspect of Rett syndrome that was selected by 84% of caregivers as most important for improvement by a possible new therapeutic. Caregivers emphasized how improving communication would help address many other symptoms as well.

"If she could speak and tell me in her own words, "Dad, I need to go to the bathroom," just the amount of dignity that would give her." ~ AJ, parent of an 11-year-old girl living with Rett syndrome

"For us, finding a treatment that improves her ability to communicate would be a godsend. Just to know what's bothering her when she's in pain (or what she wants for breakfast!) would be life-changing." ~ David K., comment submitted online

"The communication and speech - if we could improve that with some reliability for [our daughter], she certainly could inform us to so many of the other symptoms that we're dealing with." ~ Patty, parent of a 15-year-old daughter living with Rett syndrome.

MAGNOLIA

Impaired hand use or repetitive hand movements

Impaired hand use or repetitive hand movements were the aspect of Rett syndrome selected for improvement by a possible new therapeutic by 52% of caregivers. Caregivers described how improved hand use would foster independence and support non-verbal communication.

"Purposeful hand use … would open up so many doors for [our daughter]… So that she can have independence to be able to help feed herself, help turn a page of a book, to look at a book, simple things like that. But also, I think that it would go even further and help with communication because I know that if she had use of her hands, she can point to what she wants, point to where it hurts to tell me if something's hurting on her, point to picture cards to tell me what she needs and wants." ~ Hailey, parent of a 3-year-old daughter living with Rett syndrome

"To add rationale to the goal of purposeful hand movement, I'd like to add that it would allow the affected individual to play with toys, do art projects, and increase the ability to have more complex interactions with others. This is so important for general well being and positive psychological growth." ~ Lynn O., comment submitted online

"Hand use could give her the autonomy and also dignity (being fed by your parent at age 10 in a restaurant is not fun)." ~ Lena C., comment submitted online

"I would also be grateful for improved hand use, to the point that she can do some self care, basically just have some more independence." ~ Heidi, parent of a 16-year-old living with Rett syndrome

Mobility or balance difficulties

Mobility or balance difficulties including walking, crawling, weight bearing for transfers, were the aspect of Rett syndrome selected for improvement by a possible new therapeutic by 36% of caregivers.

"As a caregiver, you want the most for your child. You want them to experience the freedom to be able to do things that their peers would be able to do. Being able to walk around in the field with safety, I think is one of the crowning achievements that a caregiver could have for their child. That's why it's important." ~ Allen, parent of a 5-year-old daughter living with Rett syndrome

"She would be able to play and exercise and do so much more if she could walk without so much assistance." ~ Alysson W., comment submitted online

"I long to be able to take a walk with my daughter and hear her tell me how her day was or even what she wants to eat for dinner." ~ Allycia S., comment submitted online

Seizures

Seizures were the aspect of Rett syndrome selected by 31% of caregivers as important for improvement by a possible new therapeutic.

"Our hope for her is to effectively treat the seizure so she can feel good and enjoy life with more good days. We hope that some communication might be possible, even if only facial expressions. We miss her big smile." ~ Leslie G., parent of a 43-year-old daughter living with Rett syndrome.

Gastrointestinal issues

Gastrointestinal issues were the aspect of Rett syndrome selected by 25% of caregivers as important for improvement by a possible new therapeutic. This includes improvements to constipation, acid reflux, bloating, and air swallowing,

"If our children did not suffer chronic constipation the savings to the health insurers as a whole would be incredible, second only to the improved quality of life.

- *No rushing a child to the ER because they have not passed stool in over 3 days, despite intervention;*
- *No causing your child pain on a regular basis due to enemas, laxatives (which cause gas pain), suppositories (which burn) or digital disimpaction;*
- *No GI emergencies such as perforated bowel and ensuing surgeries;*
- *Less chance of a twisted bowel and, again, surgery;*
- *Less chance of death due to an unknown bowel obstruction, perforation or twisted bowel."* ~ Melinda L., comment submitted online

BECCA

Breathing difficulties

Breathing difficulties were the aspect of Rett syndrome selected by 23% of caregivers as important for improvement by a possible new therapeutic.

> *"If there was one single day where she didn't wake up gasping for air, that would be a dramatic improvement in all of our lives."* ~ AJ, parent of an 11-year-old girl living with Rett syndrome

> *"We would like to find a medication to address her breathing issues … She hyperventilates and breath holds constantly throughout the day."* ~ Wendy P., comment submitted online

Emotional/behavioral problems

Emotional behavioral problems were the aspect of Rett syndrome selected by 11% of caregivers as important for improvement by a possible new therapeutic.

> *"If her anxiety were to decrease this would decrease behavioral issues, increase her social options and greatly enhance the quality of her life. … Without severe behavioral issues there is the chance at a more normal family life-being included in gatherings, having a babysitter, not becoming so isolated."* ~ Melinda L., comment submitted online

SADIE

Other responses

The remaining poll responses were selected by less than 10% of caregivers as one of their top three aspects of Rett syndrome to be addressed by a therapeutic. Movement disturbances including tremors, spasms and abnormal eye movements, and eating or swallowing were aspects of Rett syndrome each selected by 9% of caregivers as important for improvement by a possible new therapeutic. Additional aspects include: muscle tone abnormalities, including high tone or rigidity, selected by 8% of caregivers; sleep disturbances selected by 4% of caregivers; spine conditions, including scoliosis and kyphosis, selected by 2% of caregivers; heart issues including long QT selected by 1% of caregivers; dental issues and low bone density and fractures were not selected by any of the caregivers; other aspects of Rett syndrome were selected by 1% of caregivers as important for improvement by a possible new therapeutic. Few comments were generated.

> *"My one hope is that there would be a medication to stop her tremor so she could hold things without dropping them and she could feed herself."* ~ Collette O'D, comment submitted online

> *"I would also love a treatment that would give her back the ability to chew food, as it is difficult to always make sure pureed food is available or carried with us on outings."* ~ Deanna A., comment submitted online

Other

Caregivers of individuals living with Rett syndrome identified areas of additional unmet need.

Areas of unmet need were repeatedly mentioned throughout the meeting: including males or non-typical mutations in clinical trials, finding a cure for Rett syndrome, the need for treatments that result in improvements to Rett syndrome, more accurate endpoints for clinical trials.

Including males or those with non-typical mutations in clinical trials

"It is beyond disappointing that boys are all but forgotten about when it comes to Rett syndrome. The fact that there aren't equal opportunities for trials, studies, etc. Is maddening." ~ Rick O., comment submitted online

A cure for Rett syndrome

"[A cure] can mean a lot of different things for a lot of different people, but if it hasn't been made abundantly clear, Rett syndrome is devastating, full stop. We want future treatments to come with greater velocity and given the staggering nature of it, I think we have the opportunity to be a little bit more bold in pursuit of some more exotic things like gene therapies. I think from what we've heard today, this is a community that will go to great lengths, traveling to the ends of the earth, based on a hope of a treatment." ~ Allen, parent of a 5-year-old daughter living with Rett syndrome

"It's incredibly difficult to just cope with the fact our daughter has difficulty breathing, eating, sleeping, moving, digesting. We try to get her therapies to make her the most comfortable she can be. But in all honesty, our biggest hope is for a cure." ~ Alex, parent of a 3-year-old daughter living with Rett syndrome

"We are looking for a cure. If we cannot have that, we're looking for significant functional improvement - walk unassisted, communicate, increase functional use of her hands, and reduce seizures by 50-75% with minimal medications. - Julie N., comment submitted online

Therapies that result in even minor improvements would result in enormous quality of life benefits for individuals living with Rett syndrome

This point generated so many comments throughout the meeting that it is being emphasized again.

"Even if there is a tiniest improvement in any of the symptoms, whether that's improved quality of sleep or seizure control or better ability to swallow and eat, all of that helps with the quality of life, not only for [our daughter] and girls like her, but everybody else." ~ Anemish, parent of an 18-year-old daughter living with Rett syndrome.

"If drugs were to become available and if they were to show improvements in only one symptom, for example, improved sleep, this would be such a fantastic outcome. ... A good night's sleep, a word spoken, hands that work better or even a step taken." ~ Caryn H., comment submitted online

"Improvement in the symptoms would be a great source of comfort. Better communication, less motor difficulties, and improvement in cognition would increase the child's independence and reduce the stress and workload of the caregivers that comes with taking care of a person with special needs." ~ Sonal D., comment submitted online

More meaningful endpoints for Rett syndrome clinical trials

"The scoring methodologies didn't really capture the true improvement that she had in so many different areas." Melinda's daughter's positive changes including improved behavior and mood, being able to speak a sentence, and being able to draw. "These things were not captured by a point system. It didn't really capture the true measure of improvement... So the measuring system that's being used, yes, we need one, but there has to be another way to capture the true improvements." ~ Melinda, parent of a 28-year-old daughter living with Rett syndrome

"While key research focuses on genetic therapy and disease modification, a parent learns that key quality of life issues drive day to day priorities - infections (pneumonia), seizures control, and mobility (esp. scoliosis). Please discuss important Quality of Life endpoints that could lead to FDA approved labeling for such key elements." ~ Christopher G., comment submitted online

HANNAH

INCORPORATING PATIENT INPUT INTO A BENEFIT-RISK ASSESSMENT FRAMEWORK

The FDA uses a Benefit-Risk Assessment Framework which includes decision factors such as the analysis of condition, current treatment options, benefit, risk, and risk management. The Framework provides an important context for drug regulatory decision-making and includes valuable information for weighing the specific benefits and risks of a particular medical product under review.

Table 1 speaks to the challenges and burdens that individual living with Rett syndrome endure. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Option to be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of this unique condition for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for Rett syndrome. The data resulting from this meeting may help inform the development of Rett syndrome-specific clinically meaningful endpoints for current and future clinical trials, as well as encourage additional researchers and industry to investigate options for Rett syndrome treatments.

The information presented captures the perspectives of people living with Rett syndrome presented at the March 11, 2022, meeting, as well as polling results and comments submitted before, during and after the meeting through the online portal.

Note that the information in this sample framework is likely to evolve over time.

TABLE 1 Rett syndrome Benefit-Risk Table

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION/ IMPACTS ON ACTIVITIES OF DAILY LIVING	**Rett syndrome is characterized by a long and diverse list of symptoms which manifest differently in each individual. Families deal with eight or more symptoms at any time.** **The inability to communicate/speech impairment is the top area of concern,** followed by impaired hand use or repetitive hand movements, severe gastrointestinal issues, seizures, mobility and balance issues, eating and swallowing difficulties, sleep disturbances, emotional/behavioral problems, breathing difficulties, spine conditions, movement disturbances, dental issues, muscle tone abnormalities, heart issues, low bone density. Patients are often in pain and discomfort and struggle with infections and lengthy hospitalizations. Rett syndrome symptoms are constantly changing and are often interrelated. Individuals living with Rett syndrome experience dramatic regressions and unexpected setbacks throughout their lives.	**Rett syndrome interferes with all activities of daily life. The care requirements for individuals living with Rett syndrome are enormous.** Individuals with Rett syndrome have apraxia, a neurological disorder that prevents them from speaking or moving, even though they may have a strong desire and capacity to do so. They are cognitively aware, and many go through great efforts to communicate with their caregivers. Individuals with Rett syndrome require care every day throughout their entire lives. Caregivers worry about their loved one's future care, disease progression, and premature mortality or sudden death of their loved one.
CURRENT TREATMENT OPTIONS/ PROSPECTS FOR FUTURE TREATMENTS	**Treatments to specifically address Rett syndrome are urgently needed.** All treatment is currently palliative. Each individual with Rett syndrome requires many types of medications, therapies, supports and equipment to address each of their symptoms, yet these only help somewhat or very little. Caregivers are desperate for new therapies and are willing to try anything, including investigational medications, off-label drugs and any other approaches that could support improvement. **The burden of Rett syndrome and the therapies required to address symptoms is tremendous for individuals living with Rett syndrome and for their caregivers and families.** Therapies are essential for maintaining skills, and without constant effort in each area, individuals with Rett syndrome will regress. Appointments with specialists and therapists, as well as providing daily care requires much effort and is time-consuming for caregivers and families.	**In addition to a cure, disease-modifying medications and effective treatments for Rett syndrome are desperately needed.** **Functional improvements in communication/ speech and hand use are the aspects of Rett syndrome ranked as most important for new therapeutics.** That said, even minor functional improvements -- saying a few words, the ability to grasp or touch an object, initiation of movement -- will contribute to autonomy and improve the quality of life for people with Rett syndrome. Additional areas of unmet therapeutic need include clinical trials for males and improved endpoints for clinical trials

See the voice of the patient report for a more detailed narrative.

CONCLUSION

RSRT and the IRSF sincerely thank the participants and attendees at the EL-PFDD meeting and those who provided post-meeting commentary. Their voices help us all better understand Rett syndrome and its impacts.

We conclude with the voices of caregivers speaking for individuals living with Rett syndrome.


ANN

"[Our daughter] is 52, and has missed many life experiences like graduations, proms, wedding, and having her own children as we dreamt about. Rett took that away. She is a tremendous source of joy and love, yet Rett has caused a lifetime of hardships. Many, many children with Rett syndrome don't reach half her age." ~ Jack, parent of a 52-year-old daughter living with Rett syndrome

"Becca is frankly living on a knife edge, and it would take very little to tip the scales against her, but she repeatedly asserts through her spirit and maturity that hers is a life worth saving. … Becca is eking out a beautiful life, fighting against every aspect of this difficult disorder. Becca and the rest of us, can't wait for a day when Rett syndrome --even if it can't be cured -- can at least dampen enough to give us the chance to see just how much our daughter can accomplish with a little less going against her." ~ Brian, parent of a 14-year-old daughter living with Rett syndrome

I cannot impress on the FDA enough how much Rett syndrome robs from an individual and their family, and how much real therapeutics are needed. Rett syndrome is not a disability, it is an inability." ~ Lena C., comment submitted online

"I can only imagine what she could do and what kind of quality of life she could have if we could find treatments and therapies that could improve the other symptoms related to Rett Syndrome." ~ Claire M., comment submitted online

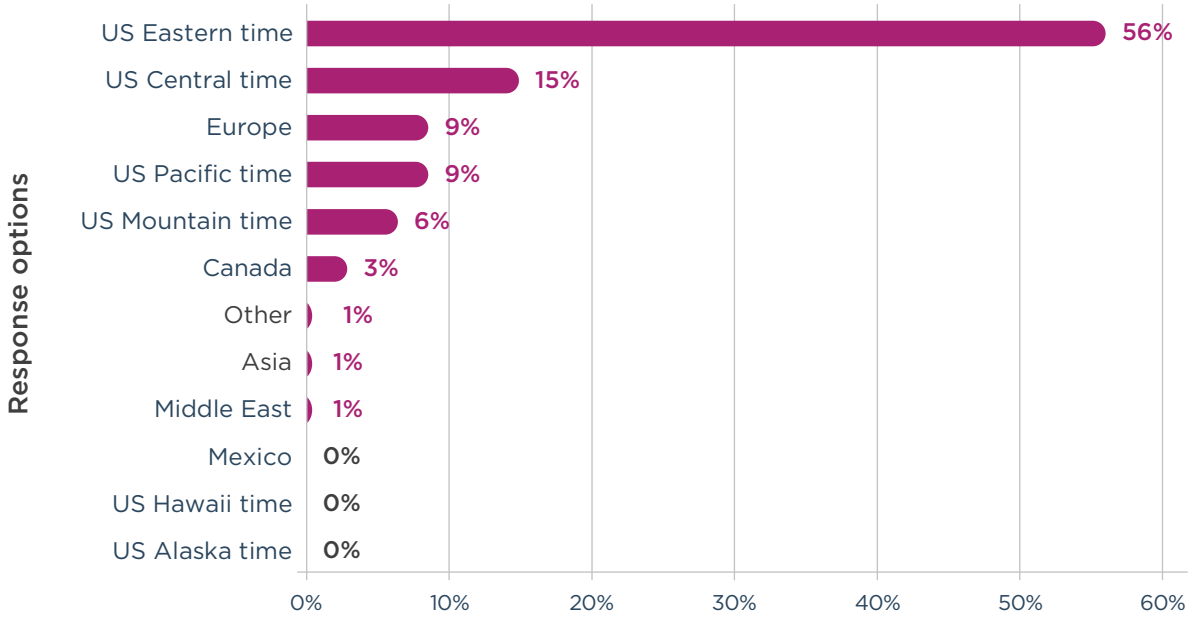
"We enjoyed every good moment and we fought through every hard one. We lived life with a child that was significantly ill, and [our son] was selfless through it all. His life was taken way too soon, but his work is not done. His mission is to reach you, to reach the experts, to reach the science, to bring a cure to all those suffering from Rett. Thank you." ~ Jenna, parent of a 7-year-old son who died from complications of Rett syndrome

APPENDIX 1: DEMOGRAPHICS

The graphs below include all attendees who chose to participate in online voting. The number of affected individuals and caregivers who responded to each polling question is shown below the X axis (N=x).

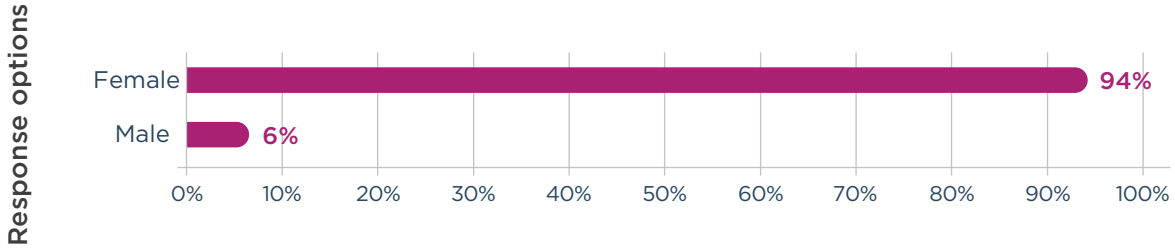
While the response rates for these polling questions is not considered scientific data, it provides a snapshot of those who participated in the EL-PFDD meeting and is intended to complement the live and pre-recorded comments throughout the meeting.

Question 1. Where do you currently reside?



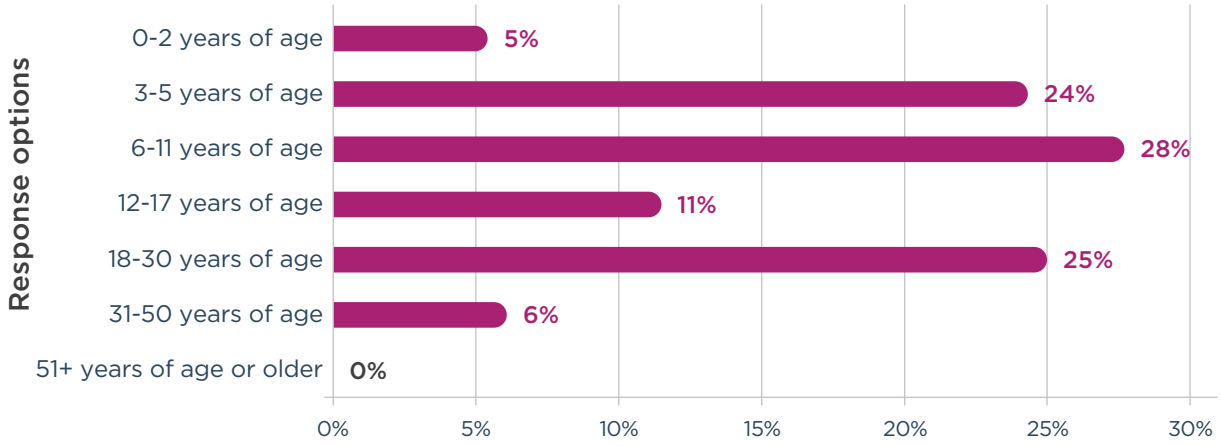
Percentage of respondents who selected each response option (N=141)

Question 2. Is your loved one with Rett syndrome:



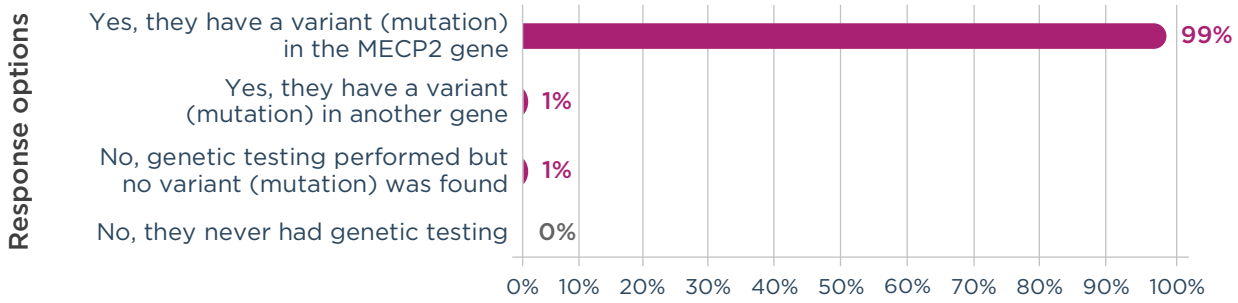
Percenage of respondents who selected each response option (N=128)

Question 3. How old is your loved one?



Percentage of respondents who selected each response option (N=148)

Question 4: Does your loved one diagnosed with Rett syndrome have a genetic diagnosis?



Percentage of respondents who selected each response option (N=154)

APPENDIX 2: MEETING AGENDA

10:00 AM	Welcome and Overview *Dominique Pichard, MD, International Rett Syndrome Foundation* *Monica Coenraads, Rett Syndrome Research Trust*
10:05 AM	Opening Remarks *Dr. Wilson Bryan, FDA*
10:15 AM	Background on Rett Syndrome *Dr. Eric Marsh, Children's Hospital of Philadelphia*
10:30 AM	Introduction and Meeting Overview *James Valentine, Hyman, Phelps & McNamara, meeting moderator*
10:35 AM	Audience Demographic Polling *James Valentine, Hyman, Phelps & McNamara*

Session 1: Rett Syndrome Patient Voices: Symptoms and Daily Impacts

10:45 AM	Panelist presentations
11:10 AM	Audience polling and discussion
12:30 PM	Lunch Break
1:00 PM	Introduction to afternoon session

Session 2: Rett Syndrome Patient Voices: Current and Future Treatments

1:05 PM	Panelist presentations
1:30 PM	Audience polling and discussion
2:45 PM	Summary Remarks *Larry Bauer, Hyman, Phelps & McNamara*
2:55 PM	Closing and Next Steps *Dominique Pichard, MD, International Rett Syndrome Foundation*

All times are Eastern Daylight Time

APPENDIX 3: MEETING DISCUSSION QUESTIONS

Topic 1: Living with Rett syndrome: Disease Symptoms and Daily Impacts

1. Of all the symptoms and health effects of Rett syndrome, which 1-3 symptoms have the most significant impact on your loved one's life?
2. How does Rett syndrome affect your loved one on best and on worst days?
3. How has your loved one's symptoms changed over time? How has the ability to cope with the symptoms changed over time?
4. Are there specific activities that are important that your loved one cannot do at all or as fully as they would like because of Rett syndrome?
5. What do you fear the most as your loved one gets older? What worries you most about your loved one's condition?

Topic 2: Perspective on Current and Future Approaches to Treatment

1. What are you currently doing to manage your loved one's Rett syndrome symptoms?
2. How well do these treatments treat the most significant symptoms and health effects of Rett syndrome?
3. What are the most significant downsides to your loved one's current treatments and how do they affect daily life?
4. Short of a complete cure, what specific things would you look for in a treatment for Rett syndrome? What factors would be important in deciding whether to use a new treatment?

APPENDIX 4: PANEL PARTICIPANTS, DISCUSSION STARTERS AND CALLERS

Session 1: Living with Rett syndrome: Disease Symptoms and Daily Impacts

Parent and caregiver testimonials

- Stephanie, parent of a 7-year-old daughter living with Rett syndrome
- Alex and Sebastian, parents of a 3-year-old daughter living with Rett syndrome
- Brian, parent of a 14-year-old daughter living with Rett syndrome
- Jack, parent of a 52-year-old daughter living with Rett syndrome
- Jenna, parent of a 7-year-old son who died from complications of Rett syndrome

Zoom discussion starters

- Dmitri, parent of a 12-year-old daughter living with Rett syndrome
- Sarah M., parent of a 9-year-old daughter living with Rett syndrome
- Sarah C., parent of a 14-year-old daughter living with Rett syndrome
- Usree, parent of a 6-year-old daughter living with Rett syndrome
- Ben, parent of a 3-year-old daughter living with Rett syndrome

Callers

- Melinda, parent of a 28-year-old daughter living with Rett syndrome.
- Kate, parent of a 14-year-old son living with Rett syndrome
- Bill, parent of a 4-year-old daughter living with Rett syndrome
- Matthew, parent of a 14-year-old daughter living with Rett syndrome
- Mickey, parent of a 24-year-old daughter living with Rett syndrome
- Hollis, parent of a 9-year-old daughter with Rett syndrome

Session 2: Perspective on Current and Future Approaches to Treatment

Parent and caregiver testimonials

- Leslie G., parent of a 43-year-old daughter living with Rett syndrome
- AJ, parent of an 11-year-old daughter living with Rett syndrome
- Heidi, parent of a 16-year-old daughter living with Rett syndrome
- Jennifer, parent of a 15-year-old daughter living with Rett syndrome
- Leslie M., parent of a child who passed away at the age of 5 from Rett syndrome complications

Zoom discussion starters

- Patty, parent of a 15-year-old daughter living with Rett syndrome
- Becki, parent of an 11-year-old daughter living with Rett syndrome
- Allen, parent of a 5-year-old daughter living with Rett syndrome
- Hailey, parent of a 3-year-old daughter living with Rett syndrome
- Colleen, parent of a 24-year-old daughter living with Rett syndrome

Callers

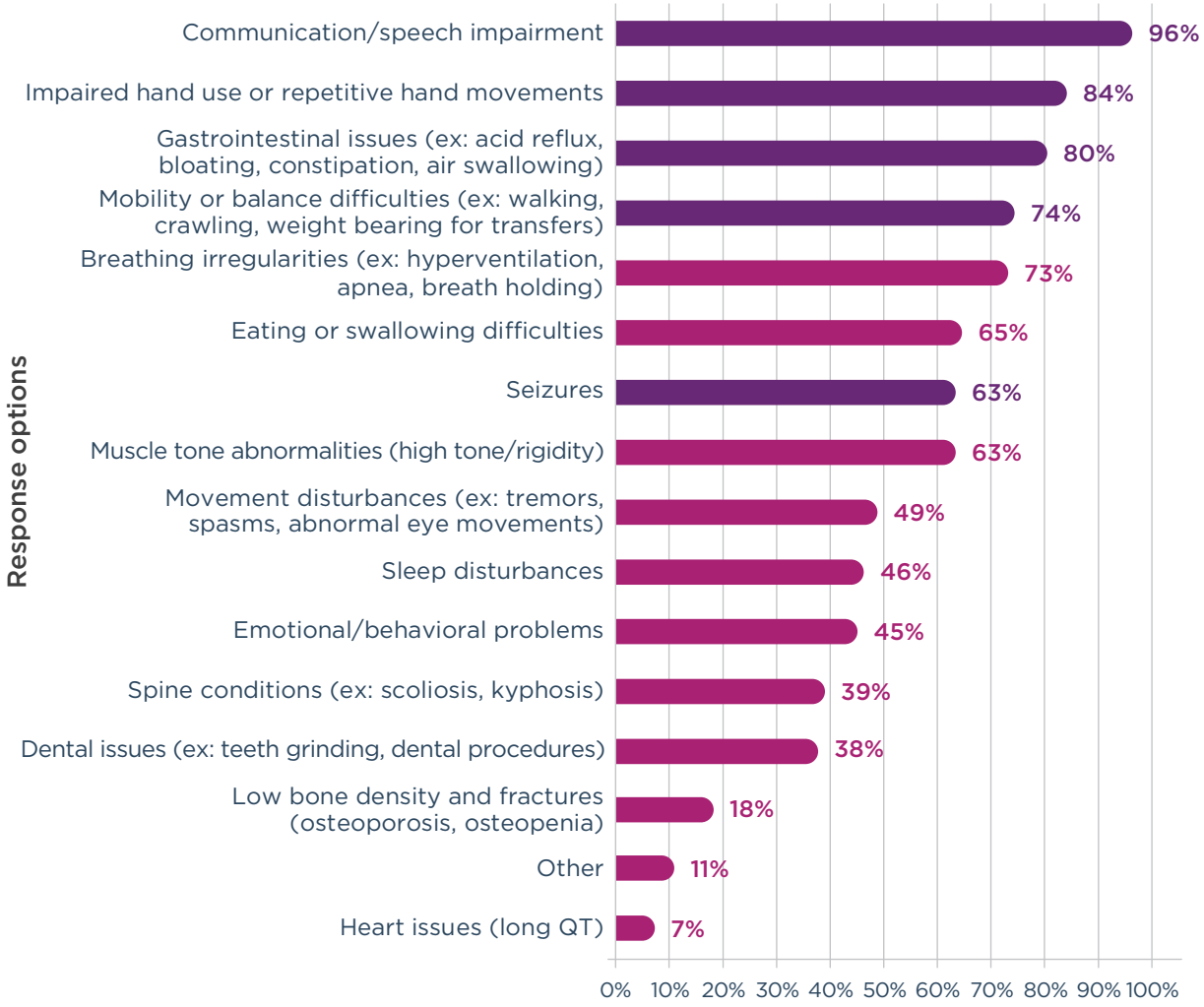
- Heather, parent of a 5-year-old daughter living with Rett syndrome
- Nida and Anemish, parents of an 18-year-old daughter living with Rett syndrome
- Wendy, parent of a 21-year-old daughter living with Rett syndrome
- Robin, parent of a 21-year-old daughter living with Rett syndrome
- Colleen, parent of a daughter living with Rett syndrome
- Melinda, parent of a 28-year-old daughter living with Rett syndrome

APPENDIX 5: SESSION 1 POLLING RESULTS

These graphs include those attendees who chose to participate in online voting. The number of patients who responded to each polling question is shown below the X axis. For most questions, poll respondents could select more than one response. The total of poll responses is also shown below the X axis.

While the response rate data for these polling questions is not considered scientific data, it provides a snapshot of who participated in the EL-PFDD meeting and is intended to complement the live and pre-recorded comments throughout the meeting.

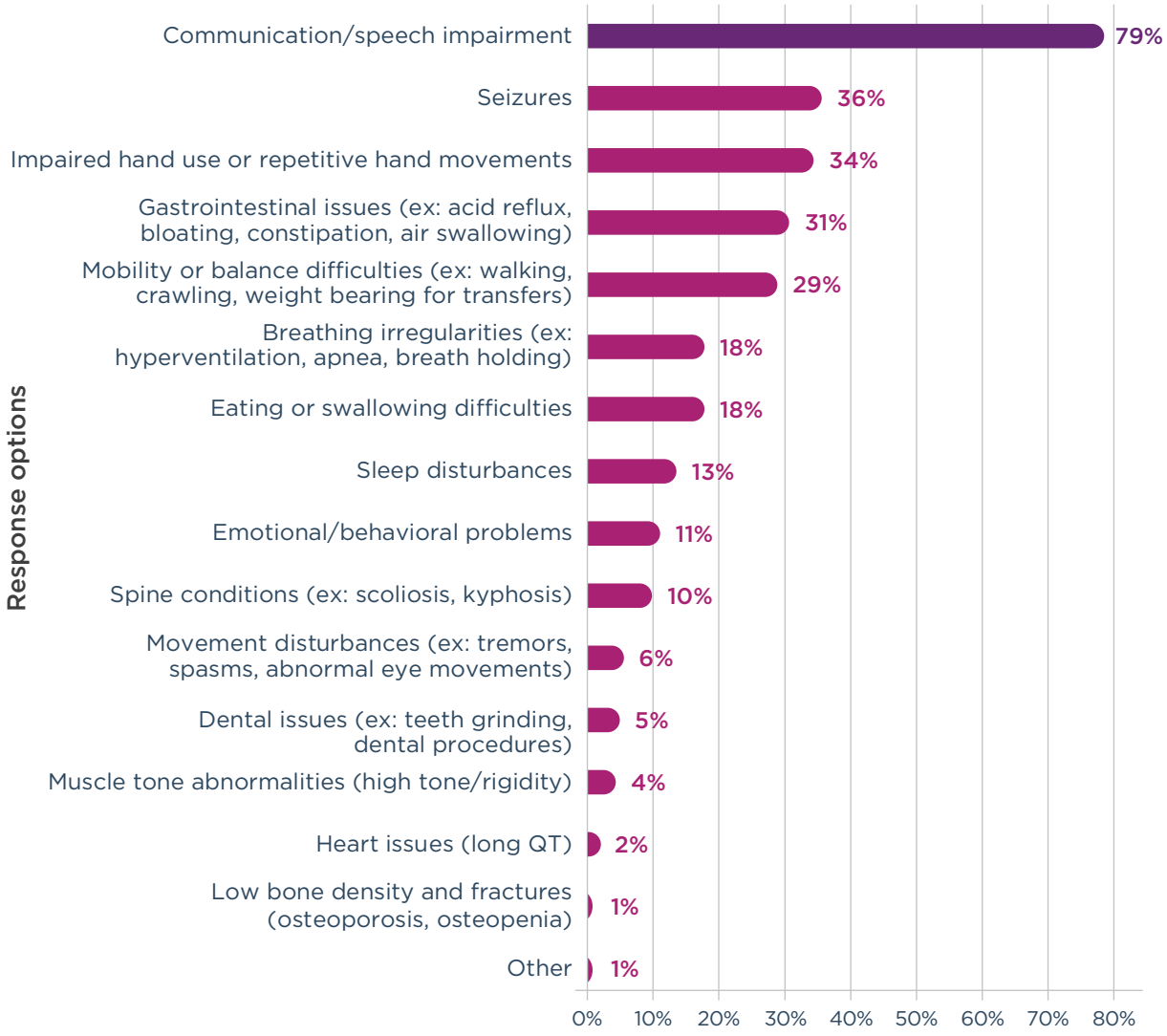
Question 1. Which of the following Rett syndrome-related health concerns does your loved one have or have had? Select ALL that apply



Percentage of respondents who selected each response option (N=82). Total responses = 700.

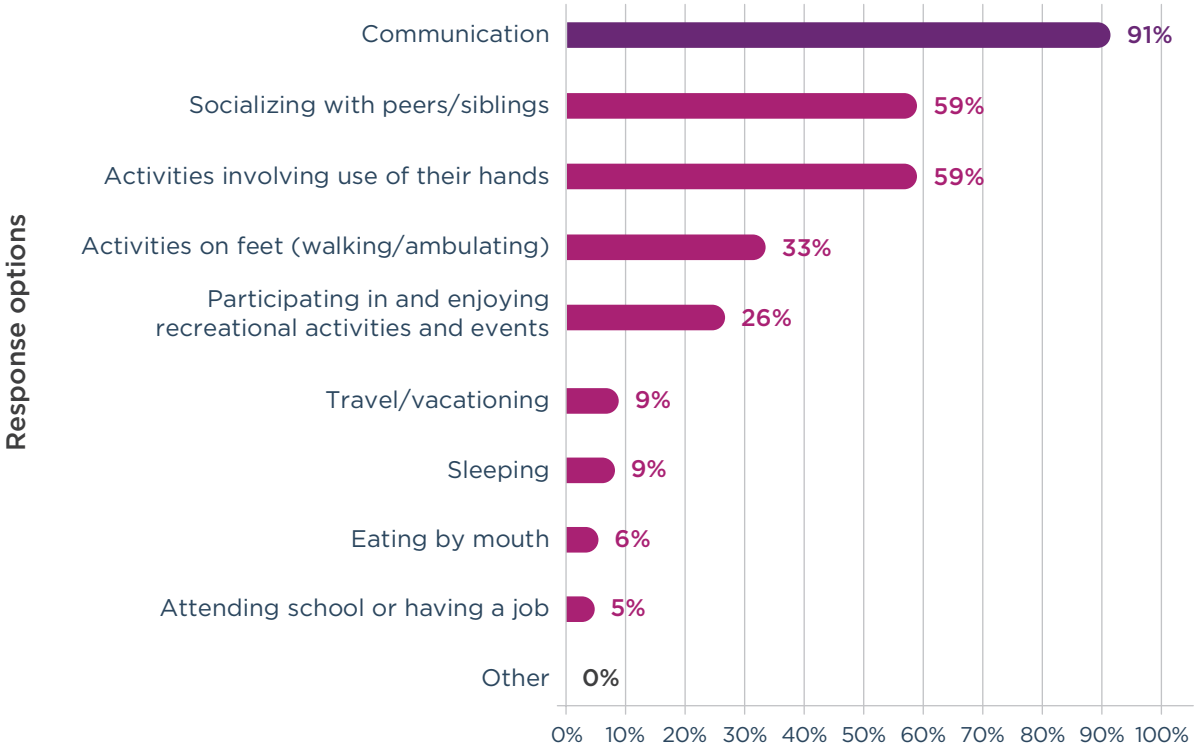
Note that respondents each selected an average of 8.5 symptoms or health concerns.

Question 2. Select the TOP 3 most troublesome Rett syndrome-related health concerns that you have or have had. Select up to 3



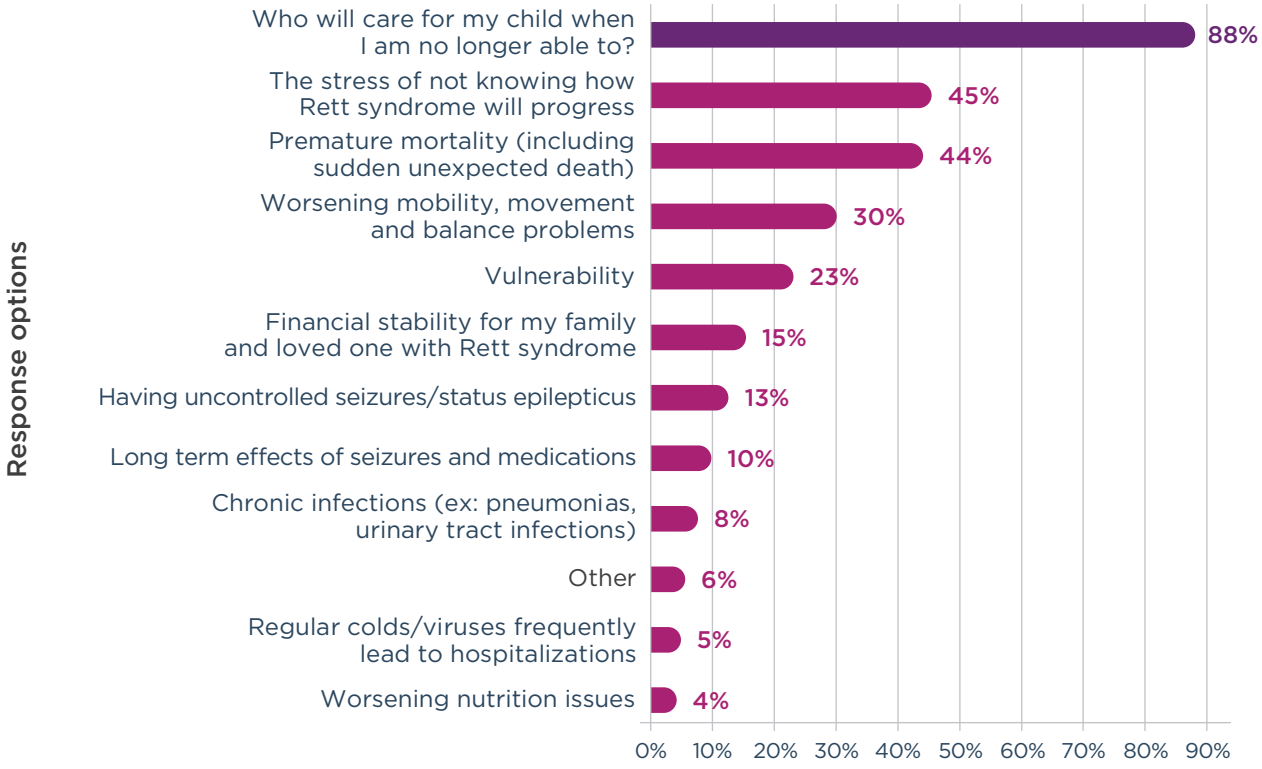
Percentage of respondents who selected each response option (N=163). Total responses = 484.

Question 3. What specific activities of daily life are most important to you that your loved one is NOT able to do or struggles with due to Rett syndrome? Select TOP 3



Percentage of respondents who selected each response option (N=138). Total responses = 410.

Question 4. What worries you most about your or your loved one's condition in the future? Select TOP 3



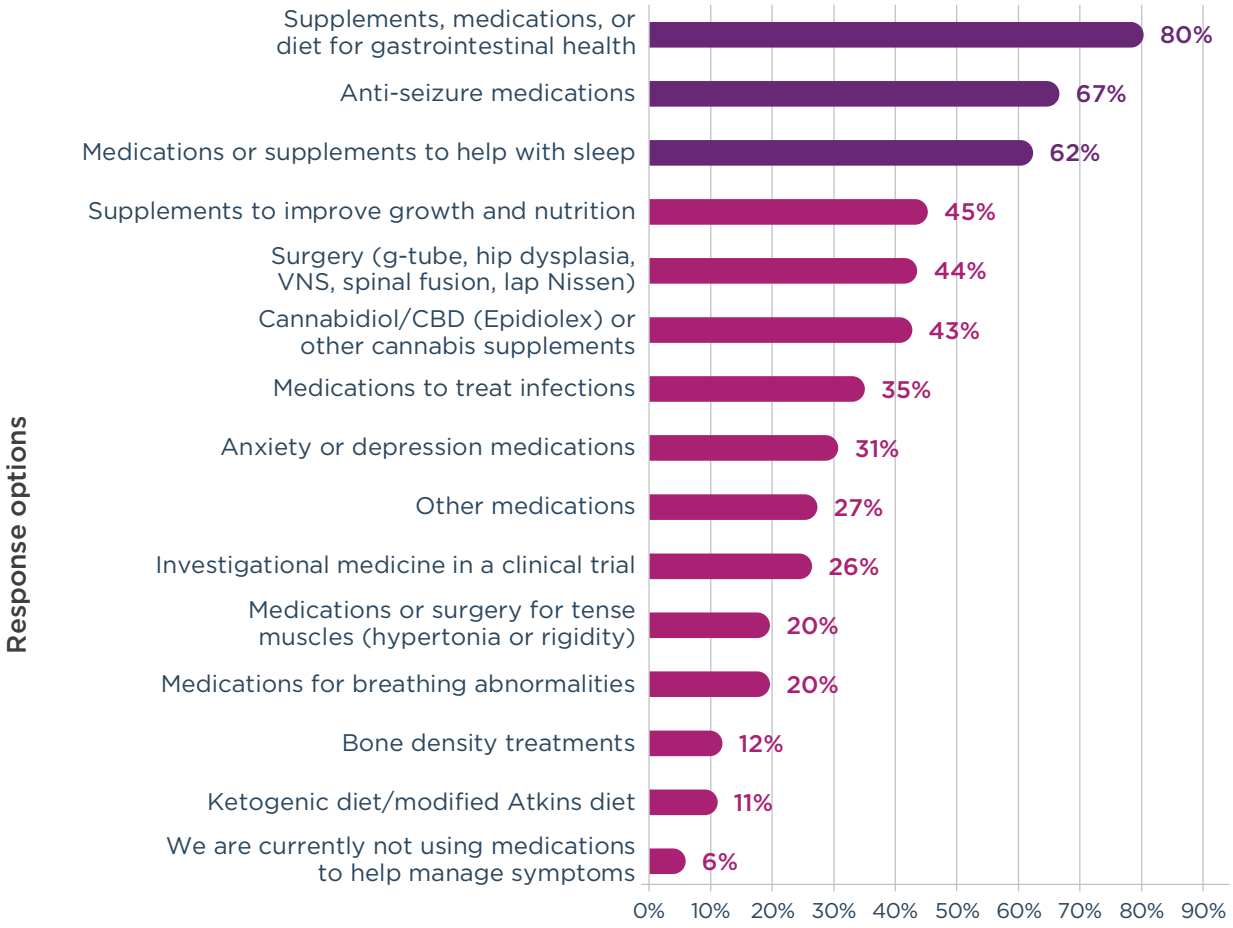
Percentage of respondents who selected each response option (N=143). Total responses = 416.

APPENDIX 6: SESSION 2 POLLING RESULTS

These graphs include those attendees who chose to participate in online voting. The number of patients who responded to each polling question is shown below the X axis. For most questions, poll respondents could select more than one response. The total of poll responses is also shown below the X axis.

While the response rate data for these polling questions is not considered scientific data, it provides a snapshot of who participated in the EL-PFDD meeting and is intended to complement the live and pre-recorded comments throughout the meeting.

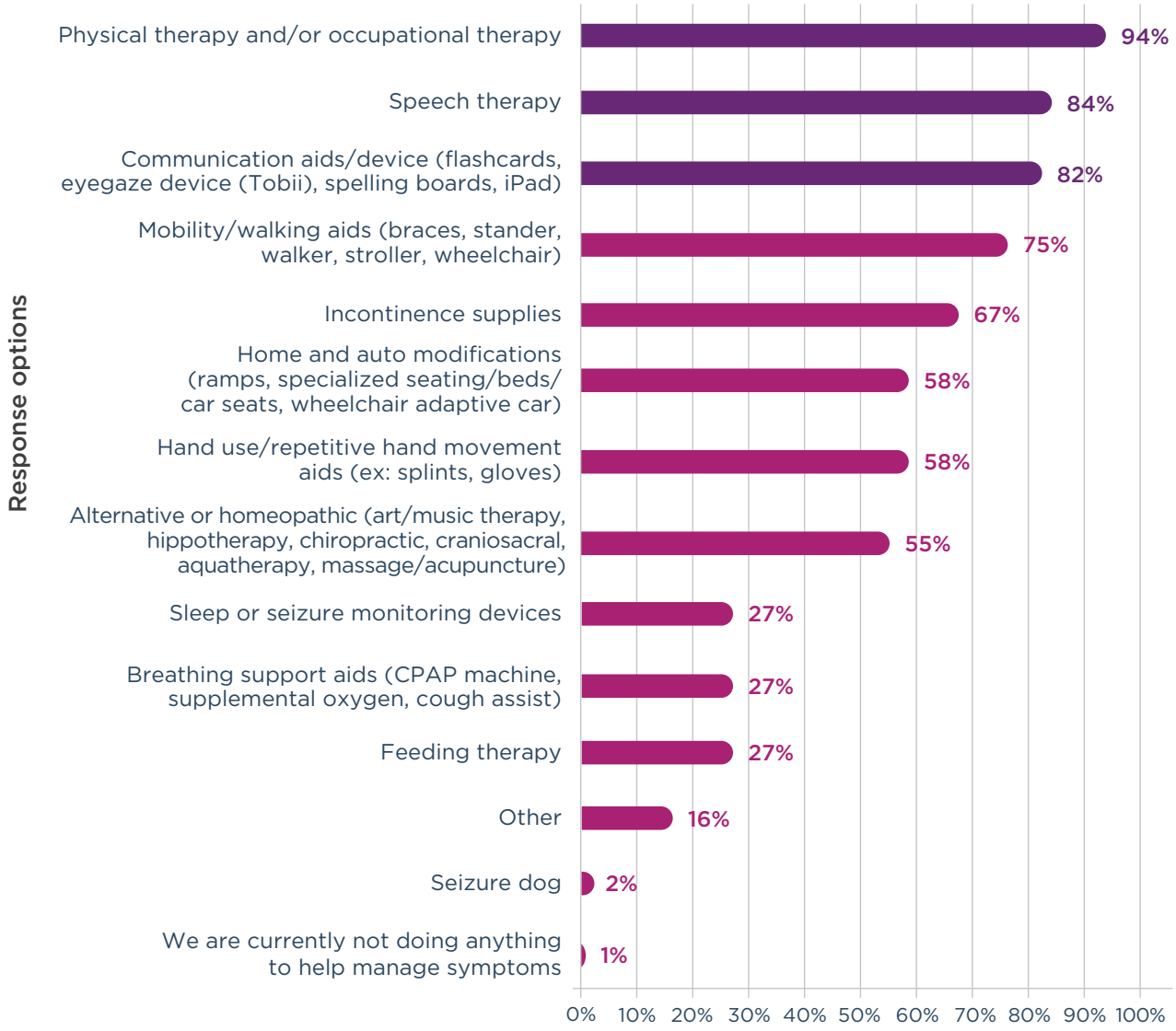
Question 1. What medications or medical treatments have you used to treat symptoms associated with Rett syndrome? Select ALL that apply



Percentage of respondents who selected each response option (N=117). Total responses = 619.

Each respondent selected an average of 5.3 different medications or medical treatments.

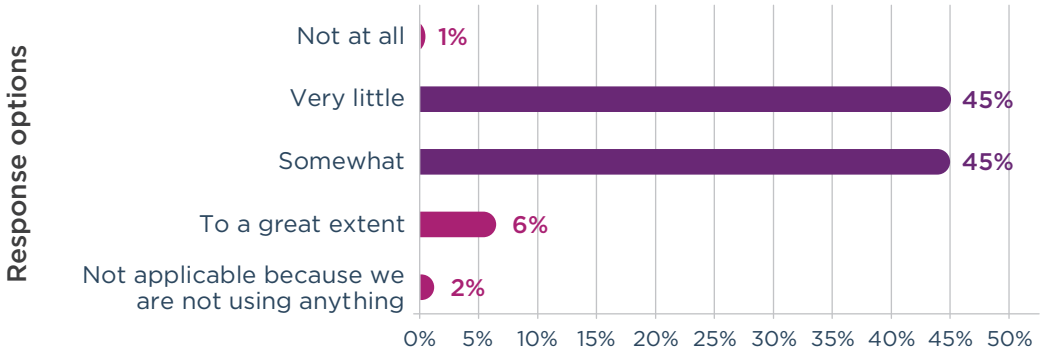
Question 2. Besides medications and medical treatments, what are you currently doing to help manage the symptoms of Rett syndrome? Select ALL that apply



Percentage of respondents who selected each response option (N=104). Total responses = 699.

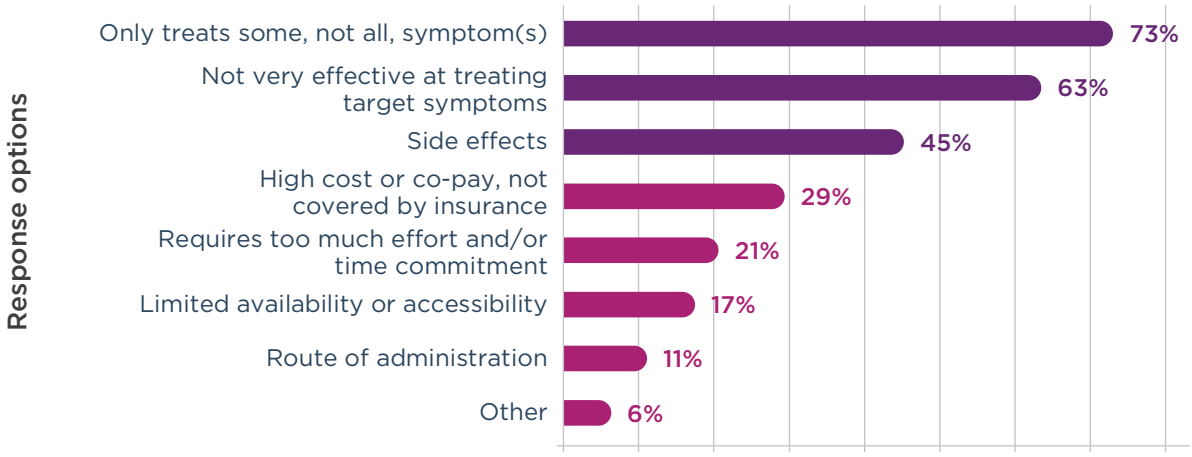
Each respondent selected an average of 6.7 different approaches to address Rett syndrome.

Question 3. How well does your current regimen control your loved one's disease overall?

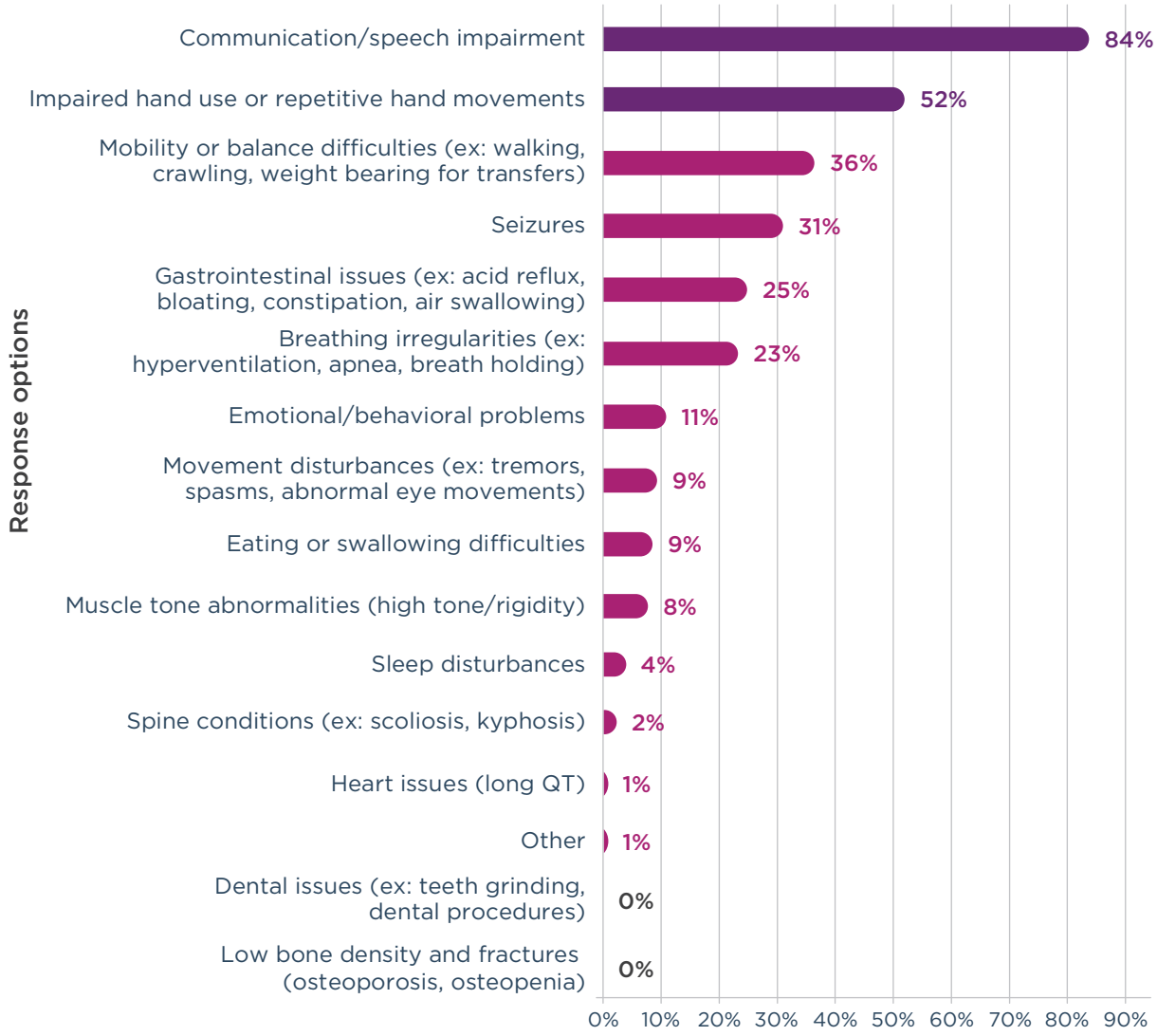


Percentage of respondents who selected each response option (N=139)

Question 4. What are the biggest drawbacks of your current approaches? Select up to 3



Question 5. Which aspects of Rett syndrome would you rank today as most important for a possible new therapeutic to improve? Select TOP 3



Percentage of respondents who selected each response option (N=129). Total responses = 381.