Every Gain, Expanding Possibilities: Caregiver Insights on Meaningful Improvement in Rett Syndrome Gene Therapy

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Aims

To explore meaningful improvements associated with gene therapy in the following domains: fine motor function, gross motor function, and communication

To explore the perceived impacts of meaningful change in functional abilities on child's and caregiver's QoL

Background

- The clinical presentation of Rett syndrome is heterogeneous – how can clinical efficacy be evaluated to account for effects in multiple symptoms and multiple severities?[1]
- Across these heterogeneities, most caregivers report that functional impairments have the greatest impact on patient and caregiver QoL; i.e., fine motor function, gross motor function, and communication[2,3]
- Caregivers value even incremental improvements in communication and fine and gross motor function, as these can enhance their child's autonomy and reduce caregiving demands[4]
- Deeper understanding regarding caregiver perspectives on meaningful improvements —while simultaneously considering gene therapy's risks and limitations—will help to inform the development assessment protocols for investigating gene therapy for Rett syndrome

Methods

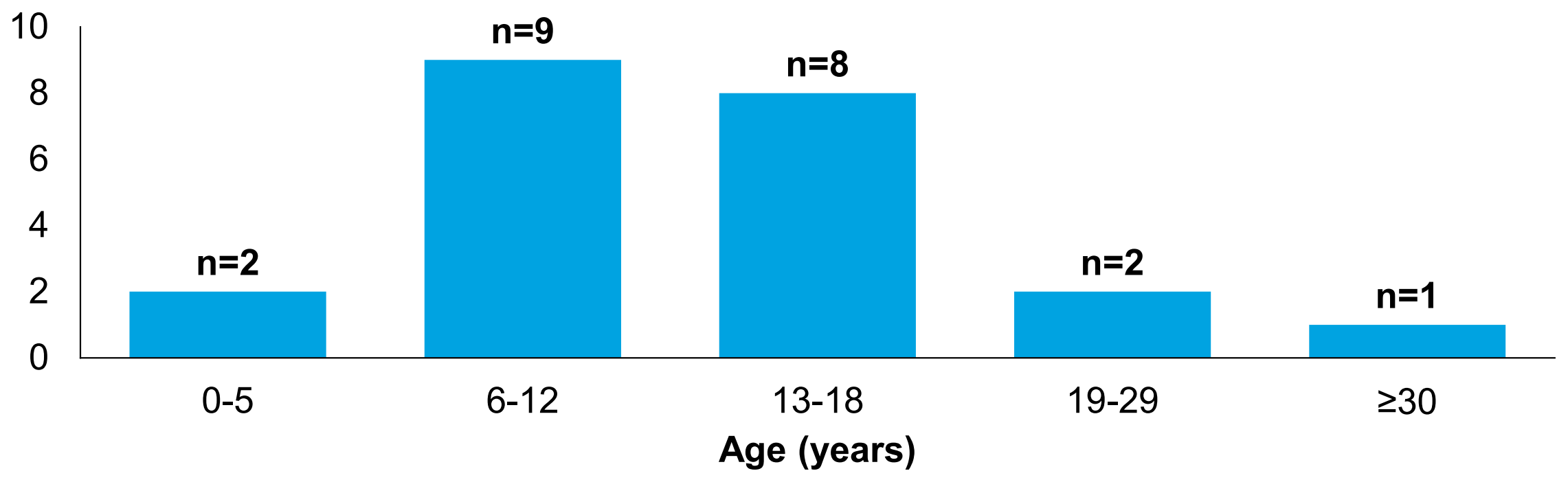
- U.S.-based caregivers of individuals with Rett syndrome were recruited via email by IRSF and the RSRT
- Semi-structured, 1:1 interviews were conducted via Microsoft Teams
- Caregivers were advised that gene therapy can only be administered once, and provided with a summary of the potential risks and limitations of gene therapy
- Interviews were recorded, transcribed, anonymized and analyzed using directed content analysis using a pre-determined coding framework
- This qualitative study was designed to explore:
  - Impact of Rett syndrome on day-to-day life on both caregivers and children
  - Meaningful improvement in fine motor function, gross motor function, and communication domains, and gain/regain of nearly 30 key developmental milestones, and why that would be important

Results

Participants

- A total of 22 U.S.-based caregivers of individuals with classic Rett syndrome (aged 5–39 years) participated (Figure 1)

Figure 1: Age distribution of individuals with Rett syndrome



- While all individuals were reported to be able to communicate via eye gaze and over half had some ability to walk, relatively few patients were able to purposefully and consistently use their hands (Figure 2)

Figure 2: Overview of child's current abilities

Fine Motor Function
- 68% cannot reach, grasp or hold an object
- 23% finger feed and/or hold objects <50% of the time
- 9% finger feed and hold objects >50% of the time

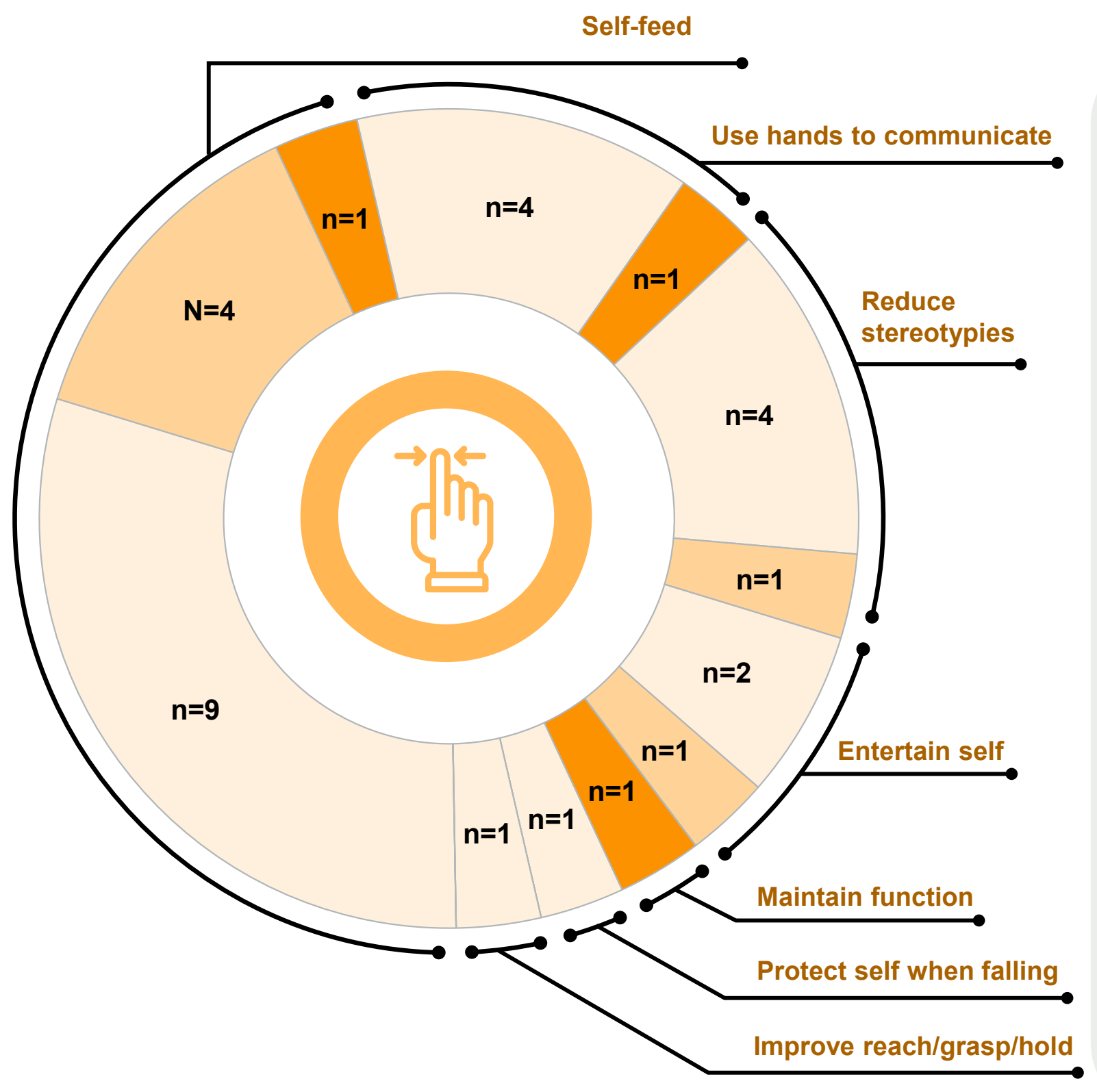
Gross Motor Function
- 45% are not able to walk with or without support
- 18% walk with support
- 36% walk independently

Communication
- 86% communicate only through eye gaze with or without AAC
- 14% use a few simple words (e.g., yes/no) and communicate via eye gaze with or without an AAC

Fine motor function

- Improving fine motor function and reducing stereotypies were top meaningful improvements in fine motor function reported by caregivers (Figure 3)

Figure 3: Meaningful fine motor function improvements reported by caregivers



> **"Feeding herself, entertaining herself… being able to flip pages or purposefully hold a book, change the channel on a remote... Things that just give her independence… would be a game changer for us."**
> – Caregiver of 8-year-old with purposeful hand use

> **"I would love for her to be able to express some kind of preference. She's almost 17, I don't know what toys she might be interested in, but if she was able to indicate by reaching, that would be meaningful."**
> – Caregiver of 17-year-old without purposeful hand use

> **"If she was able to feed herself [including using utensils with assistance]…I can't even tell you what that would do for me, to not sit and have to feed her. It just frees up a lot of time and also I think it would be huge for her self esteem."**
> – Caregiver of 15-year-old without purposeful hand use

Note: Some caregivers provided >1 response.

Gross motor function

- Caregivers prioritized enhancing existing abilities
  - Ambulatory: Improving walking distance, increasing walking speed, having more balance
  - Non-ambulatory: Sitting without support longer, having more stability

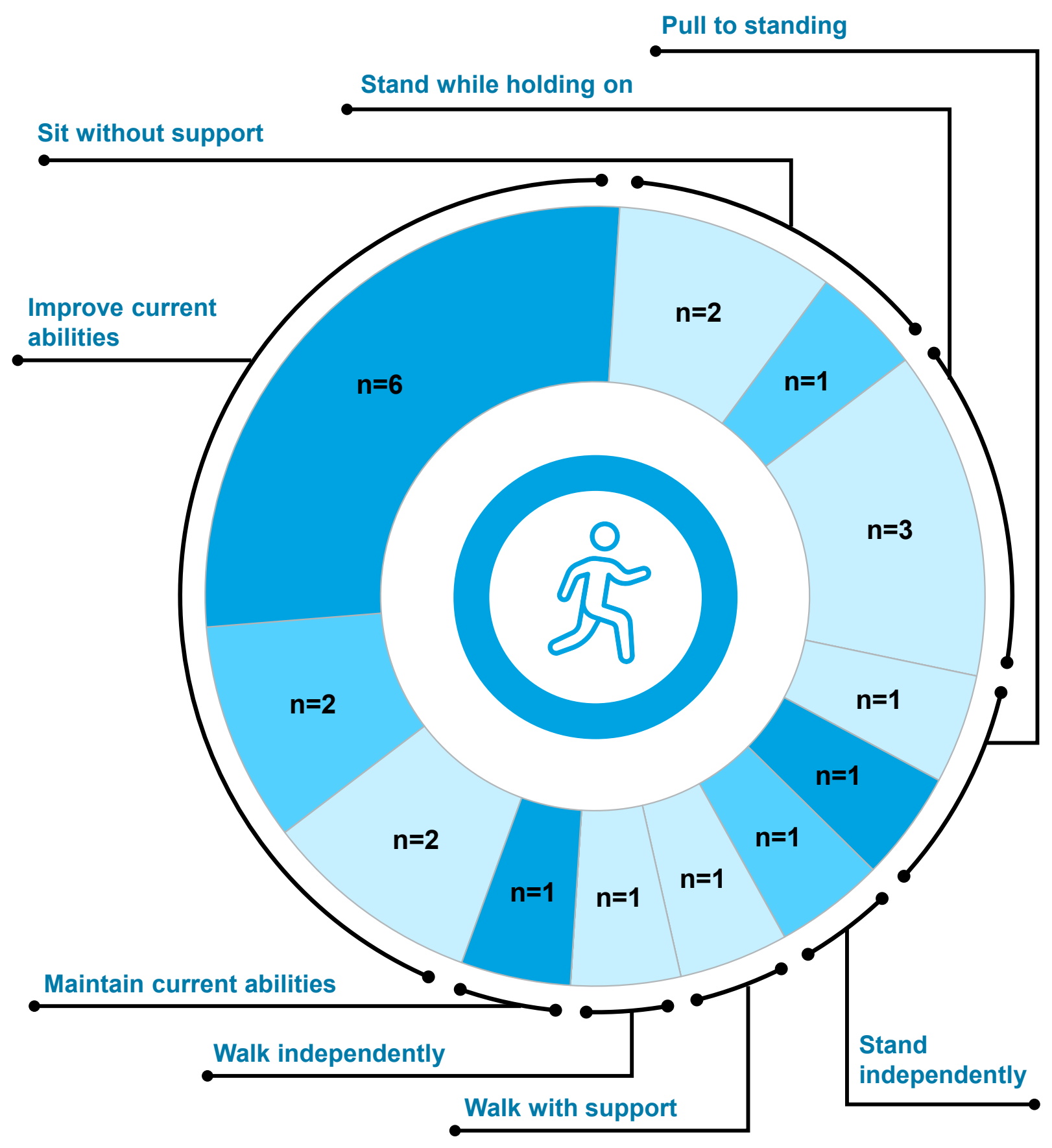
Figure 4: Meaningful gross motor function improvements reported by caregivers

> **"…if we got a safe and secure sitting position from her….[t]hat would be a win. We would be able to have her sitting and not have to be right next to her. We could have her at the dining table with us."**
> – Caregiver of non-ambulatory 5-year-old

> **"[Standing with support] Yeah, that would be very, very meaningful. Just having more independence. Not always having to have our full assistance there."**
> – Caregiver of ambulatory 7-year-old

> **"[Walking] would be amazing for her overall health, not to be in a wheelchair. And it would completely change our lives as a family. It would give us a lot more access to different activities that we can't do now."**
> – Caregiver of non-ambulatory 17-year-old

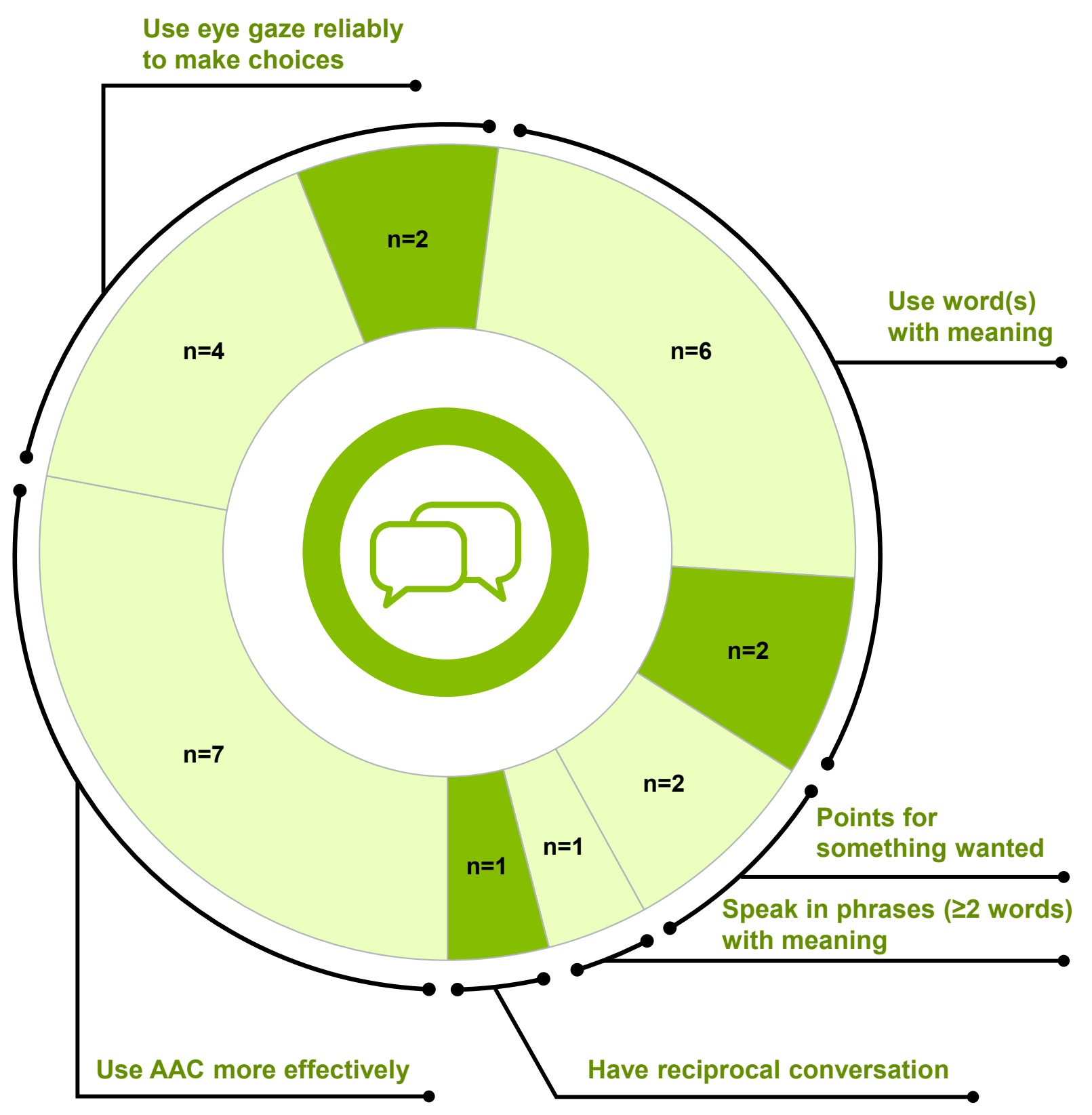
Note: Some caregivers provided >1 response.



Communication

- Using eye gaze with more accuracy, consistency, and meaning was considered a priority by caregivers
- Ability to communicate with even a small number of words (e.g., yes, no) was meaningful

Figure 5: Meaningful communication improvements reported by caregivers



> **"It would be incredible having your kid be able to advocate for themselves. Whether it's what we want to hear or not, but it would be incredible."**
> – Caregiver of 5-year-old who communicates via eye gaze

> **"I never heard my daughter say one word in her entire life, so that's a pretty, pretty big area for us if she could. But if it's just five to ten words without AAC would be incredible."**
> – Caregiver of 16-year-old who communicates via eye gaze

> **"Well, the device is a whole internal world of language, and I would really like to see her master that technology and take it to where she wants it to go …If she could change the subject and go someplace else and say 'I want to talk about this, I want to talk about that.'"**
> – Caregiver of 17-year-old who communicates via eye gaze

Note: Some caregivers provided >1 response.

Meaningful Improvements

- According to caregivers, the gain or regain of a developmental milestone would be a meaningful functional improvement post-gene therapy, improving abilities to perform activities of daily living

Milestone	Importance
Fine Motor Function	
Reach for a toy	• Supports communication through more intentional expression of wants/needs (compared to eye gaze)
Hold a bottle	• Provides autonomy and shows progress toward ability to drink from a bottle independently
Used raking grasp to retrieve an object **Used pincer grasp to retrieve an object**	• Provides autonomy and shows progress toward self-feeding • Enables more enriching activities, play and engagement with their surroundings
Transfer an object from one hand to another	• Demonstrates improved fine motor function that could strengthen over time
Ability to finger feed **Use utensils to eat without assistance** **Drink from a cup without assistance**	• Enables independence and reduces mealtime burden for caregivers • Empowers individual to meet her own needs, providing autonomy over when and how much they eat and drink • Supports more typical family dining at home or in public
Use spoon/fork to eat with assistance	• Shows progress towards ability to eat independently
Gross Motor Function	
Come to sitting	• Eases daily tasks, such as getting dressed • Provides more independence, e.g., allowing daughter to sit up in bed once she's awake
Sit with support*	• All currently had this skill, so it was not considered a meaningful improvement
Sit without support	• Improves safety and enables independence in everyday activities (playing, mealtimes)
Pulled to standing **Standing while holding on**	• Provides functional autonomy and enables independence in everyday activities, reducing the physical burden of caregiving • Increases mobility and improves overall health of individual
Walk independently **Stand independently** **Walk with support**	• Provides functional autonomy and enables independence in everyday activities, reducing the physical burden of caregiving • Enables greater leisure and travel opportunities for families • Increased stability and balance reduce safety concerns
Climb up/down stairs with or without help	• Reduces caregiver and financial burden (i.e., need for adaptive equipment) • Improves ability to navigate different surfaces (steps, curbs, building entrances)
Run 10 feet without falling	• Gaining this level of function was meaningful and almost unimaginable
Communication	
Fixes and follows objects with eyes*	• All currently had this skill, so it was not considered a meaningful improvement
Points to something they want	• Enhances ability to communicate preferences, likes and dislikes
Follows a command with or without a gesture	• Increases participation in tasks and social engagement • Enhances safety (e.g., "stop/watch out")
Can identify body parts	• Enables ability to show if/where something hurts
Uses words with meaning	• Facilitates more decisive choice-making, greater agency and self-expression • Reduces frustration and friction in daily life • Minimizes "guessing game" and guilt caregivers feel when they are unable to understand
Speaks in 2-word phrases	• Increases self-advocacy for needs/wants • Strengthens relationships and connections for a more fulfilling social life
Can identify colors*	• Most caregivers did not find this to be a meaningful outcome of gene therapy

**Not included in the Developmental Milestone Assessment based on caregiver feedback.*

> **"I mean obviously it's super exciting because there are no other [disease modifying] treatments…We're feeling like gene therapy is the next frontier. The best hope for any kind of meaningful improvement. I feel cautiously hopeful."**
> – Caregiver of 17-year-old

Conclusions

- Findings consistent with recent research on developmental and epileptic encephalopathies, also associated with complex and severe functional impairments[5,6]
- Caregivers reported that improvements in fine motor function, gross motor function, and communication guide their interest in seeking gene therapy
  - Caregivers valued gain/regain of developmental milestones from gene therapy
  - Incremental improvements were perceived as supporting child autonomy, safety, social interactions, pare burden of care and quality of life
- Caregivers estimated that the gain or regain of developmental milestones would enable their child's ability to perform everyday activities
- This data informed the use of the Developmental Milestone Assessment in a gene therapy clinical trial (REVEAL)

Key Takeaway

Key outcomes for caregivers of people with Rett syndrome that would guide decisions to seek gene therapy include achieving developmental milestones (e.g. gain/regain of functional abilities) supporting greater autonomy for their child and assist with activities of daily living and communication, thereby enhancing quality of life and reducing the demands of caregiving

Taysha
GENE THERAPIES

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Abbreviations: AAC, augmentative and alternative communication device; IRB, institutional review board; IRSF, International Rett Syndrome Foundation; RSRT, Rett Syndrome Research Trust; U.S., United States of America

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