



Poster #266

NGN-401, a Novel Regulated AAV9 Gene Therapy, Demonstrates Clinically Meaningful Improvements in Hand Function in a Phase 1/2 Study in Rett Syndrome

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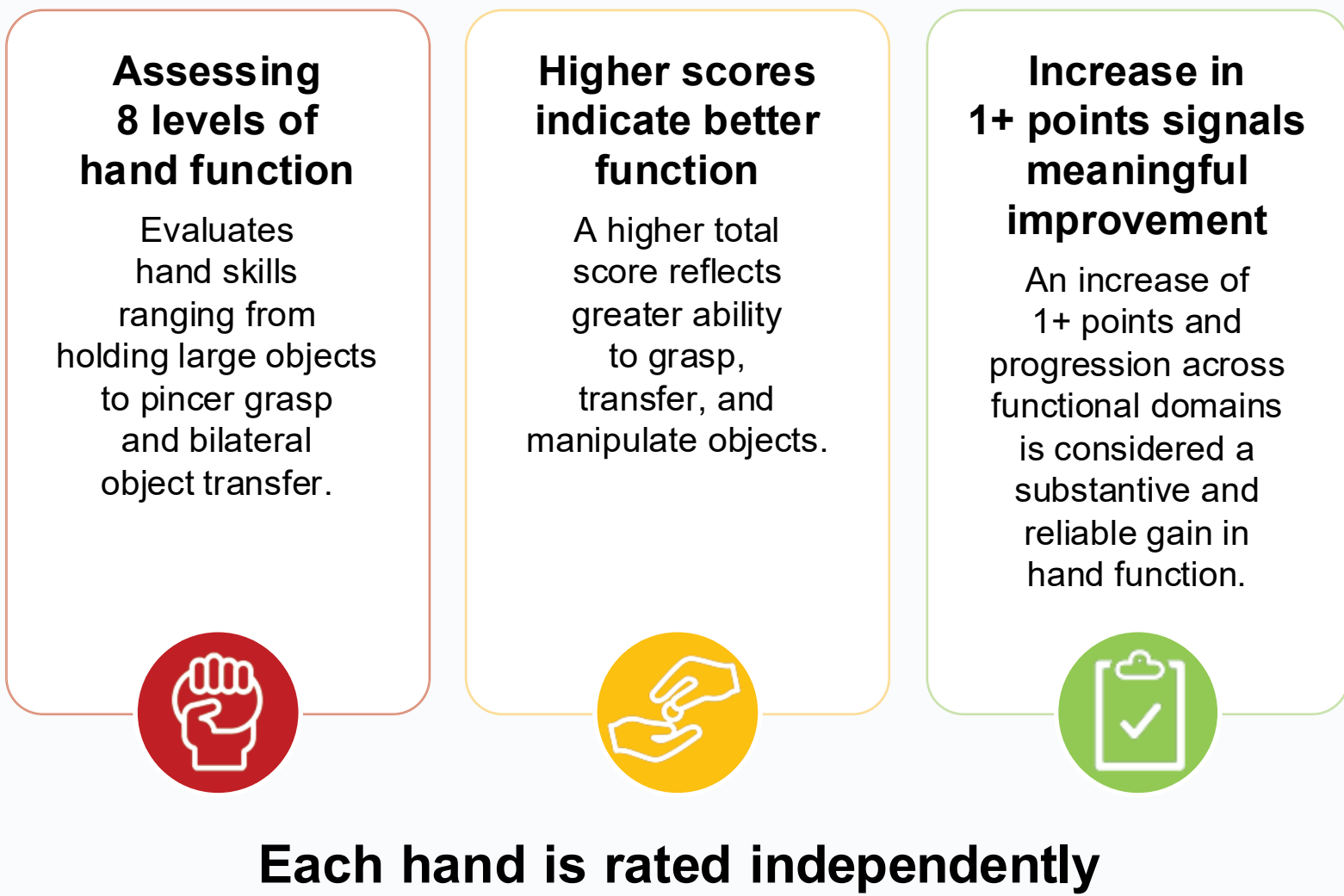
INTRODUCTION

- Rett syndrome (RTT) is a rare neurodevelopmental disorder caused by loss-of-function variants in the *MECP2* gene encoding MeCP2, a protein critical for normal function in the brain and nervous system.^{1,2}
- In RTT, loss of purposeful hand use (e.g., grasp, transfer, goal-directed hand movements, engagement in activities of daily living) has substantial impacts on patients and caregivers.^{3,4}
- Based on natural history data, simple developmental milestones are lost, some rarely re-acquired, and more complex skills are not acquired post-regression.^{1,2,5,6}
- NGN-401 is an investigational AAV9 gene therapy that delivers the full-length human *MECP2* transgene, incorporating EXACT™ transgene regulation technology designed to enable controlled MeCP2 expression on a cell-by-cell basis, and is administered intracerebroventricularly for the treatment of RTT.^{7,8}
- The data presented here show improvement in hand function in participants that received NGN-401 in the Phase 1/2 trial.

METHODS

- The Phase 1/2 open-label trial (NCT05898620) in females with classic RTT, age ≥4 years, with a baseline Clinical Global Impression – Severity (CGI-S) score of 4–6, is evaluating the safety, tolerability, and efficacy of NGN-401.⁸
- 10 participants received 1E15 vg NGN-401 (age 4–10 years cohort, n=8; age ≥11 years cohort, n=2).
- The data cutoff was June 16, 2026, yielding a minimum of 12 months and up to 30 months of follow-up across the 10 participants.
- Hand function was assessed in 2 ways:
 - Through developmental milestones based on the criteria in the Embolden™ registrational trial evaluating NGN-401.⁹
 - The Rett Syndrome Hand Function Scale (RSHFS)¹⁰, a validated tool that measures hand function in 8 levels of increasing sequential complexity. A higher RSHFS score indicates better hand function (**Figure 1**).

Figure 1. The RSHFS assesses hand function.



RSHFS analysis

- RSHFS testing was videotaped in clinic, and scores were assessed by central independent raters.
- Replicable and best attained scores were analyzed relative to baseline, to account for variability across visits (e.g., fatigue, illness, attention, apraxia) and align with established responder frameworks in rare neurological diseases.^{11,12}
- Reproducibility of best score was confirmed via ≥2 documented central ratings and/or centrally reviewed videos performed outside the assessment. Repeat confirmation was not required when the best score occurred at the most recent assessment as it was deemed an emergent skill.

Table 1. Phase 1/2 baseline participant demographics.

Characteristic	All participants (N=10)
Age at dosing, years, range	4–18
Baseline CGI-S score*	4–6
Genetic variant severity	Mild to severe
Time post-dosing	12–30 months
Baseline hand function†	RSHFS score <7: 90%

*Score of 4 indicates 'Moderately ill'; score of 5 indicates 'Markedly ill'; score of 6 indicates 'Severely ill'. †RSHFS score of 1 indicates unable to grasp objects, scores 2–6 indicate skills using one hand, scores 7–8 indicate more complex single and bilateral hand skills. CGI-S, Clinical Global Impression – Severity scale; RSHFS, Rett Syndrome Hand Function Scale.

References

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RESULTS

- All participants (100%, n=10/10) demonstrated a gain in hand function either by improvement in RSHFS (n=8), improved grasp (n=1), and/or the acquisition of a new hand function developmental milestone (n=1).
- Of the 9 participants with significantly impaired hand function at baseline (RSHFS <7), 89% (n=8/9) achieved at least a 1-point gain from the baseline/first assessment, with many demonstrating larger gains of ≥2 and ≥3 points in the RSHFS total score (**Figure 2**). Post-treatment scores increased by 1.8 points on average for both dominant and non-dominant hands (**Figure 2B and 2C**).
 - Of the participants with no observable hand function in at least one hand at baseline/first assessment (RSHFS score of 1, n=7), 100% (n=7/7) showed improvements (**Figure 2B and 2C**).
 - Most participants 78% (n=7/9) demonstrated bilateral improvements in RSHFS score (**Figure 2D**).
- A participant who had less impaired baseline hand function (RSHFS score=7) demonstrated advancement in the precision of grasping small objects (**Figure 4**) rather than an increase in score.

Figure 2. RSHFS score improvements.

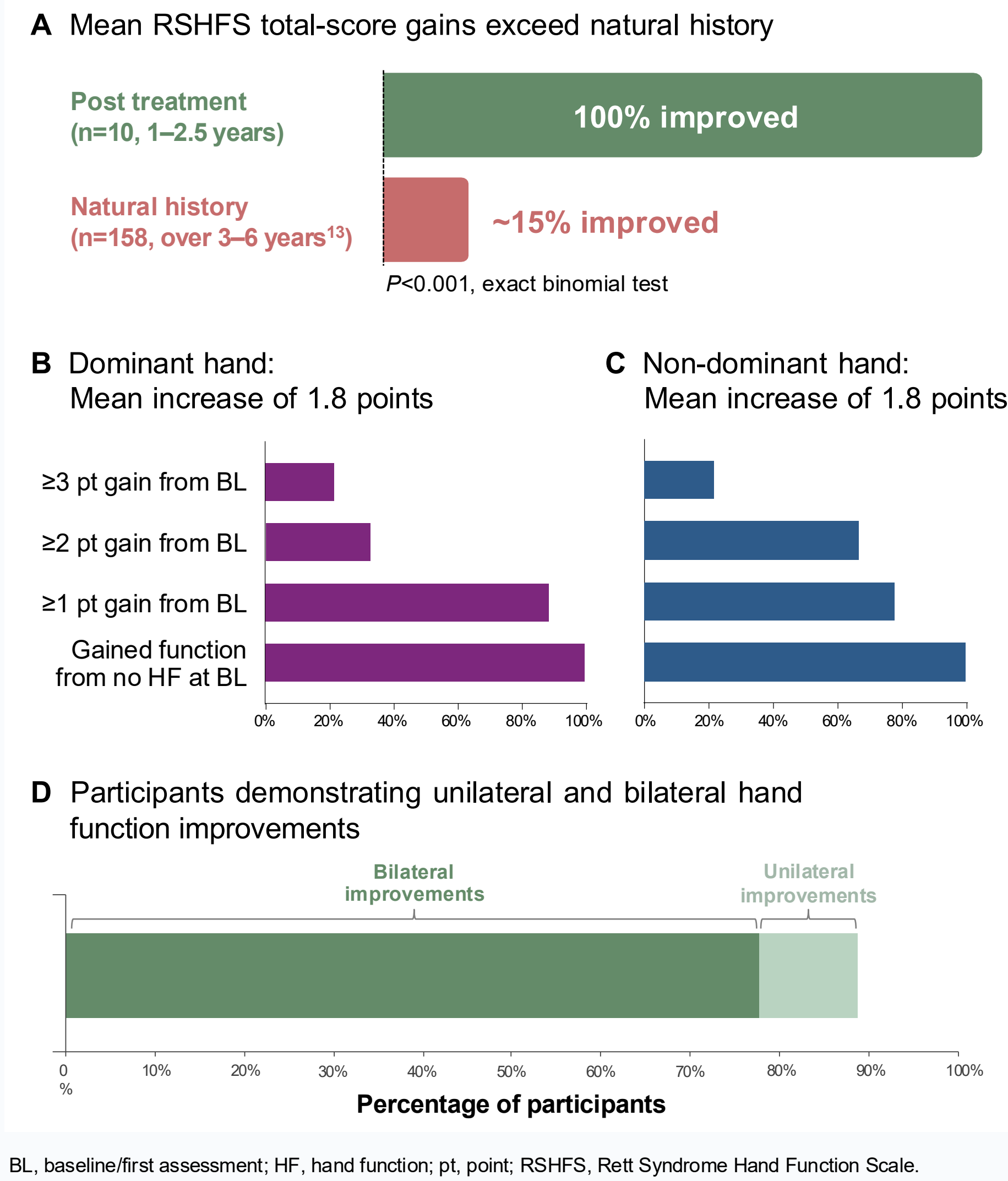
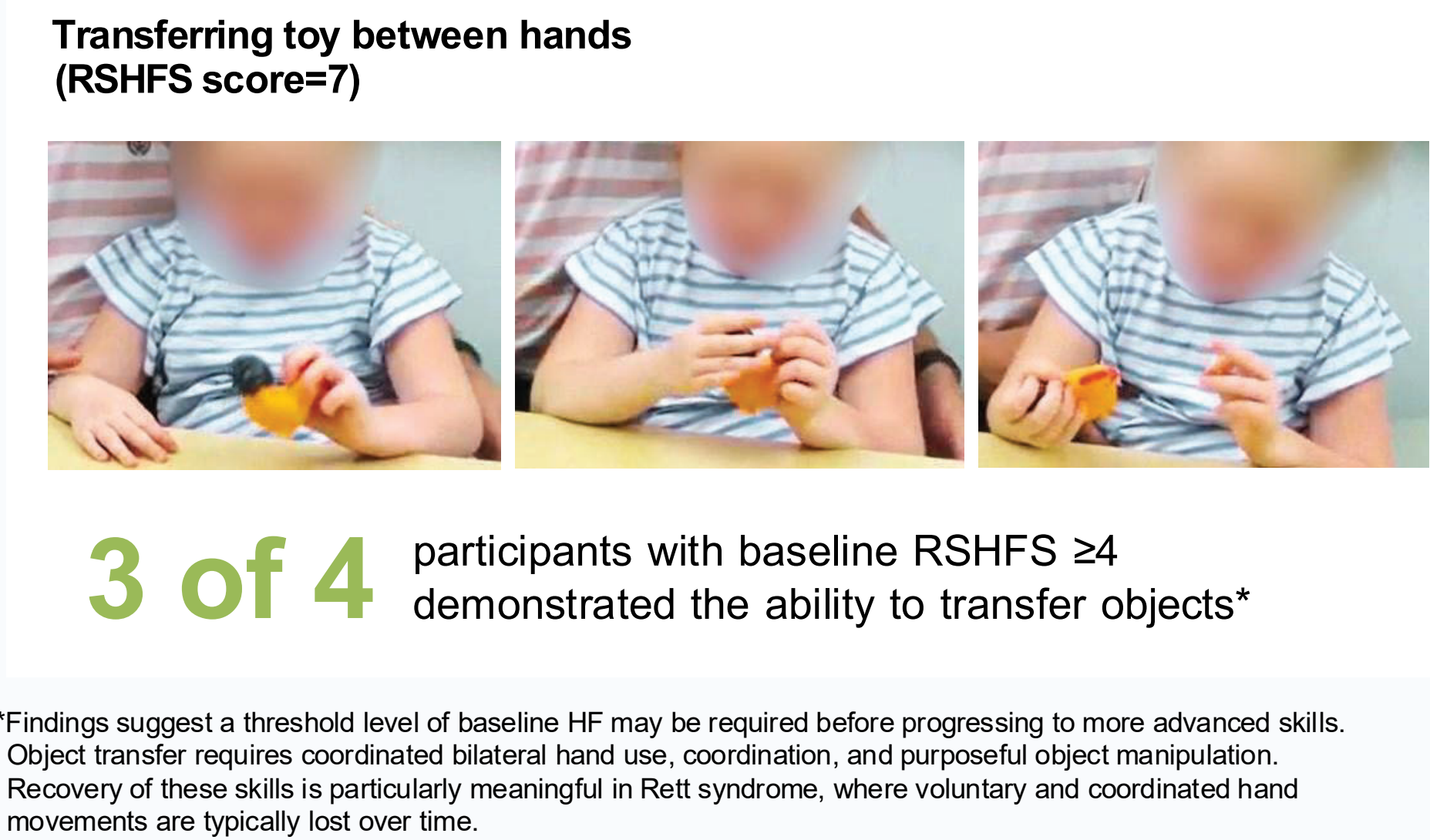


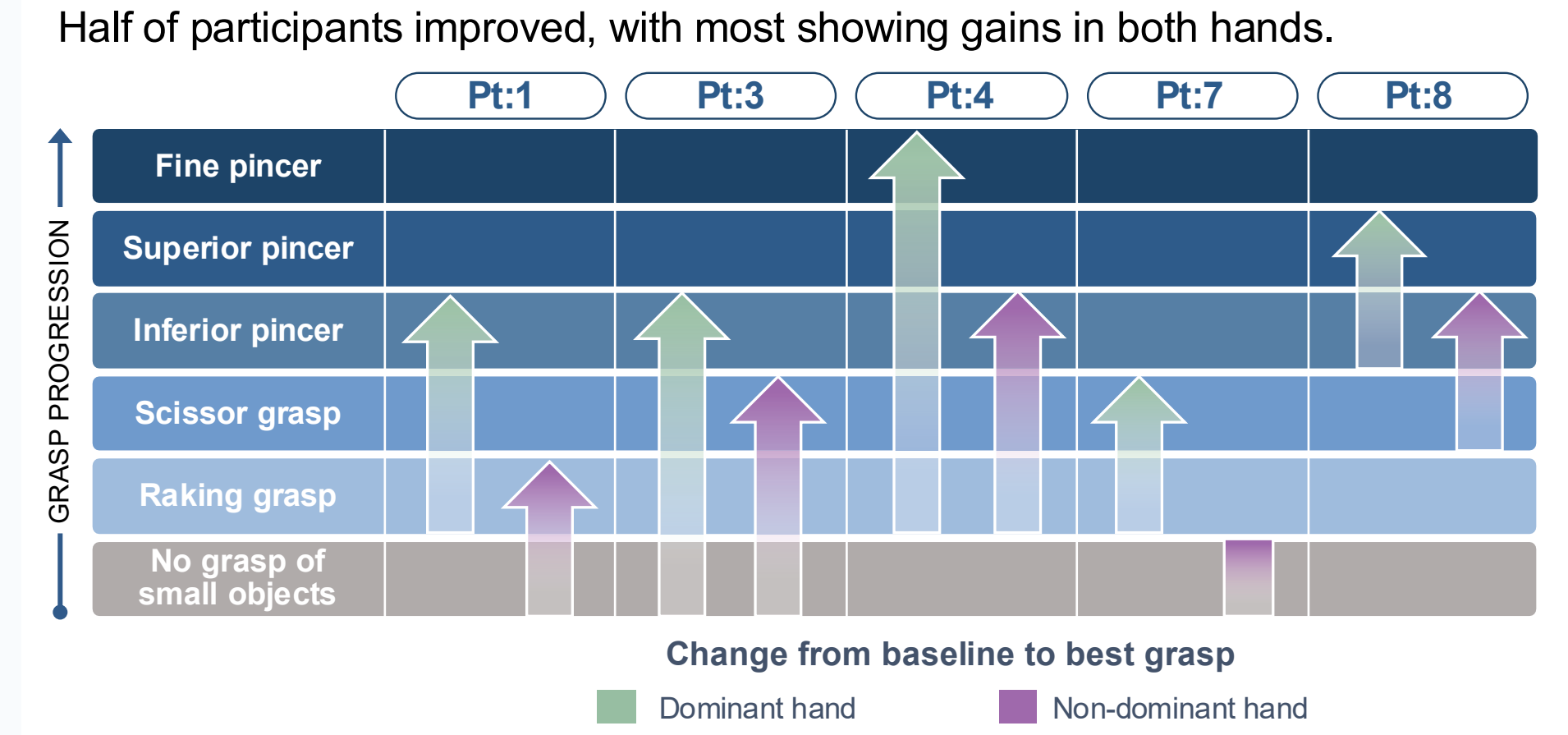
Figure 3. Bimanual hand use gained by participants who grasped objects with one hand.



KEY CONCLUSIONS

- Treatment with NGN-401 resulted in clinically meaningful improvement in hand function in a disorder where hand function is not expected to improve.¹³
- Hand function gains were observed in 100% of participants, with improvements in both hands seen in the majority, supporting functioning in daily life.
- Most participants achieved hand-function milestones in a hierarchical manner, including emergence and refinement of pincer grasp and object transfer, reflecting more fine motor control, coordination, and dexterity.
- Real-world examples demonstrate how hand function improvements translate into purposeful, goal-directed hand use that positively impacts everyday life, such as playing, eating independently, joining in family outings, and engaging in family activities.
- These functional gains align with caregiver priorities, highlighting the importance of improved hand use for independence and reduced caregiving burden.⁴

Figure 4. Progression toward more refined grasp patterns of small objects.



For participants 1 and 3, the RSHFS assessment was introduced into the study subsequent to study start. Baseline grasp was confirmed via an alternative in-clinic video assessment and was centrally rated for confirmation. Progression from bilateral raking grasp to bilateral pincer represents higher-order fine motor control. Gains in hand function meaningfully impact everyday life activities and gain of these skills is particularly important to patients and caregivers. Pt, participant; RSHFS, Rett Syndrome Hand Function Scale.

Figure 5. Improved grasping and new abilities of bilateral hand use enabled meaningful play.

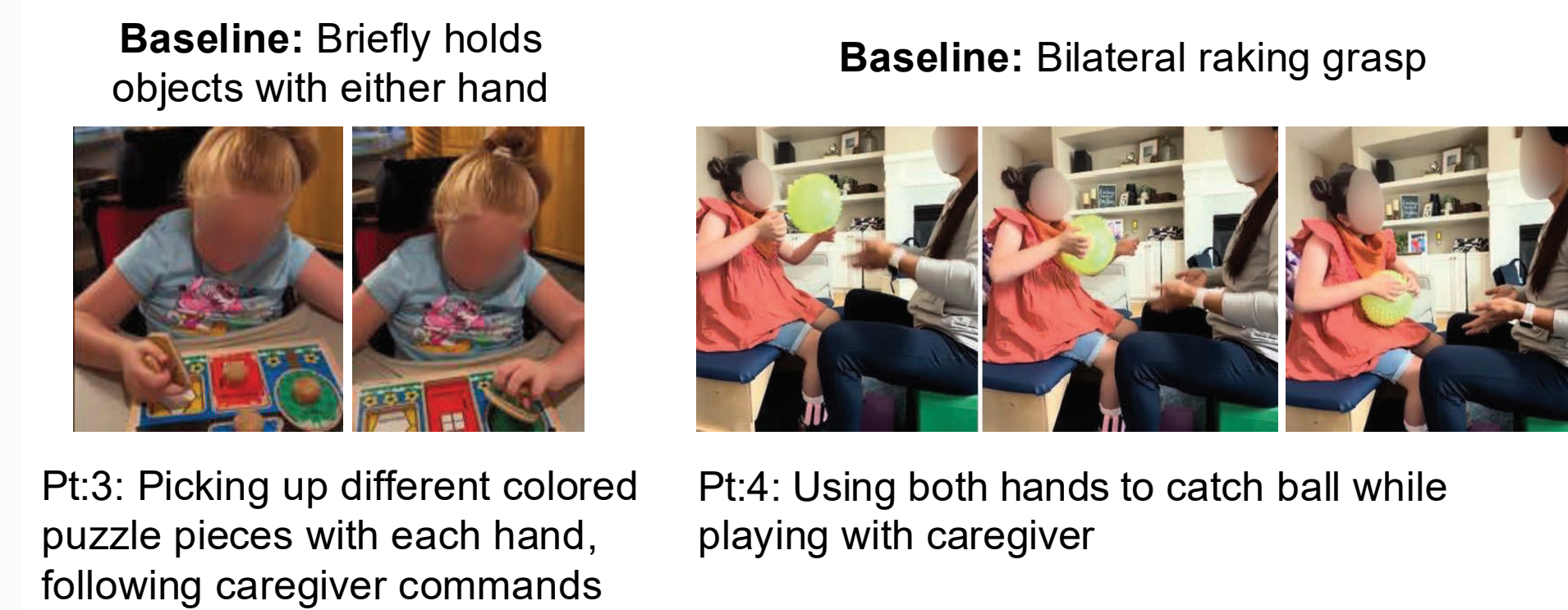


Figure 6. Gains in hand function enabled independent self-feeding at mealtimes.

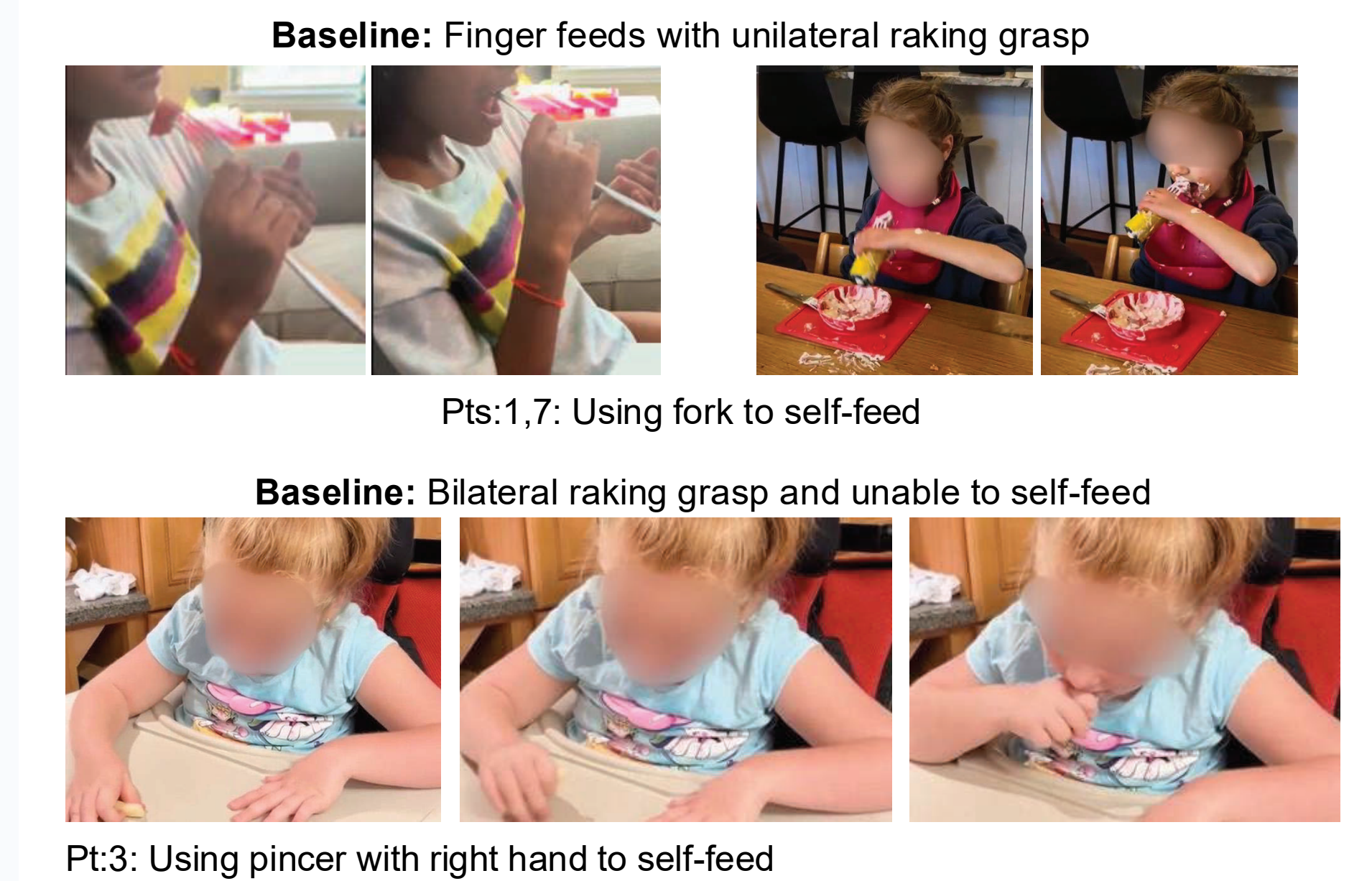
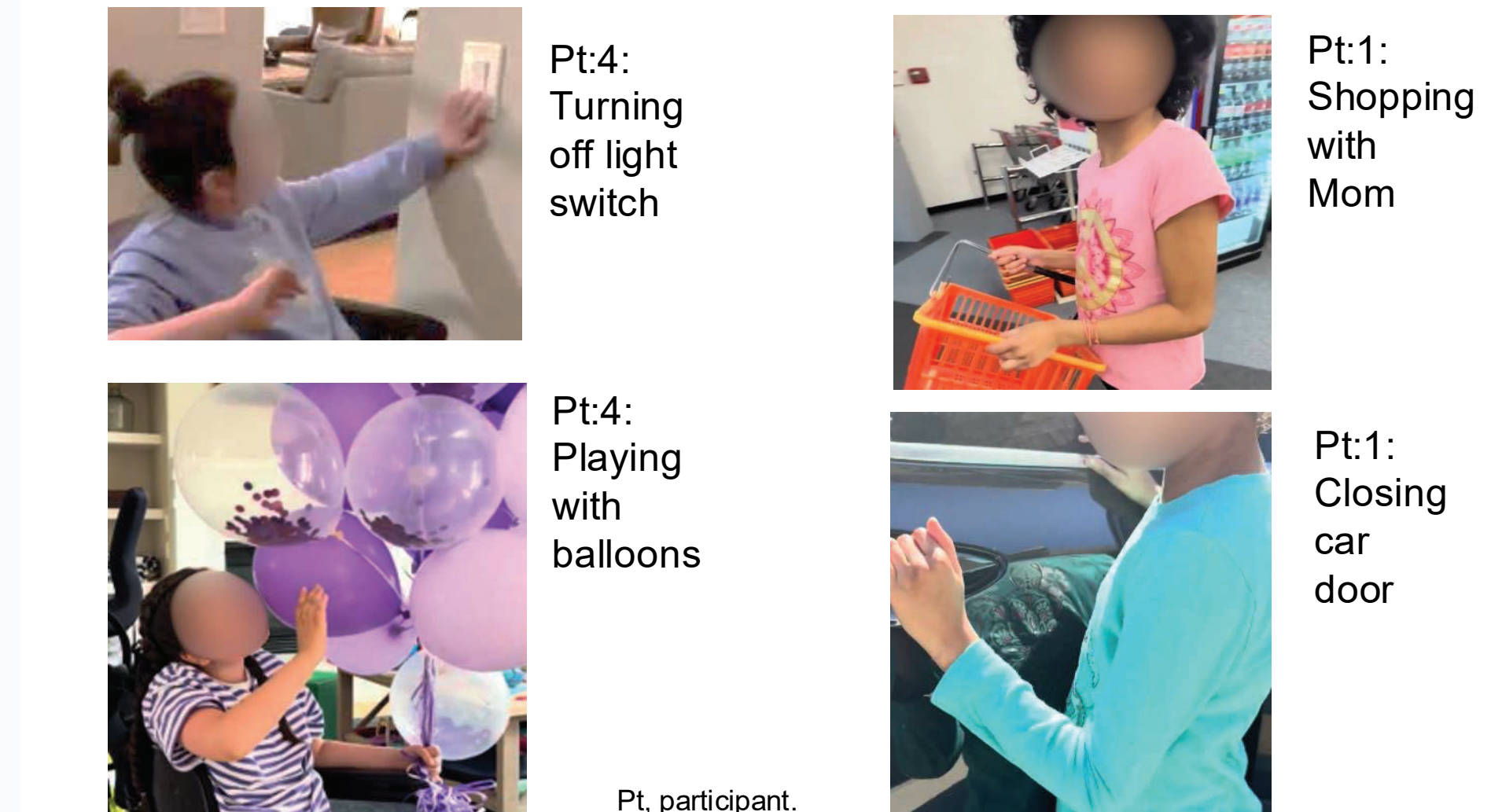


Figure 7. New hand skills and bimanual coordination translated to real-world participation in family routines and celebrations.



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