Title: Creatine Transporter Deficiency and Potential Outcome Variables for the Severely Impaired

Authors: Judith S Miller, Rebecca P Thomas, Kaitlin Mulray, Daniel Fichter, Kristen Cunningham, Ranita Anderson, Aleksandra Bruchey, Robert J Davis, Audrey Thurm, Monica E Calkins

Introduction: Creatine Transporter Deficiency is a rare X-linked disorder associated with severe developmental impairments. It was first identified in 2001, and little is known about the natural history. We assessed a sample of individuals with CTD to identify potential clinical endpoints that would be meaningful to families and responsive to change in a treatment trial.

Method: We studied 20 males with CTD (age 1-21 years) using parent questionnaires and interviews, record reviews, and in some cases (n=7) direct testing. From parents we gathered: earliest concerns, top 3 current concerns, the path to diagnosis, co-occurring medical or behavioral conditions, developmental course, and intervention history. From direct testing we explored content overlap and ease of administration across several norm-referenced and criterion-referenced developmental tests (Mullen, Vineland-II, Peabody, PLS-5, DASH-3). We administered these tests regardless of chronological age – our oldest participants still obtained relatively low raw scores on these measures.

Results: Parents’ top concerns included: Language, negative behaviors, independence skills, attention, and emotion regulation. Across the developmental tests there was significant redundancy, with many nearly identical activities and prompts. In the end, the combination of the Mullen and Vineland appeared to be the most efficient manner of presenting the types of activities and prompts across the domains prioritized by parents.

We then attempted to model a pre-post intervention analysis with a 12-month interval. We plotted our current Vineland raw scores and standardized scores. For each participant, we then calculated the increase in raw scores that would result in a statistically significant improvement in standardized scores, defined as a post-intervention standardized score that would exceed the confidence interval range of the pre-intervention score. For example, if the current standardized domain score and confidence interval was 7+/-2, then a statistically significant post-intervention standardized domain score would be 11+/-2.

We found that, across the domains of the Vineland a raw score increase of 3-58 points would be needed to achieve statistically significant differences in an individual participant’s standardized scores pre- and post-intervention. We conducted a similar analysis with the Mullen, and found a 10-39 increase in raw score would be needed to approximate a statistically significant increase in scores.

Discussion: For CTD, parents rated skill development as the most meaningful endpoint. Our results suggest that the Vineland and Mullen provided the activities and prompts to measure foundational skills for severely impaired individuals, regardless of chronological age. Relatively large increases in raw score points are needed to ensure statistically significant changes in an individual’s functioning relative to the psychometric properties of the instruments. However, raw score increases of a much smaller magnitude might indicate clinically significant skill development that would be meaningful to families.