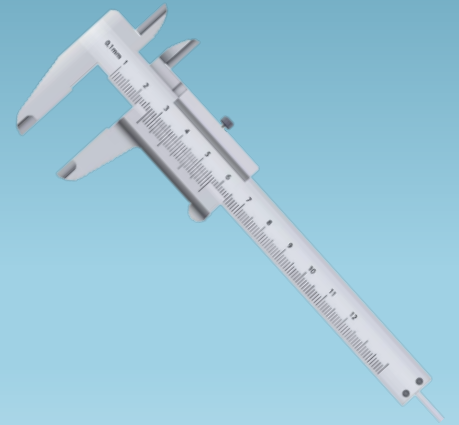


Rare diseases – rare outcomes

Measuring “better” for DEE patients with severe impairments



Anne T. Berg, PhD
Northwestern-Feinberg School of Medicine



DEEs, they're not just for seizures anymore.

Non-seizure outcomes as primary trial targets
How do we get there?



Which measures can be used to test whether there is improvement?

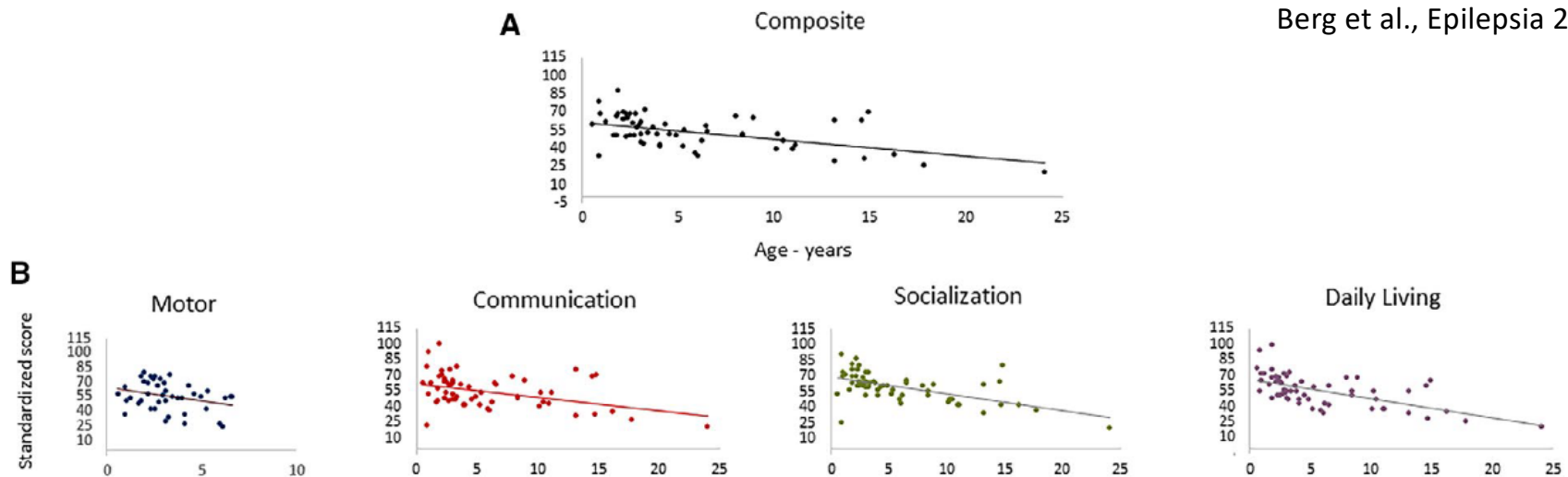
On-line Outcomes Measures Boutique



Vineland
Bayley
ADOS
BRIEF
WISC
Mullens
WISC
BITSEA
PEDS-QL
CBCL
ABC

Consequences of On-line Shopping!

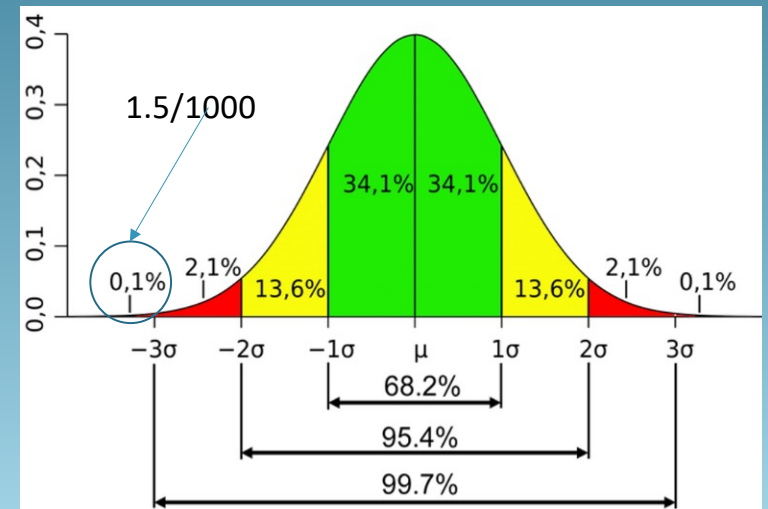
- Vineland-II from Simons Searchlight, SCN2A Cohort
 - Standardized scores decrease with age
 - Regression?
 - Plateauing?
 - Slow acquisition of skills



Standardized scores in the SCN2A cohort

- Simons Searchlight
- SCN2A proband recruitment
 - With or without epilepsy
- 64 probands (50 with epilepsy)
- Median age: 49m (IQR 28 to 101)
- Mean standardized Vineland-II scores,
 - Composite: 54
 - Motor: 56
 - Communication: 54
 - Socialization: 59
 - Daily living skills: 55

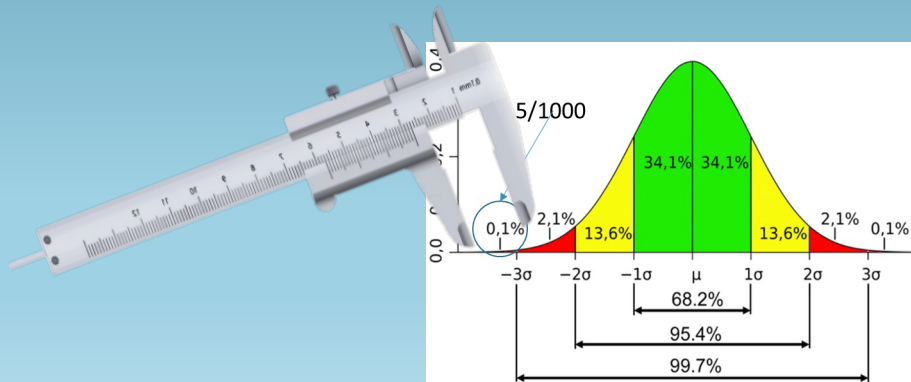
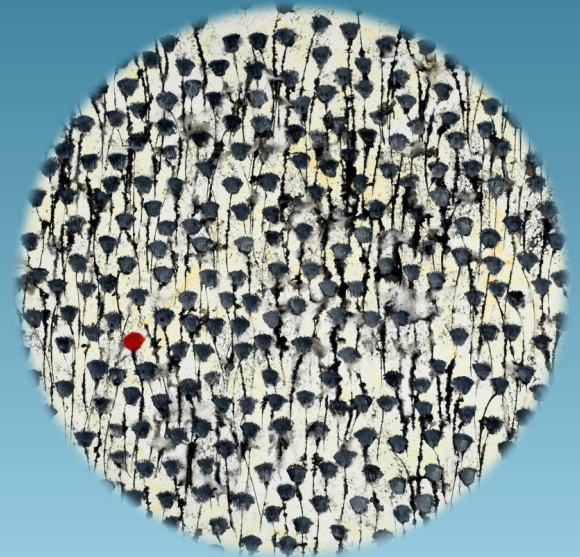
~ -3SD < mean



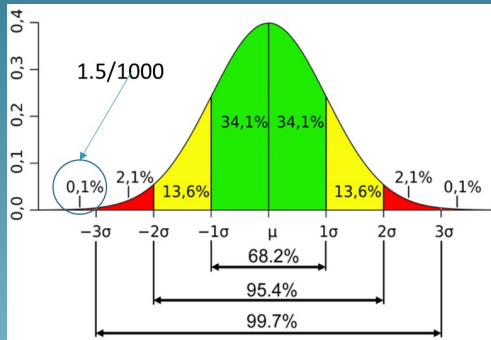
Berg et al., Epilepsia 2020

Rare Diseases have Rare Outcomes!

- How do we measure 3SD below the mean?
 - Reliably
 - Validly
 - Sensitive to change



What does better look like 3SD below the mean?



We don't need to measure
Milestones. We need to measure
"Inch-stones."

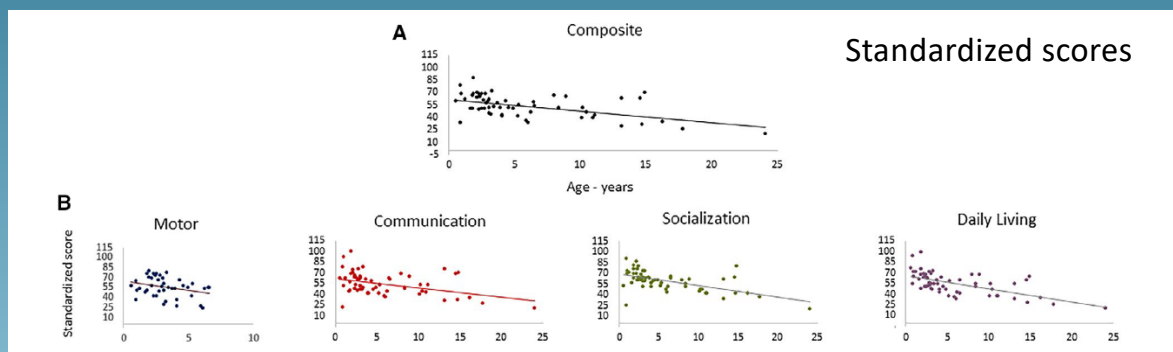
Gabi Conecker & JayEtta Hecker
DEE-P Connections



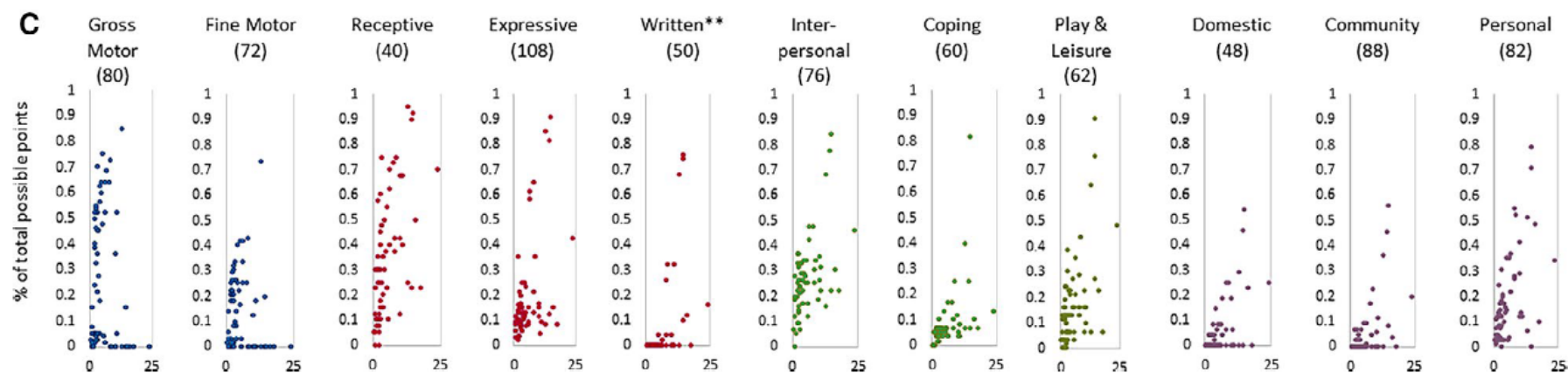
Strategies to address the -3SD situation

- Alternative scoring
- Out of intended age range
- Create measures *de novo*

1) Alternative scoring – Simons SCN2A Cohort, Vineland-II

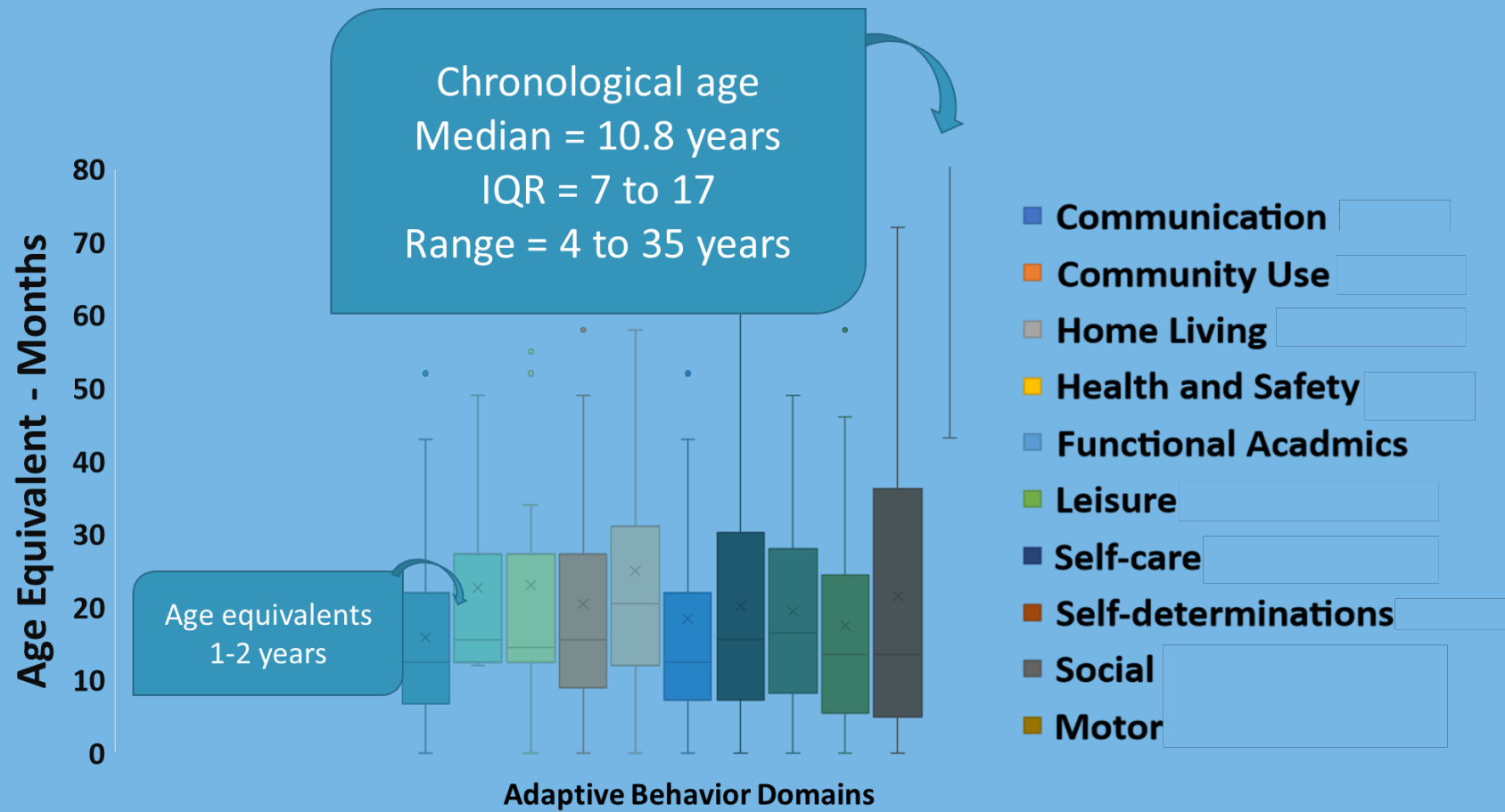


Alternative (raw) scores



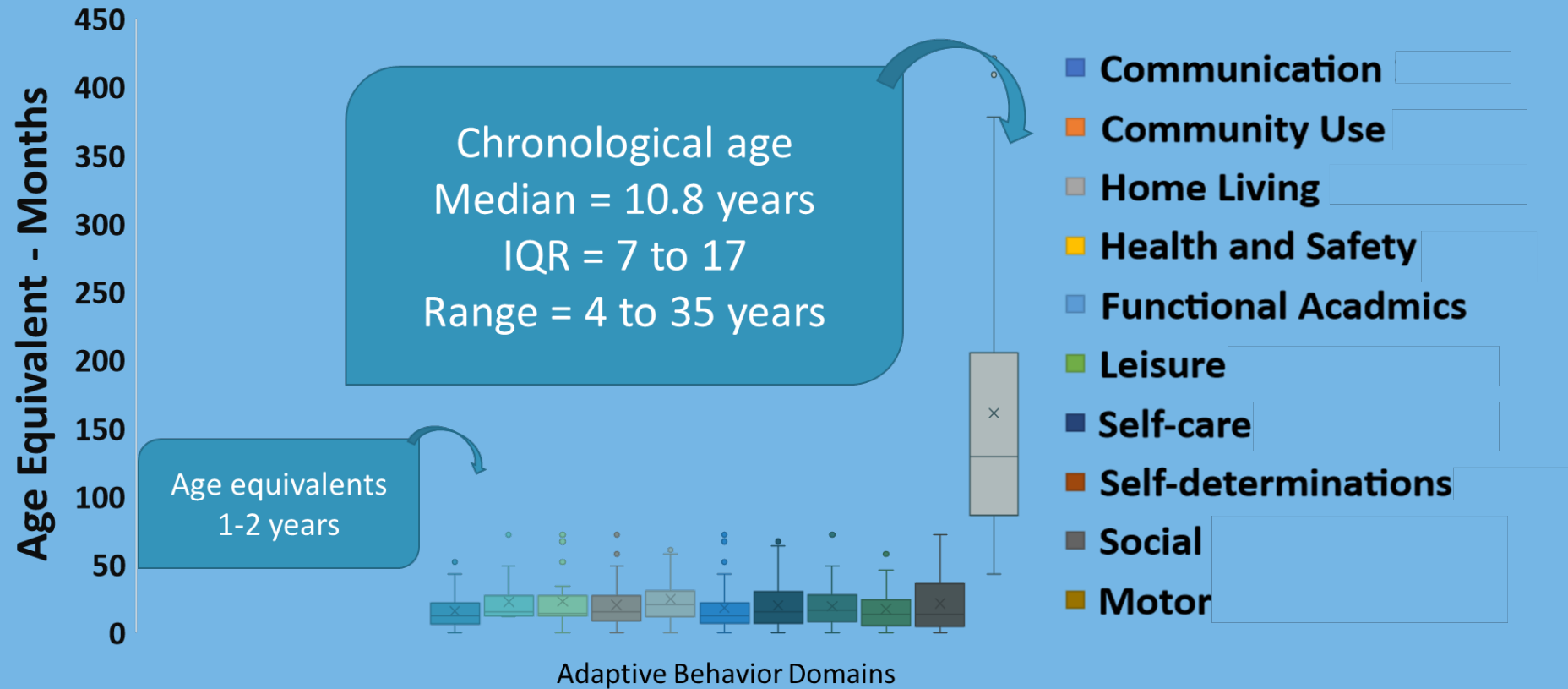
2) Out of intended age range

- The Ability Study
- 1-time assessment of 125 children and young adults with
 - Dravet syndrome
 - Lennox-Gastaut Syndrome
 - KCNB1-DEE
 - KCNQ2-DEE
 - SCN2A-DEE
- Adaptive Behavior Assessment System 0-5 years (ABAS)
 - 125 young people with severe developmental & encephalopathic epilepsies.
 - 36 Lennox-Gastaut Syndrome
 - Chronological age 10.8 years (IQR 7.4 – 17.1)



In preparation

Age Equivalents in Months – ABAS 0 -5

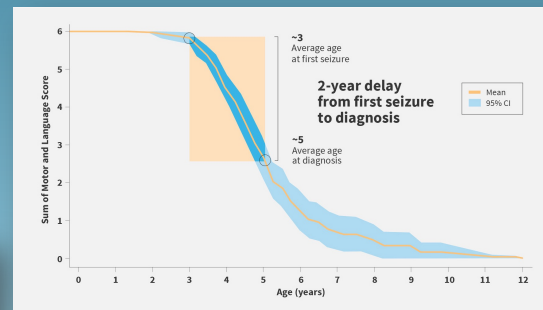


3) Create de *novo*– a lot of work

Assessment of a Clinical Trial Metric for Rett Syndrome: Critical Analysis of the Rett Syndrome Behavioural Questionnaire

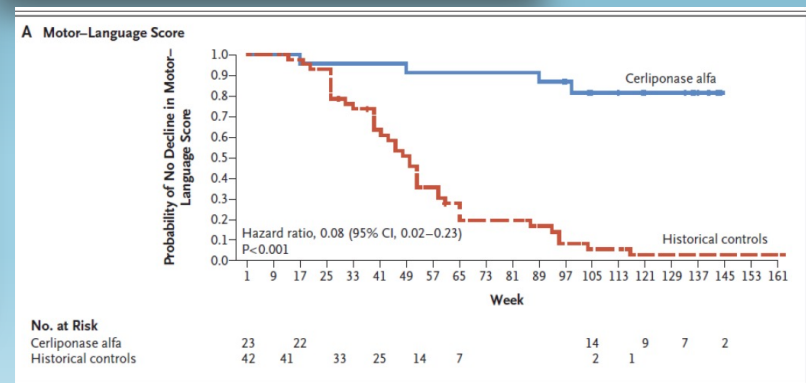
Wei Hou, PhD^a, Usree Bhattacharya, PhD^b, Wisnu A. Pradana^b,
Daniel C. Tarquinio, DO, MS-Cl^{c, e}

Ped Neurol, 2020



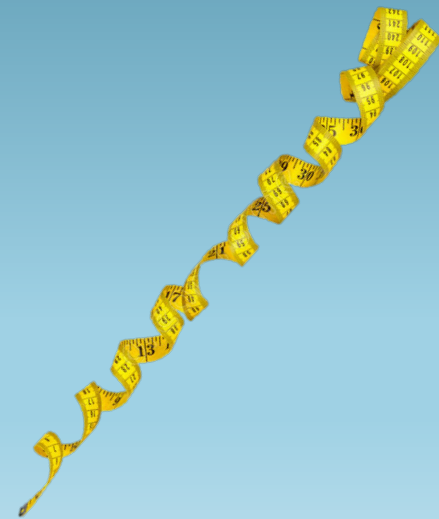
Motor function	Language function
3 Normal Grossly normal gait. No prominent ataxia, no pathologic falls.	3 Normal Apparently normal language. Intelligible and grossly age-appropriate. No decline noted yet.
2 Clumsy, falls Independent gait, as defined by ability to walk without support for 10 steps. Will have obvious instability, and may have intermittent falls.	2 Abnormal Language has become recognizably abnormal; some intelligible words; may form short sentences to convey concepts, requests, or needs.
1 No unaided walking Requires assistance to walk, or can crawl only.	1 Minimal Hardly understandable. Few intelligible words.
0 Immobile Can no longer walk or crawl.	0 Unintelligible No intelligible words or vocalizations.

Neuronal ceroid lipofuscinosis: Schulz, NEJM, 2018



De novo measures: advantages and disadvantages

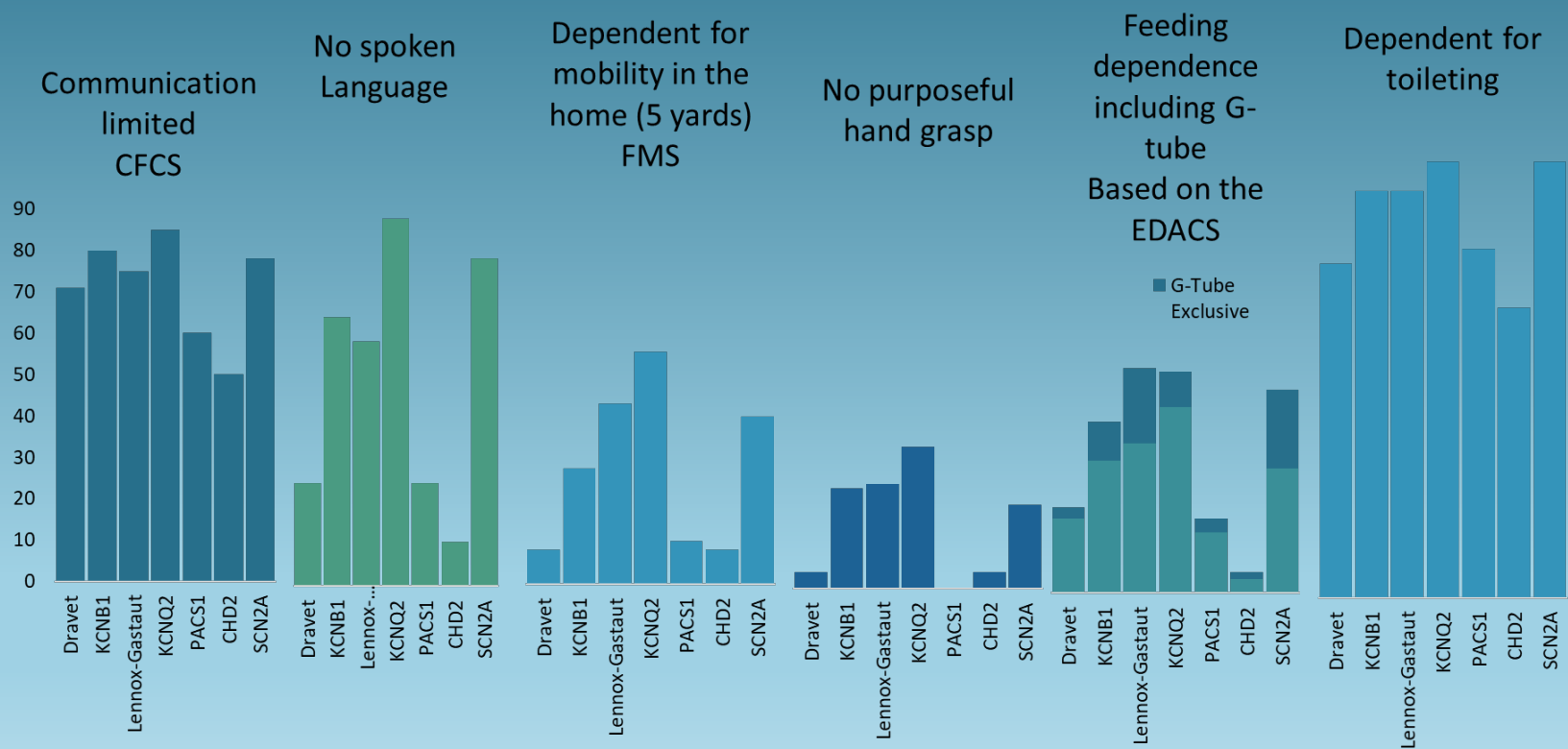
- + Precise for the disease of interest (NCL)
- Does not always work as intended (Rett syndrome)
- Huge effort and resources needed
- Limited to that disease
 - Do we always need a disease-specific measure?



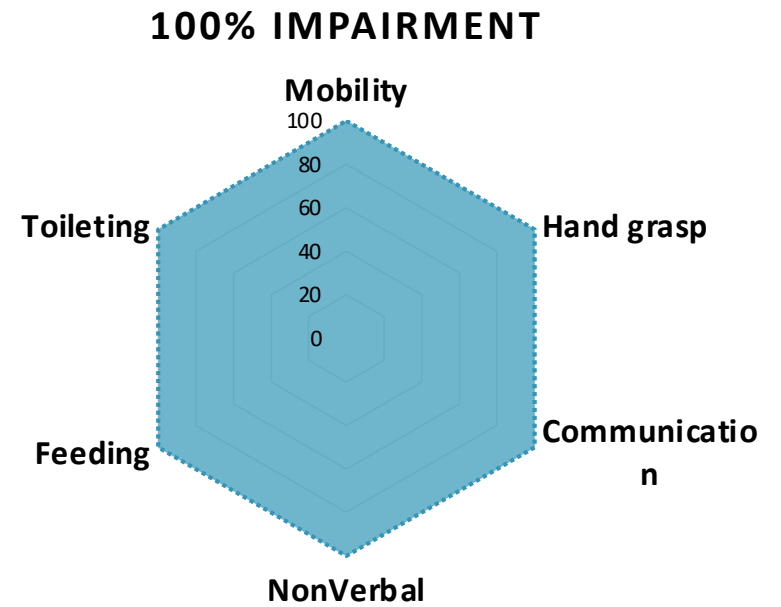
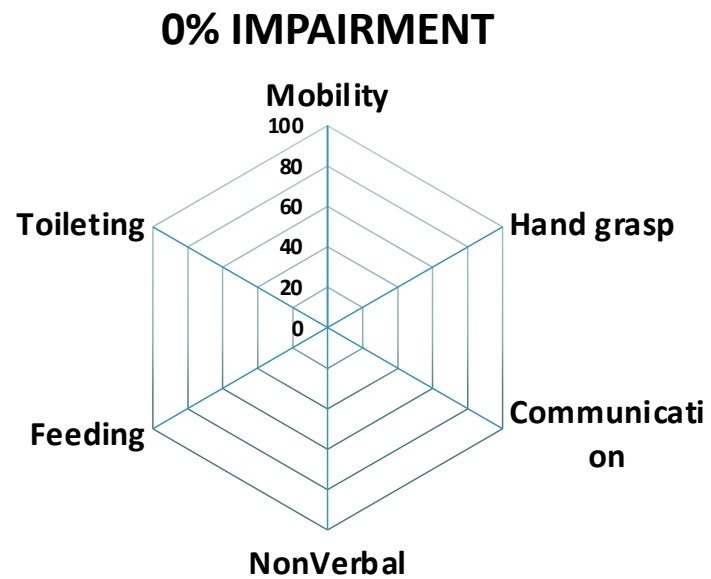
Which measures can be used to test whether there is improvement?

- **Scope it out first**
- Natural History survey
 - Online, parent-identified domains, parent-reported outcomes
 - Dravet Syndrome
 - Lennox-Gastaut Syndrome
 - KCNQ2-DEE
 - KCNB1-DEE
 - CHD2-DEE
 - PACS1-DEE
 - SCN2A - separately

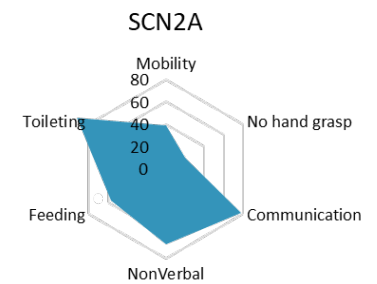
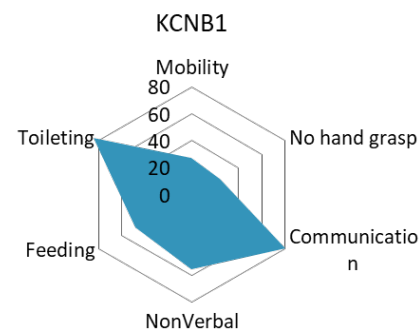
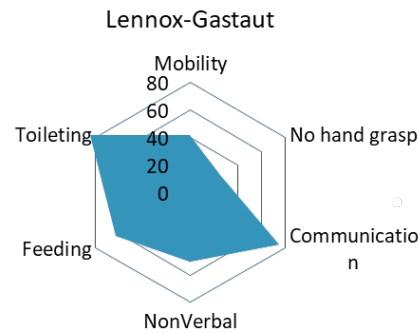
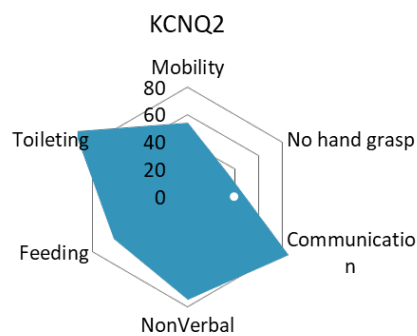
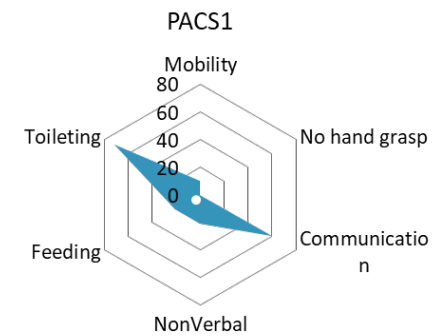
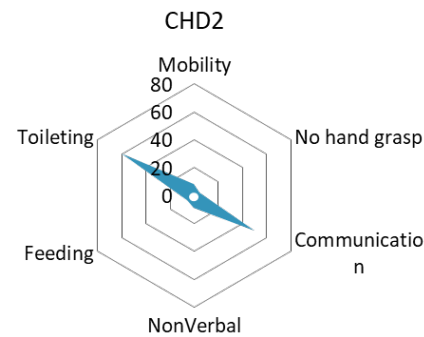
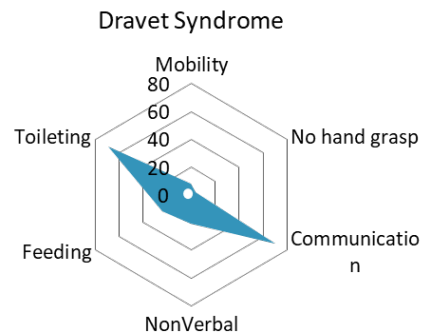
FUNCTIONAL DISABILITIES IN SELECTED DEES



Radar Plots

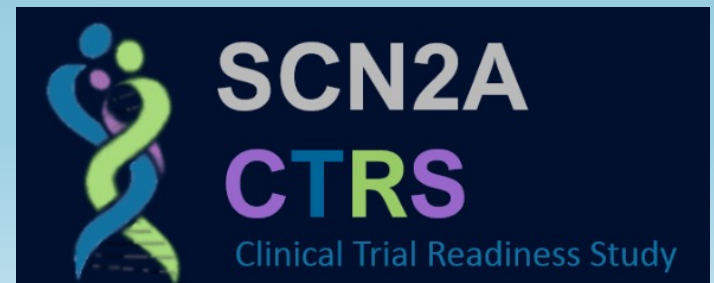


Profiles of severe-profound impairment

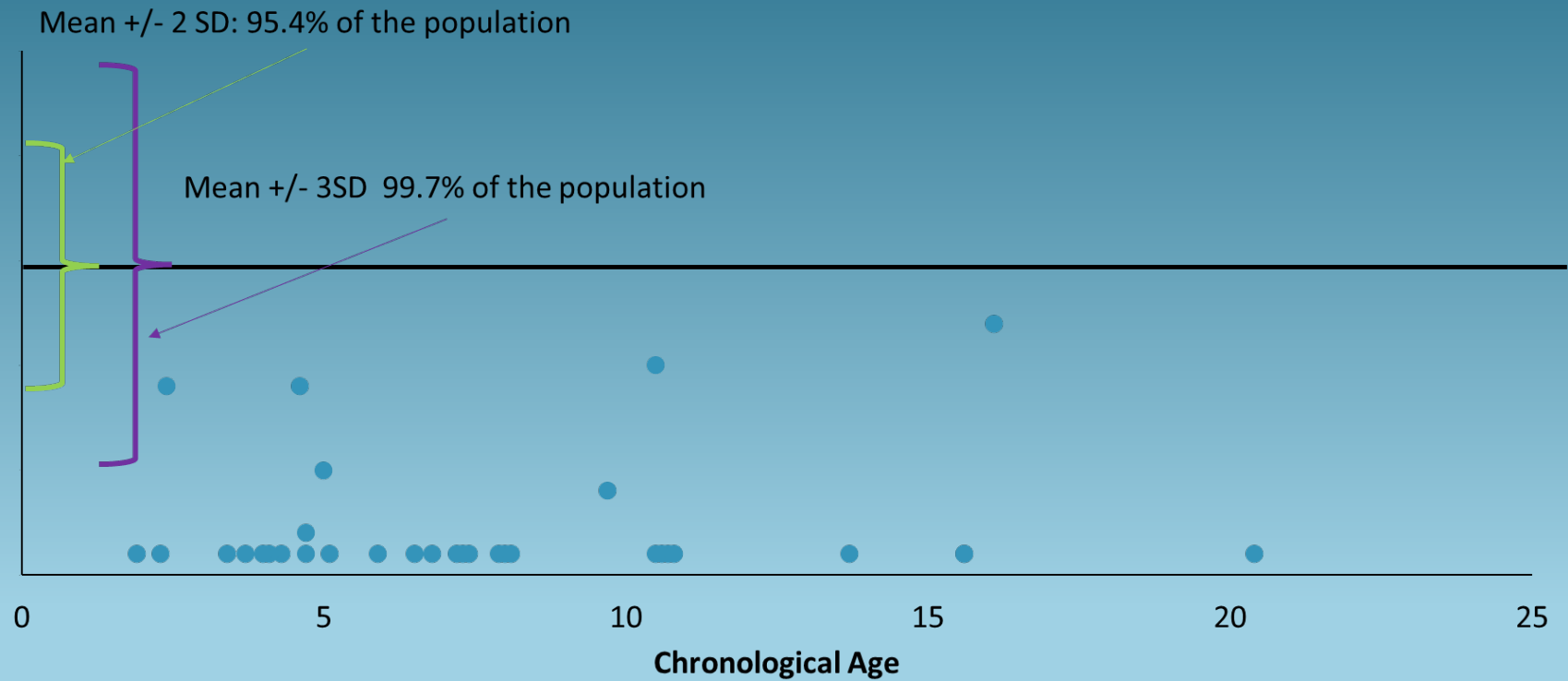


How to get there?

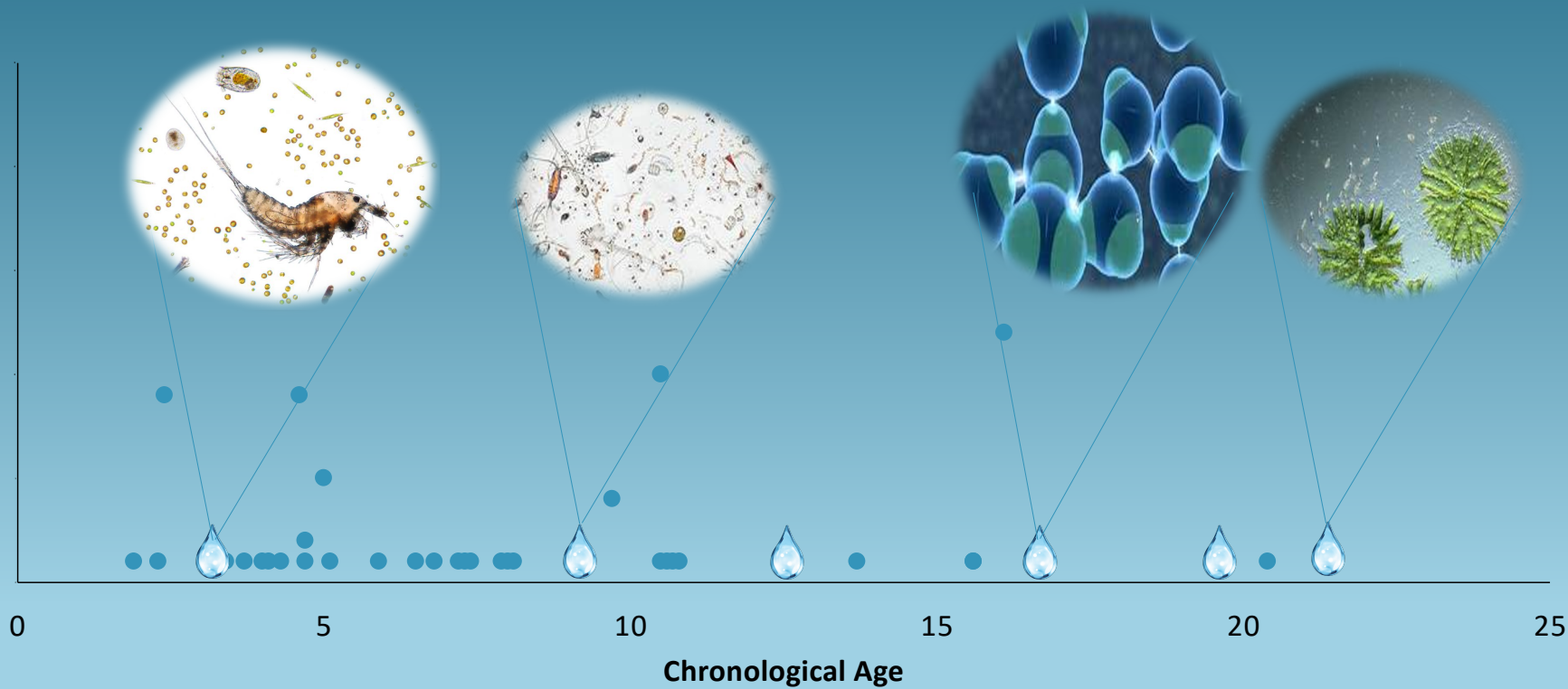
- Listen to the experts, people living with DEE
 - Focus in on critical outcomes
 - Uni-dimensional
- Engage professional in physiatry, autonomic medicine, speech&language pathology, palliative care
- Identify, adapt, create appropriate measures
- **Trial measures in intended population**
 - Ability Study
 - SCN2A Clinical Trials Readiness Study (CTRS)



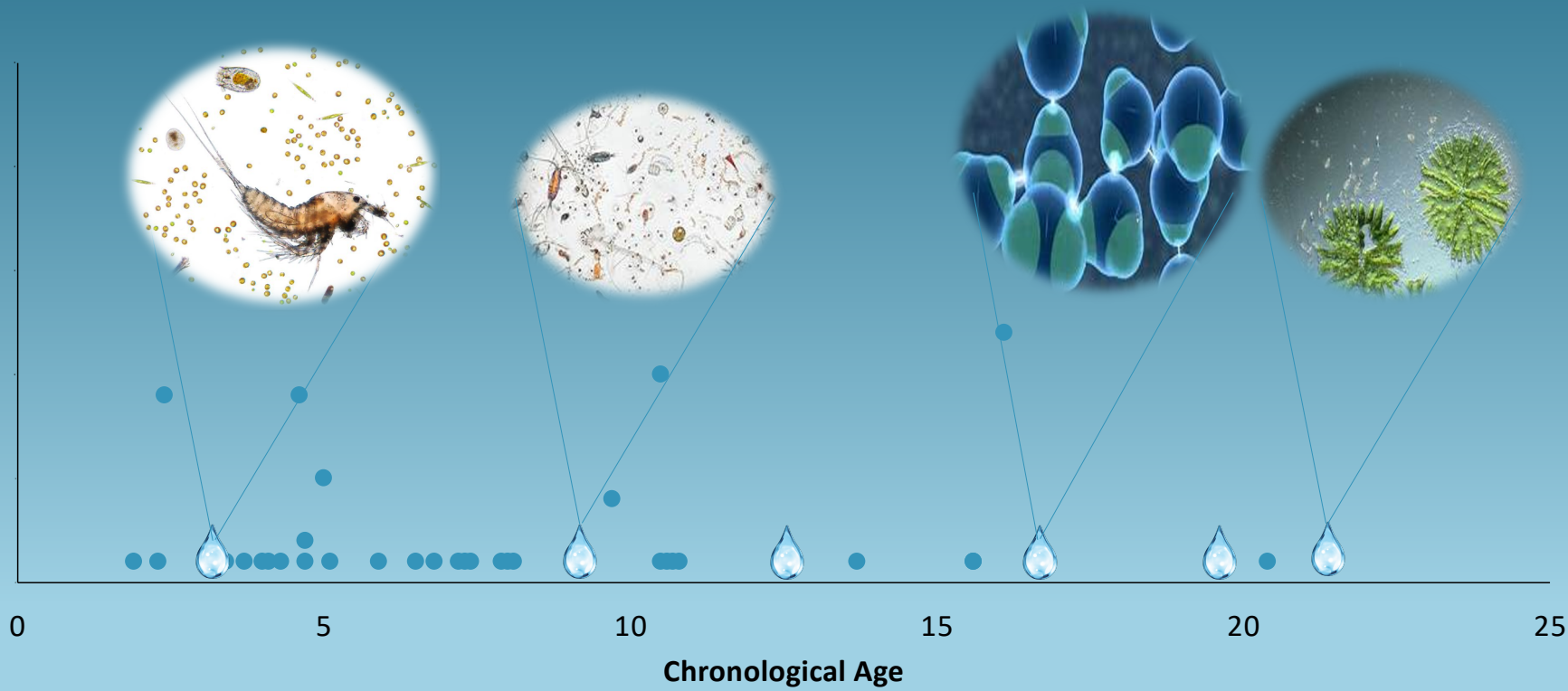
Standardized measure of a function



Preliminary data

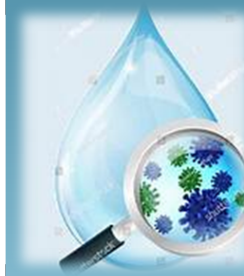
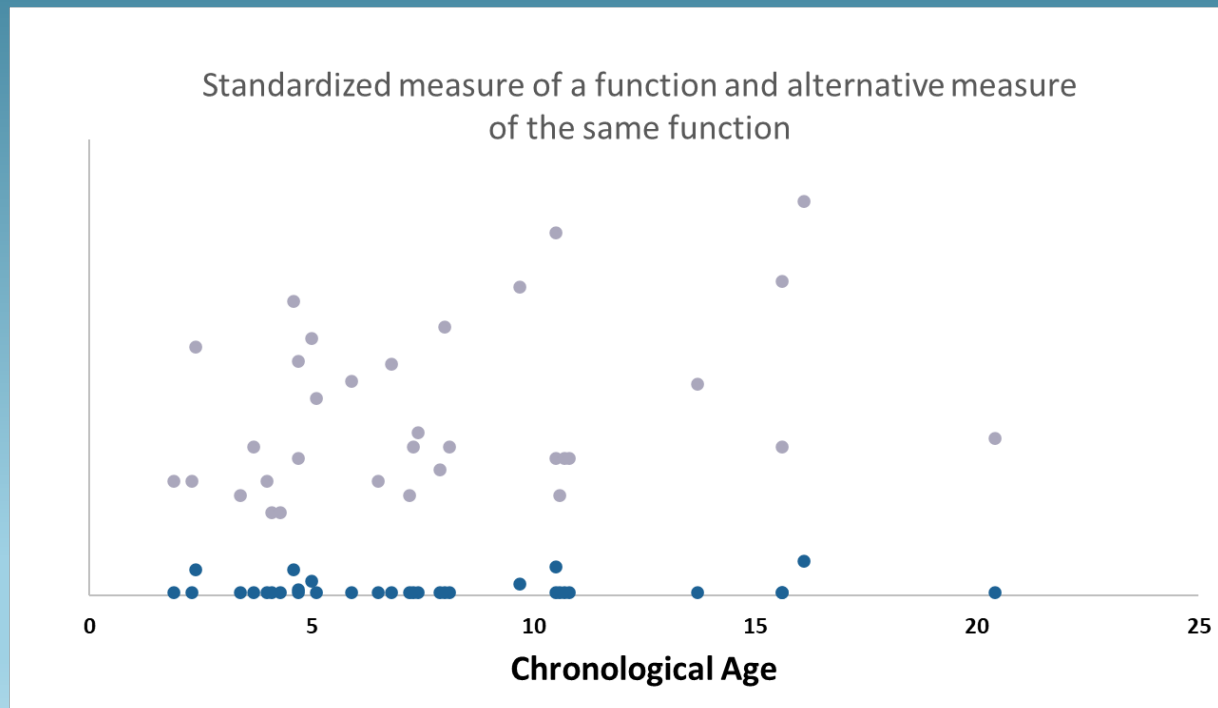


Preliminary data



Preliminary data

Standardized measure of a function and an alternate measure



Preliminary data

Measuring better at -3SD?

- Listen to the experts, people living with DEE
 - Focus in on critical outcomes
 - Uni-dimensional
- Engage professional in physiatry, autonomic medicine, speech&language pathology, palliative care
- Identify, adapt, create appropriate measures
- Trial measures in intended population
 - Ability Study
 - SCN2A Clinical Trials Readiness Study (CTRS)
- **Get the results into the scientific community**
 - Familiarity
 - Buy-in

