



The Inchstone Project

Community Update

March 25, 2024



What is The Inchstone Project?

Mission: To make clinical development more inclusive by developing a battery of FDA-approved Clinical Outcome Assessments within 5 years that are:

- psychometrically sound,
- sensitive to meaningful change, and
- fit-for-purpose for severe DEEs

Assure every person, regardless of the severity of their disease, can have even their smallest achievements, or inchstones, counted.



Agenda

- Recap of Inchstone Vision and Approach
- Highlights and Importance of Results from DEE Parents Speak Survey
 - Overview of Parent Speak survey
 - Overview of Parent Priorities and Areas of Impairment
 - Analysis of Qualitative Data from Parent Speak survey
 - Quality of Life Scores
 - Developmental Quotients
 - Awareness and Responsiveness
 - Cortical Visual Impairment
 - Sample PAG Dashboard
- Open discussion/ Q&A
- Continuing Ways to engage
 - Upcoming Focus groups
 - FDA Listening session
 - Expanded clinical assessments

The Inchstone Project Team



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3 Phases of The Inchstone Project



Working Hypotheses of The Inchstone Project

Need/challenge

More sensitive and validated outcome measures are essential for progress in precision medicine (PM)

Developing assessment tools disease by disease is unsustainable. Doing this together gets us all closer to PM faster.

Inchstone R&D

DEEs and severe NDDs have many common characteristics and similar priorities for improvement

Development of an Inchstone COA Battery validated for use across the DEEs/severe NDDs will

- improve meaningful inclusion of DEEs in trials
- improve efficiency & effectiveness of trials

Participants and Characteristics of DEE Parent Speak Study




Enrollment criteria for Priorities Survey

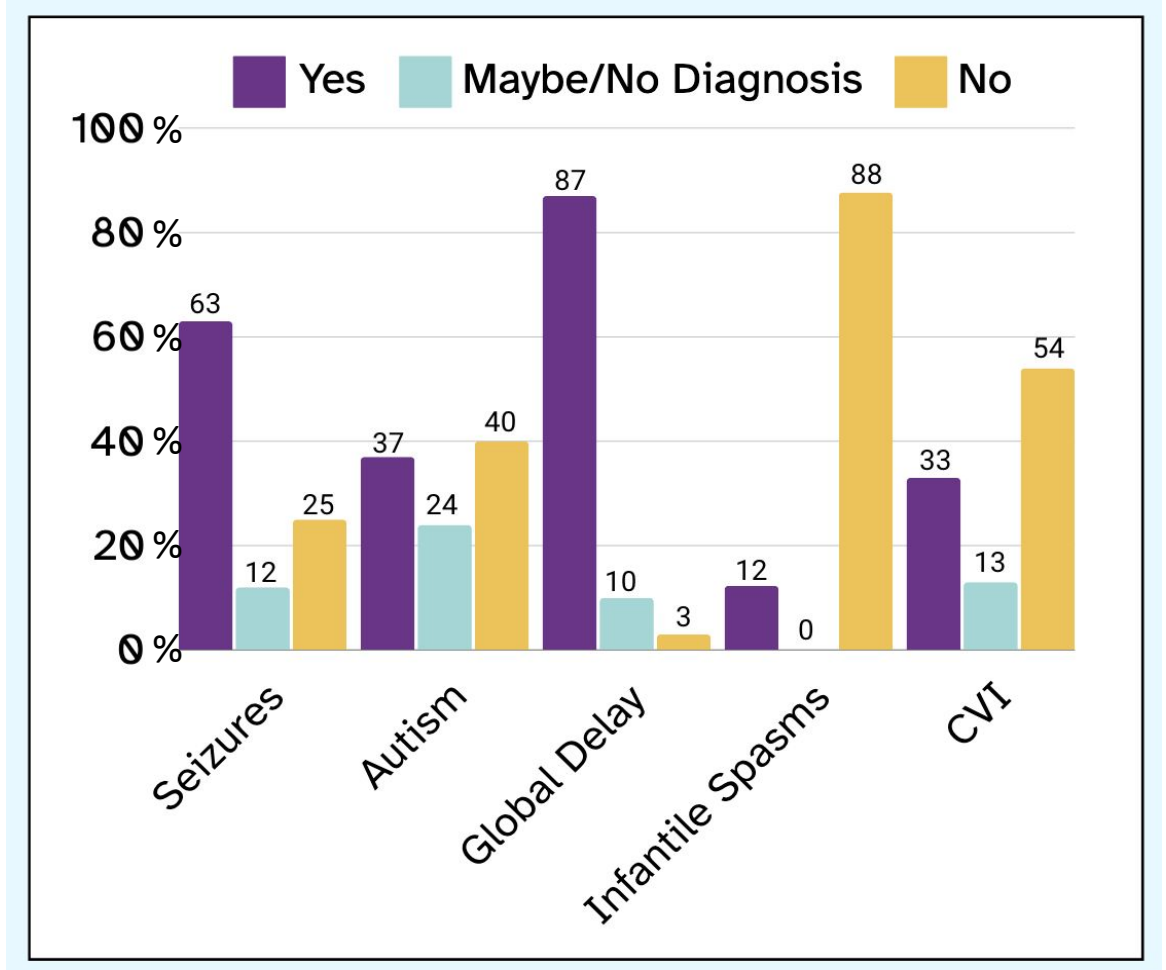
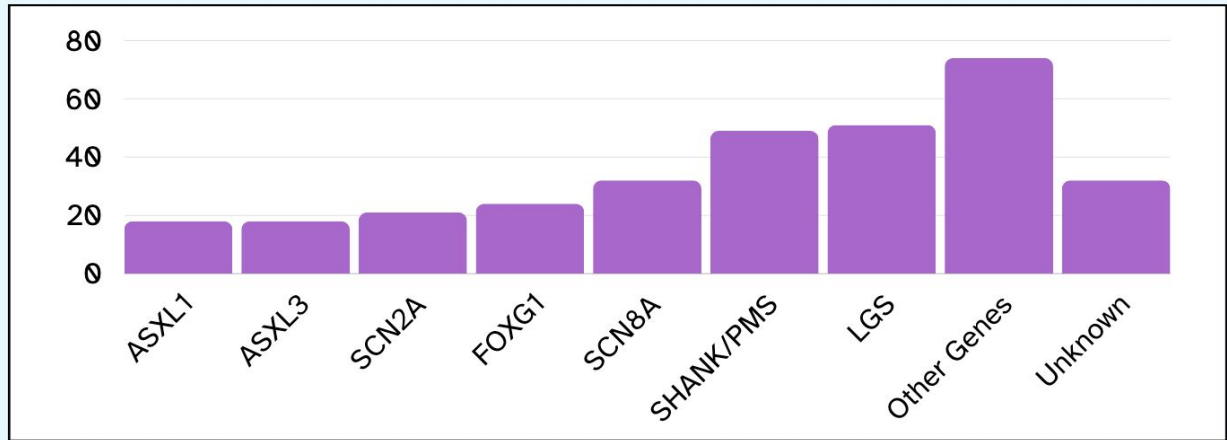
- Initial
 - At least 1-year old
 - Have very **severe communication challenges**.
 - Unable to walk or unable to feed self (including g-tube dependent)
 - Have one or more of: seizures, developmental delay, intellectual disability, autism
- After Sept 13, 2023 and the LGS meeting
 - At least 1-year old
 - Have very **severe communication challenges**.
 - ~~Unable to walk or unable to feed self (including g-tube dependent)~~
 - Have one or more of: seizures, developmental delay, intellectual disability, autism

DEE Parents Speak Survey Overview

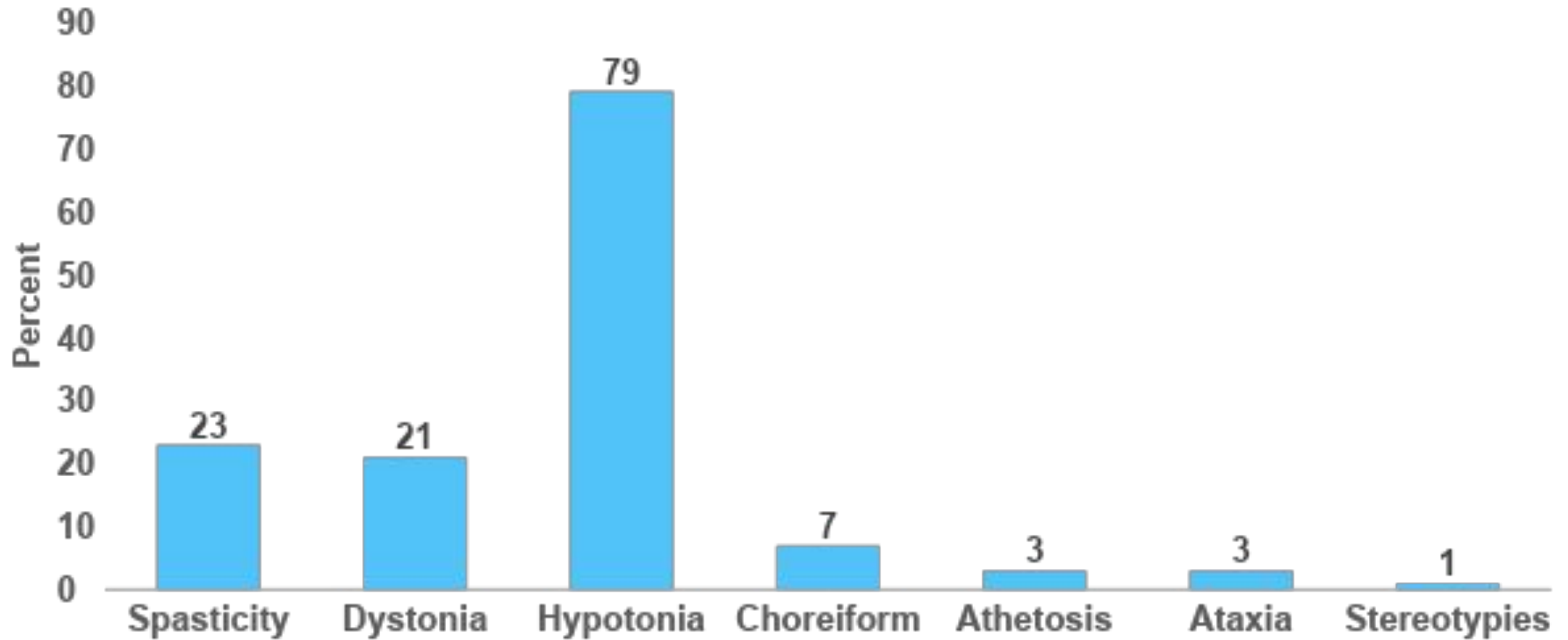
 **Total**
268

 **Sex**
56% Female

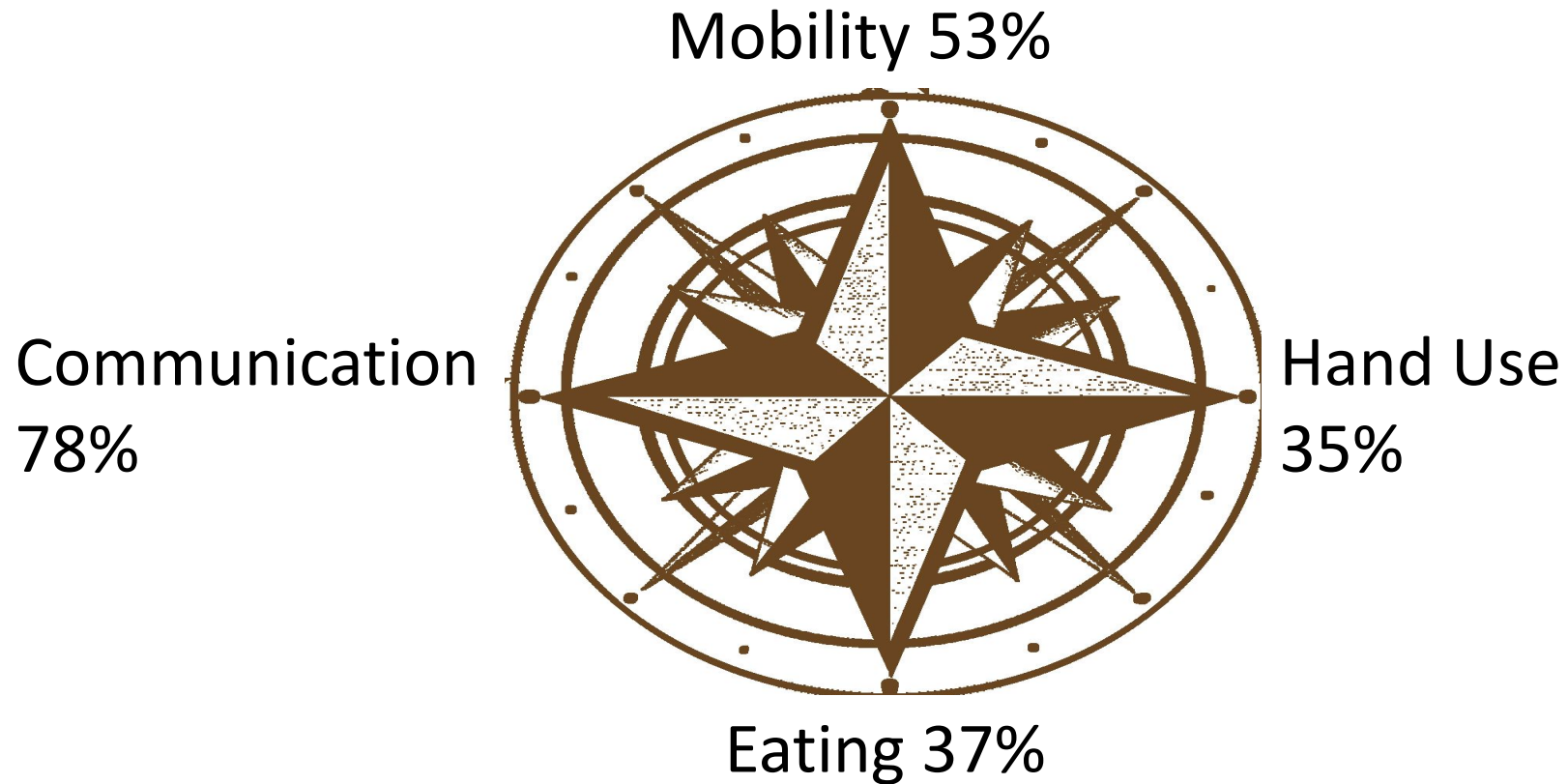
 **Average Age**
8.7



Muscle and Tone Disorders

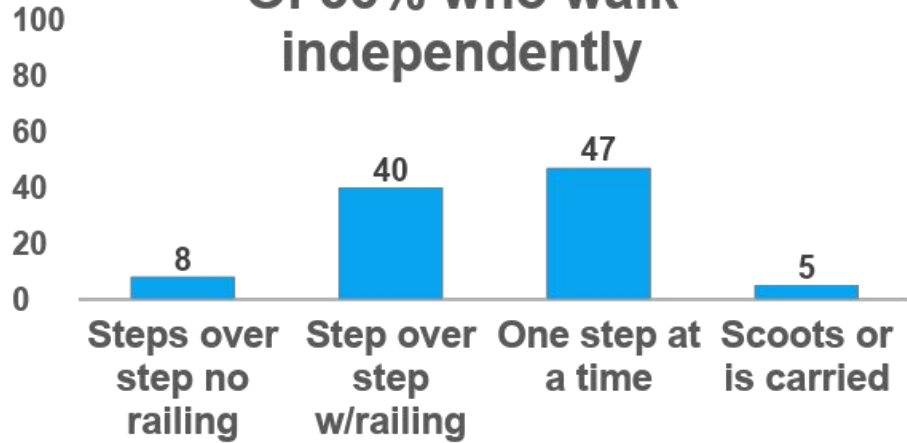


Severe to Profound Impairment: Compass Points of Function

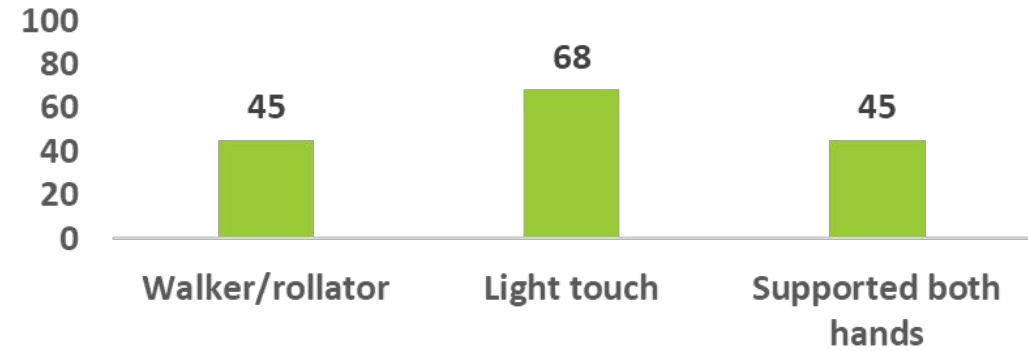


Mobility – 2 years and older

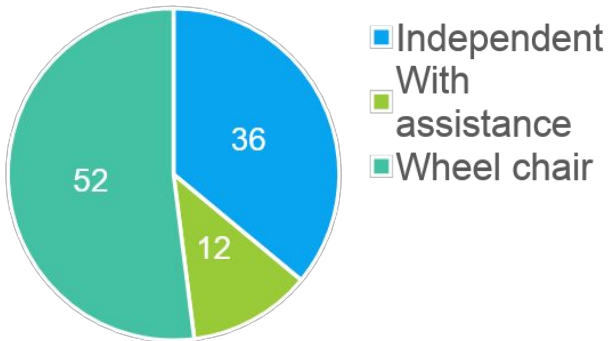
Of 36% who walk independently



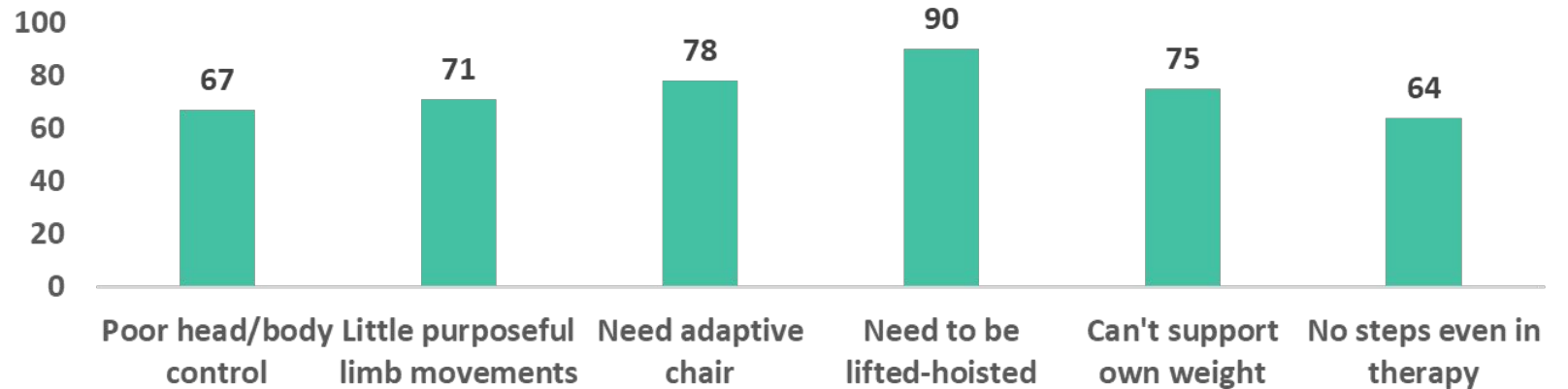
Of the 12% who walk with assistance



Walking, <5 yards

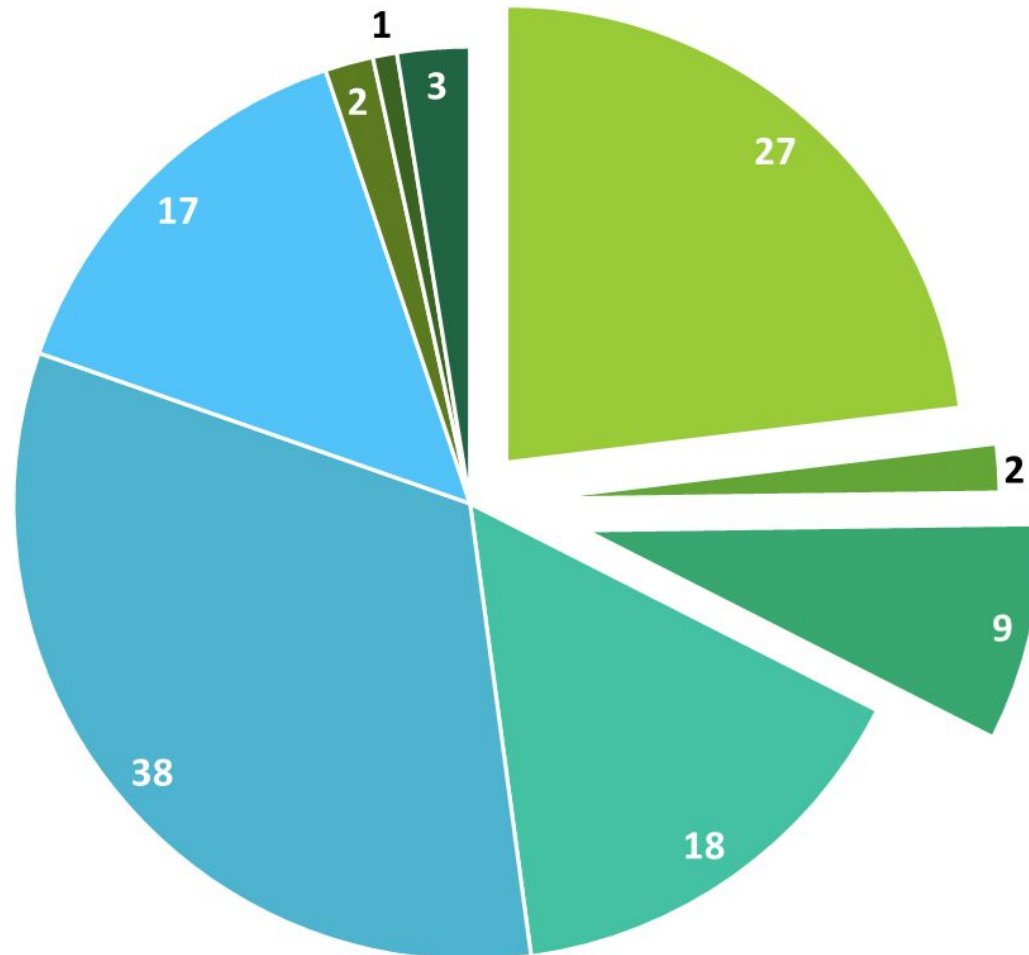


Of 52% requiring a wheelchair/stroller in the home



Communication

Primary Mode of Communication



- Speech
- Signs
- AAC
- Gestures
- Sounds
- Eye gaze
- Facial exp/Body movement
- Mix
- Non



Aides and Assistive Devices

Therapeutic stroller
74%



AFOs **62%**



Medical bed/crib
35%



Therapeutic chair
41%



Rollator - Walker
24%



Arm-wrist brace
14%



Medical lift or hoist
18%

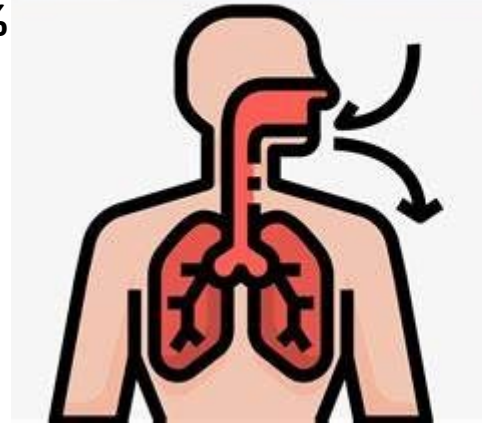


Other Devices

AAC 39%



Other breathing
aides 10%



CPAP device
7%



Cough assist device
11%



Corrective lenses
32%



Noise cancellation
head phones
14%

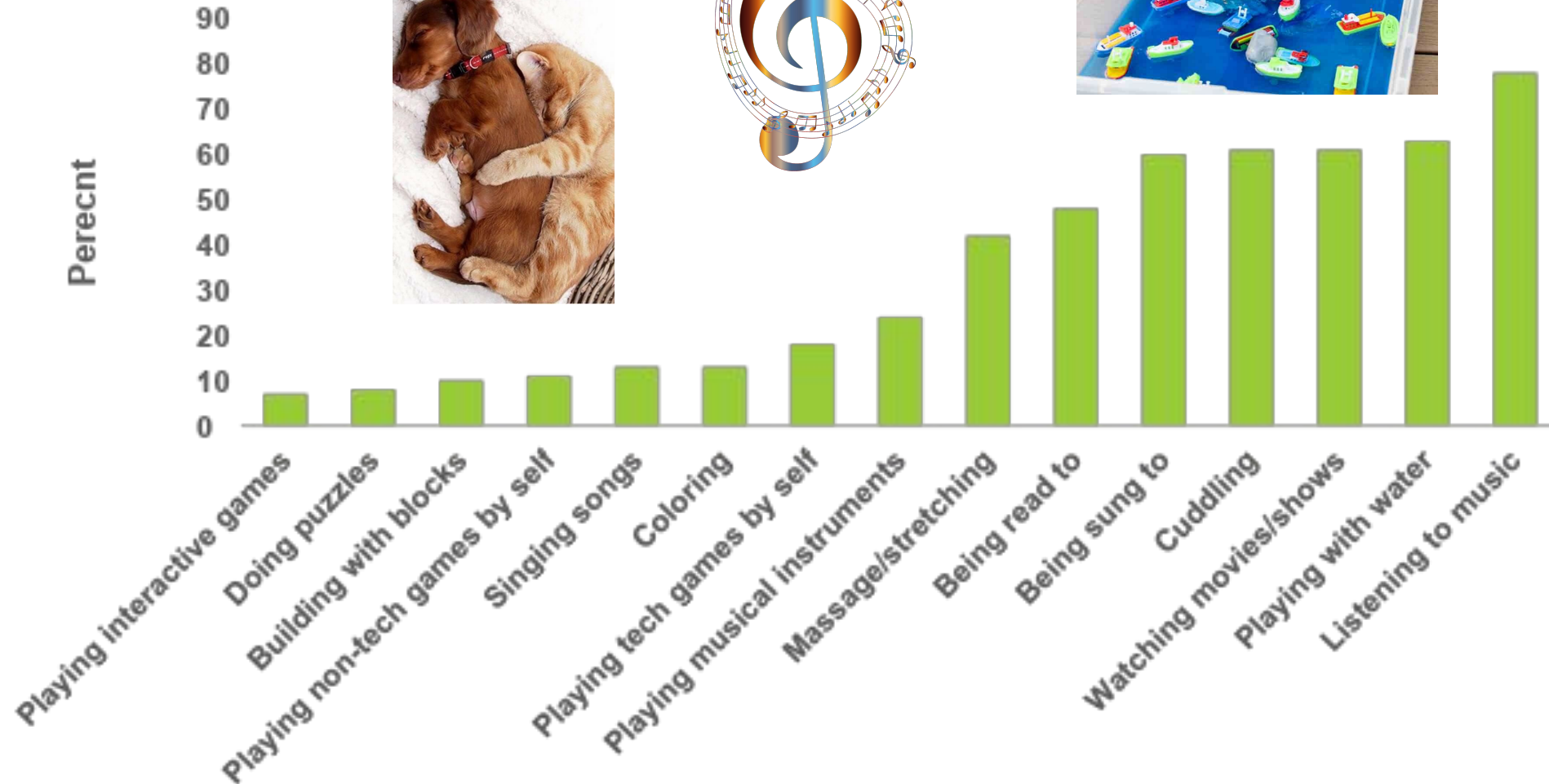
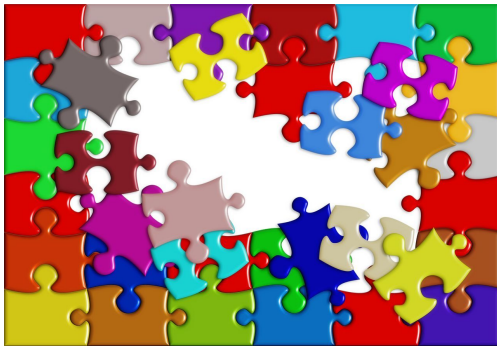


Suction device
24%



Activities enjoyed

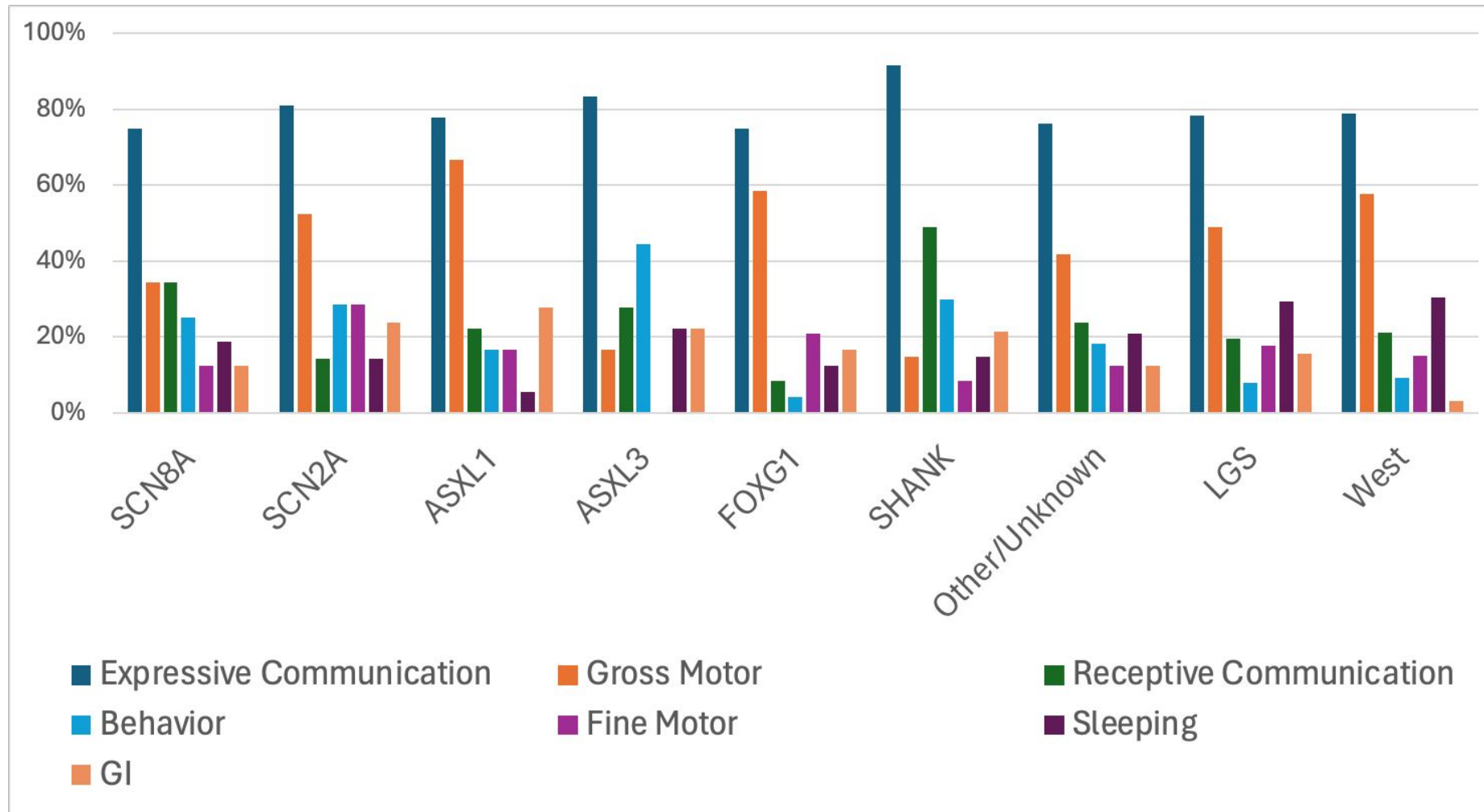
Passive activities were indicated more often for the most impaired participants



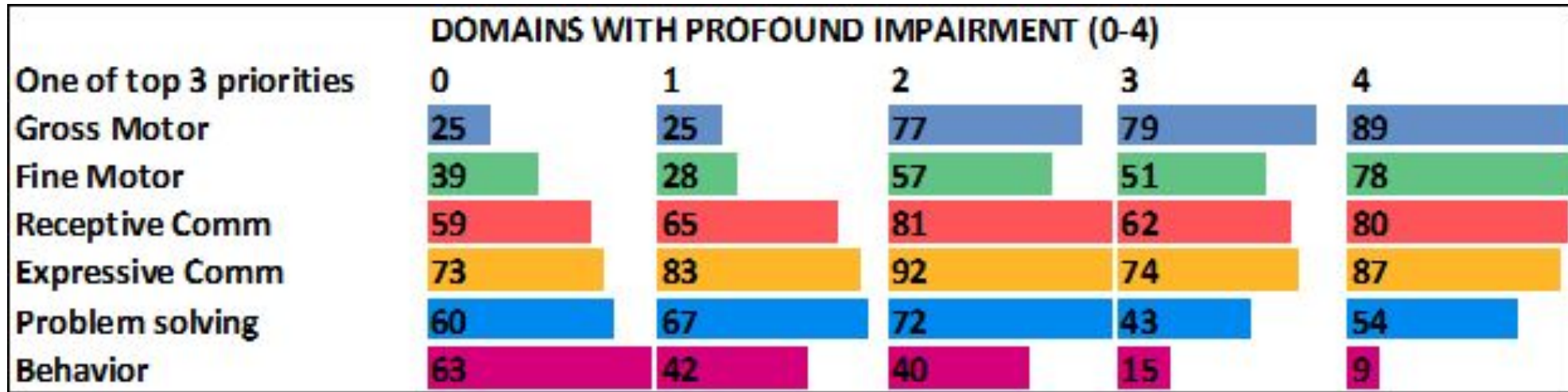
Priorities by: Disease Group & Level of Severity



Communication is top priority across disease groups



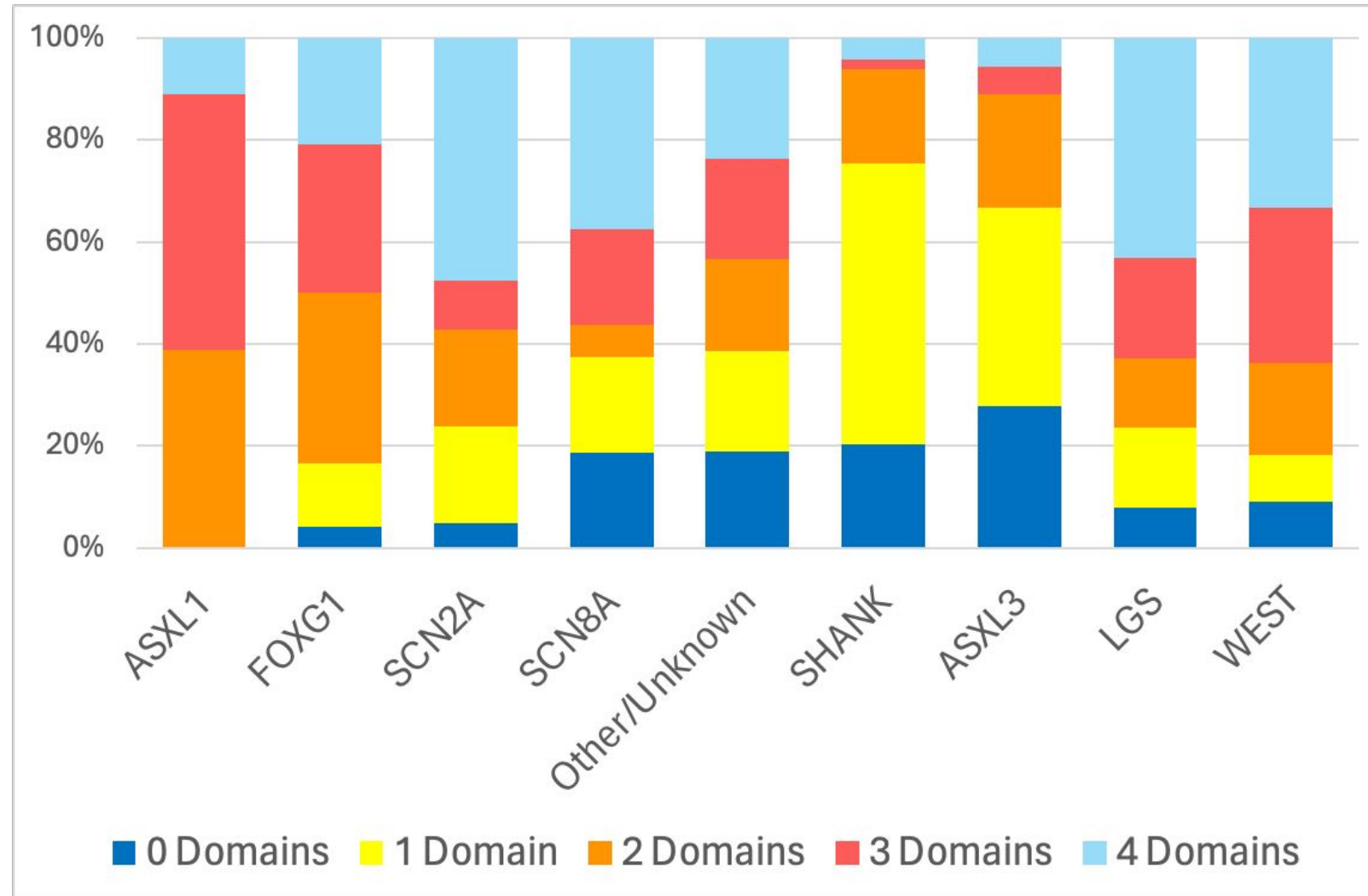
Priorities change based on disease severity



Communication as a priority is consistent between gene groups and is the top priority regardless of the number of domains with severe impairments

Gross motor and fine motor are bigger priorities as number of severe domains increases, while behavior decreases as a priority as number of severe impacts increases

Number of domains with profound impairment by gene/epilepsy groups



Analysis of Qualitative Data from DEE-Wide Survey



Q40. If you could improve just one aspect of your child's condition of those listed above, what would you choose? We are specifically interested in the domains we just asked you about above but there is room for additional possibilities at the end of this section.

- Use of arms and legs and trunk - Gross motor skills
- Use of fingers and wrists - Fine motor skills
- Understanding others - receptive communication
- Expressing self to others - expressive communication
- Eating safely without risk of choking
- Feeding self independently, without help from another
- Vision
- Alertness, responsiveness, and attention
- Reasoning and problem solving
- Problems falling or staying asleep or waking up in the morning
- Sleepiness during the day, trouble staying awake
- Behavioral and emotional self-regulation
- Interacting with and responding to others - social engagement
- GI problems - constipation, gut dysmotility
- Movement disorder
- Dysautonomias
- Pain

Q41. Could you describe your child's current abilities and activities in this first area **Expressing self to others - expressive communication**?

Q42. What would be the smallest improvement or step forward in this area that would be important to you or your child terms of your child's well-being, function, or quality of life?

Please try to be objective as possible. What would someone who does not know your child that well be able to observe?

Q43. Why would this small improvement be important to you/your child?

Q44. If you could improve one other aspect of your child's condition, what would you choose? We are specifically interested in the domains we just asked you about above but there is room for additional possibilities at the end of this section.

For example - Expressive Communication

Q45 - What would you see?

It is difficult to understand her basic needs

Q46 - What is better?

Is she in actual pain, does she have gas, or is it positional when she seems unable to engage in activities?

Q47 - Why?

It would aid in intervention, if we understood the source, we could offer either medicine, a shift in position, or some other intervention

Total number of wishes = 807

Wish Name	All	ASMs	Autism	LGS	ASXL1	ASXL3	FOXG1	SCN2A	SCN8A	SHANK	XXXOT
Expressive Comms	211	137	83	40	14	15	18	17	24	43	80
Gross Motor Skills	102	79	14	25	12	3	14	11	11	7	44
Receptive Comms	73	34	39	10	4	5	2	3	11	23	25
Behavior	59	33	37	4	3	8	1	6	8	14	19
Sleep Problems	46	30	16	15	1	4	3	3	6	7	22
GI Problems	45	30	18	8	5	4	4	5	4	10	13
Feeding Independently	43	26	13	7	4	6	6	1	3	5	18
Fine Motor Skills	35	27	10	9	3	0	5	6	4	4	13
Social Engagement	35	25	17	6	2	3	1	1	9	6	13
Eating Safely	28	17	12	4	1	0	2	2	4	8	11
Alertness	24	16	9	4	2	0	2	3	1	1	15
Vision	22	15	3	4	0	1	4	4	2	2	9
Reasoning	16	9	6	1	1	1	0	0	3	4	7
Movement	12	8	2	1	0	0	6	0	1	2	3
Reduce Pain	11	10	2	3	1	2	2	0	3	0	3
Sleepiness	10	10	2	5	0	0	0	0	1	1	8
Dysautonomias	7	5	1	3	1	0	0	1	1	0	4
TOTAL	269	175	99	51	18	18	24	21	32	50	106

Code	Description	Number	Percentage
EC19	Basic communication of needs/wants	56	26.29
EC30	Express pain/hurt/discomfort	38	17.84
EC62	Communicate – aided – not specified	35	16.43
EC45	Communicate body– limbs (hand gestures, pointing, waving, kicking, moving feet, push button)	32	15.02
EC21	Communication - not specified	30	14.08
EC60	Communicate – words – not specified	21	9.86
EC20	Express feelings	20	9.39
EC32	Communicate Yes/No	19	8.92
EC41	Consistency of communication	13	6.10
EC57	Communicate – words – single	12	5.63
EC49	Communicate – vocalisation (squealing, moaning, yelling, grunting, laughing, crying, babbling)	10	4.69

Quality of Life Scores Across Disease Groups

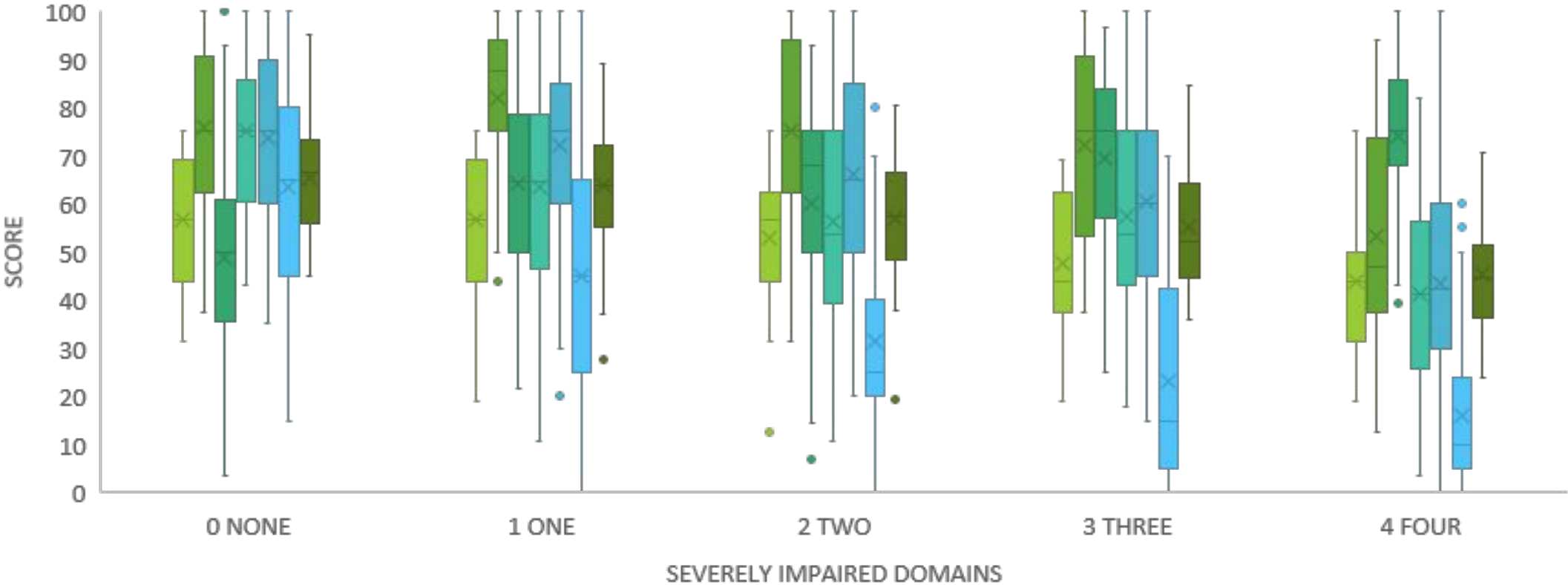


Quality of Life Scores by Burden of Impairment

n=215

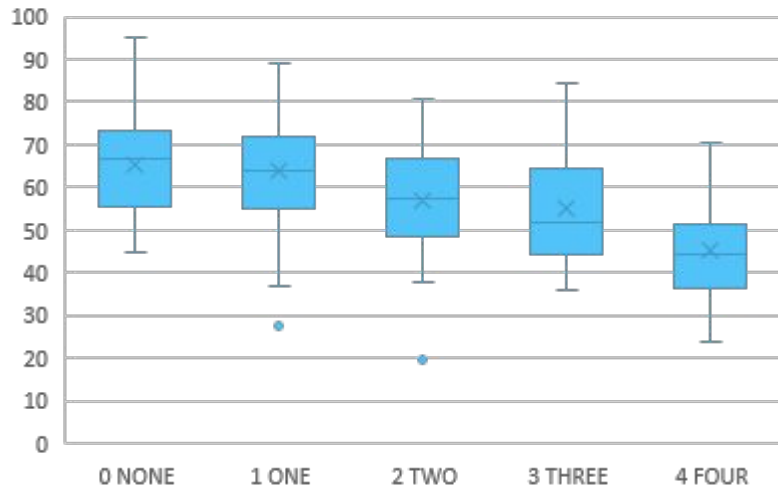
Quality of life scores by burden of impairment (age ≥ 3 years)

- Physical Health
- Positive Emotions
- Negative Emotions
- Social Interactions
- Leisure&Outdoors
- Independence
- Overall QOL

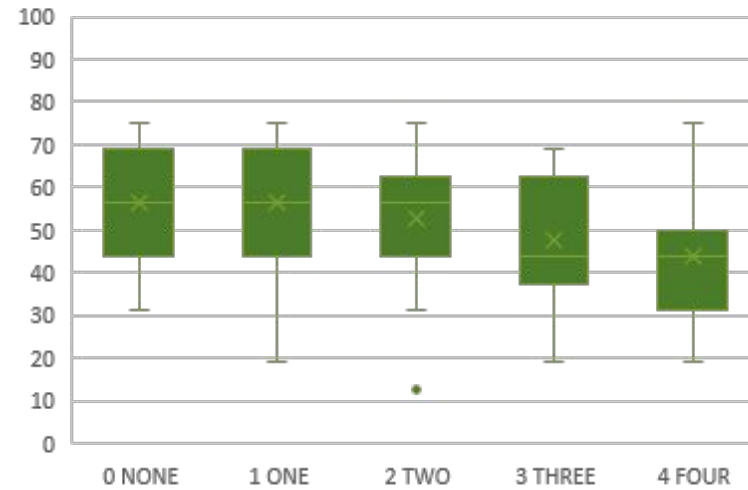


Quality of Life Score by Domains and Impairments

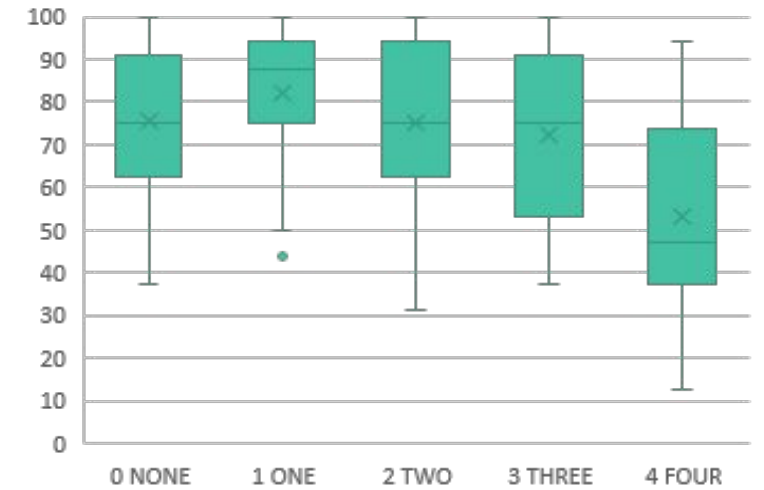
Overall Quality of Life



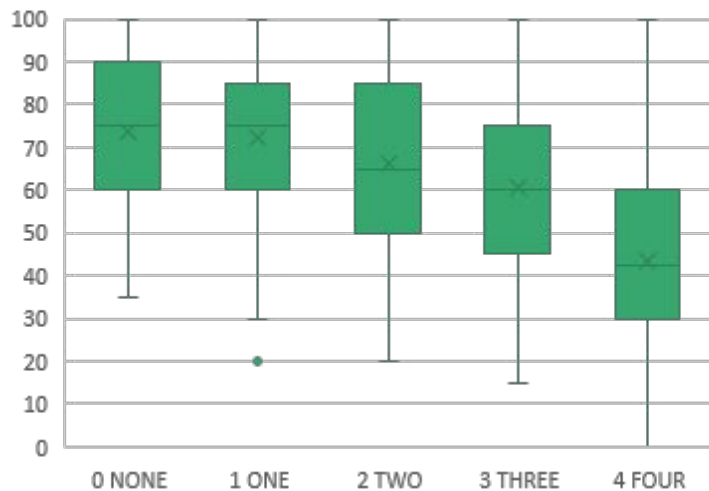
Physical health



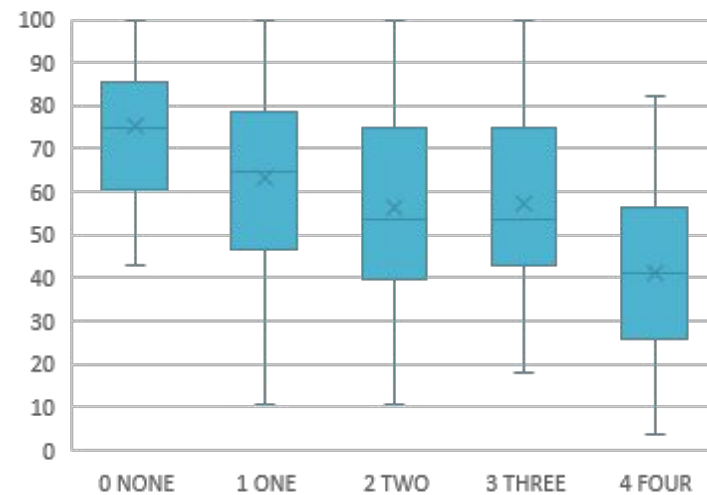
Positive emotions



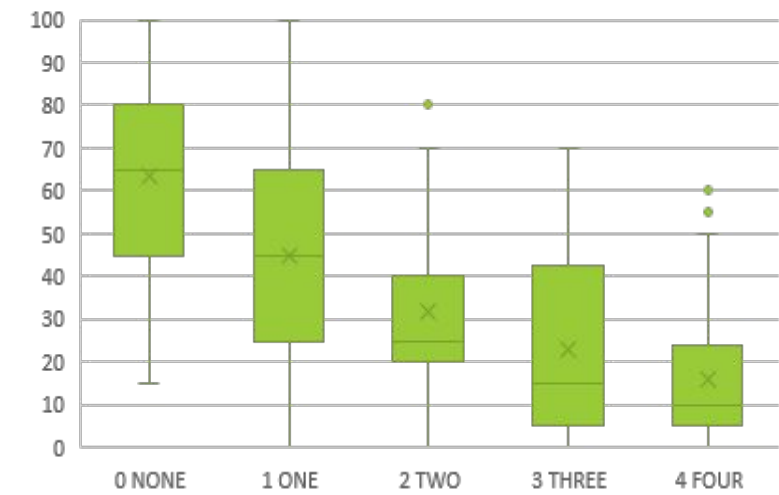
Leisure & Outdoors



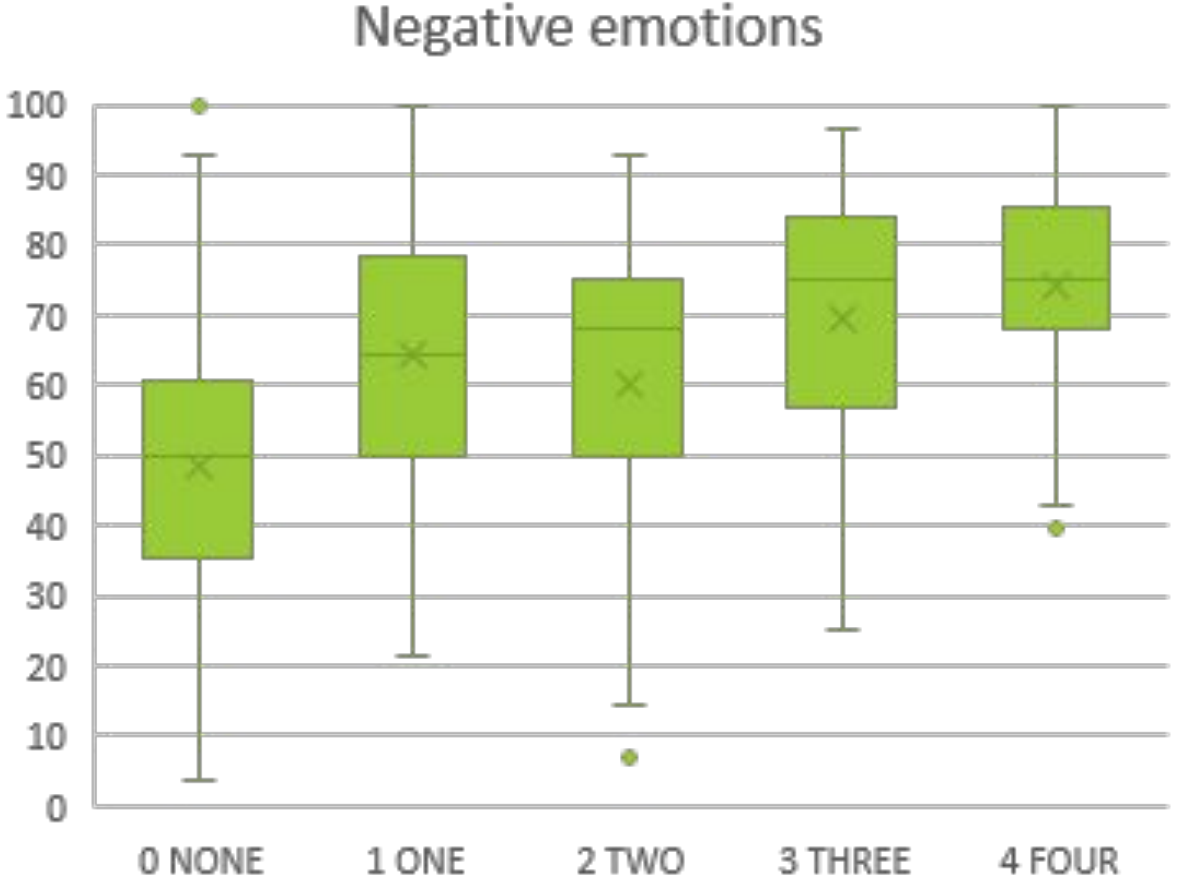
Social interactions



Independence



Quality of Life Score by Domains and Impairments



Development Quotient Across Disease Groups



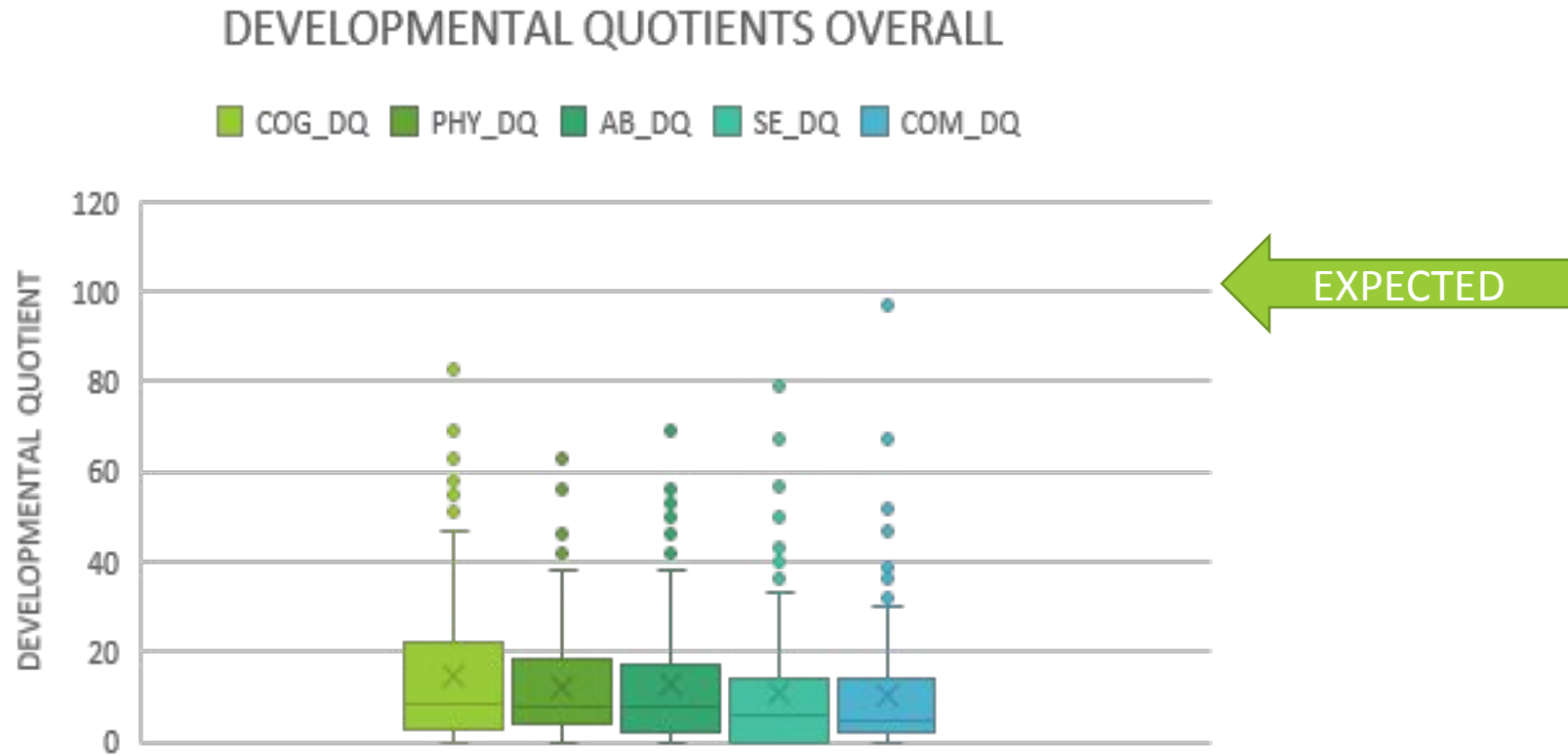
Developmental Profile-4

Caregiver rating of development in 5 areas:

- Cognitive
- Communication
- Physical
- Social-Emotional
- Adaptive Behavior

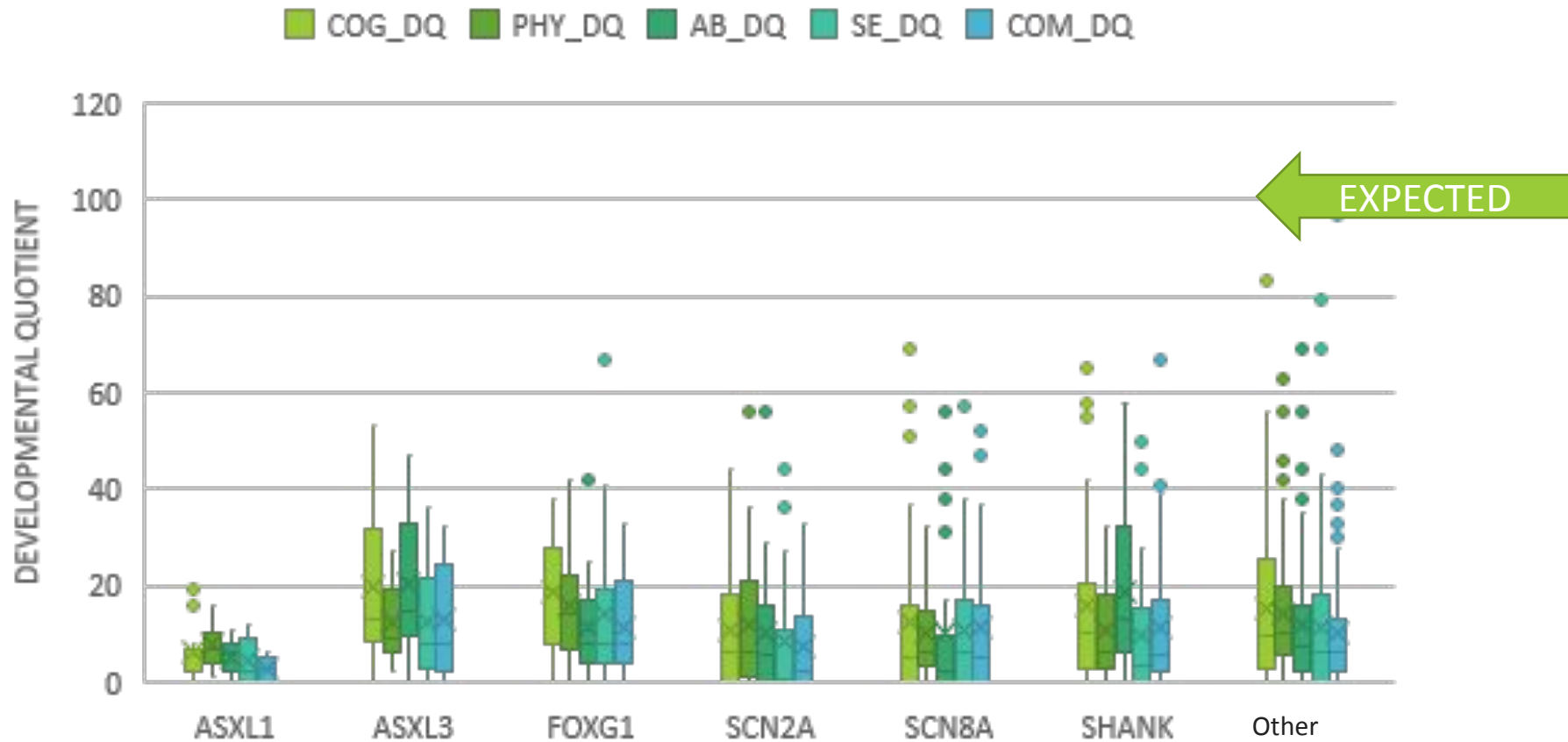
Developmental Quotients (DQ) - Overall

n=222

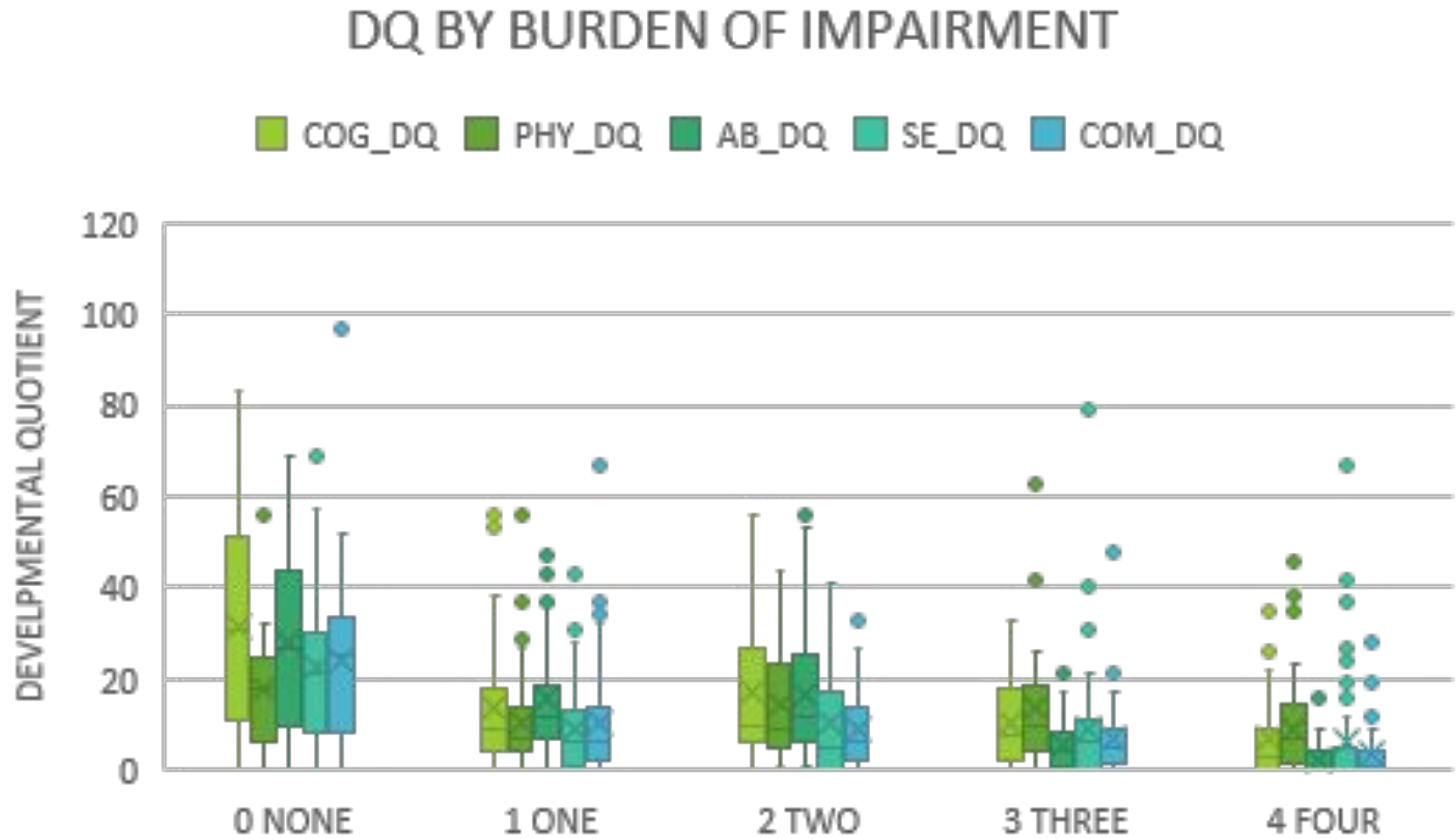


DQ by Gene Group

DEVELOPMENTAL QUOTIENTS BY GENE GROUPS

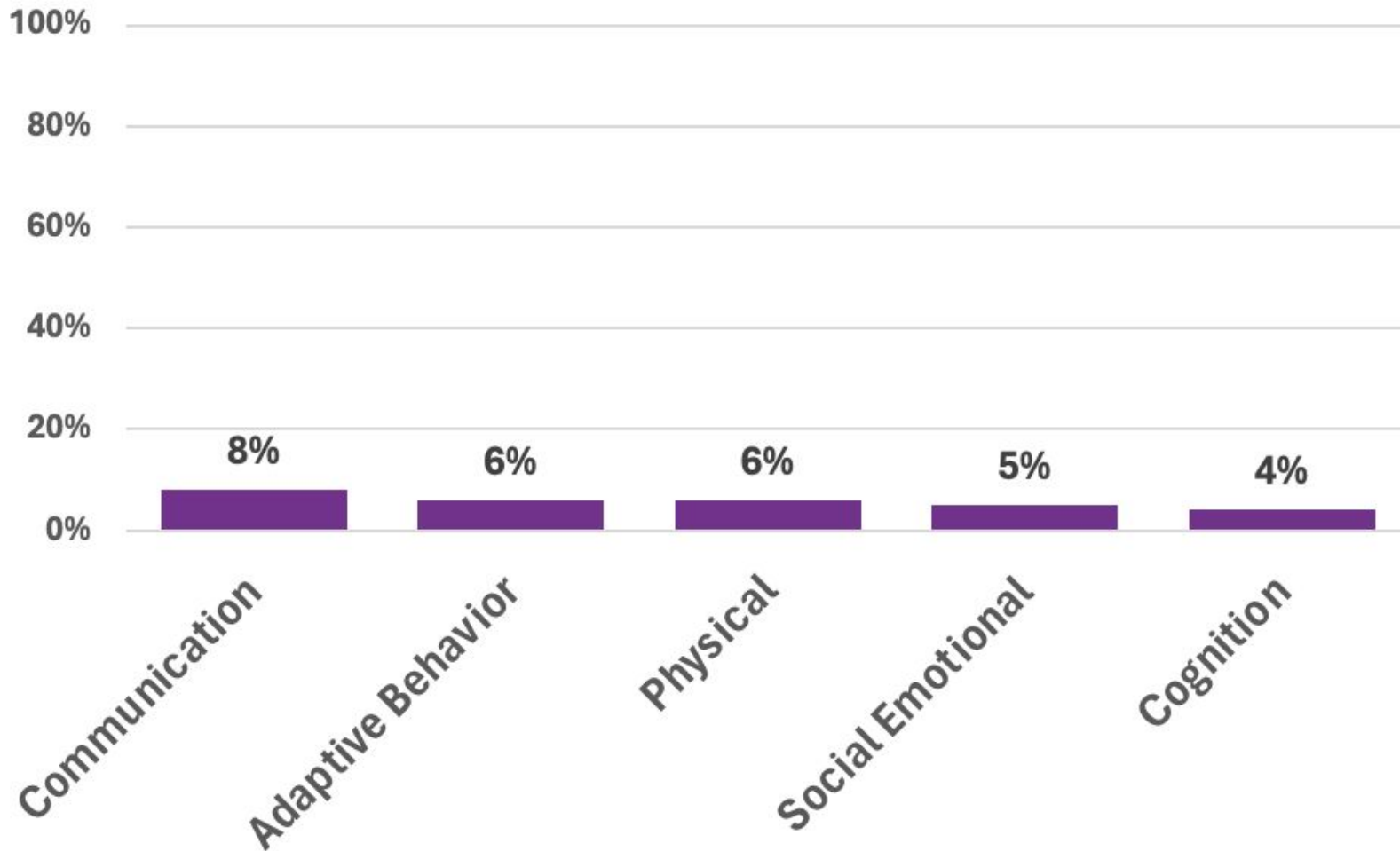


DQ by Number of Profoundly Impacted Domains



DP4 Raw Scores

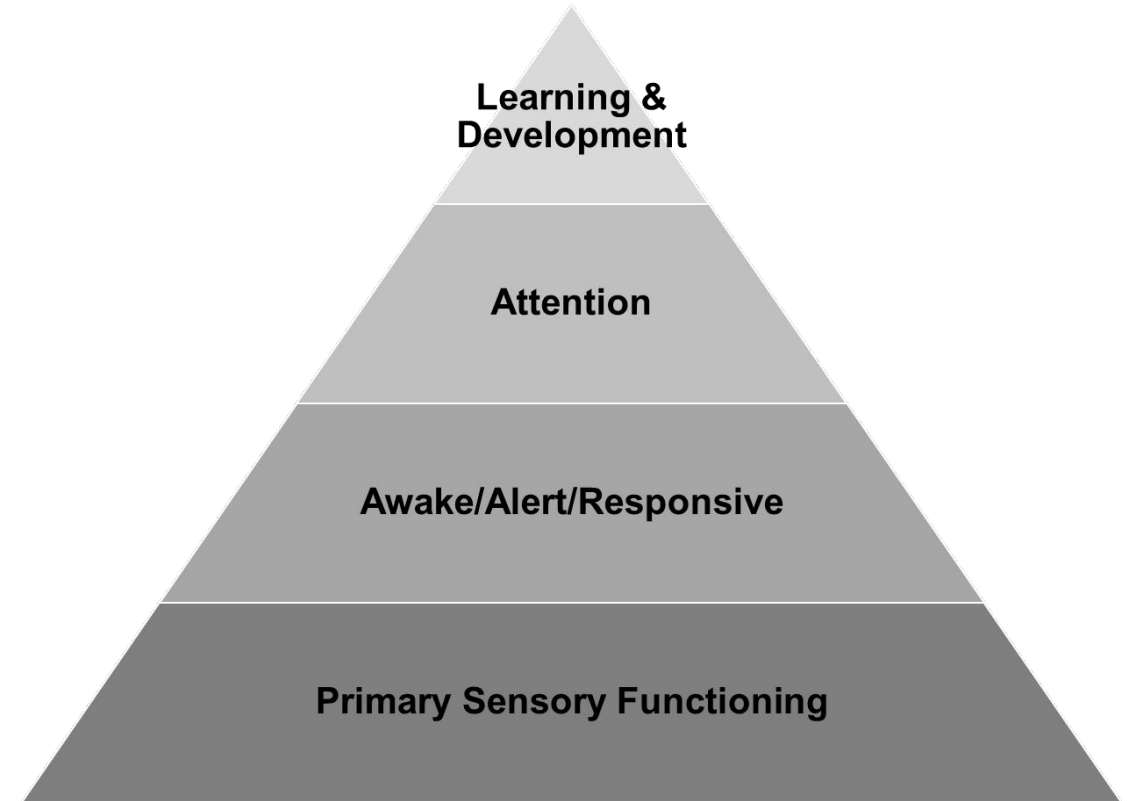
Percentage of sample scoring at floor



What percent of kids scored at the floor (0) for each of the DP4 categories?

Awareness and Responsiveness

*What does it look like
when your child is
having a good day?*



Targeting **alertness, awareness, responsiveness** may be important and meaningful to measure for those who are severely impaired

Caregiver Responsivity Inventory (CRI)

(Ludwig et al. adapted from Wolff et al, 2019)

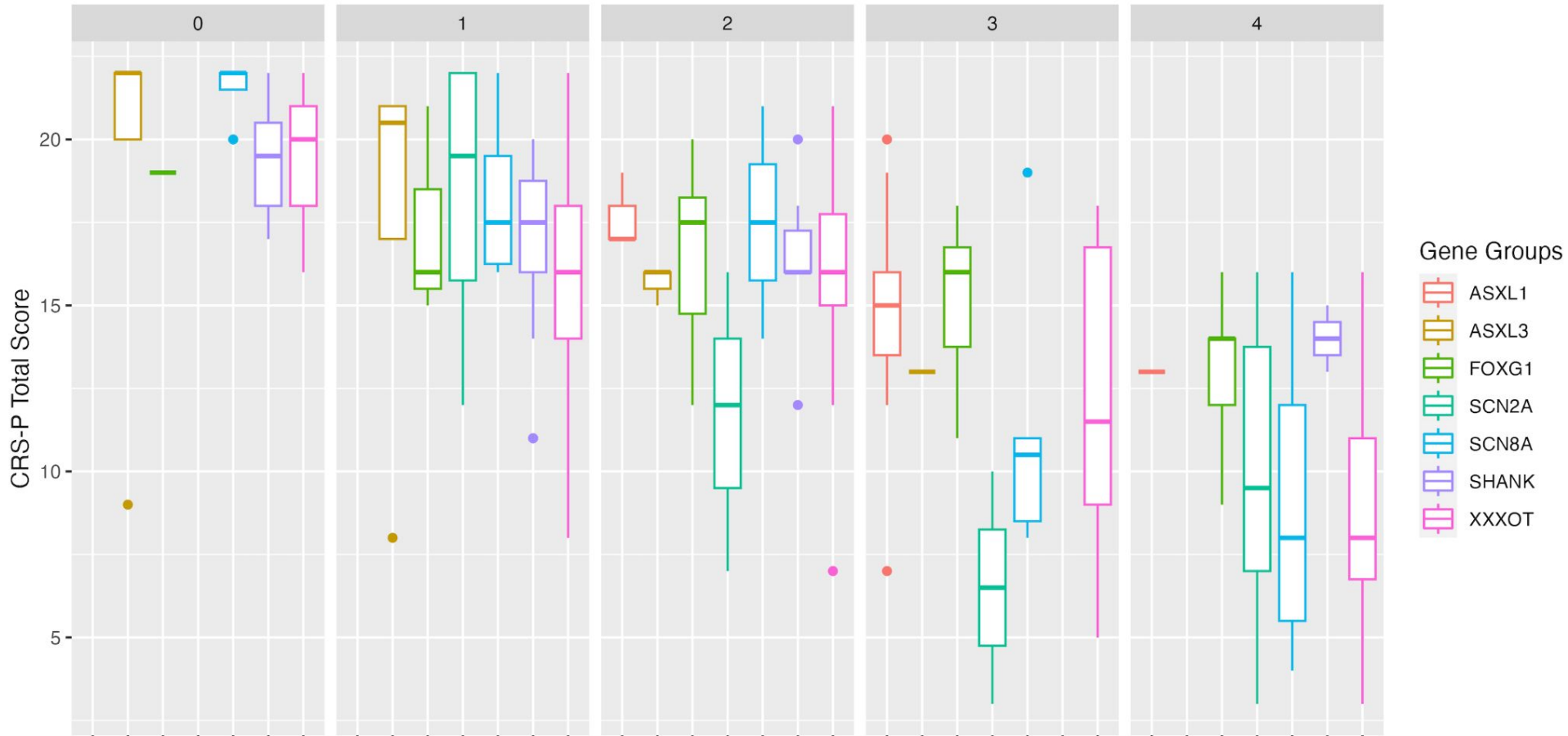
Domain	Average
Auditory (0-4)	2.22
Visual (0-5)	3.63
Motor (0-6)	4.33
Vocal (0-3)	1.96
Communication (0-2)	0.67
Arousal (0-3)	2.21
Total (0-23)	14.84 (no ceiling/ floor)

- **Auditory**
 - Does your relative move their head or eyes towards the location of a sound? **Yes.**
- **Visual**
 - Is your relative able to recognize two objects that are presented to them? **Yes.**
 - Is your relative able to follow with their eyes? **Yes.**
- **Motor**
 - Does your relative move their hand to grasp an object and hold it? **Yes.**
- **Vocal**
 - Does your relative produce sounds? **Yes.**
- **Communication**
 - Does your child cry or smile? **Yes.**
- **Arousal**
 - Does your relative usually keep their eyes open independently during school or therapies? **Yes.**

Distribution of scores

Distribution of CRS-P Total Scores

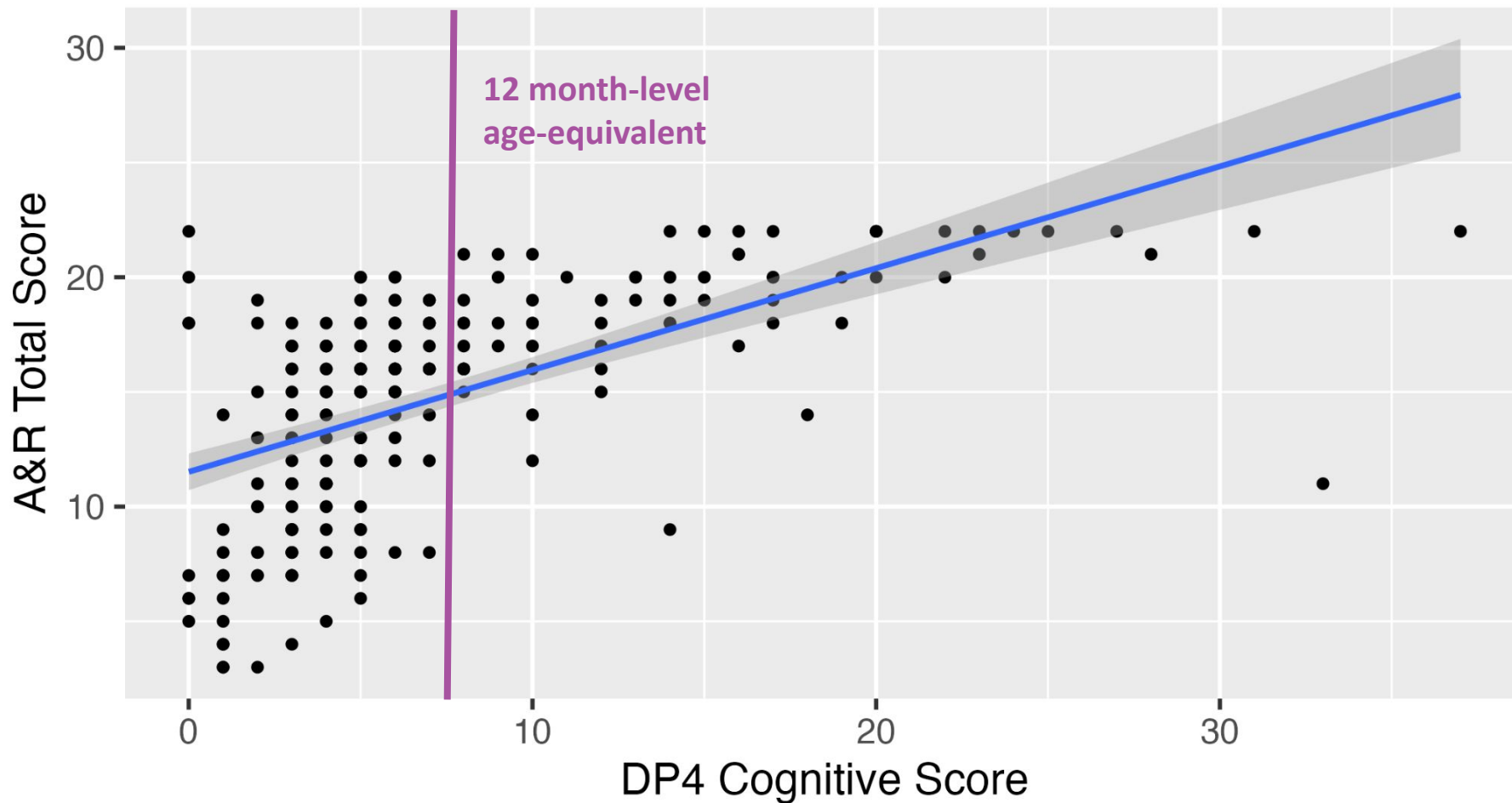
Gene Group and Number Severely Impacted Domains



Takeaway:

**Responsivity
decreases with
more severe
impairment.**

Correlation with DP4 scores



Takeaways:

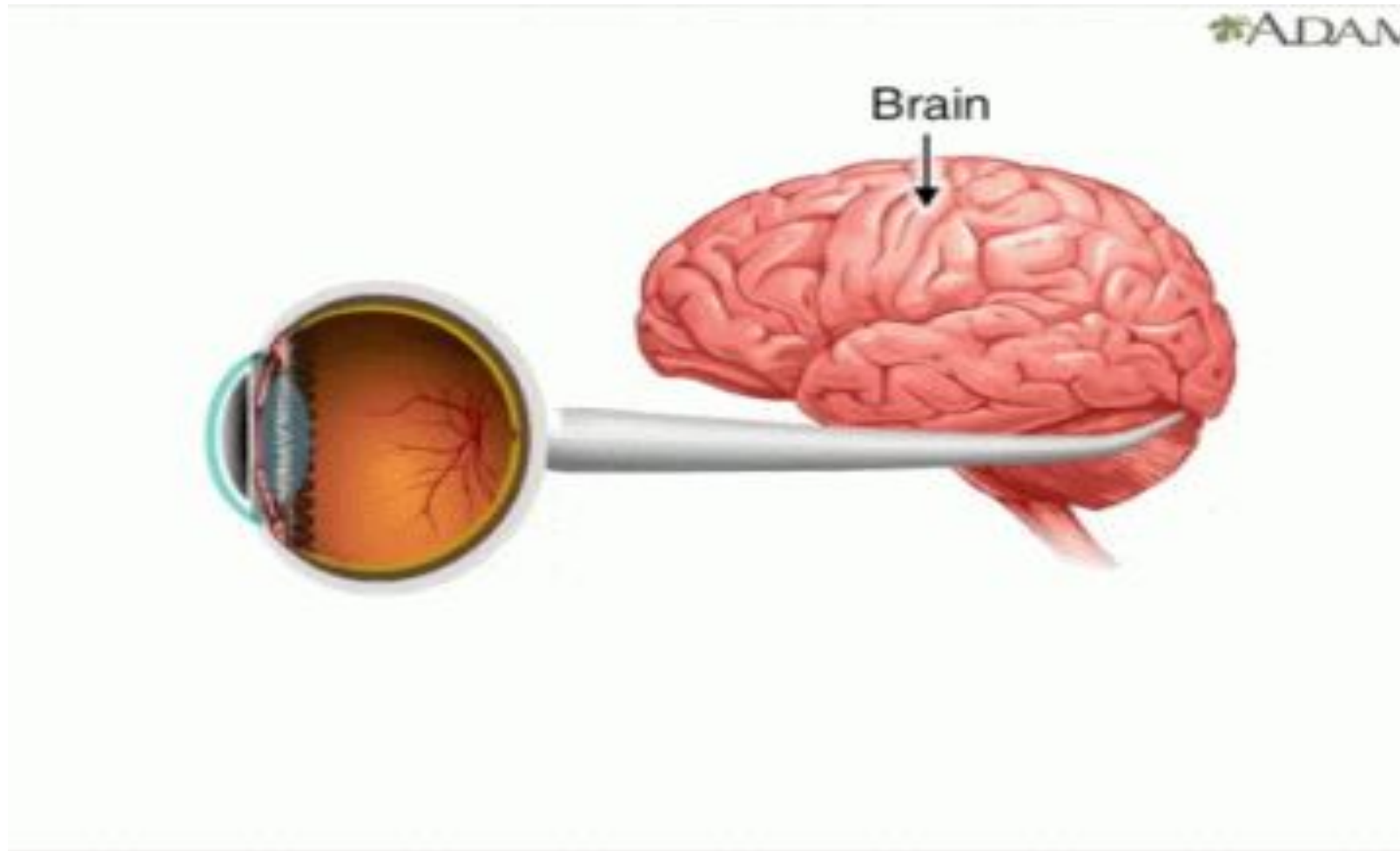
Responsivity increases with more cognitive ability.

The CRI shows far more variability in scores than the DP-4 for those below a 12 month-level.

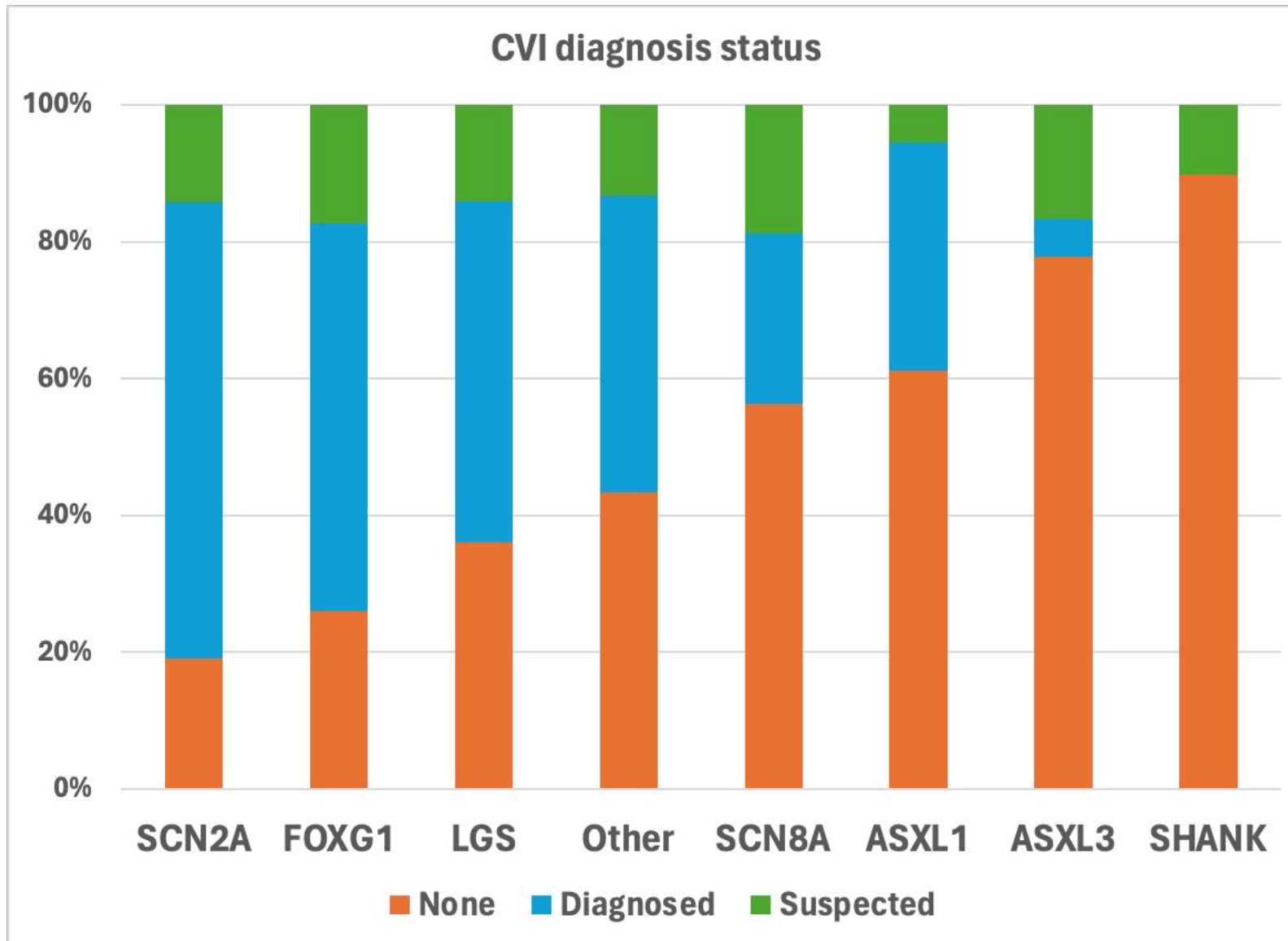
Cortical Visual Impairment



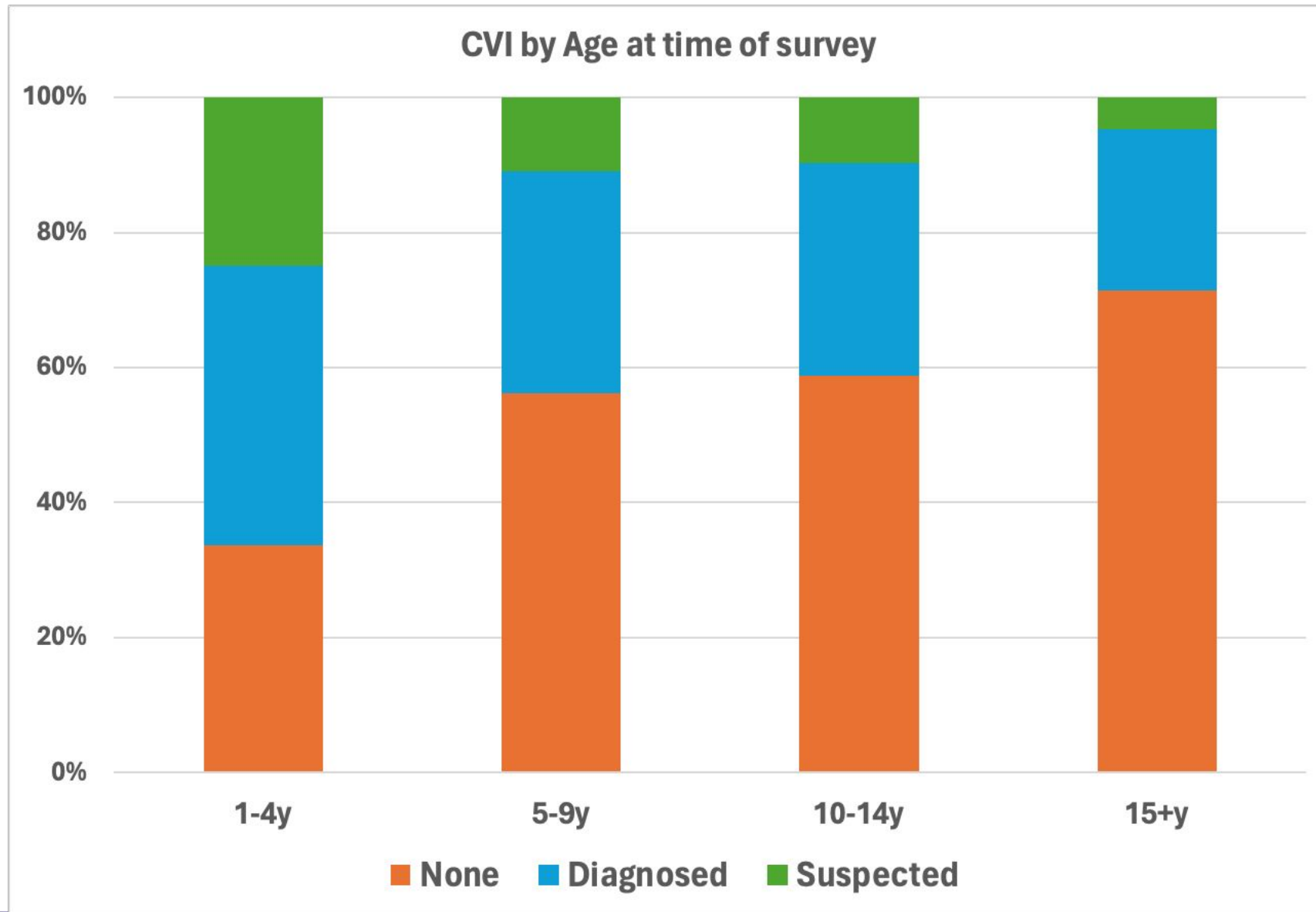
Cortical/Cerebral Visual Impairment



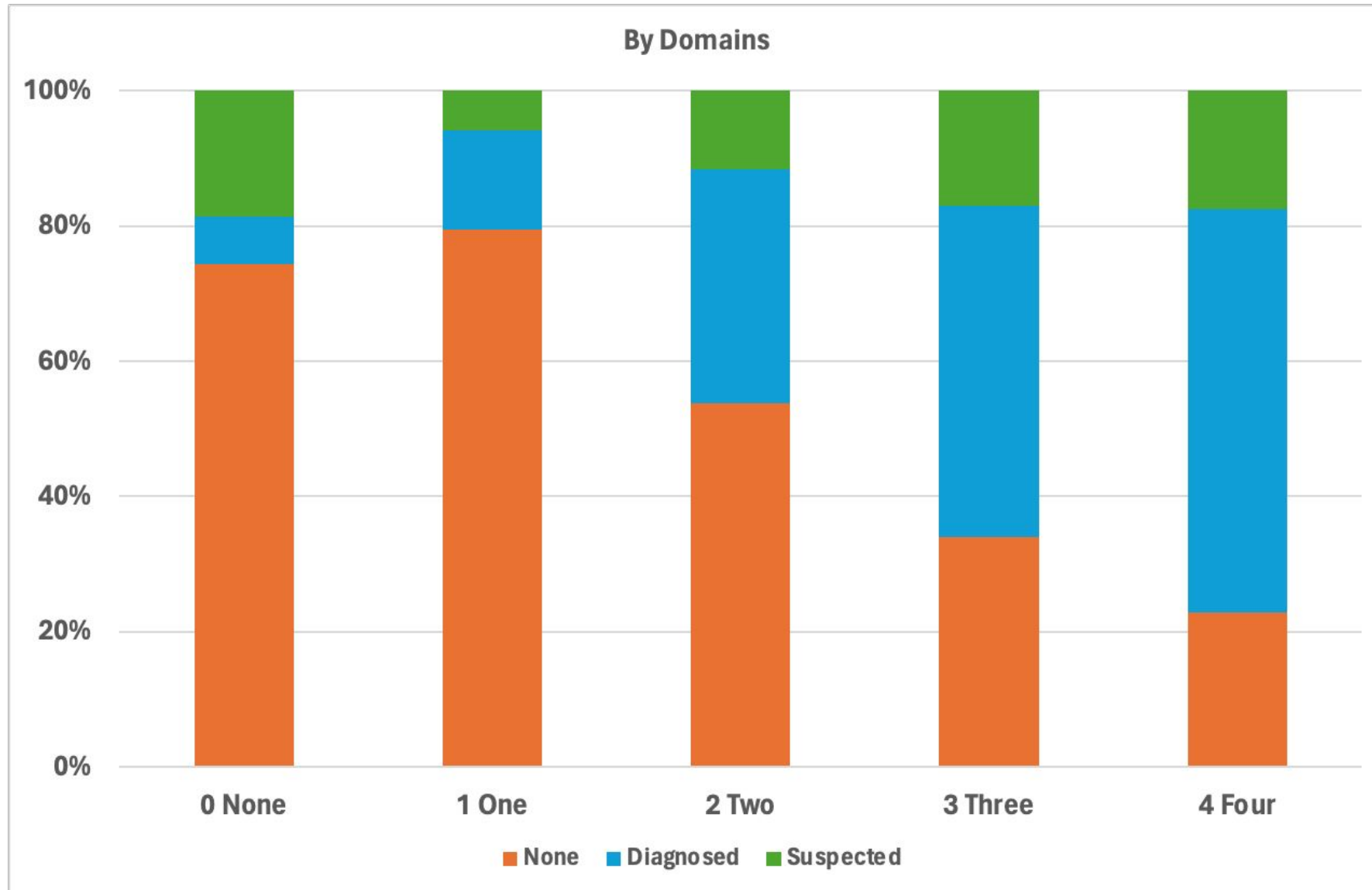
CVI by Gene Group



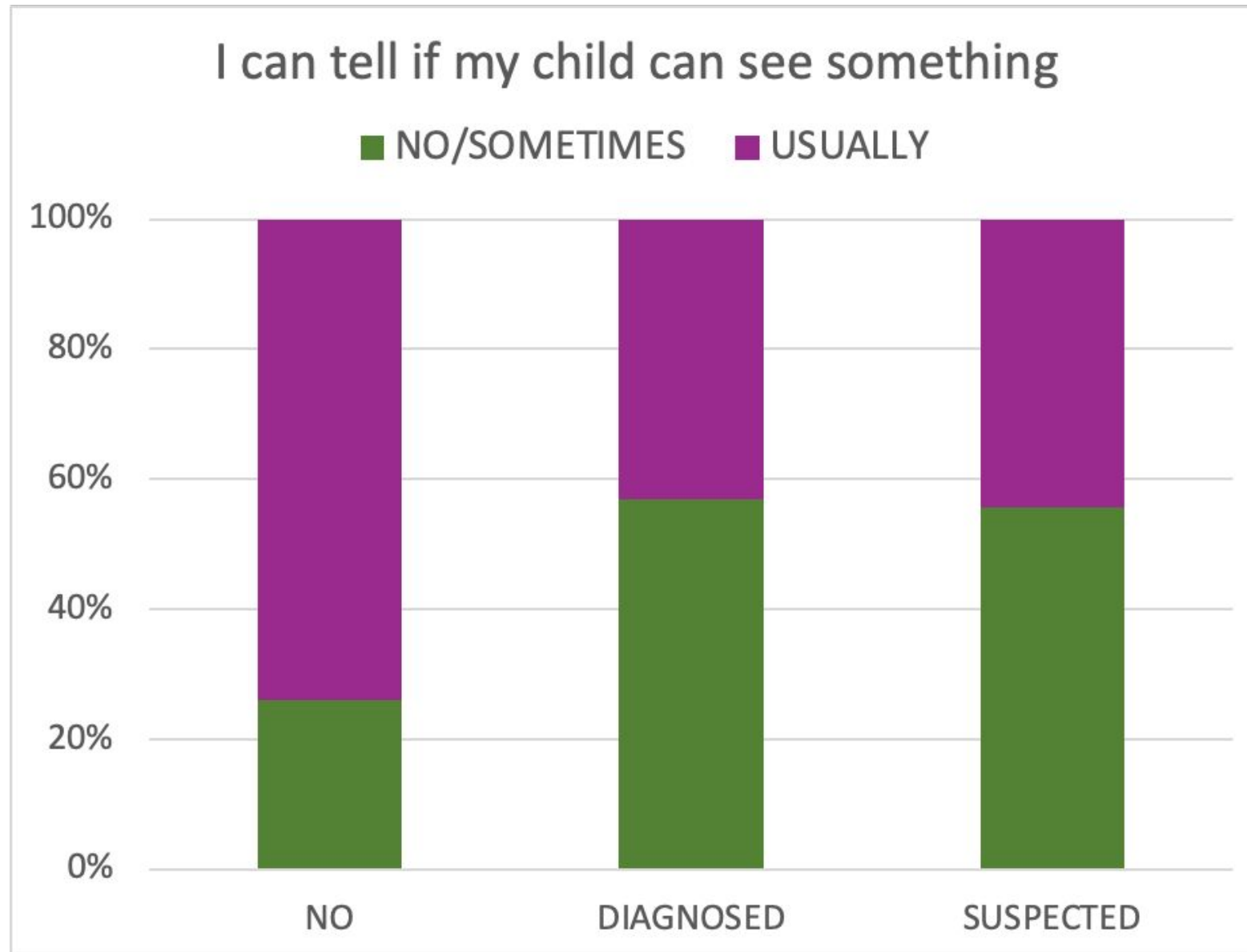
CVI diagnosis differs by age at time of survey



CVI diagnosis increases with number of impairments



Ability to Tell if My Child Can See Something by Diagnosis Status



The Importance of Vision in Communication



- Non-ocular impairment in visual processing
“Software” issue
- Color
- Movement
- Fields
- Latency
- Complexity
- Environment
- **Faces**
- Light
- Novelty
- Reaching



VINELAND-3 – early communication items

- Looks at caregiver who is gesturing to get attention
- Responds appropriately to 3+ facial expressions

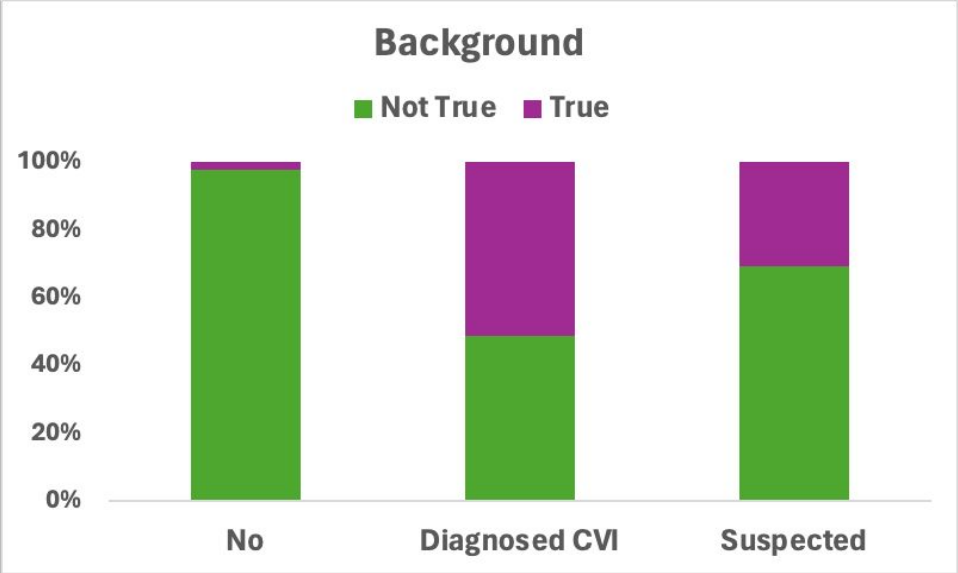
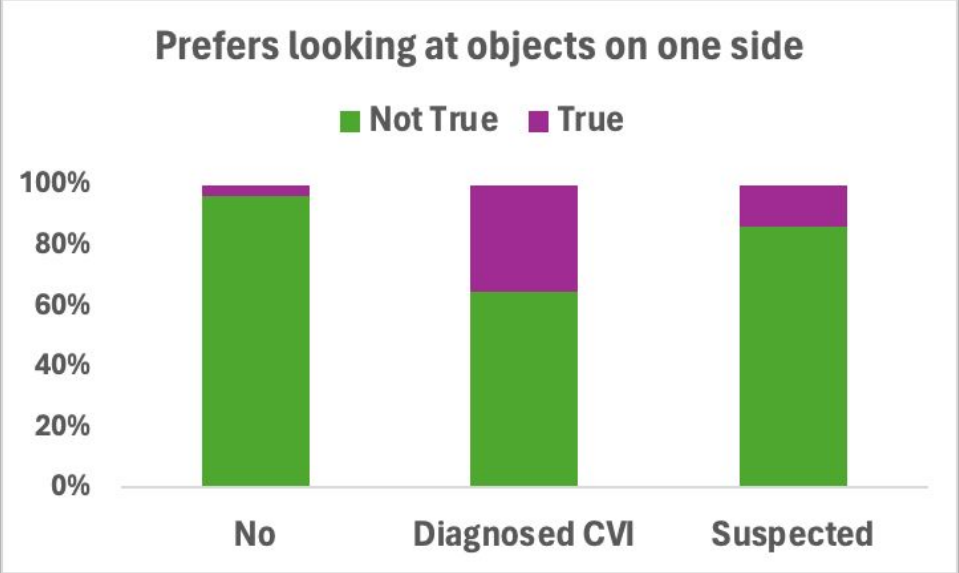
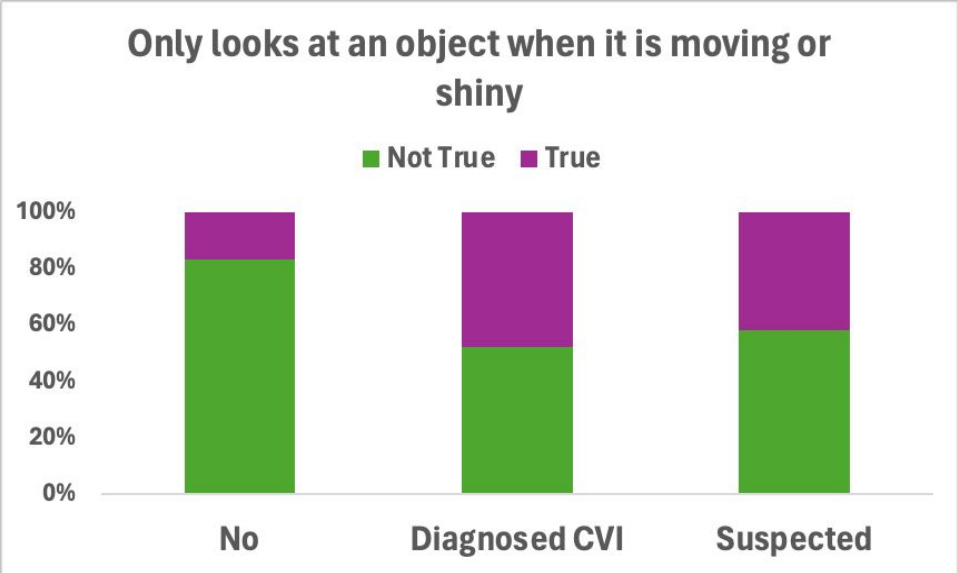
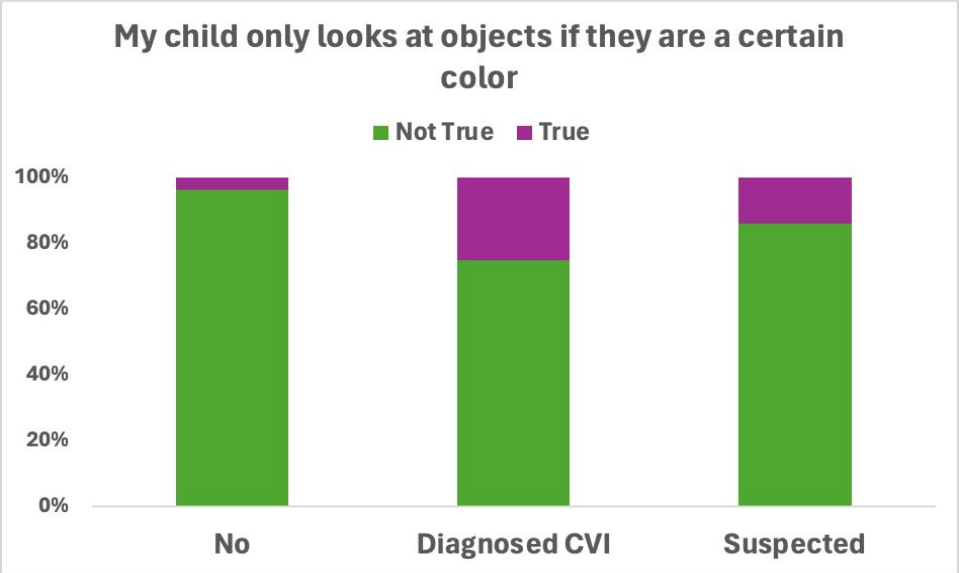
CSBS

- Does your child smile or laugh while looking at you?
- When you look at and point to a toy across the room, does your child look at it?

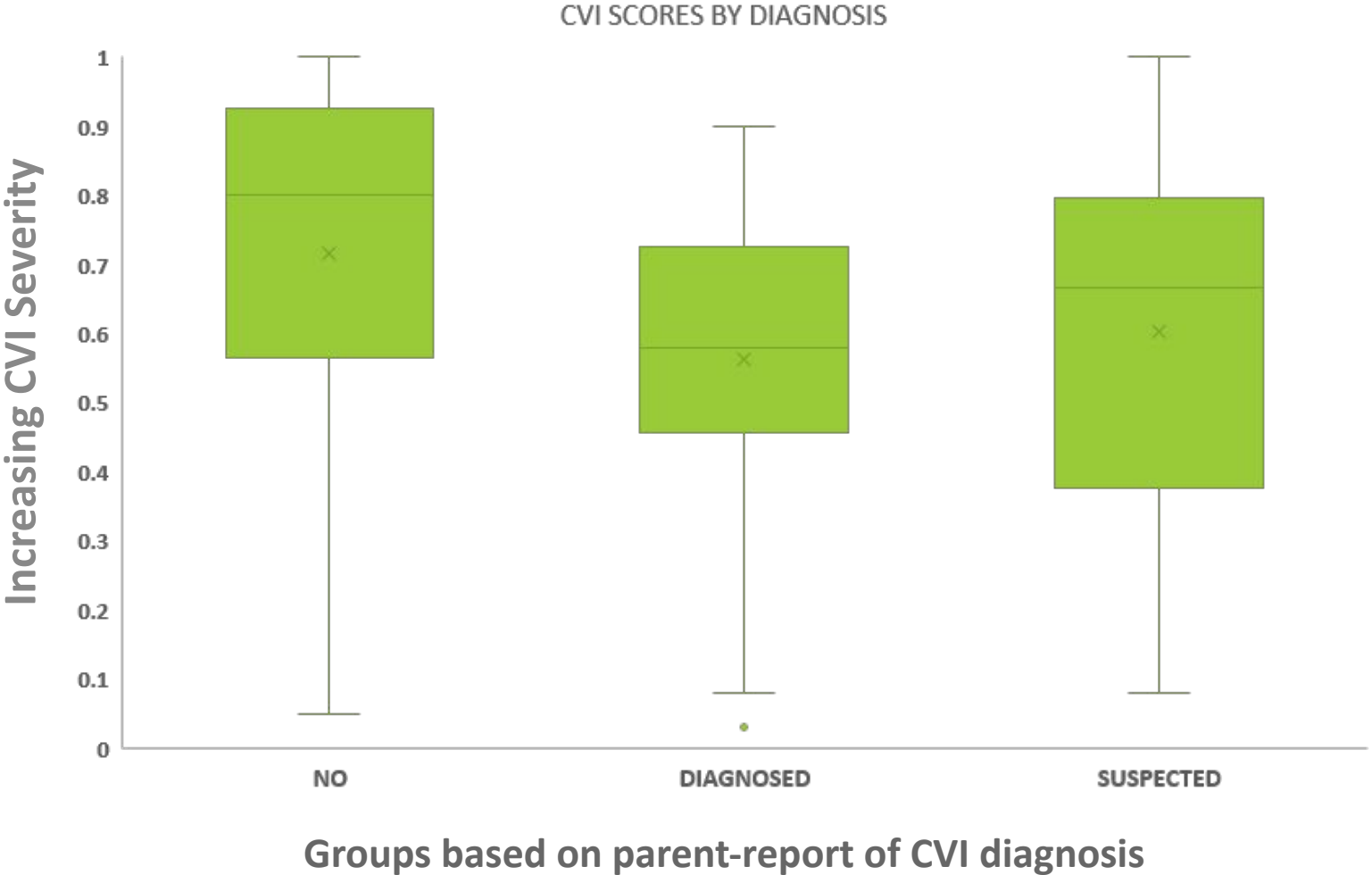
mCHAT

- When you smile at your child, does he or she smile back at you...?
- Does your child look you in the eye when you are talking to him or her, playing with him/her....?

Factors Affecting My Child's Vision by Diagnosis Status



Novel Parent-Report Measure of CVI Severity Based on the CVI Range: Scores by CVI Diagnosis Status



These initial findings are promising and exciting, but there is more work to be done to validate the measure

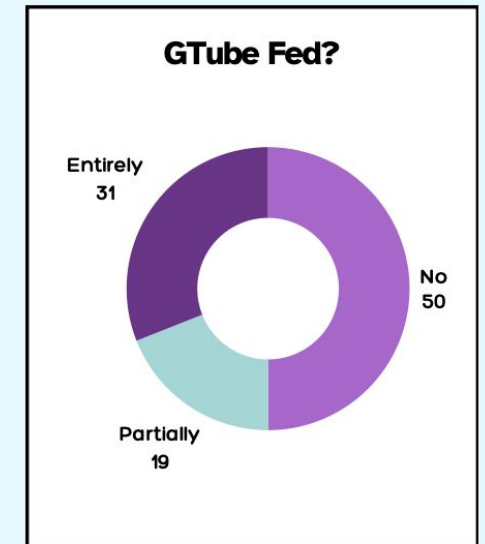
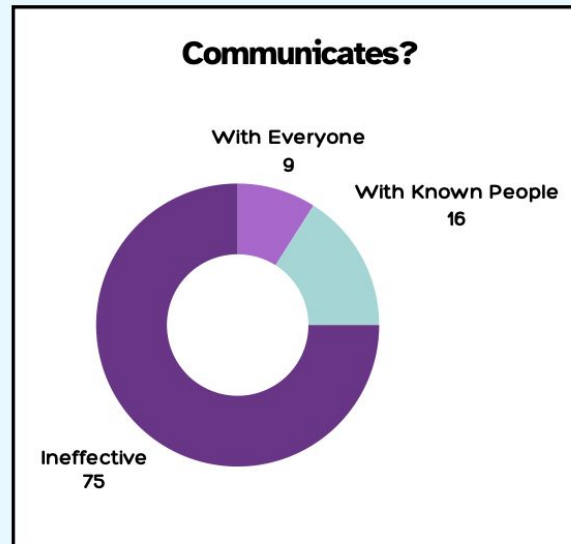
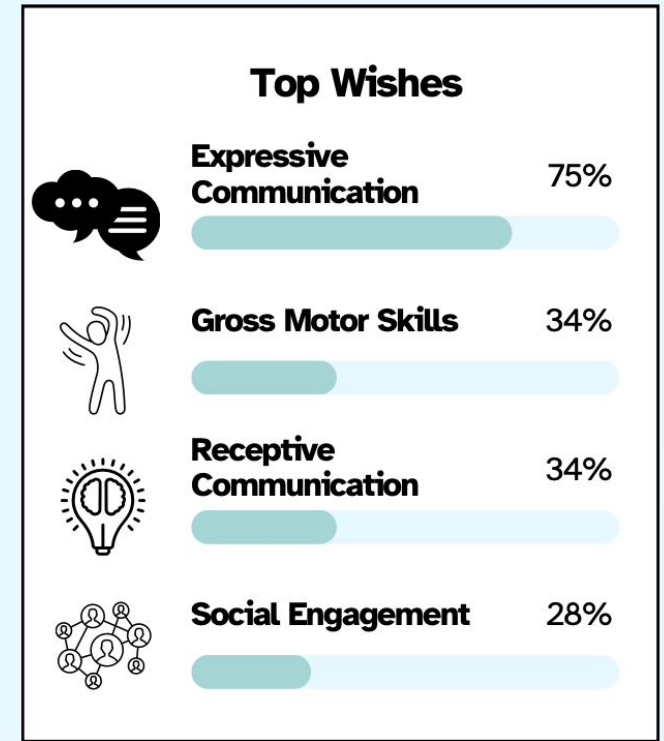
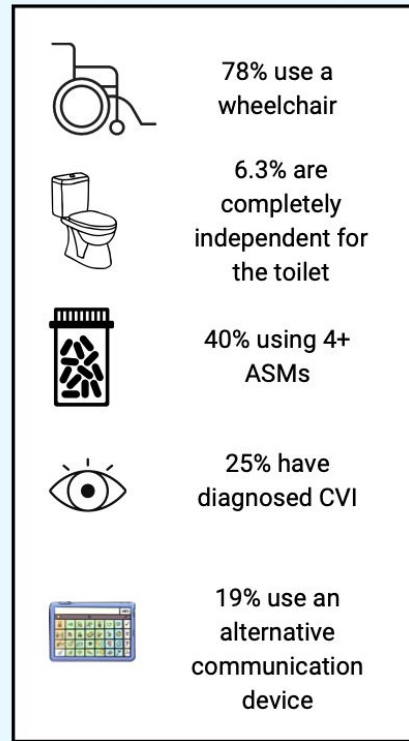
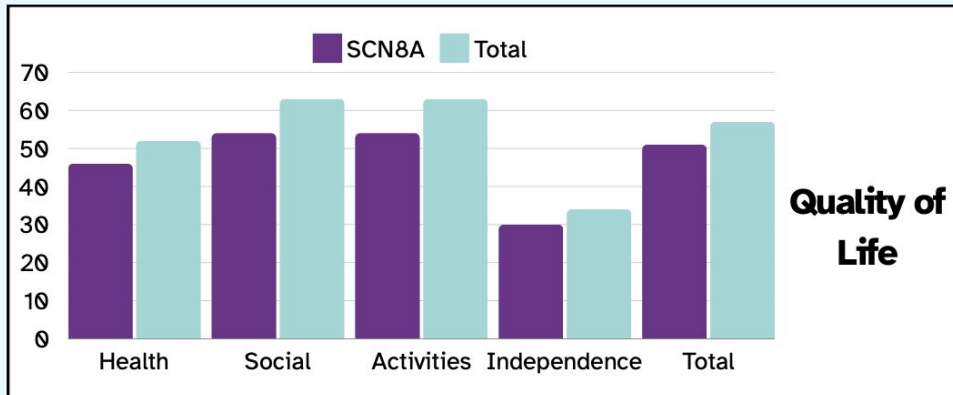
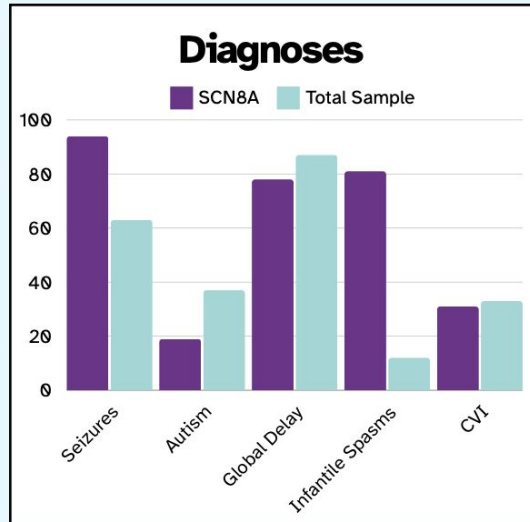
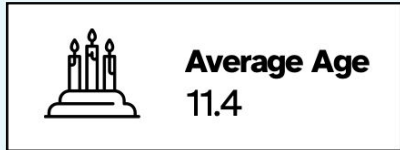
Community Profiles of Disease Groups with >20 Participants



SCN8A

Inchstone Results

This report provides both a broad overview of our SCN8A sample, as well as key highlights from the survey results.



LGS

Inchstone Results

This report provides both a broad overview of our LGS sample, as well as key highlights from the survey results.



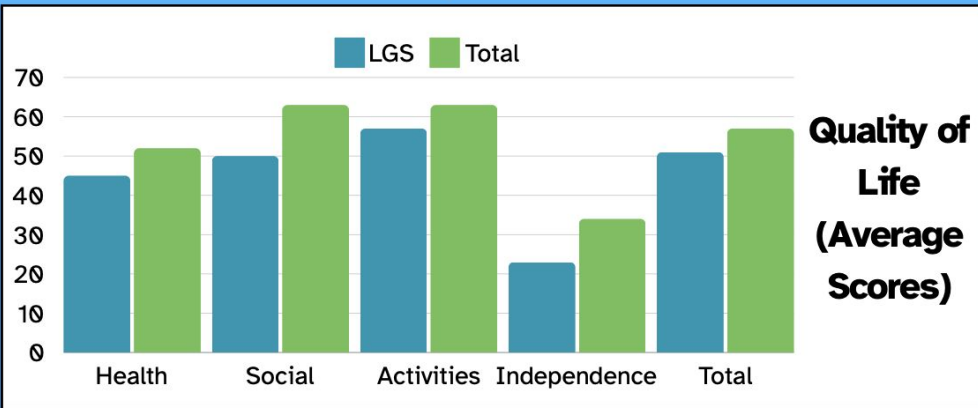
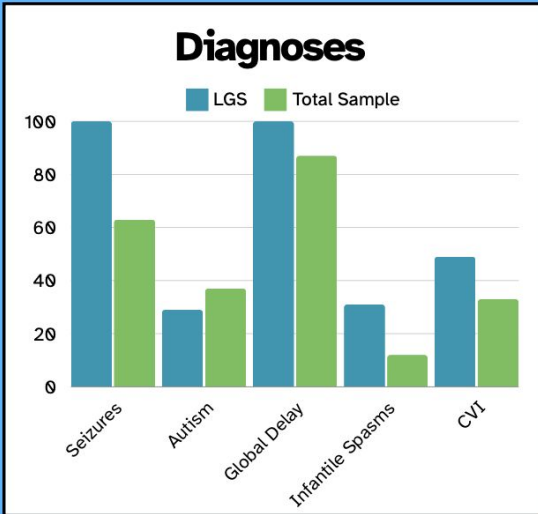
Total
51



Average Age
12



Sex
51% Female



92.2% use a wheelchair



0% are completely independent for the toilet



65% using 4+ ASMs



50% have diagnosed CVI



19% use an alternative communication device

Top Wishes



Expressive Communication 80%



Gross Motor Skills 51%



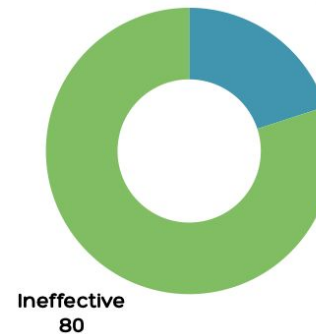
Sleeping 31%



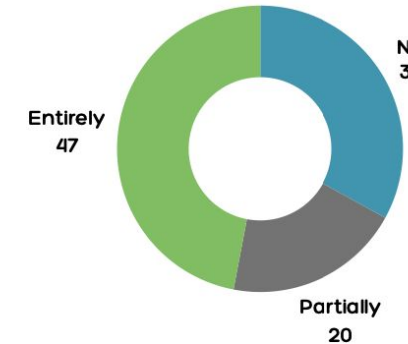
Receptive Communication 20%

Communicates?

With Known People
20



GTube Fed?





THE INCHSTONE PROJECT

Q&A

Discussion

Continuing Opportunities to Help Advance Work of The Inchstone Project

Focus Groups

Entirely virtual, led by one of our DEE researchers

We will have 5 separate sessions

Cognition

Quality of Life

Vision

Awareness and Responsiveness

Priorities and Impacts

If you participated in the DEE Parents Speak Survey and indicated you were open to joining the post-survey focus groups, we will be in touch soon with additional details

This isn't another survey, but a chance for your feedback on the process and a key part in understanding the limitations and room for improvement in current and developing instruments



Proposing FDA Listening Session for DEEs and Severe NDDs

- **Listening Session:** 90 min informal, non-regulatory meetings between FDA staff and patients
- **Participants:** Caregivers, advocates, community representatives, and FDA staff
- **Purpose:** Share patient experiences, perspectives, and needs related to their health or a disease
- **Benefits:** Helps FDA connect with under-represented communities and understand patient needs

Opportunity to participate in expanded clinical assessments

Kennedy Krieger - Contact Natasha at: LudwigResearch@kennedykrieger.org

or

Nationwide - Contact Mary at: Mary.Wojnaroski@nationwidechildrens.org



The Inchstone Project is Recruiting for a New In-Person Study

The Inchstone Project is recruiting for a **new in-person research study to explore better ways to measure abilities in individuals with severe neurodevelopmental disabilities.**

Children and adults with 1) severe to profound intellectual disability (ID) or global developmental delay (GDD) and 2) either severe motor impairments (i.e., unable to walk independently) and/or a gastrostomy tube may be eligible for participation in this study.



Interested families are encouraged to contact the study team to learn more and to complete a short screening survey to check eligibility at: LudwigResearch@kennedykrieger.org

This study has been approved by the Johns Hopkins School of Medicine (IRB IRB00382308)

Principal Investigator: Natasha Ludwig, PhD

THE INCHSTONE PROJECT

Confirmed 2024 Industry Partners



Jazz Pharmaceuticals.



2022 Industry Partners



Jazz Pharmaceuticals.



2023 Industry Partners



Jazz Pharmaceuticals.





THE INCHSTONE PROJECT

Thank you!

Reach out anytime with questions or ideas: gabi@d-de.org