Use of Bayley-III and online screening tools to characterize early childhood behavioral phenotype in boys with Duchenne muscular dystrophy

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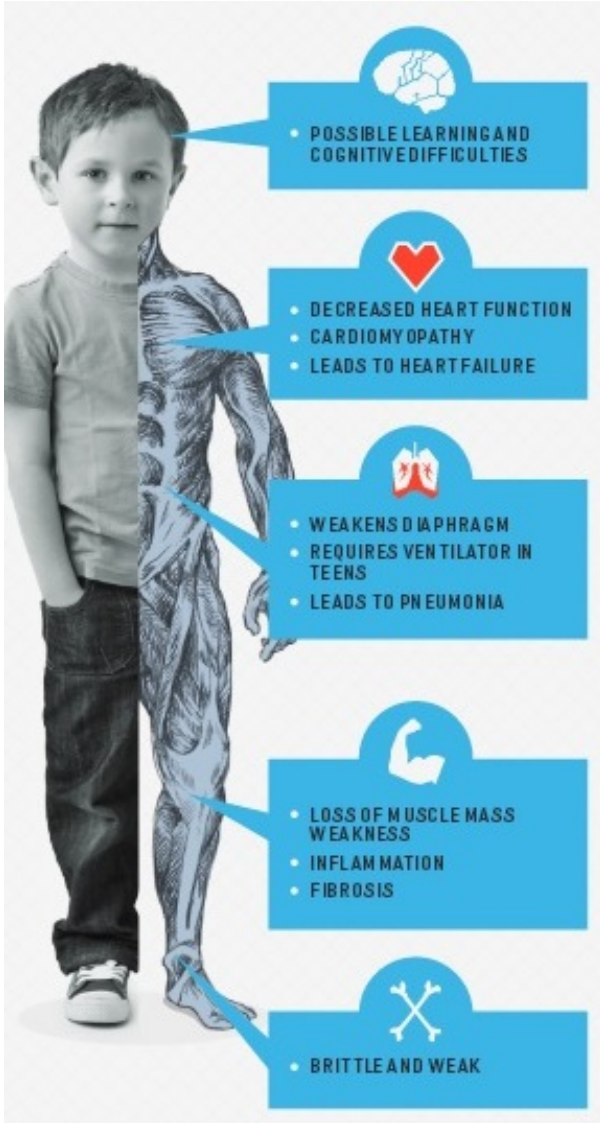
DMD: A Multisystem Disorder



Duchenne Muscular Dystrophy as a Developmental Disorder

- Cognitive Delays
  - 1-1.5 SD below the mean with same distribution
  - 1/3 cognitively delayed (Cyrulnik et al., 2008; Daoud et al., 2009)
- Language Delay
  - Often first sign of DMD (Lundy et al., 2007; Kaplan, Osborn, & Elias, 1986)
- Social/Behavioral Delay
  - Higher incidence of boys with ADD, ADHD, OCD (Poysky, 2007; Hendriksen & Vles, 2008; Hinton et al., 2006)
- Estimated prevalence of DMD/ASD comorbidity in the literature is ***between 3.1-19.6%***

Developmental assessments for children with DMD*

- **Monitor physical and developmental milestones** and **be aware of DMD-specific neurodevelopmental and neuropsychological issues**, such as the increased prevalence of intellectual disability, attention-deficit hyperactivity disorder, and autism spectrum disorder
- Refer to a psychologist for psychological and neuropsychological **assessments and interventions** when appropriate
- Refer to a speech-language pathologist for suspected delays
- Help the family with **special educational needs** (eg, in the USA, plans include the Individualized Education Programs and 504 plans)
- Identify **community resources** that might enhance individual and family functioning and coping, such as local social service agencies and patient advocacy organizations

D. Birnkrant et al.* ***Diagnosis and management of Duchenne muscular dystrophy, part 3**: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet 2018*

Developmental assessments for children with DMD

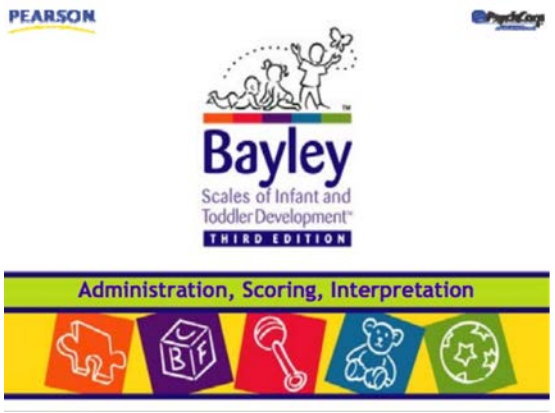
- **Neuropsychological evaluations** should be done when **cognitive delays**, **difficulties with emotional and behavioral regulation**, or **concerns about social skills** exist;
- **Neuropsychological evaluations** should be **considered within the first year of diagnosis** to establish a baseline
- **Re-evaluations should be done every 2–3 years** to monitor developmental progress and response to interventions

D. Birnkrant et al.* ***Diagnosis and management of Duchenne muscular dystrophy, part 3**: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet 2018*

Study 1: MDA Clinical Research Network Study of Infants and Young Boys with DMD

(Connolly et al., 2013 & 2014)

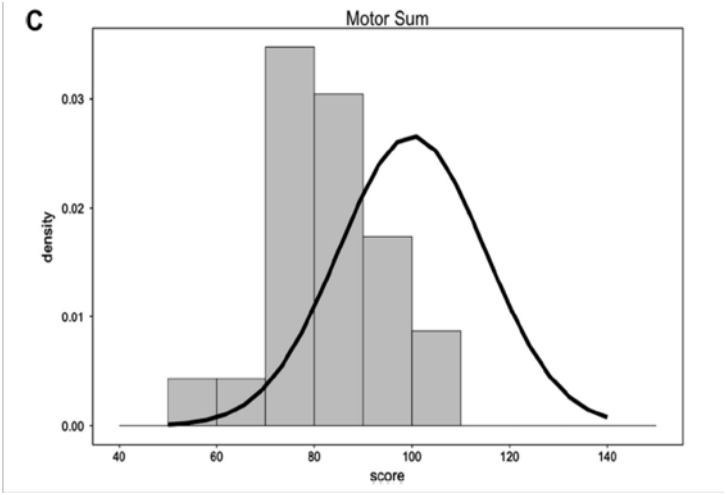
- Multisite study – 6 locations
- 24 boys with DMD enrolled under 36 months of age at BL
  - Mean = 22.8 months
  - Range 4.4 – 35.9 months
- Bayley-III assessments at:
  - Baseline (N = 24)
  - 6 months after baseline (N = 19)
  - 12 months after baseline (N = 12)



Baseline Distribution of Bayley-III Composite Scores

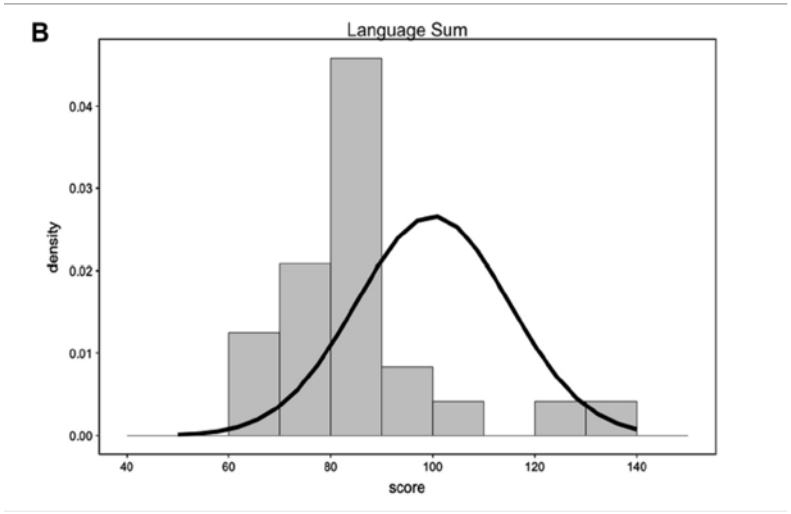
(Connolly et al., 2013)

MOTOR



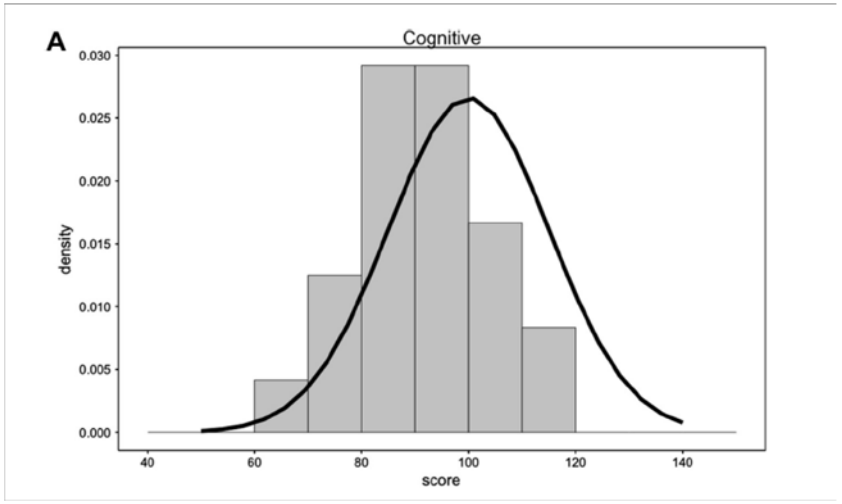
p≤.0001

LANGUAGE



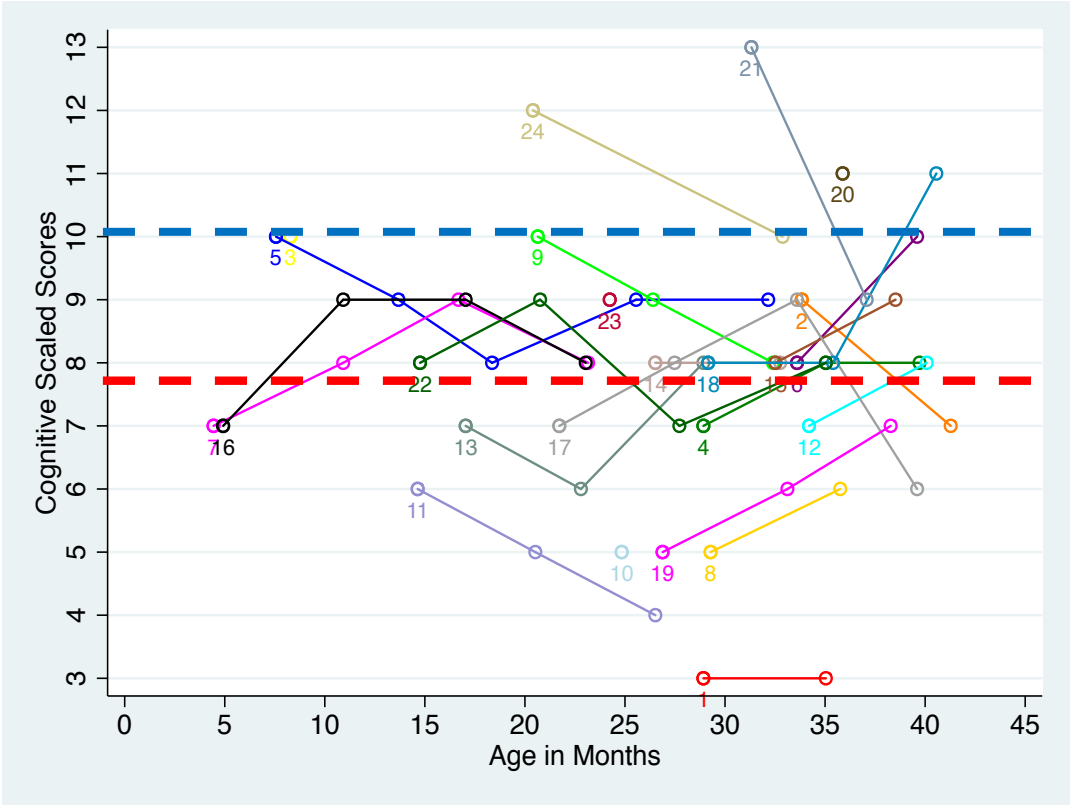
p≤.0001

COGNITIVE



p≤.0001

Longitudinal Bayley-III Cognitive Scaled Scores demonstrate stability over time on average



Typical Score 10

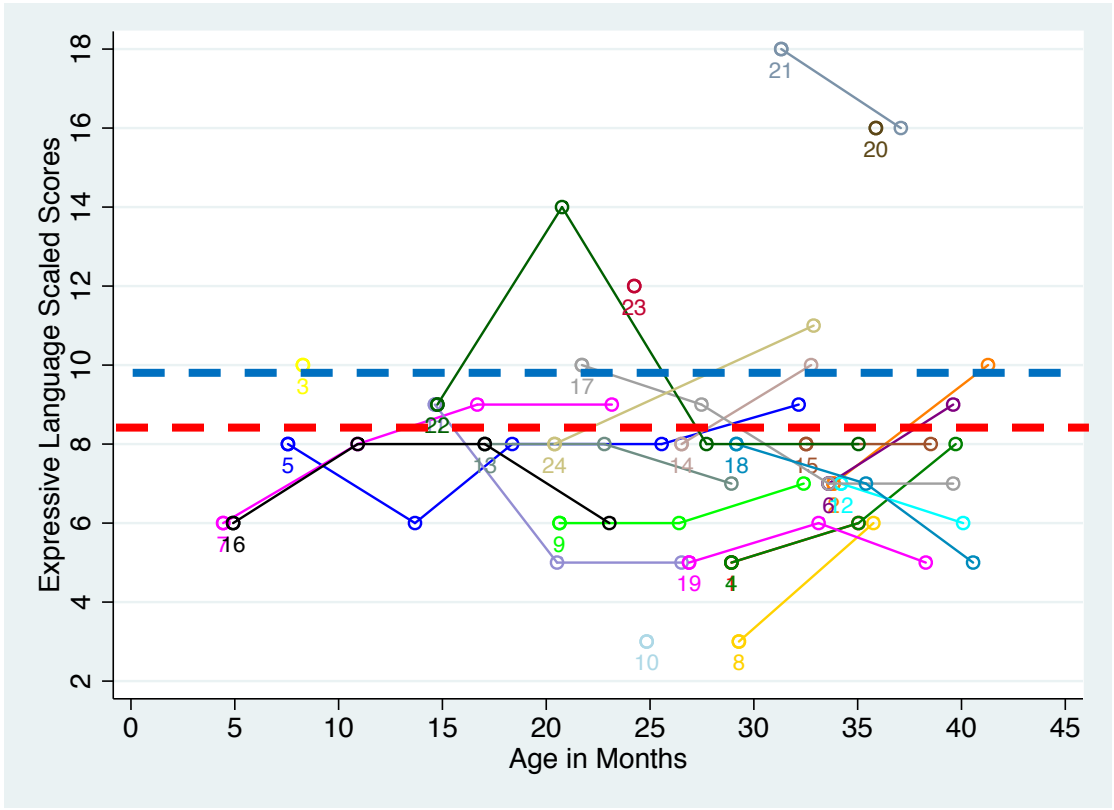
DMD Score 7.9

Table 14. Results of Unconditional Means Model (No Growth) of Bayley-III Cognitive Subscale Scores for Boys with DMD by Age in Months (N=24; Number of Observations = 61)

Coefficient (SE)	Unconditional Means Model
Fixed Effects	
Intercept	7.93***
Linear Slope	
Quadratic	
Random Effects	
Level-1:	
Within-person	1.21
Level-2:	
Intercept	2.98
Linear slope	
Quadratic	
Goodness of Fit	
-2 Log Likelihood	230.7
AIC	236.7
BIC	240.2

~ p <.10, * p<.05, ** p<.01, *** p<.001

Longitudinal Bayley-III Expressive Language Scaled Score deficits also demonstrate stability over time



Typical Score 10

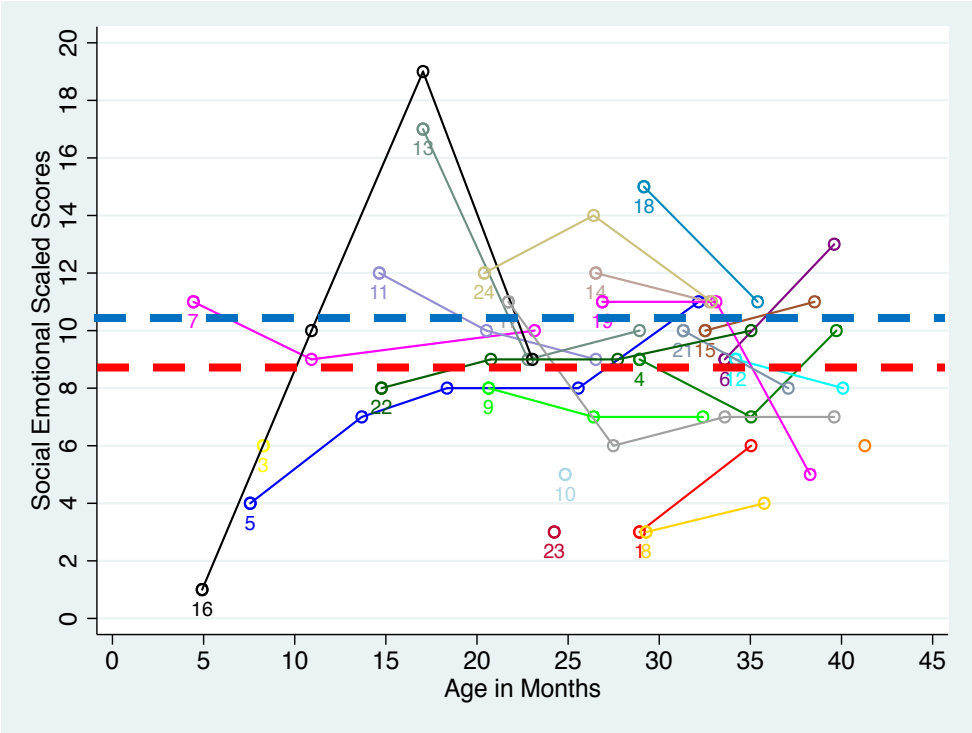
DMD Score 8.1

Table 20. Results of Unconditional Means Model (No Growth) of Bayley-III Expressive Language Subscale Scores for Boys with DMD by Age in Months (N=24; Number of Observations = 61)

Coefficient (SE)	Unconditional Means Model
Fixed Effects	
Intercept	8.14***
Linear Slope	
Quadratic	
Random Effects	
Level-1:	
Within-person	2.49
Level-2:	
Intercept	7.54
Linear slope	
Quadratic	
Goodness of Fit	
-2 Log Likelihood	278.9
AIC	284.9
BIC	288.4

~ p <.10, * p<.05, ** p<.01, *** p<.001

Longitudinal Bayley-III Social Emotional Scaled Score deficits are variable but stable



Typical Score 10

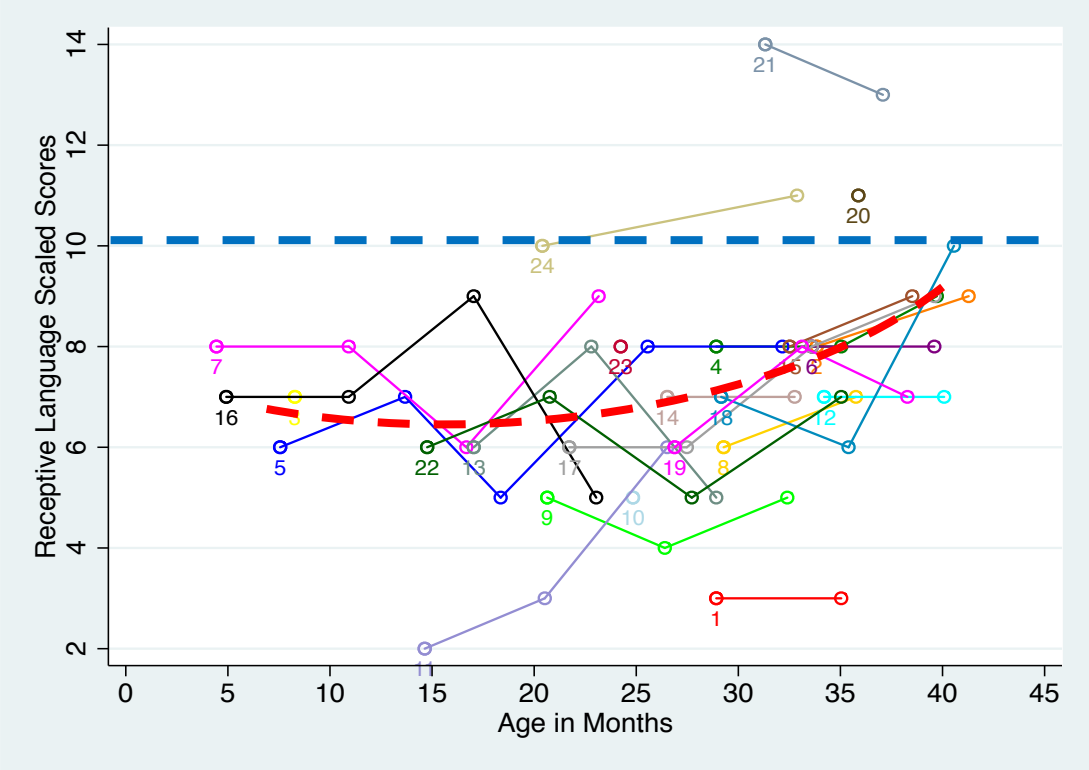
DMD Score 8.8

Table 23. Results of Unconditional Means Model (No Growth) of Bayley-III Social Emotional Subscale Scores for Boys with DMD by Age in Months (N=24; Number of Observations = 63)

Coefficient (SE)	Unconditional Means Model
Fixed Effects	
Intercept	8.86***
Linear Slope	
Quadratic	
Random Effects	
Level-1:	
Within-person	9.69***
Level-2:	
Intercept	1.26
Linear slope	
Quadratic	
Goodness of Fit	
-2 Log Likelihood	302.7
AIC	308.7
BIC	312.2

~ p <.10, * p<.05, ** p<.01, *** p<.001

Longitudinal Bayley-III Receptive Language Scaled Scores show delay that improves with age



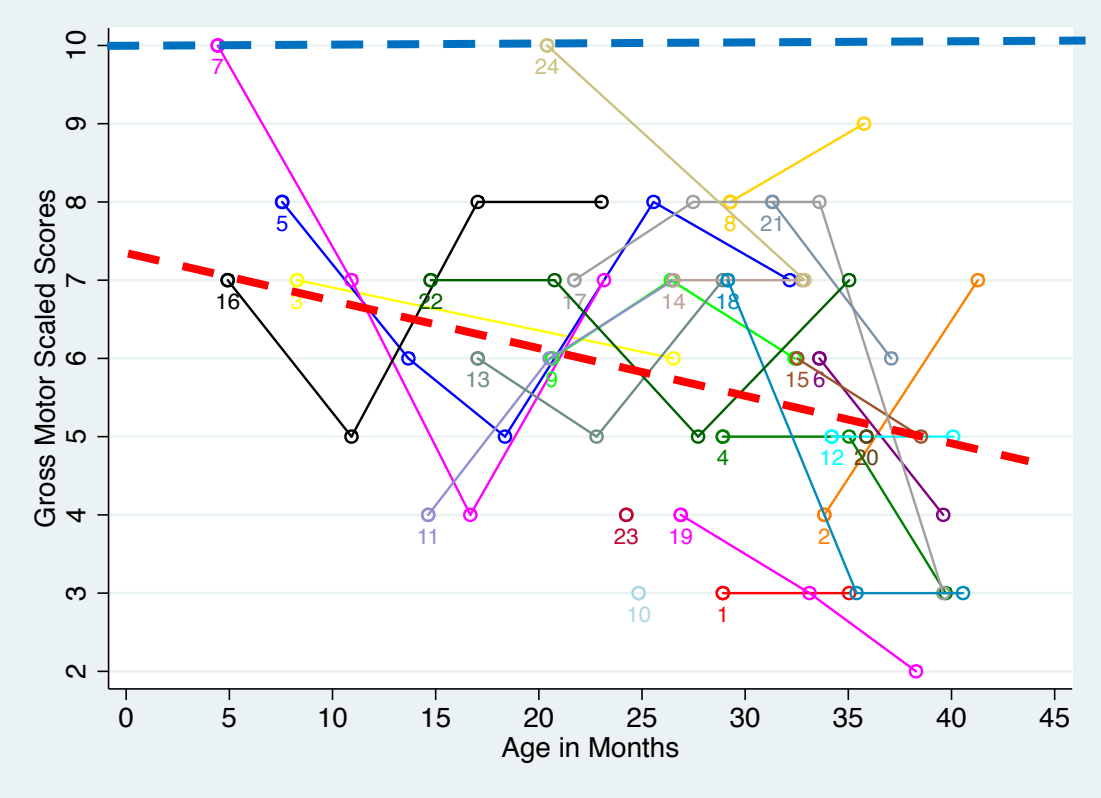
Typical Score 10

Table 17. Results of Quadratic Model with Random Intercept of Bayley-III Receptive Language Subscale Scores for Boys with DMD by Age in Months (N=24; Number of Observations = 61)

Coefficient (SE)	Quadratic Model without Random Intercept
Fixed Effects	
Intercept	6.62***
Linear Slope	0.0619*
Quadratic	0.0034*
Random Effects	
Level-1:	
Within-person	1.25***
Level-2:	
Intercept	3.3861
Linear slope	
Quadratic	
Goodness of Fit	
-2 Log Likelihood	234.4
AIC	244.4
BIC	250.3

~ $p<.10$, * $p<.05$, ** $p<.01$, *** $p<.001$

Longitudinal Bayley-III Gross Motor Scaled Scores show decline with advancing age



Typical Score 10

Table 8. Results of Linear Model with Random Intercept of Bayley-III Gross Motor Subscale Scores for Boys with DMD by Age in Months (N=24; Number of Observations = 62)

Coefficient (SE)	Quadratic Model without Random Intercept
Fixed Effects	
Intercept	6.15***
Linear Slope	-0.067**
Quadratic	
Random Effects	
Level-1:	
Within-person	2.32
Level-2:	
Intercept	0.65
Linear slope	
Quadratic	
Goodness of Fit	
-2 Log Likelihood	240.9
AIC	248.9
BIC	253.6

~ p <.10, * p<.05, ** p<.01, *** p<.001

Study 2 Methods: National online survey using common ASD-focused and developmental *screening* tools

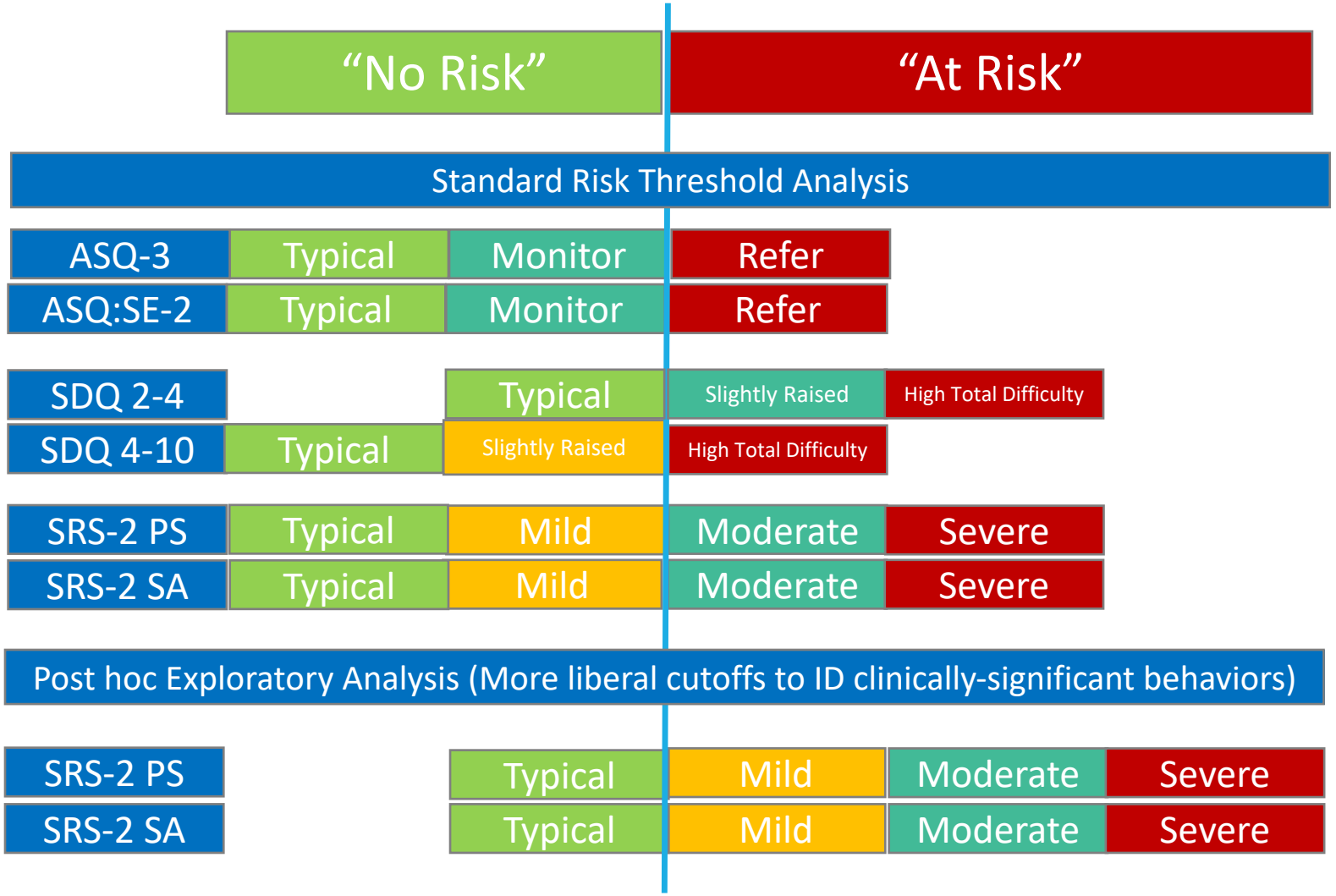
DMD Group

- N = 45 Boys
- Age: Mean 58.6 mos.; 18.1-83.3 mos.
- 27 States
- 28.9% have 3+ children
- 57.7% of respondents & 33.4% of partners have college or grad degree
- 13.3% with income <$20K
- 40% with income ≥$100K

Control Group

- N = 39 Boys
- Mean 48.0 mos.; 18.6-82.1 mos.
- 12 States
- 15.6% have 3+ children
- 97.4% of respondents & 70.5% of partners have college or grad degree
- 0% with income <$20K
- 69% with income ≥$100K

Screening Tools and Cutpoints for "At Risk" Classification



The percentage of boys with DMD who score in the "At-Risk" range on ASQ-3 and ASQ:SE-2 developmental screeners is higher than that of unaffected boys

Table 41. Fisher's Exact Test of ASQ-3 Subscale Scores & ASQ:SE-2 Total Scores for the DMD Group in comparison to Control Group (One-tailed at .05 significance level)

Screener [Subscale]	DMD Group Proportion in "At Risk" Category (%)	Control Group Proportion in "At Risk" Category (%)	Significance level/ p value (1-sided)	Post-hoc Power (α=.05)
ASQ-3 Communication	4/23 (17.4)	0/29 (0)	*0.033	63.9%
ASQ-3 Gross Motor	19/23 (82.6)	2/29 (6.9)	**<0.001	100%
ASQ-3 Fine Motor	8/23 (34.8)	1/29 (3.4)	*0.014	84.6%
ASQ-3 Problem Solving	5/23 (21.7)	1/29 (3.4)	0.053	53.6%
ASQ-3 Personal Social	10/23 (43.5)	1/29 (3.4)	**0.001	94.9%
ASQ:SE-2	11/31 (35.5)	1/33 (3.0)	**0.001	92.9%

*95% confidence interval or .05 significance level
**99% confidence interval or .01 significance level

Strengths and Difficulties Questionnaire shows DMD boys score more frequently in "At-Risk" range for Emotion, Conduct and Peer Difficulties.

Table 20. "No Risk" and "At Risk" Subtotals for DMD & Control Group for each SDQ Subscale and Results of Fisher's Exact Tests (SDQ 2-4 & SDQ 4-10 ratings combined)

	Emotional Symptoms		Conduct Problems		Hyperactivity		Peer Problems		Prosocial Score		Total Difficulties Score	
	No Risk	**At Risk**	No Risk	**At Risk**	No Risk	**At Risk**	No Risk	**At Risk**	No Risk	**At Risk**	No Risk	**At Risk**
DMD (N=38)	32	**6**	29	**9**	25	**13**	27	**11**	33	**5**	26	**12**
Control (N=32)	32	**0**	30	**2**	27	**5**	29	**3**	31	**1**	30	**2**
p-value	*0.021		*0.045		0.066		*0.039		0.144		**0.008	
Power	67.2%		51.3%		48.0%		53.1%		31.3%		77.2%	

SDQ 2-4 High Risk & Very High Risk combined for "At Risk" category for this study; SDQ 4-10 High Risk category considered "At Risk" for this study
Fisher's Exact Test (1-tailed) (α=.05)
*95% confidence interval
**99% confidence interval
Bolded numbers included in "At Risk" category

Social Responsiveness Scale-2 screening tool shows increased incidence of "At Risk" behaviors in boys with DMD using standard *and* more liberal cutoffs

Moderate & Severe Risk

Mild, Moderate & Severe Risk

	SRS-2 "At Risk"				SRS-2 Liberal "At Risk" Cutoff			
SRS-2 Subscale	DMD Ratio (%) in Moderate & Severe Risk Range	Control Ratio (%) in Moderate & Severe Risk Range	p value (1-tailed)	Post hoc Power (α=.05)	DMD Ratio (%) in Mild, Moderate & Severe Risk Range	Control Ratio (%) in Mild, Moderate & Severe Risk Range	p value (1-tailed)	Post hoc Power (α=.05)
Social Awareness	5/37 (13.5%)	6/30 (20%)	0.499	6.1%	8/37 (21.6%)	6/30 (20%)	0.567	3.6%
Social Cognition	5/37 (13.5%)	1/30 (3.3%)	0.186	29.3%	8/37 (21.6%)	1/30 (3.3%)	0.053	60.0%
Social Communication	5/37 (13.5%)	2/30 (6.7%)	0.186	29.3%	9/37 (24.3%)	2/30 (6.7%)	0.089	48.9%
Social Motivation	8/37 (21.6%)	2/30 (6.7%)	**0.013	81.2%	12/37 (32.4%)	2/30 (6.7%)	*0.030	75.3%
Restricted Interests & Repetitive Behavior	7/37 (18.9%)	1/30 (3.3%)	0.081	50.0%	10/37 (27.0%)	1/30 (3.3%)	*0.023	76.9%
Social Communication & Interaction	5/37 (13.5%)	1/30 (3.3%)	0.186	29.3%	11/37 (29.7%)	1/30 (3.3%)	*0.015	83.4%
Total Score	6/37 (16.2%)	1/30 (3.3%)	0.123	39.6%	11/37 (29.7%)	1/30 (3.3%)	*0.015	83.4%

Conclusions

- **Connolly Bayley studies:**
  - Early ***stable deficits*** in cognitive, expressive language, and social emotional domains in addition to gross motor concerns.
  - ***Receptive language often improves with age.*** Many kids begin to "catch up" with peers by 3-4 years of age though this is variable.
  - ***Gross motor declines from infancy onward.*** This contradicts the common perception that strength/functional decline begins in middle childhood.
  - Children with Bayley Gross Motor scale deficits ***may warrant evaluation*** for neuromuscular disease.
- **Online screener study:**
  - ASQ-3, ASQ-SE, SDQ and SRS-2 ***all show areas of concern in young children with DMD***.
  - ASQ-3 may ***identify risks of fine and gross motor delays*** and may help parents with concerns to gain access to earlier DMD diagnostics
  - While they ***do not diagnose autism***, screening tools demonstrate at-risk behaviors in communication, social communication and motivation, personal conduct, peer relationship and restricted interest/repetitive behavior domains associated with autism spectrum disorders.
- Some behaviors ***may pose significant challenges in daily living*** and may be ***modifiable with early intervention programs.***

Clinical Implications

- ***Instead of "watch and wait",*** infants and toddlers with developmental delay concerns and motor delays/weakness ***should be evaluated by pediatricians for presence of neuromuscular disease (including DMD)***.
- Present focus of many neuromuscular providers is on strength and motor maintenance but ***cognitive and social function should also be systematically addressed***.
- Screening tool use could ***increase potential for parents to self advocate for earlier social/cognitive diagnostics*** by identifying concerning behaviors.
- Potential for ***earlier preschool intervention to address social and behavioral challenges*** with family and peers.
- Need to ***advocate to get DMD on list of "Established Conditions"*** for each state to improve service eligibility for preschool and early school programs.

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Parent Project Muscular Dystrophy
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