Duchenne Muscular Dystrophy

Path to Newborn Screening

JERRY R. MENDELL, M.D.

Muscular Dystrophy Association

Fighting Muscle Disease

2012 MDA Muscle Disease Symposium on Newborn Screening for DMD
September 11th - 12th, 2012

Symposium Chairs:

Jerry R. Mendell, M.D.
Nationwide Children's Hospital
Columbus, OH

Michele A. Lloyd-Puryear, M.D., Ph.D.
National Institute Child Health and Human Development, Bethesda, MD

Wednesday, September 12, 2012

8:30 – 8:45 am Welcome and Goals for Meeting
SANJAY BIDICHANDANI, MBBS, Ph.D, Vice President–Research, MDA

8:45 – 9:00 am Significance for the addition of DMD to the Uniform Panel
R. RODNEY HOWELL, M.D., FAAP, FACMG, University of Miami

9:00 – 9:30 am Evidence-based Review: Description and summary of the SACHDNC process
ALEX KEMPER, M.D., MPH, M.S., Duke University

9:30 – 10:00 am Case Example: Adding SCID to the Uniform Panel
AMY BROWER, Ph.D., American College of Medical Genetics

10:00 – 10:15 am What are we screening? Description of DMD Disease Process
CRAIG MCDONALD, M.D., University of California, Davis

10:15 – 10:45 am Newborn Screening for DMD: Summary of NBS findings in Ohio; General principles outlined in the Calonge, *et al*. commentary in *Genetics in Medicine*, including performance metrics
JERRY MENDELL, M.D., Nationwide Children's Hospital and The Ohio State University

11:00 – 11:15 pm DMD Implementation of CK Screening: Possibilities and Challenges for a State
RAM CHANDRASEKAR, Ph.D., Ohio Department of Health

11:15 – 11:30 pm Treating DMD
FRANCESCO MUNTONI, M.D., FRCPCH, FMedSci, University College London

11:30 – 12:15 pm On the Horizon: Current and Future DNA Testing Methods
ROBERT WEISS, Ph.D., University of Utah
MADHURI HEGDE, Ph.D., Emory University

1:30 –2:30 pm Panel Discussion from Presentations to include discussion of:

- Performance of screening test and other quality assurance measures
- Diagnosis
- Follow-up and management protocols

JOHN PORTER, Ph.D, NINDS (Moderator)
MICHELE CAGGANA, Sc.D., New York State Dept. of Health
FRED LOREY, Ph.D., California Department of Public Health)
JEFFREY BROSCO, M.D., Ph.D., University of Miami
SCOTT GROSSE, Ph.D., Centers for Disease Control and Prevention

2:45 – 3:45 pm Public and Provider Education
ANNIE KENNEDY, MDA (Moderator)
PAT FURLONG, PPMD
ROBERT SAUL, M.D., Greenwood Genetic Center (and AAP)
BRUCE KORF, M.D., Ph.D., University of Alabama, Birmingham (and ACMG)
NICOLE JOHNSON, Sc.M., CGC, Johns Hopkins School of Medicine

3:45 – 5:00 pm Discussion of next steps: Questions to be answered; barriers to be addressed before implementation of DMD newborn screening

PIERO RINALDO, M.D., Ph.D., Mayo Clinic
MICHELE LLOYD-PURYEAR, M.D., Ph.D., NICHD

5:00 pm Adjourn

Scheduled Participants

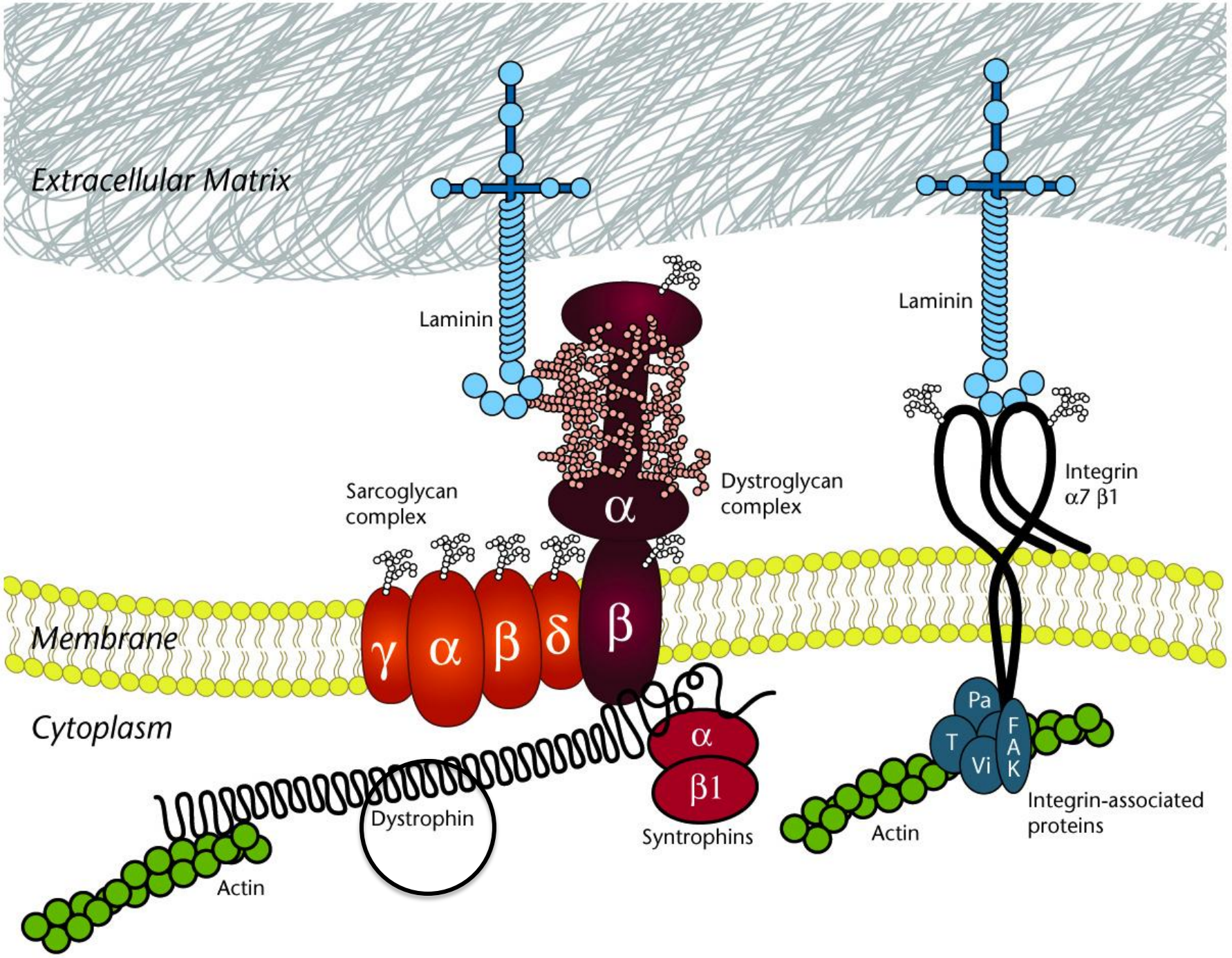
Barbara Adam, M.S.	Centers for Disease Control and Prevention
Sanjay Bidichandani, M.B.B.S., Ph.D.	Muscular Dystrophy Association
Julie Bolen, Ph.D., M.P.H.	Centers for Disease Control and Prevention
Jeffrey Brosco, M.D., Ph.D	**University of Miami**
Amy Brower, Ph.D.	**American College of Medical Genetics**
Michele Caggana, Sc.D.	**New York State Department of Health**
Ram Chandrasekar, Ph.D.	**Ohio Department of Health**
Anne Connolly, M.D.	**Washington University School of Medicine**
Kevin Flanigan, M.D.	Nationwide Children's Hospital
Pat Furlong, RN	**Parent Project Muscular Dystrophy**
Scott Grosse, Ph.D.	**Centers for Disease Control and Prevention**
Madhuri Hegde, Ph.D.	**Emory University**
R. Rodney Howell, M.D., FAAP, FACMG	**University of Miami**
Nicole Johnson, Sc.M. CGC	Johns Hopkins School of Medicine
Allison Kassir	King & Spalding LLP
Alex Kemper, M.D., M.P.H., M.S.	**Duke University**
Annie Kennedy	**Muscular Dystrophy Association**
Bruce Korf, M.D., Ph.D	**University of Alabama, Birmingham and American College of Medical Genetics**
Michele Lloyd-Puryear, M.D., Ph.D	**Eunice Kennedy Shriver National Inst. of Child Health and Human Development**
Fred Lorey, Ph.D.	**California Department of Public Health (and SACHDNC)**
Amy Madsen	Muscular Dystrophy Association
Craig McDonald, M.D.	**University of California, Davis**
Paul Muhlrad, Ph.D.	Muscular Dystrophy Association
Jerry Mendell, M.D.	**Nationwide Children's Hospital and The Ohio State University**
Francesco Muntoni, M.D., FRCPCH, FMedSci	**University College London**
Glen Nuckolls, Ph.D.	National Institute of Arthritis and Musculoskeletal and Skin Diseases
C. Scott Palubiak, MBA	PerkinElmer, Inc. and American College of Medical Genetics Foundation
Melissa Parisi, M.D., Ph.D	Eunice Kennedy Shriver National Inst. of Child Health and Human Development
John Porter, Ph.D.	**National Institute of Neurological Disorders and Stroke**
Piero Rinaldo, M.D., Ph.D	**Mayo Clinic**
Rachel Salzman, D.V.M.	Stop ALD Foundation
Robert Saul, M.D.	**Greenwood Genetic Center and American Academy of Pediatrics**
Natalie Street, M.S.	Centers for Disease Control and Prevention
Ljubisa Vitkovic, Ph.D.	Eunice Kennedy Shriver National Inst. of Child Health and Human Development
Michael Watson, M.S., Ph.D., FACMG	American College of Medical Genetics (and SACHDNC
Robert Weiss, Ph.D.	**University of Utah**

Speakers

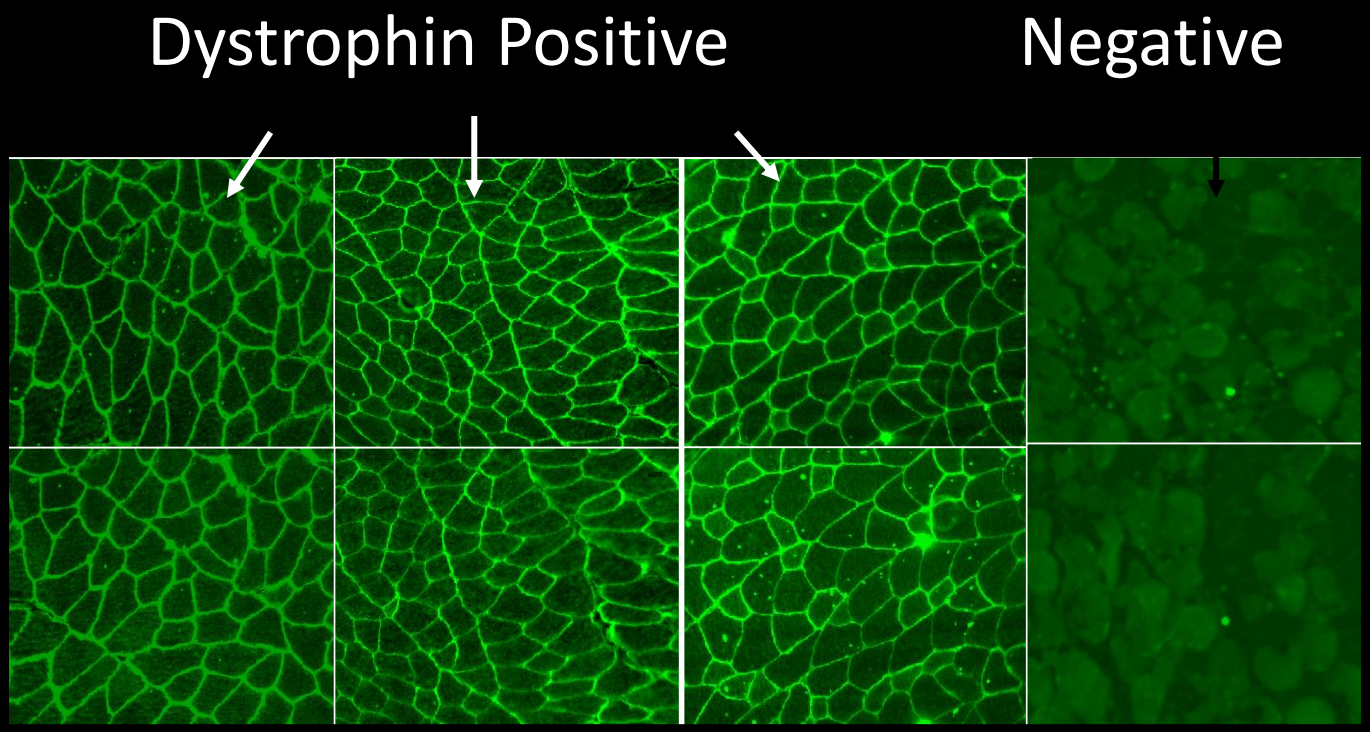
MDA Newborn Screening Symposium

- Examined all available data on DMD
  - Natural history
  - Disease pathogenesis
  - Newborn Screening method introduced in Ohio
  - Current Data on Therapy

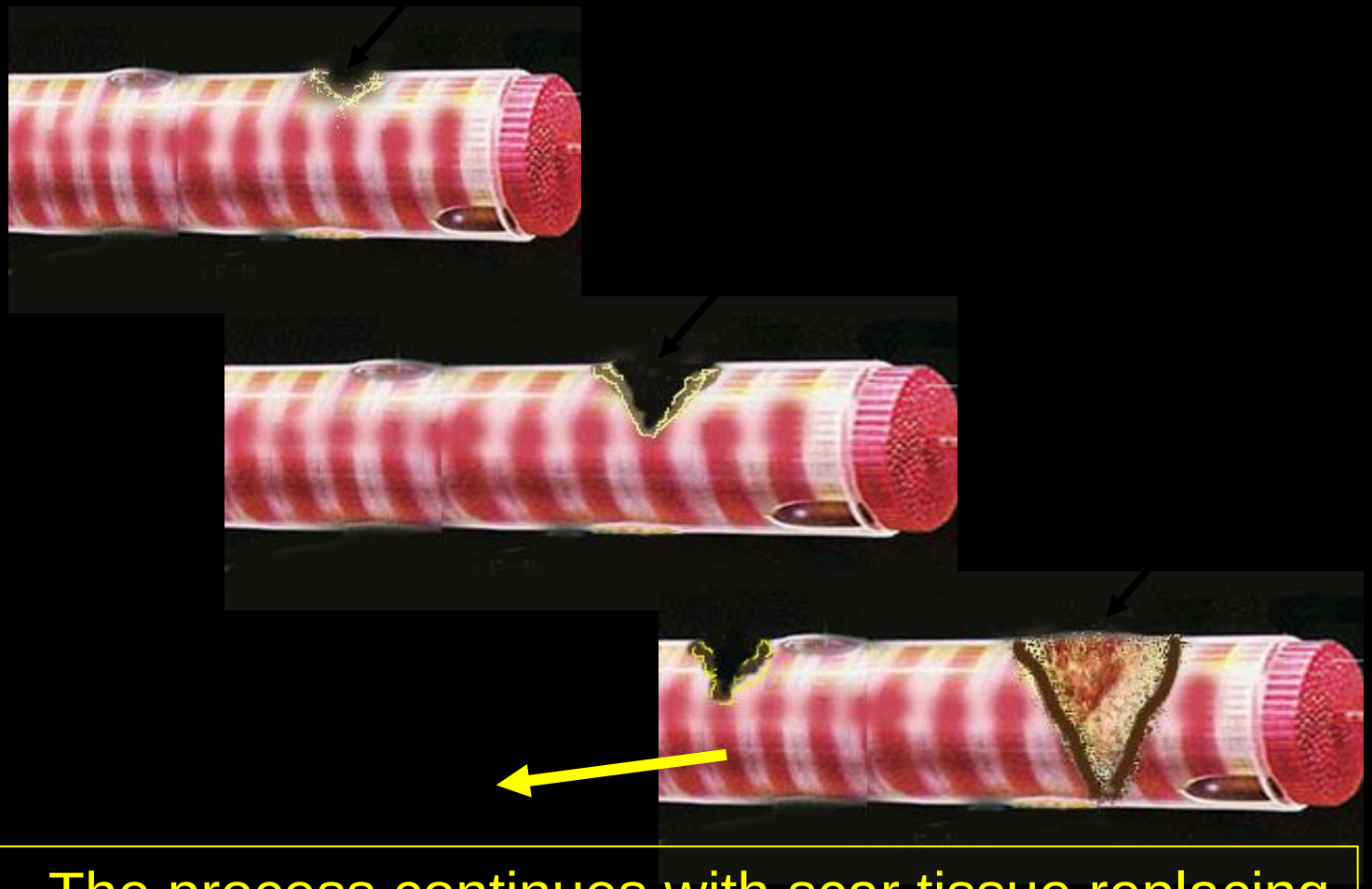
Disease pathogenesis


Extracellular Matrix
Laminin
Laminin
Dystroglycan complex
Sarcoglycan complex
Integrin α7 β1
α
γ
α
β
δ
β
Membrane
Cytoplasm
α
β1
Syntrophins
Dystrophin
Actin
Actin
Pa
T
Vi
FAK
Integrin-associated proteins

Dystrophin Covers and Protects Muscle

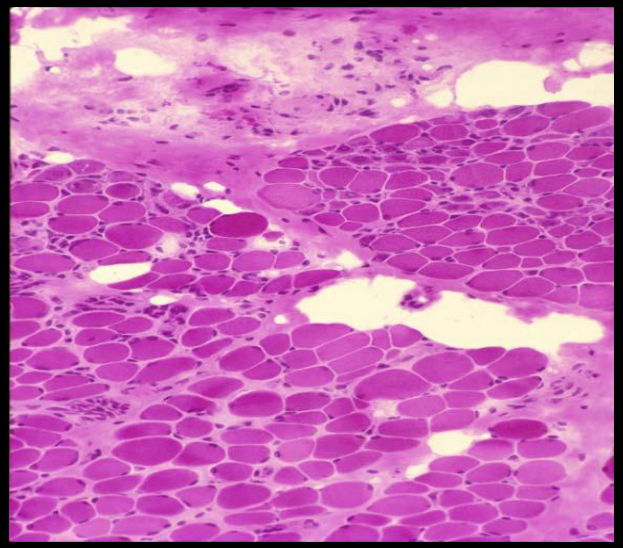


Consequences of Absent Dystrophin

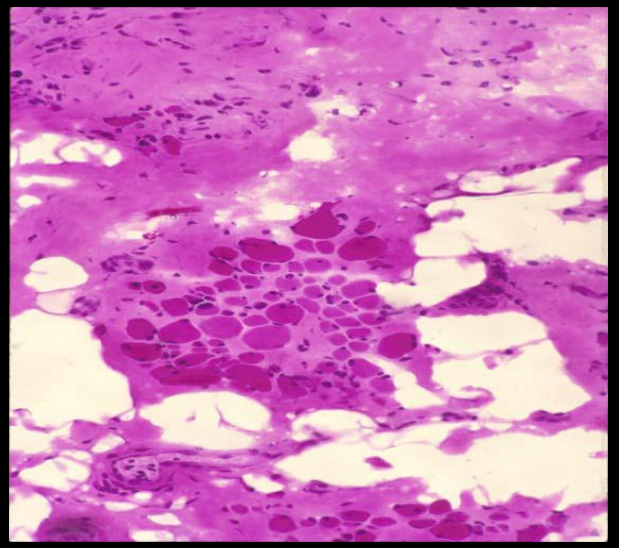


- The process continues with scar tissue replacing lost muscle fibers causing muscular dystrophy

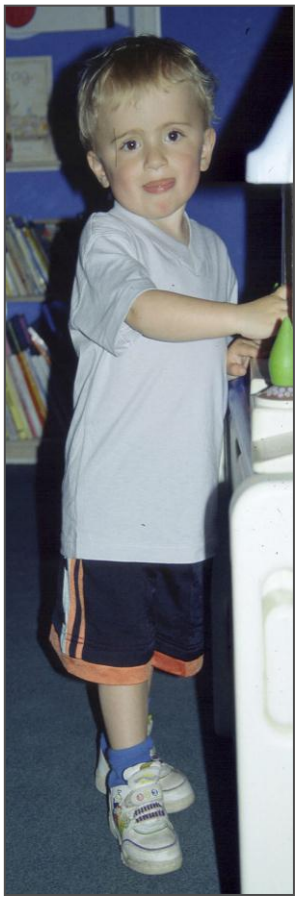
3 year old DMD



9 Year old DMD

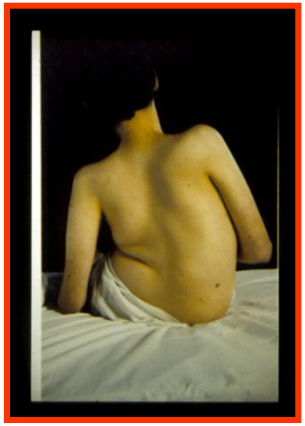


Normal 3 year old



DMD: Pre-Steroid Era

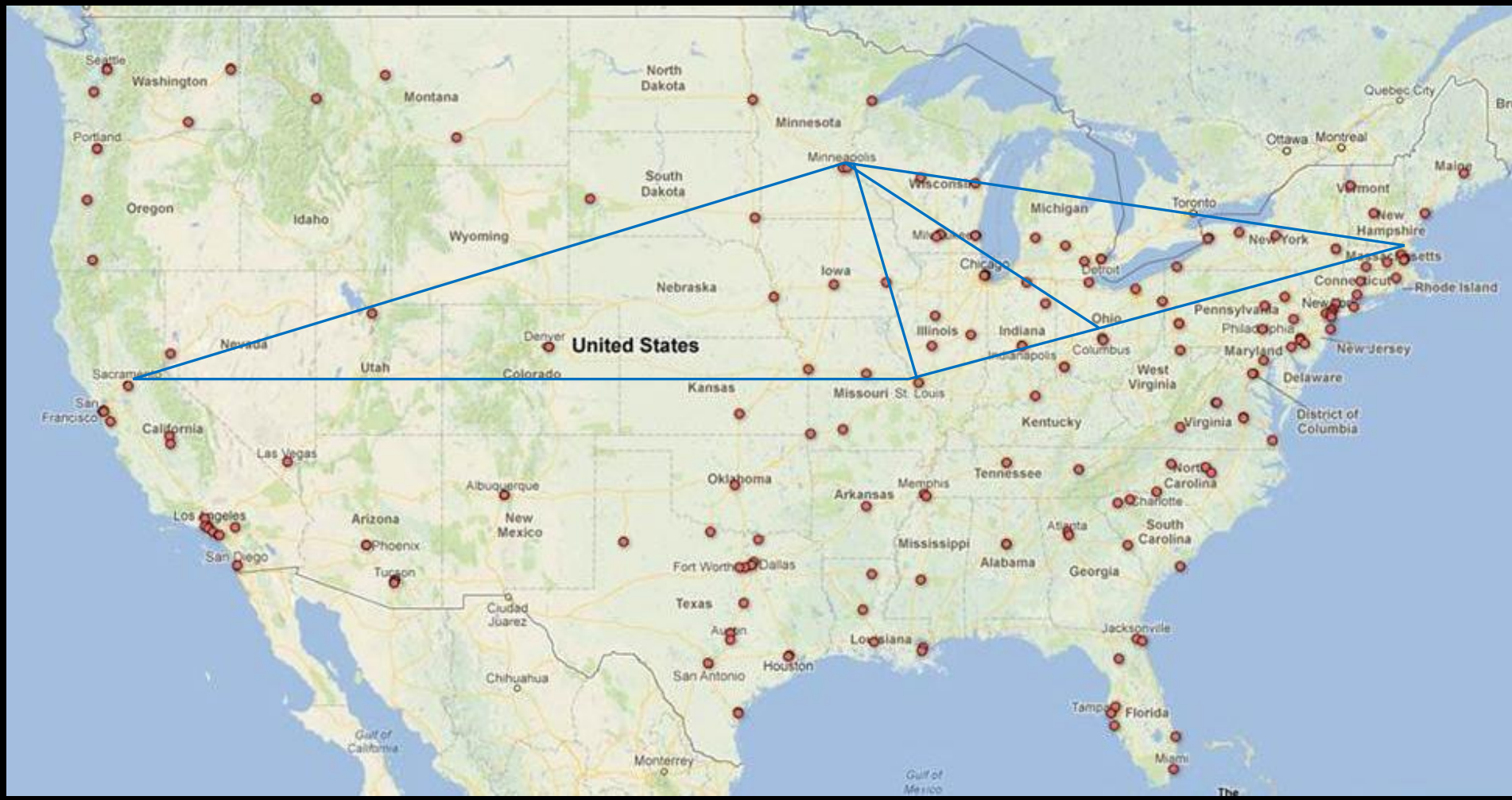
- Delayed milestones: walk at ≥15 months
- At 2.5 years: not as active as his peers, walks on toes.
- At 3.5 years frequent falls, difficulty going upstairs
- unable to run or jump
- Mean age at diagnosis: **4 yrs 9 months**
- Wheelchair dependent Age 9.5
- Onset of scoliosis Age 12
- Age 17 frequent chest infections and dilated cardiomyopathy
- Age 19 death due respiratory failure



Validating Infant Natural History

Clinical Research Network
PI: Anne Connolly
Washington U
St. Louis Children's

MDA Duchenne Clinical Research Network

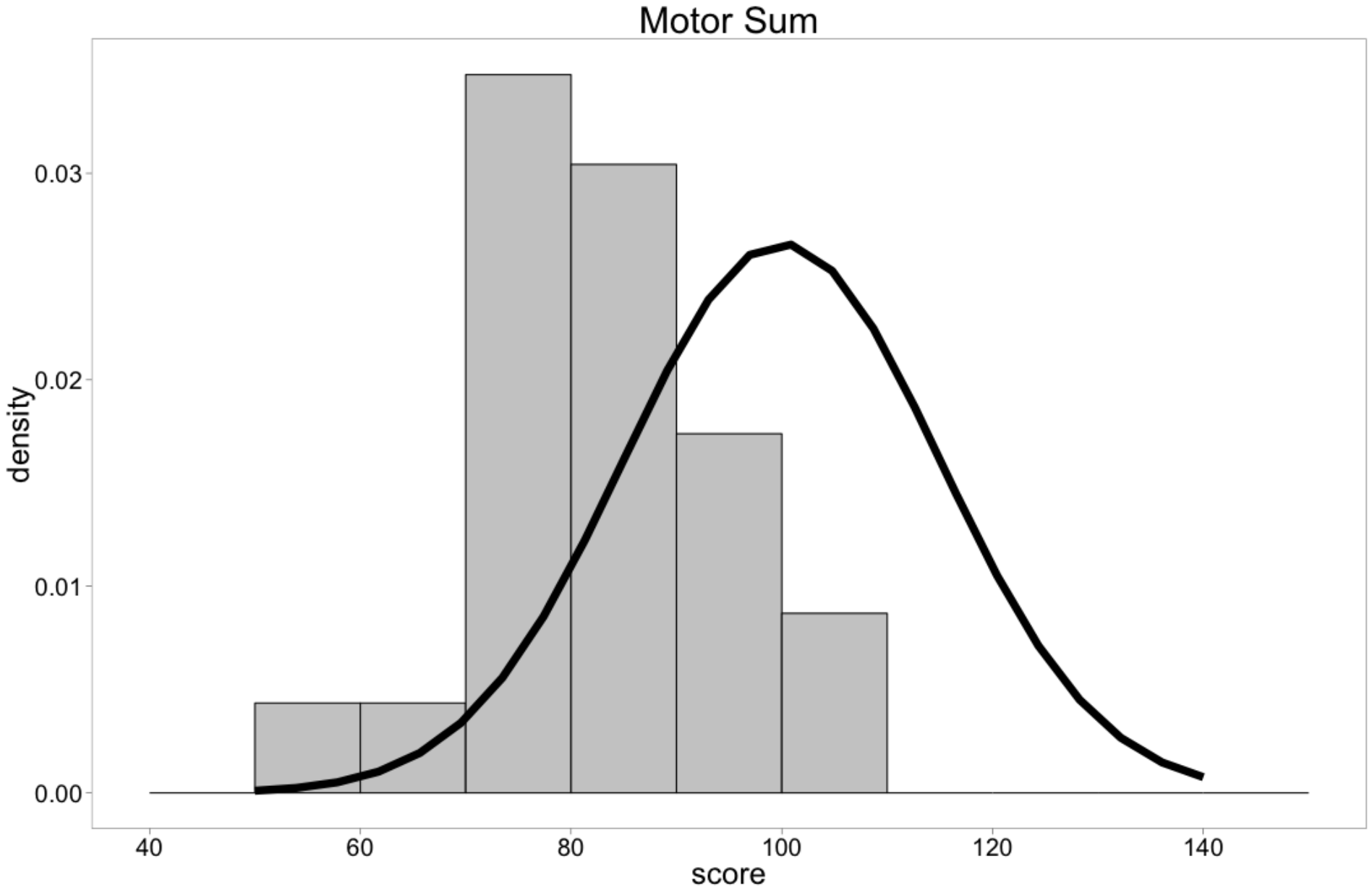


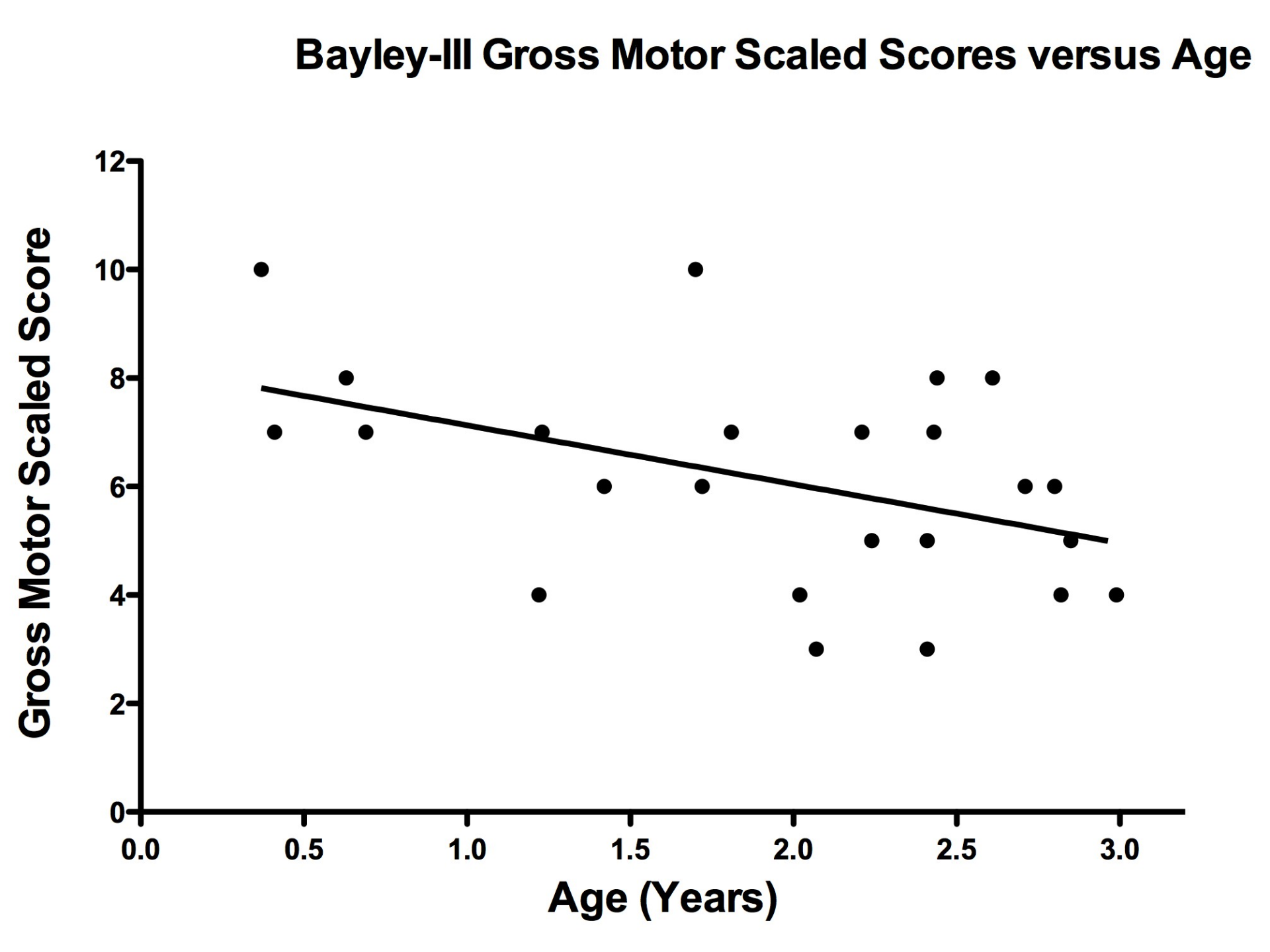
Participants in Infant Natural History Study

Subject	Age (years)	Family History	Mutation	Exon(s)	Frame
1	0.37	Yes	Deletion	3-32	In
2	0.41	No	Deletion	3-41	In
3	0.63	Yes	Deletion	45	Out
4	0.69	Yes	Nonsense* (c.615T>A; p.TyrX)	7	Out
5	1.22	Yes	Duplication	2	Out
6	1.23	Yes	Deletion	45-50	Out
7	1.42	Yes	Deletion	46-50	Out
8	1.7	No	Deletion	12	Out
9	1.72	Yes	Deletion*	46	Out
10	1.81	Yes	Deletion	45-50	Out
11	2.02	No	Deletion	58	Out
12	2.07	Yes	Deletion*	8-9	Out
13	2.21	Yes	Nonsense (c.2353C>T; p.Gln785X)	19	Out
14	2.24	No	Deletion	51-57	Out
15	2.41	No	Deletion	53-55	Out
16	2.41	No	Deletion	45	Out
17	2.43	No	Deletion	49-52	Out
18	2.44	No	Deletion	58-64	Out
19	2.61	Yes	Deletion	18-25	In
20	2.71	No	Deletion	46-52	Out
21	2.8	No	Nonsense (c.2791G>T; p.Glu931X)	21	Out
22	2.82	No	Deletion	45	Out
23	2.85	Yes	Deletion	12-44	Out
24	2.99	No	Deletion	17	Out

Bayley-III Motor Assessment of Infants and Young Boys with DMD

SUBTEST	NORMAL	DMD	t test p value
Gross Motor Score n =24	10 ± 3	6.2 ± 1.5	t = -10.1 p = <0.0001
Fine Motor Score n = 24	10 ± 3	7.8 ± 1.9	t = -4.7 p = <0.0001
Composite Motor Score n= 24	100 ± 15	82.5 ± 8.1	t = -7.99 P = < 0.0001


Motor Sum
density
0.03
0.02
0.01
0.00
40
60
80
100
120
140
score


Bayley-III Gross Motor Scaled Scores versus Age
Gross Motor Scaled Score
12
10
8
6
4
2
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Age (Years)

History of Newborn Screening And Introduction of Two-Tier Screening in Ohio

History of NBS
Based on single-tier analysis using CK

YEAR	LOCATION	NBS/DMD		INCIDENCE
1979	New Zealand	10,000	2	1:5000
1982	Edinburgh UK	2336	0	0
1986	W Germany	358,000	78	1:4589
1988	Manitoba	172,860	26	1:5960
1989	Lyon	37,312	7	1:5330
1991	W PA USA	49,000	10	1:4900
1998	Cyprus	30,219	5	1:6002
2006	Antwerp	281,214	51	1:5500
2011	Wales UK	335,045	73	1:5266

Overall Incidence: ~1:5000

Single-Tier Paradigm

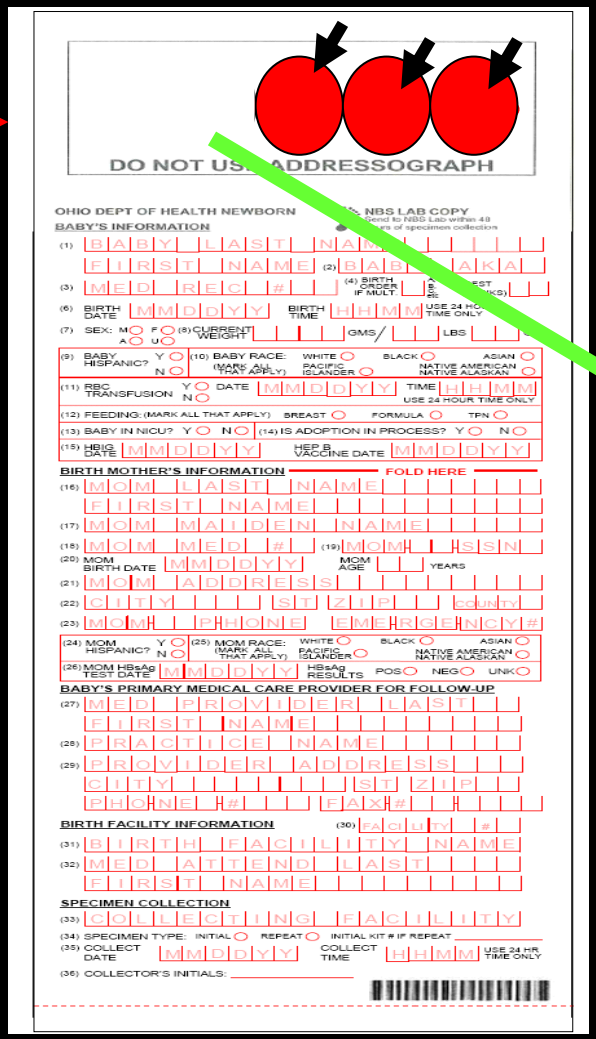
- Prototypical world-wide single-tier DMD NBS a poor fit for USA Health Care System
- CK elevation at birth on dried blood spots re-tested at 4-6 weeks (challenges without uniform Health care system)
- Persistent CK elevation results in DMD gene mutation analysis on venous blood

The Ohio Program at Nationwide Children's Hospital

- CDC Funded NCH Children's Hospital
  - Implicit was a charge to fit early hosp D/C
  - Return at 6 weeks or later for re-testing <ideal
- Program designed to complete testing at birth including both CK and DNA
  - Two-tier system of screening

Source of Blood for Testing

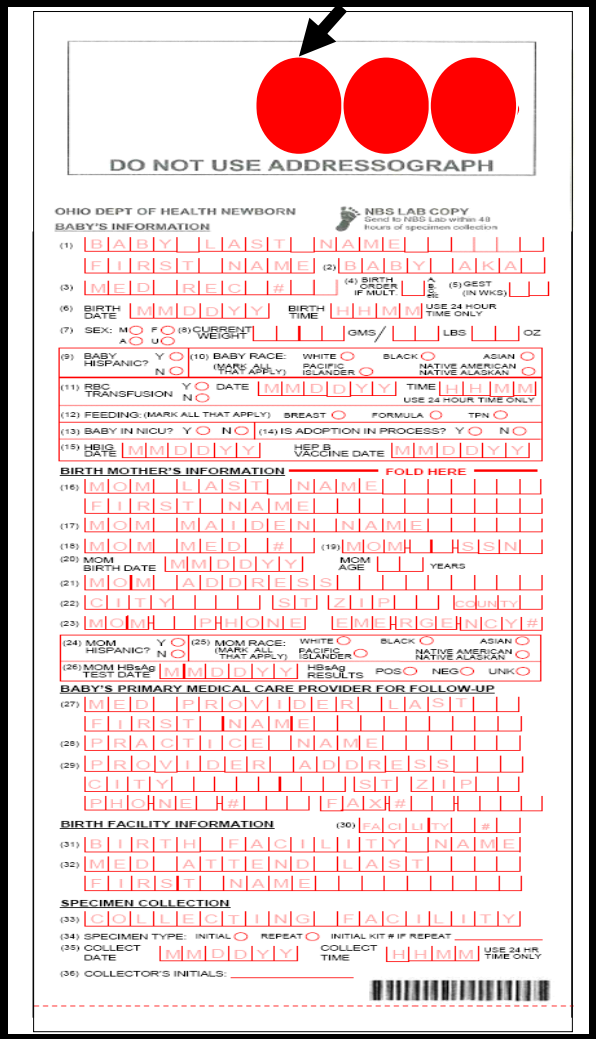
Heel Sticks
Dried Blood Spots
24-48 hrs Post Delivery



Mandated Tests:
35 including CF

Phase I: Establish Population-based range of CK

- Ohio Dept of Health (ODH)
  - Ram Chandrasekar ODH
- Analyzed 30,547 anonymous dried blood spots


DO NOT USE ADDRESSOGRAPH

OHIO DEPT OF HEALTH NEWBORN

NBS LAB COPY
Send to NBS Lab within 48 hours of specimen collection

BABY'S INFORMATION

(1) BABY LAST NAME
FIRST NAME
(2) BABY AKA
(3) MED REC #
(4) BIRTH ORDER IF MULT
(5) GEST (IN WKS)
(6) BIRTH DATE MM DD YY
BIRTH TIME HH MM
USE 24 HOUR TIME ONLY
(7) SEX: M F A U
(8) CURRENT WEIGHT GMS / LBS OZ
(9) BABY HISPANIC? Y N
(10) BABY RACE: (MARK ALL THAT APPLY) WHITE BLACK ASIAN PACIFIC ISLANDER NATIVE AMERICAN NATIVE ALASKAN
(11) RBC TRANSFUSION Y N DATE MM DD YY TIME HH MM USE 24 HOUR TIME ONLY
(12) FEEDING: (MARK ALL THAT APPLY) BREAST FORMULA TPN
(13) BABY IN NICU? Y N (14) IS ADOPTION IN PROCESS? Y N
(15) HBIG DATE MM DD YY HEP B VACCINE DATE MM DD YY

BIRTH MOTHER'S INFORMATION — FOLD HERE

(16) MOM LAST NAME
FIRST NAME
(17) MOM MAIDEN NAME
(18) MOM MED # (19) MOM SSN
(20) MOM BIRTH DATE MM DD YY MOM AGE YEARS
(21) MOM ADDRESS
(22) CITY ST ZIP COUNTY
(23) MOM PHONE EMERGENCY #
(24) MOM HISPANIC? Y N (25) MOM RACE: (MARK ALL THAT APPLY) WHITE BLACK ASIAN PACIFIC ISLANDER NATIVE AMERICAN NATIVE ALASKAN
(26) MOM HBsAg TEST DATE MM DD YY HBsAg RESULTS POS NEG UNK

BABY'S PRIMARY MEDICAL CARE PROVIDER FOR FOLLOW-UP

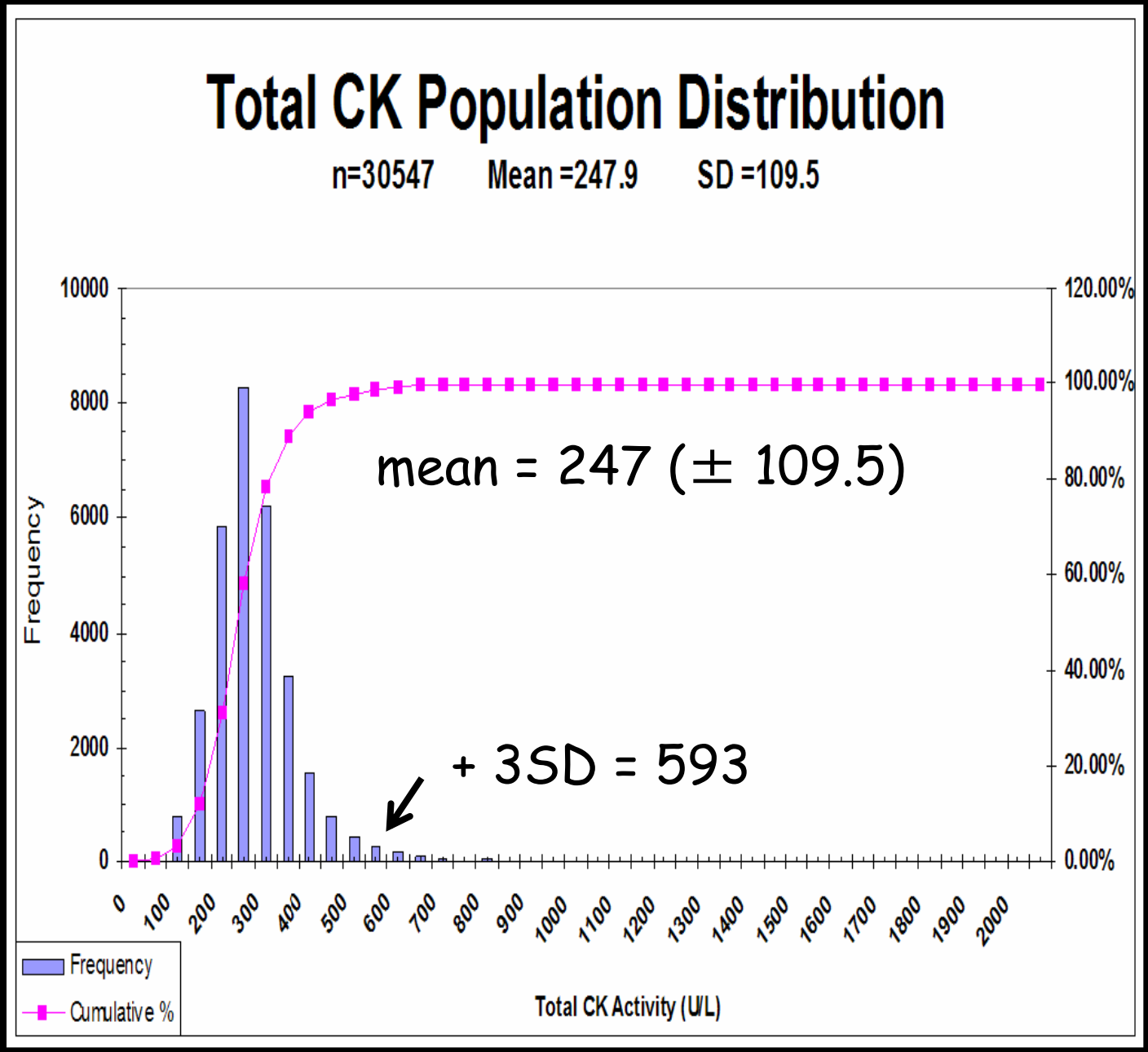
(27) MED PROVIDER LAST
FIRST NAME
(28) PRACTICE NAME
(29) PROVIDER ADDRESS
CITY ST ZIP
PHONE # FAX #

BIRTH FACILITY INFORMATION

(30) FACILITY #
(31) BIRTH FACILITY NAME
(32) MED ATTEND LAST
FIRST NAME

SPECIMEN COLLECTION

(33) COLLECTING FACILITY
(34) SPECIMEN TYPE: INITIAL REPEAT INITIAL KIT # IF REPEAT
(35) COLLECT DATE MM DD YY COLLECT TIME HH MM USE 24 HR TIME ONLY
(36) COLLECTOR'S INITIALS:


Total CK Population Distribution
n=30547 Mean =247.9 SD =109.5
mean = 247 (± 109.5)
+ 3SD = 593
Frequency
Cumulative %
Total CK Activity (U/L)
10000
8000
6000
4000
2000
0
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000

Gender, Collection Time, Weight

Group	Mean CK U/L	3 SDs CK U/L
Males	251.52	593.07
Females	246.38	587.07
< 48 hours	253.37	597.48
49-120 hours	207.56	503.19
> 120 hours	201.64	492.30
> 2500 g	250.61	593.72
2000-2499 g	231.68	586.58
< 1500 g	226.36	529.36

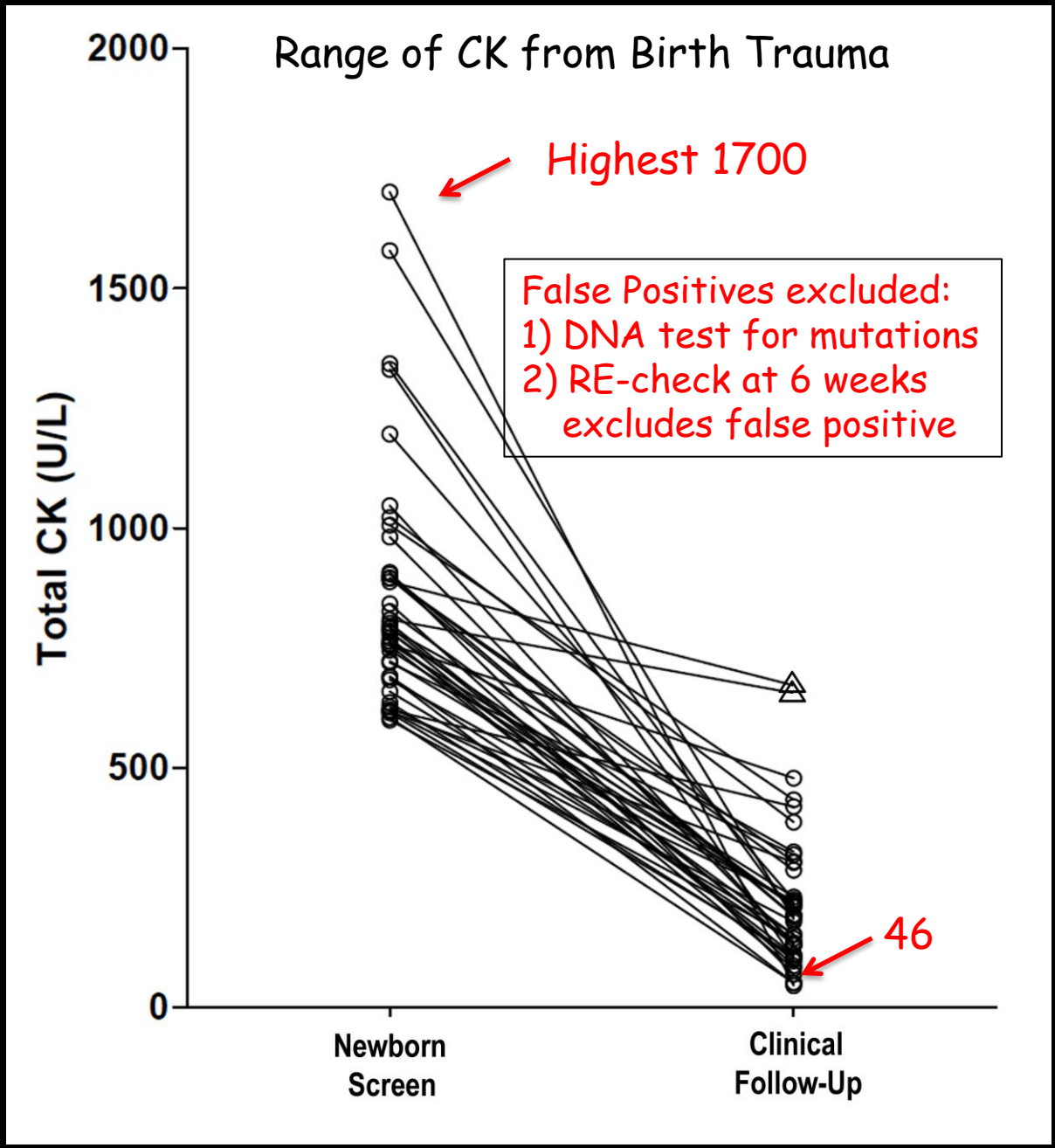
DNA Testing on DBS - Robert Weiss Ph.D.

Validation in patients with known mutations from MDA Clinic

- Venous blood taken from volunteer/consented DMD patients with known mutations and placed on dried blood spots at NCH
- Sent DBS to U of Utah Lab and results of blinded analysis reported
- 7 Exon deletions and 6 duplications all identified correctly

Phase II Screening

- Phase II screened 6,928 NBS in 4 Birthing Hospitals in Columbus and Cincinnati
  - 110 exceeded CK threshold
  - 2 above 2000 U/L (2461, 2675) both with DMD mutations
  - False positives 108/6926 = 1.6%


Range of CK from Birth Trauma
Highest 1700
False Positives excluded:
1) DNA test for mutations
2) RE-check at 6 weeks
excludes false positive
46
Total CK (U/L)
2000
1500
1000
500
0
Newborn Screen
Clinical Follow-Up

Phase III Testing

- NBS implemented at 43 birthing hospitals throughout the state of OHIO
- CK threshold raised to ≥ 750 U/L
- 10,937 Screened with 58 above threshold
  - False positive now reduced from 1.6% to 0.52%
  - Reduced need for DMD gene testing by 68%
    - Huge cost saving
- DMD mutation found in one NB with CK 2003

Phase IV Testing

- Increased sample size through anonymous screening of DBS throughout State of OHIO
- Sample size increased by 19,884 newborn males and total = 37,749
- 3 additional DMD mutations again with CK > 2000

DMD Mutations (6/37,749)

Gender	CK U/L	Gene	Mutation	Frame
Male	2462	DMD	Del ex50	Out
Male	2675	DMD	Del ex5-41	In
Male	2003	DMD	Del ex8-9	Out
Male	2466	DMD	Del ex45	Out
Male	2791	DMD	Del ex45-48	Out
Male	2688	DMD	Del ex4-7	Out

Phase IV (Extension)

- The final anonymous phase also included18,763 newborn females
- CK ≥ 2000 on 2 Females
- Total 7 males (19,884) without DMD mutations
  - Mutation analysis was expanded to include most common LGMD genes (*DYSF*, *CAPN3*, Sarcoglycans, *FKRP*)

Non-DMD Mutations

Gender	CK U/L	Gene	Mutation	Frame
female	2731	DYSF	FrmShift ex39	Out
Male	2735	SGCB	3 nt dup ex1	In
Male	2984	FKRP	pR143S missense	In

Important Outcomes

- Two-tier system fits OB practice in USA
  - Mother and child discharged in 24-48 hours
- Cost per CK =$1.00/DNA = $150
- All DMD had CK >2000 U/L
  - Threshold for DNA testing could be raised to ≥ 1000
  - Further reduce screening to 40 per 10,000
- Comparative cost for w/u of new cases in clinic: Specialist, Muscle biopsy, DNA testing = $2500-$3000
- Value Added: Other muscular dystrophy genes can be identified

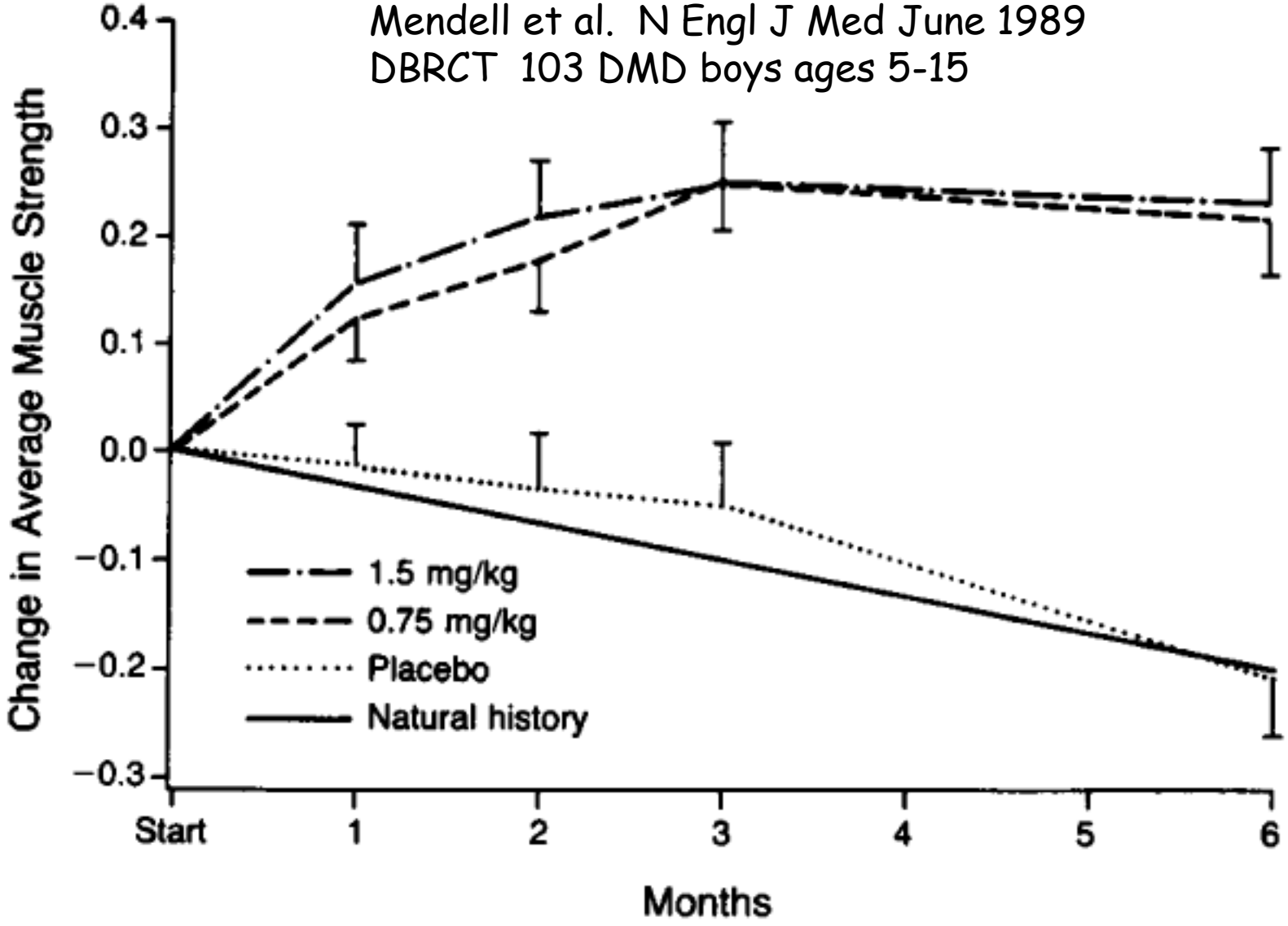
Approaches to DMD Therapy

- Glucocorticoids established as standard of care
  - Data supports early intervention based on outcomes of prolonged ambulation

- Exon skipping shown to be effective in and supports early childhood treatment

Glucorticoid Treatment in DMD

Mendell et al. N Engl J Med June 1989
DBRCT 103 DMD boys ages 5-15

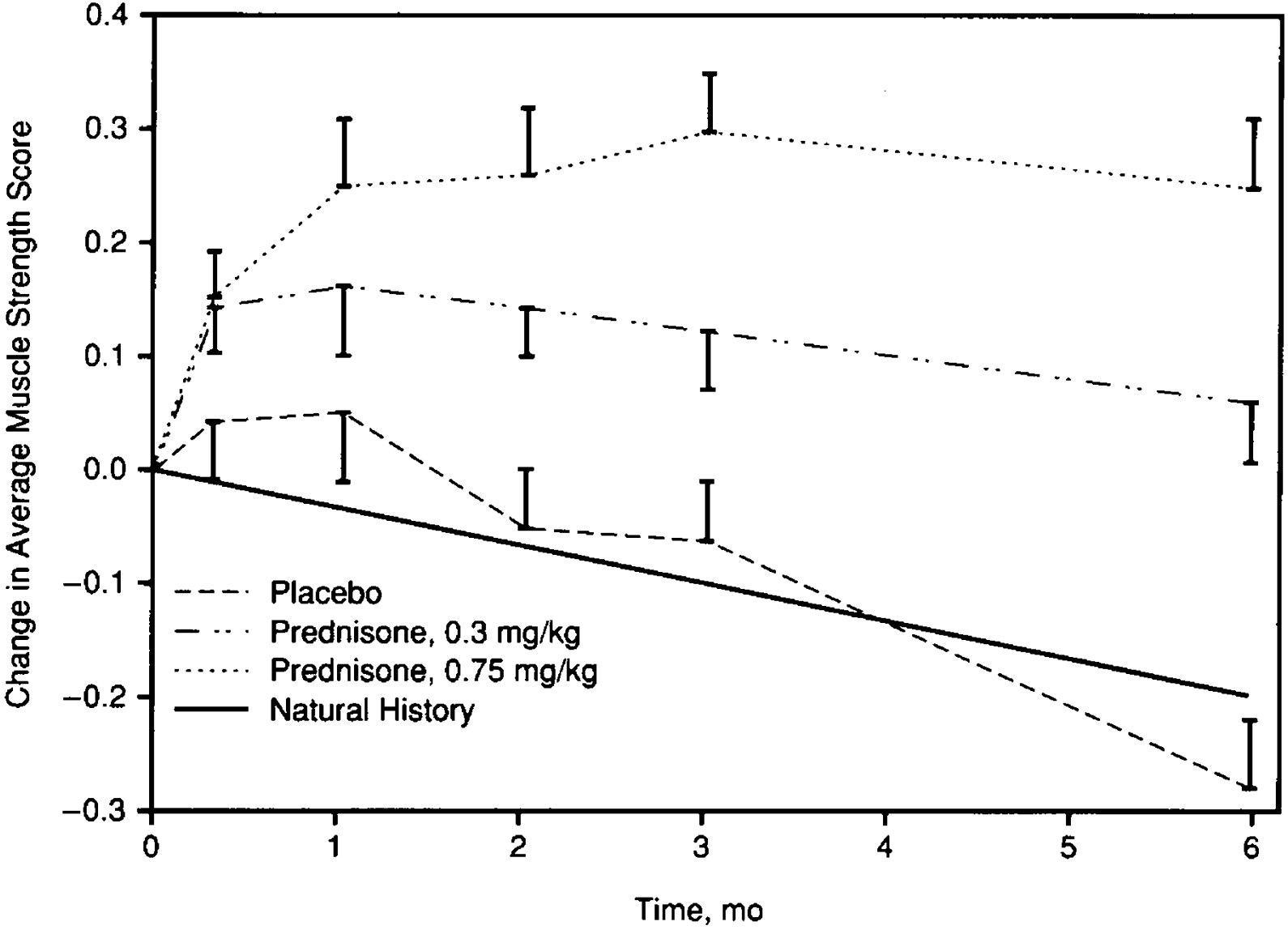


Prednisone DBRCT Clinical Outcomes 6 month Trial n = 103					
	Placebo	0.75 mg/kg	1.5 mg/kg	P values	
Muscle Strength	5.80 n = 35	6.23 n = 30	6.25 n = 30	0.0001 Pl vs 0.75	0.0001 Pl vs 1.5
Stair Climbing	7.05 s n = 18	3.87 n = 35	4.00 n = 24	0.0001 Pl vs 0.75	0.0001 Pl vs 1.5
Walk 9 m	9.68 n = 27	6.81 n = 25	7.04 n = 30	0.003 Pl vs 0.75	0.005 Pl vs 1.5
Standing from supine	6.17 n = 16	4.15 n = 18	3.43 n = 16	0.0002 Pl vs 0.75	0.0001 Pl vs 1.5
Force vital capacity	1.52	1.68	1.66	0.0004 Pl vs 0.75	0.002 Pl vs 1.5

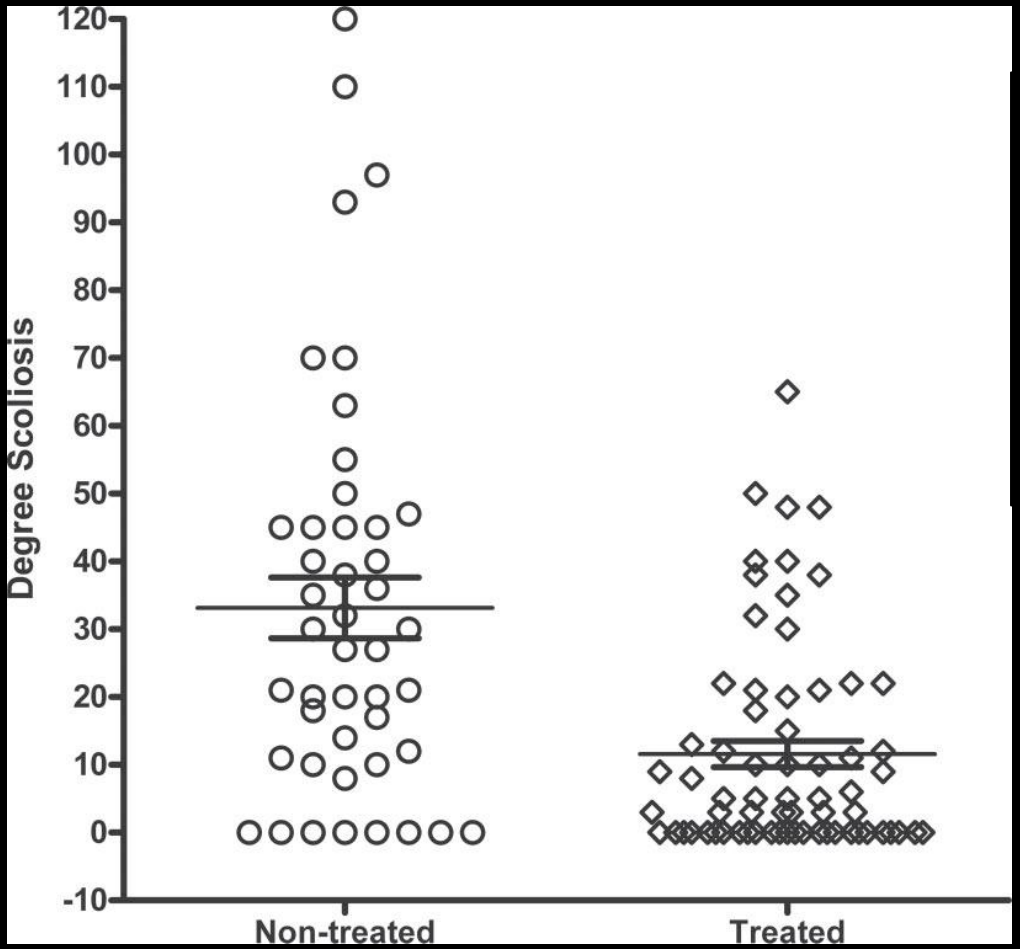
Highly Significant Improvement in Strength and Function!!

Prednisone Dose Response Curve

Griggs et al 1991



Long-Term Benefits of glucocorticoids
King et al: 2007



- N = 143 DMD boys; 75 treated
  Mean duration 8.04 years
- Mean degree of scoliosis:
  33.15 vs 11.58 treated vs untreated
- 91% of untreated scoliosis by age 9
  vs 31% pred treated ($p < 0.0001$)

What is the earliest glucocorticoid effect?

14-year Glucocorticoid Follow up in DMD
Merlini et al Muscle & Nerve 2012

Patient	Treatment age	Follow up	10 m Walk m/sec	6MWT Distance m	FVC % predicted
1	3.9	18.5y	12.5	389	73%
2	4.0	18.6y	1.11	365	65%
3	2.4	16.1y	1.0	310	>100%
4	3.3	17.0y	1.1	288	96%

Randomized Blinded Trial of weekend vs daily prednisone in DMD

Escolar et al Neurology 2011

Patient Groups	Treatment age	Follow up	Efficacy Significantly Improved at 1 year	Linear Growth
Daily Pred 0.75 mg/kg	4-10 y Ambulatory n =32	1 year	QMT 10m-walk Stair climbing p < 0.0001	Δ4.1 cm
Weekend Dosing 10 mg/kg	4-10 y Ambulatory n =32	1 year	QMT 10m-walk Stair climbing p < 0.0001	Δ6.6 cm

p = 0.002

- Validates study done 22 years before (all ambulatory patients)
- Linear growth preserved by weekend dosing

Molecular Therapy for DMD

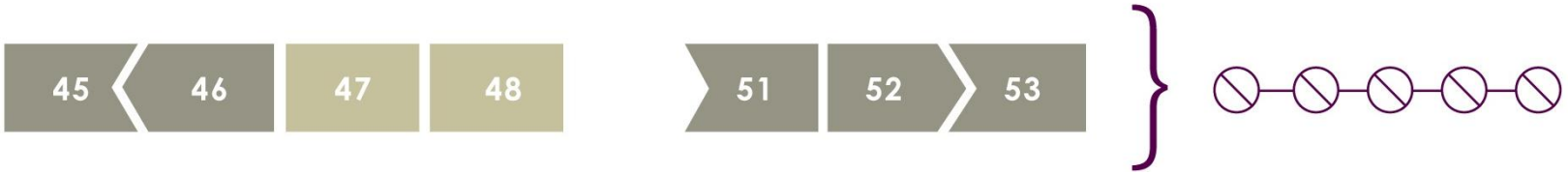
Results of 48 week Phase IIB Exon Skipping study using Eteplirsen in DMD

Jerry R Mendell, MD
Nationwide Children's Hospital

Exon-Skipping APPROACH:

Repair mRNA to restore protein translation and dystrophin production

EXAMPLE OF ETEPLIRSEN AMENABLE GENOTYPE: DELETION OF EXONS 49-50 RESULTS IN **AN OUT OF FRAME DELETION** IN mRNA

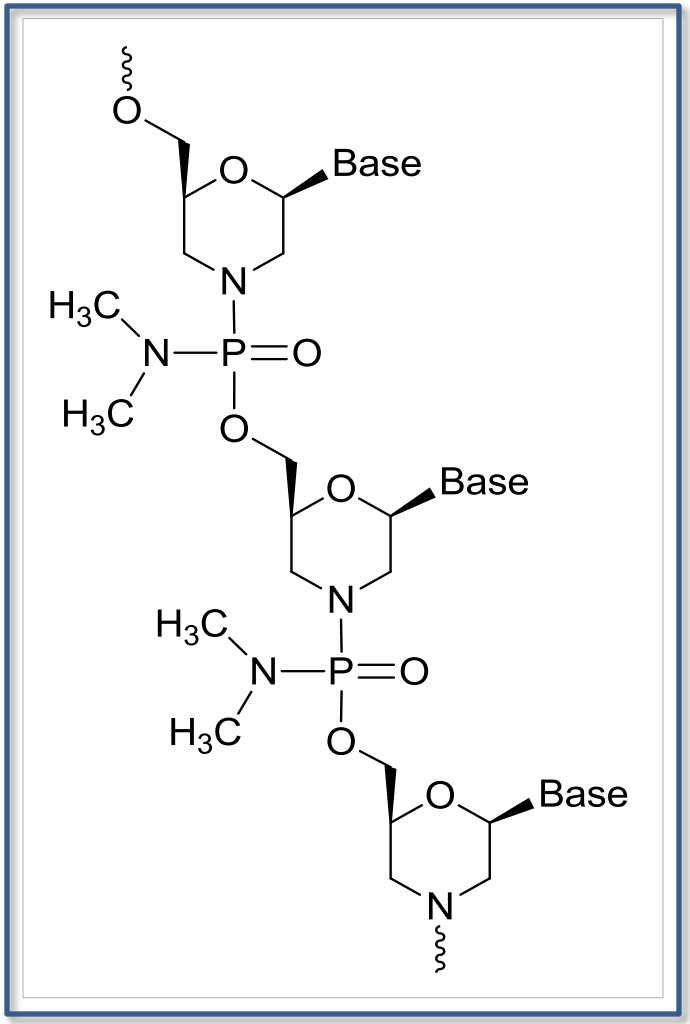


BY SKIPPING EXON 51, IN-FRAME **mRNA TRANSCRIPTION IS RESTORED**, ENABLING THE PRODUCTION OF A FUNCTIONAL DYSTORPHIN PROTEIN

Eteplirsen:

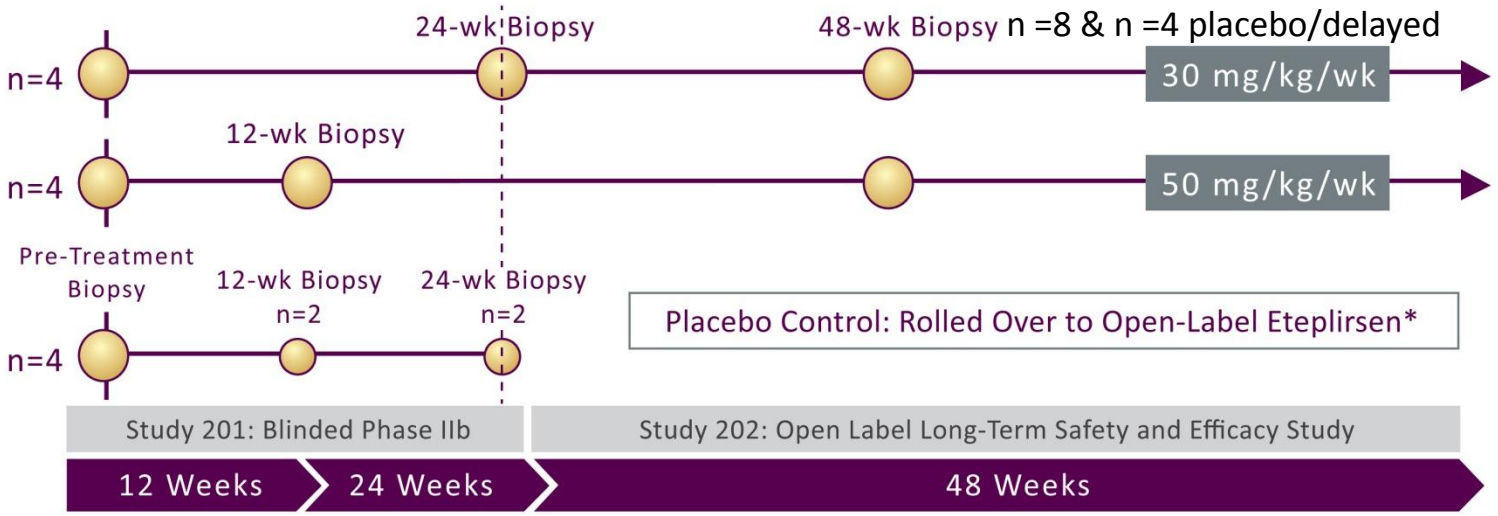
RNA modulator that permits skipping at pre-mRNA

- Morpholine Ring replaces Ribose of RNA Phosphorodiamidate morpholino oligomer (PMO)
- Plasma half-life of 2 to 6 hours
- Cleared through kidney
- Systemic administration through weekly IV infusion



Protocol Studies 201 & 202: eteplirsen Phase IIb

long-term safety & efficacy



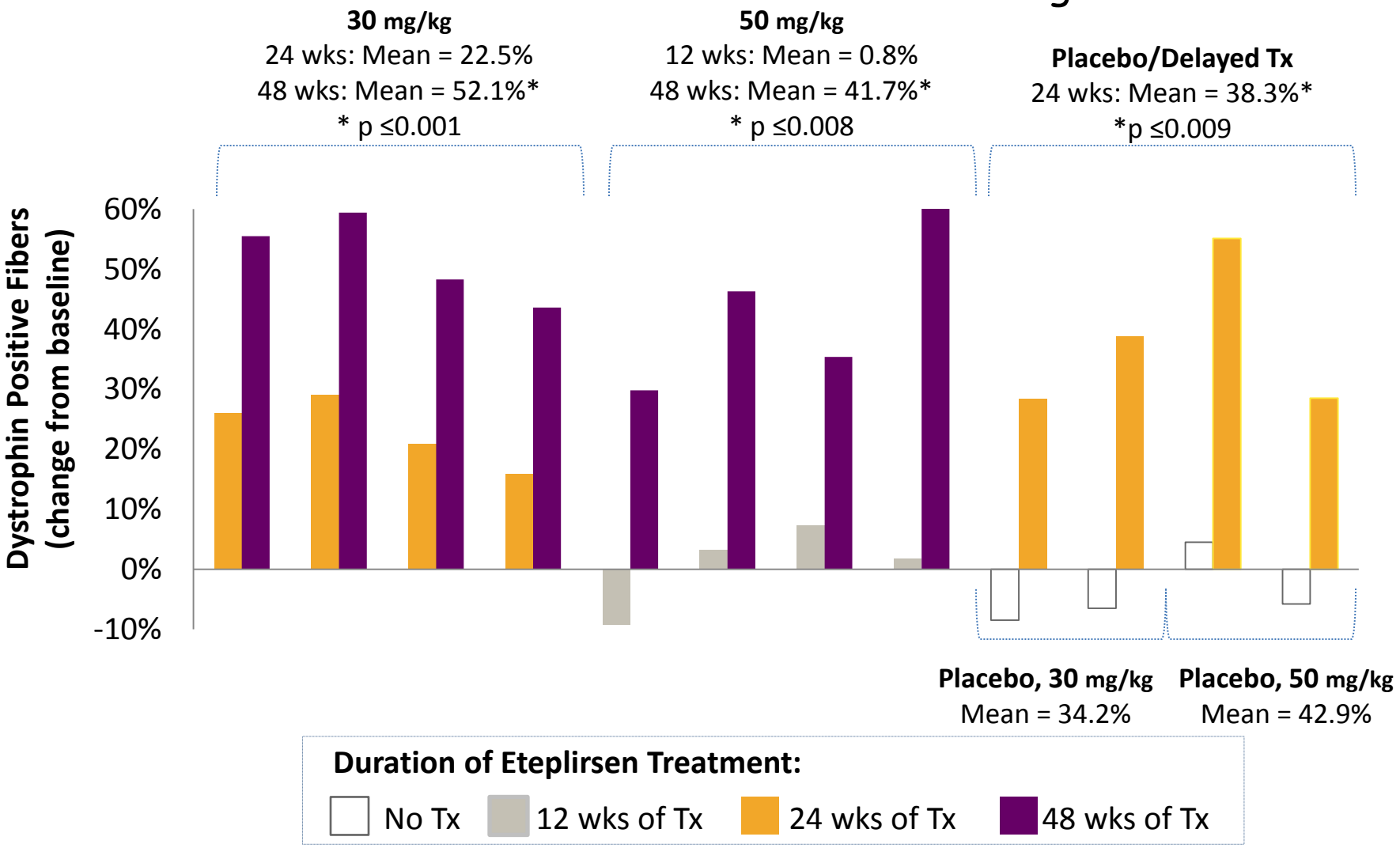
**Patients on placebo crossed over to treatment at 24 weeks referred to as the delayed-treatment group*

LONG-TERM SAFETY AND EFFICACY ASSESSED

- Biochemical measures of dystrophin: % dystrophin positive-fibers is primary study endpoint
- 6-Minute Walk Test is primary clinical outcome measure
- Safety: clinical and laboratory measures

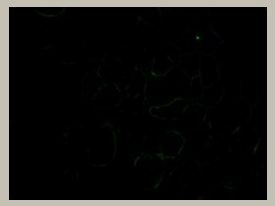
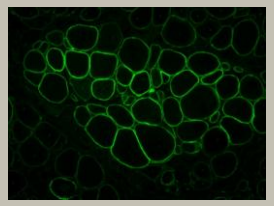
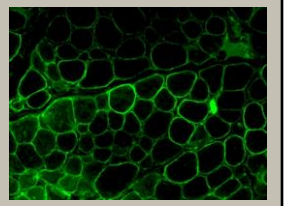
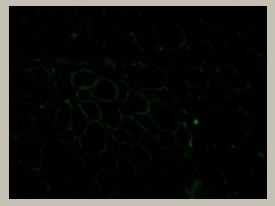
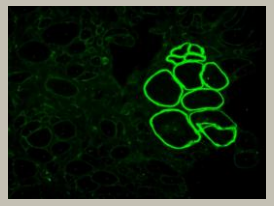
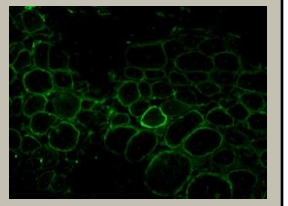
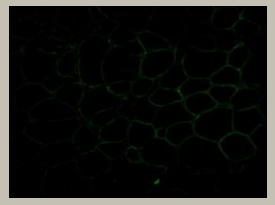
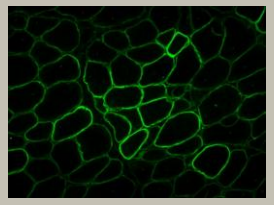
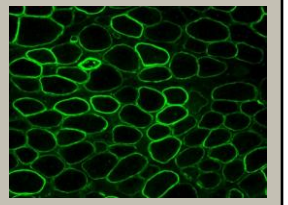
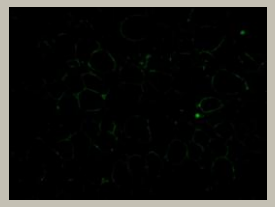
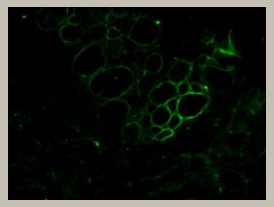
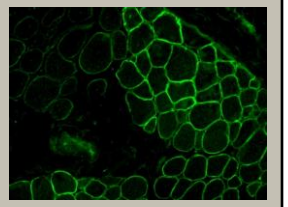
Dystrophin production from eteplirsen treatment:

observed at 24 weeks with increases through 48 weeks



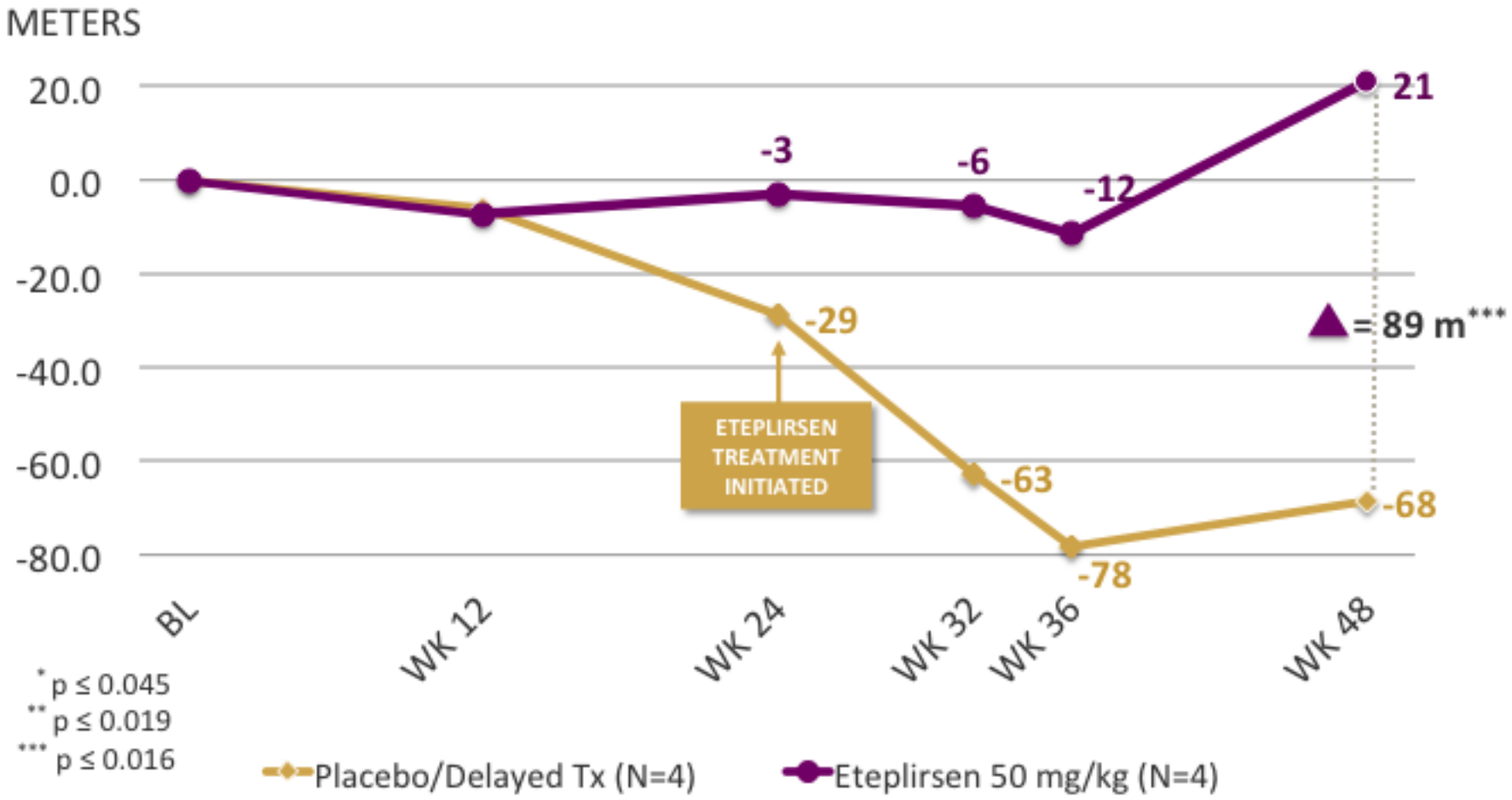
** Values based on Immunofluorescence using anti-dystrophin antibody MANDYS106*

DYSTROPHIN POSITIVE FIBERS CORRECTLY LOCALIZED AT THE SARCOLEMA

30 MG/KG			
Patient	**Pre-Tx**	**24 wks of Tx**	**48 wks of Tx**
02			
09			
06			
10			

6MWT change from baseline to week 48:

INTENT-TO-TREAT POPULATION: ETEPLIRSEN 50MG/KG VS PLACEBO



Note: Statistical analysis based on Intent-To-Treat Population using ANCOVA test

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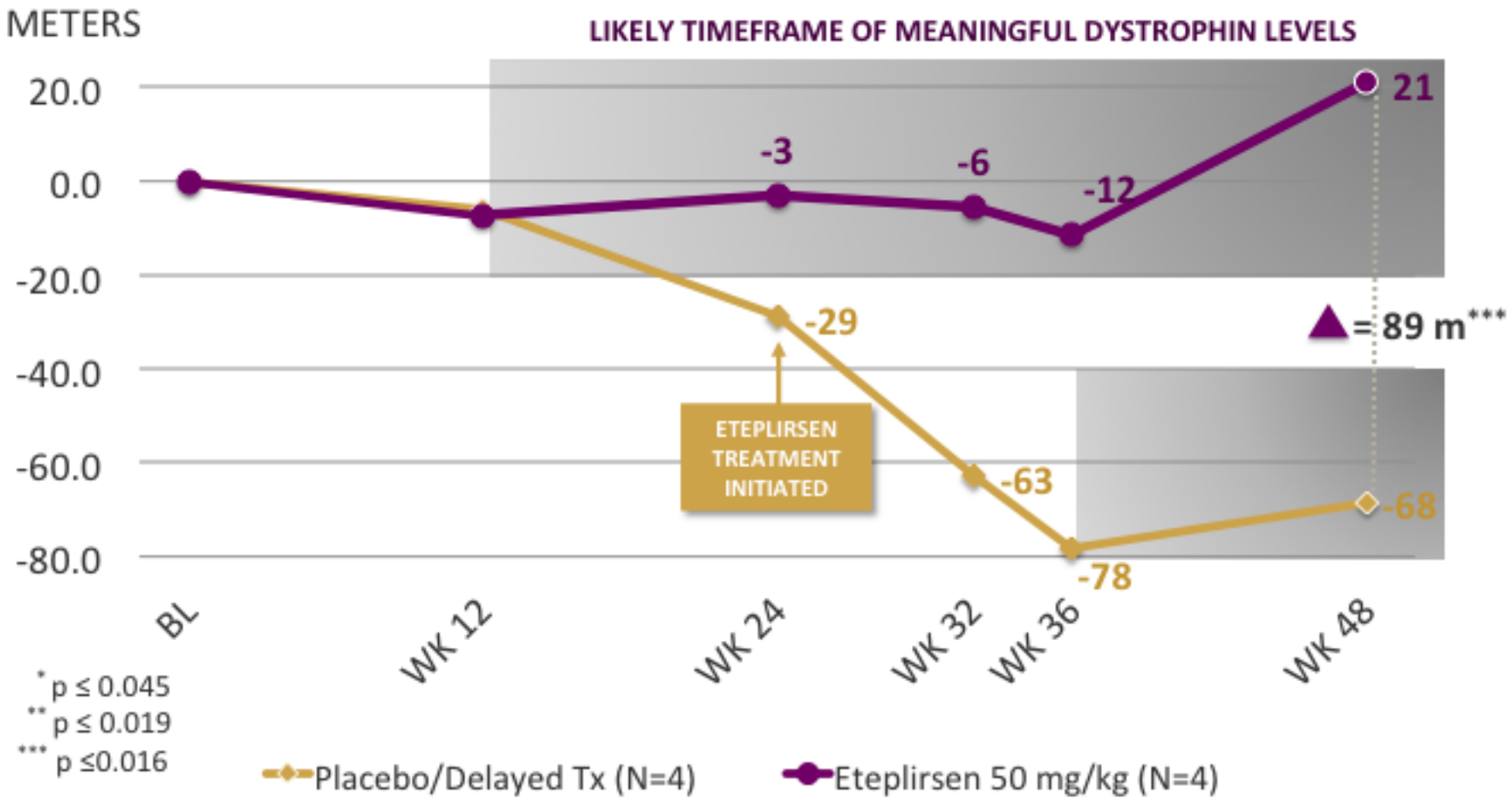

Note: Statistical analysis based on Intent-To-Treat Population using ANCOVA test

No treatment-related adverse events through 48 weeks

TREATMENT-EMERGENT ADVERS E EVENT	ETEPLIRSEN FOR 24 WKS N=12 (%)	ETEPLIRSEN FOR 48 WKS N=8 (%)	PLACEBO FOR 24 WKS N=4 (%)
Procedural pain	5 (42)	4 (50)	3 (75)
Vomiting	4 (33)	4 (50)	0
Hypokalemia	2 (17)	4 (50)	2 (50)
Cough	3 (25)	3 (38)	2 (50)
Back pain	1 (8)	4 (50)	2 (50)
Fall	2 (17)	2 (25)	1 (25)
Headache	3 (25)	1 (12)	2 (50)
Balance disorder	3 (25)	3 (38)	0
Diarrhoea	2 (17)	2 (25)	1 (25)
Dermatitis Contact	2 (17)	3 (38)	0
Pyrexia	1 (8)	2 (25)	2 (50)
Hematoma	2 (17)	2 (25)	1 (25)
Abdominal pain	1 (8)	0	2 (50)
Nausea	1 (8)	1 (12)	1 (25)
Rhinitis	1 (8)	1 (12)	1 (25)
Polyuria	1 (8)	1 (12)	0
Muscle Spasms	1 (8)	1 (12)	0
Musculoskeletal Pain	1 (8)	1 (12)	0
Proteinuria	0	0	1 (25)

ETEPLIRSEN HAS BEEN WELL TOLERATED

- No treatment- related adverse events
- No serous adverse events and no discontinuations
- No treatment related changes detected on any safety laboratory parameters including liver-specific enzymes and kidney function
- No proteinuria, change in blood coagulation profiles or thrombocytopenia observed

SUMMARY

VALID SCREENING TEST

- Highly specific/sensitive
- Low False positive rate
- Unequivocal predictive value

TREATMENT IMPROVES OUTCOMES

> 20 year hx of Glucocorticoids repeatedly validated efficacy

- Most effective when started at young age (prolongs walking; Prevents scoliosis)
- Improvement also improved by exon skipping

NATURAL HISTORY WELL DEFINED

- Well characterized in infants
- Therapy changes natural History

COST BENEFIT / RATIO

- Diagnosis in newborn period reduces cost
- Avoids diagnostic odyssey

Thank You !

NATIONWIDE CHILDREN'S

When your child needs a hospital, everything matters.℠