UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of
The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported)

March 9, 2018

CAPRICOR THERAPEUTICS, INC.
(Exact name of Registrant as Specified in its Charter)

Delaware	**001-34058**	**88-0363465**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

8840 Wilshire Blvd., 2nd Floor, Beverly Hills, CA	**90211**
(Address of principal executive offices)	**(Zip Code)**

(310) 358-3200
(Registrant's telephone number, including area code)

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR §230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR §240.12b-2).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On March 9, 2018 Capricor Therapeutics, Inc., a Delaware corporation (the "Company"), hosted a KOL Event in New York City focused on Duchenne muscular dystrophy and Capricor's current development program. A copy of the slides are attached hereto as Exhibit 99.1 and are incorporated by reference into this Item 7.01 of this Current Report on Form 8-K. Additionally, the Company has made available on its website the slides from the presentation.

The information contained in this Form 8-K (including Exhibit 99.1 attached hereto) is being furnished and shall not be deemed to be "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section and shall not be incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

99.1 Capricor Therapeutics, Inc. KOL Slide Presentation, dated March 9, 2018

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, hereunto duly authorized.

CAPRICOR THERAPEUTICS, INC.

Date: March 12, 2018

By: /s/ Linda Marbán, Ph.D.
Linda Marbán, Ph.D.
Chief Executive Officer

Key Opinion Leaders Lunch to discuss the emerging clinical paradigm in DMD focusing on gene and cell therapy.

NASDAQ: CAPR

March 9, 2018

Forward-Looking Statements

Statements in this presentation regarding the efficacy, safety, and intended utilization of Capricor's product candidates; the initiation, conduct, size, timing and results of discovery efforts and clinical trials; the pace of enrollment of clinical trials; plans regarding regulatory filings, future research and clinical trials; regulatory developments involving products, including the ability to obtain regulatory approvals or otherwise bring products to market; plans regarding current and future collaborative activities and the ownership of commercial rights; scope, duration, validity and enforceability of intellectual property rights; future royalty streams, expectations with respect to the expected use of proceeds from the recently completed offerings and the anticipated effects of the offerings, and any other statements about Capricor's management team's future expectations, beliefs, goals, plans or prospects constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Any statements that are not statements of historical fact (including statements containing the words "believes," "plans," "could," "anticipates," "expects," "estimates," "should," "target," "will," "would" and similar expressions) should also be considered to be forward-looking statements. There are a number of important factors that could cause actual results or events to differ materially from those indicated by such forward-looking statements. More information about these and other risks that may impact Capricor's business is set forth in Capricor's Annual Report on Form 10-K for the year ended December 31, 2016 as filed with the Securities and Exchange Commission on March 16, 2017, in its Registration Statement on Form S-3, as filed with the Securities and Exchange Commission on September 28, 2015, together with the prospectus included therein and prospectus supplements thereto, and in its Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, as filed with the Securities and Exchange Commission on November 14, 2017. All forward-looking statements in this press release are based on information available to Capricor as of the date hereof, and Capricor assumes no obligation to update these forward-looking statements.

Capricor KOL Speakers

- **Linda Marban, Ph.D.** – Chief Executive Officer, Capricor Therapeutics, Inc.
- **Deborah Ascheim, M.D.** – Chief Medical Officer, Capricor Therapeutics, Inc.
- **Craig McDonald, M.D.,** is professor and chair of the Department of Physical Medicine and Rehabilitation and Director of the Neuromuscular Disease Clinics at the University of California, Davis. Dr. McDonald is an internationally recognized expert in the clinical management and rehabilitation of neuromuscular diseases including DMD. He is the national PI of the Capricor HOPE-2 Trial.
- **Jeffrey Chamberlain, Ph.D.,** is professor in the Departments of Neurology, Medicine and Biochemistry and director of the Seattle Wellstone Muscular Dystrophy Center. Dr. Chamberlain is the holder of many of the key patents for microdystrophin and has been a world leader in the development of gene therapies for DMD.
- **Michelle Eagle, Ph.D.,** the managing director of ATOM International LTD, is one of the creators of, and has published extensively on, the Performance of the Upper Limb (PUL) test, a validated test for skeletal muscle function in Duchenne muscular dystrophy.
- **Pat Furlong,** is the founding president and CEO of the Parent Project Muscular Dystrophy (PPMD), the largest non-profit organization in the U.S. focused solely on Duchenne. She has spearheaded the advocacy movement in Duchenne and is a world expert on regulatory strategies for approval of products to treat the disease.

Capricor's Mission

Capricor is ***focused*** on the discovery, *development* and commercialization of ***innovative cell*** and ***exosome*** based ***therapies*** for patients with ***immune-inflammatory*** rare diseases with a focus on ***Duchenne muscular dystrophy*.**

Treatment Options for DMD are Limited

- Exon Skipping
- Gene therapy
- Utrophin
- NF-kB
- Steroids

Challenges

- EXONDYS 51 –13% of DMD population
- Gene therapy not always effective due to antibody response
- Steroids have adverse long term side-effects
- NF-kB inhibition may not be enough to mediate immune response

CAP-1002

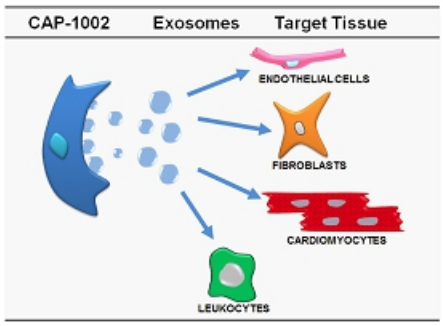
- Immunomodulatory
- Anti-fibrotic
- Pro-angiogenic
- Pro-regenerative
- Cellular Energy

We believe CAP-1002 may be used synergistically with other therapeutics aimed to treat the underlying genetic mutation with DMD

Capricor's CAP-1002 Technology

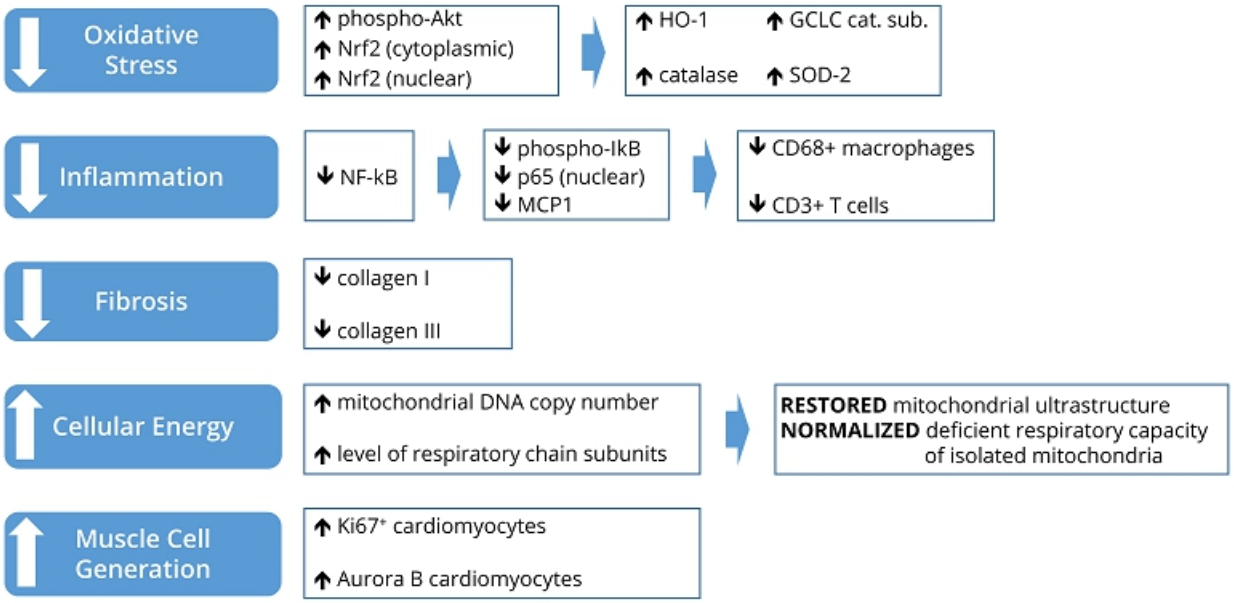
– CAP-1002 is a biologic consisting of allogeneic cardiosphere-derived cells (CDCs)

- Manufactured from donated heart muscle
- **Does not act by "stemness" – the cells do not engraft into host tissue**
- MOA: cells secrete EVs (exosomes)
  - Contain non-coding RNAs and proteins
  - Internalized by target cells
  - Stimulate diverse and lasting changes in cellular behavior



- CAP-1002 has been investigated in several clinical trials and more than 130 human subjects

Physiological Effects of CDCs in mdx Model



*CDCs have been the subject of >100 peer-reviewed papers since 2007

Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)30049-3).

Intramyocardial CDC methods

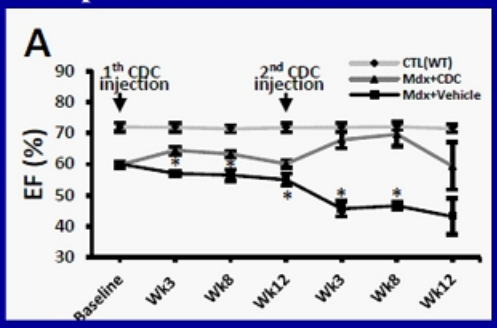
- Mouse model of DMD
  - 10 m/o *mdx* mice (n=12 per group)
  - Randomized to CDC vs vehicle
  - Followed for 6 months or longer
  - Single or repeat injection at 3 mo as noted

- CDCs
  - From background mouse strain (C57BL/10)
  - Injected intramyocardially
    (LV; 4 injection sites)

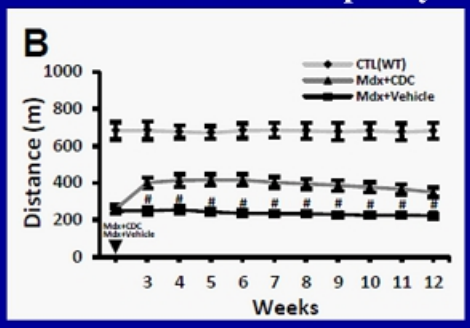
Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)30049-3

Improved function & survival in mouse model

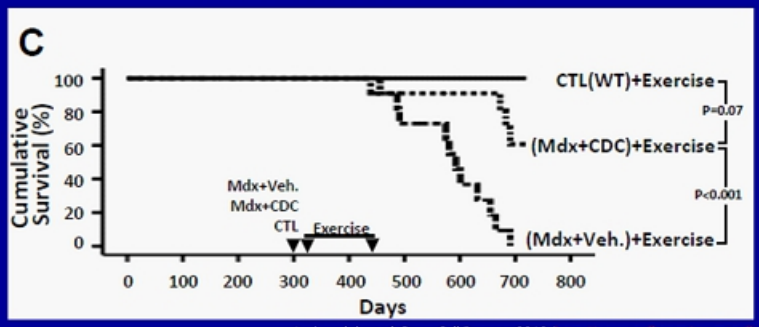
Improved cardiac function



Increased exercise capacity

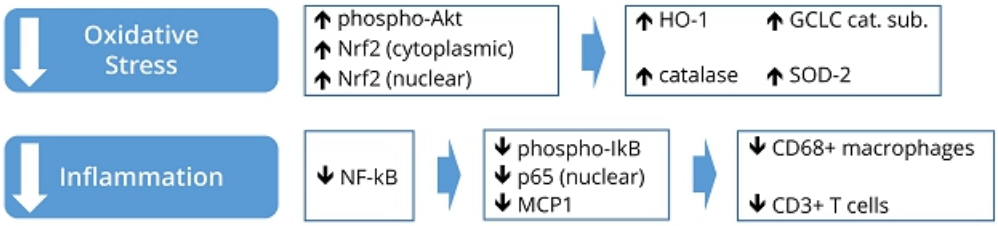


Increased survival rate



Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)30049-

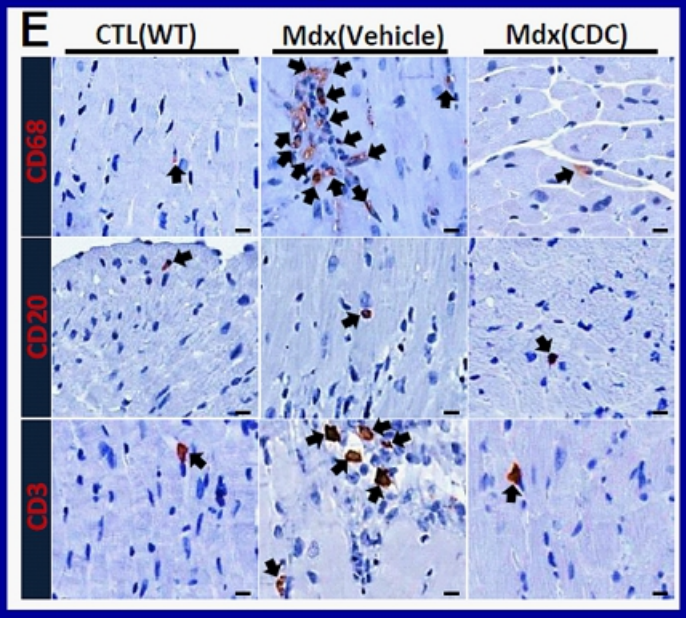
Physiological Effects of CDCs in mdx Model



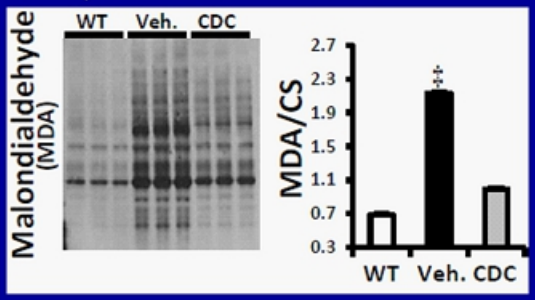
Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)30049-3).

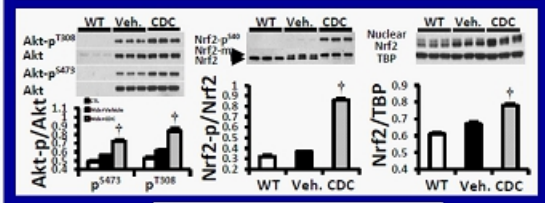
Oxidative stress & inflammation: major players in DMD

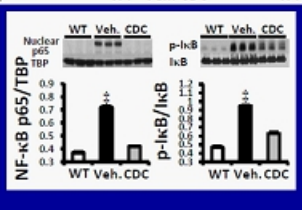
↓ Inflammatory cell infiltration



↓ Oxidative stress

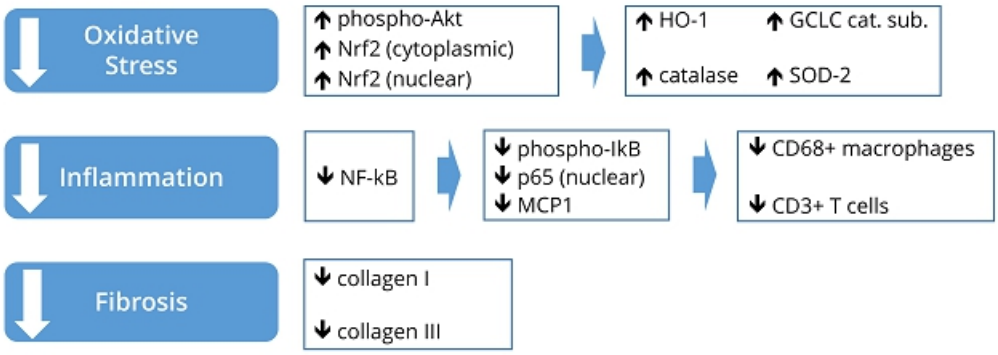






Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)30049-3).

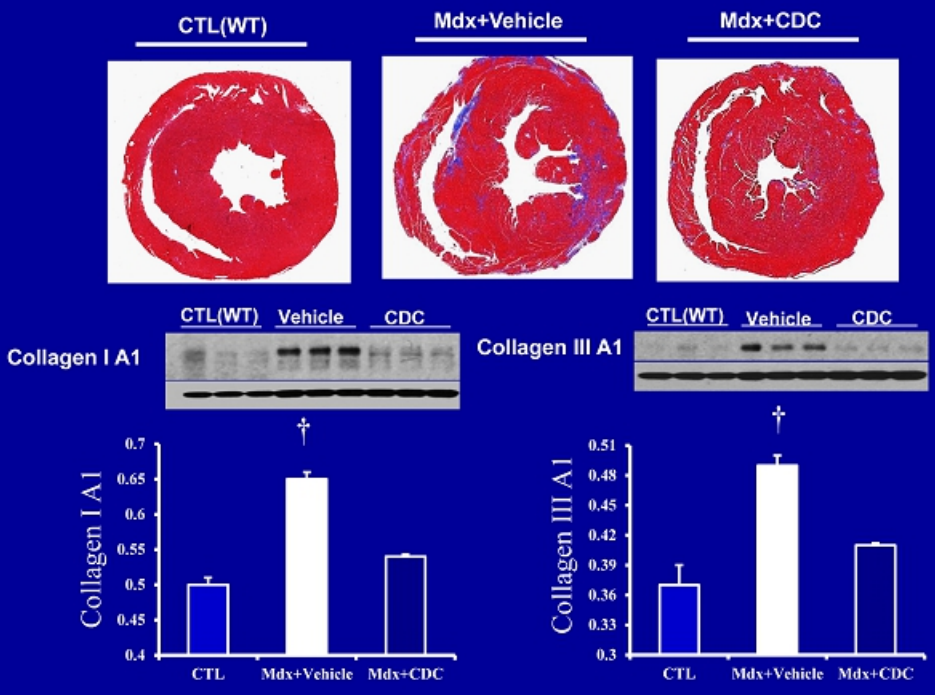
Physiological Effects of CDCs in mdx Model



*CDCs have been the subject of >100 peer-reviewed papers since 2007

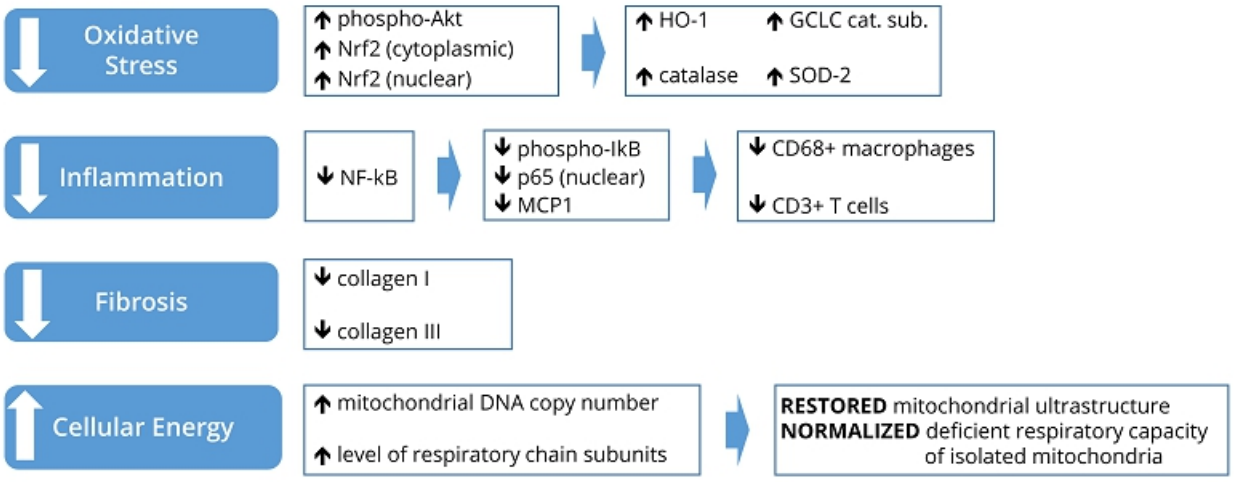
Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)30049-3).

Reduced cardiac collagen content and fibrosis



Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)

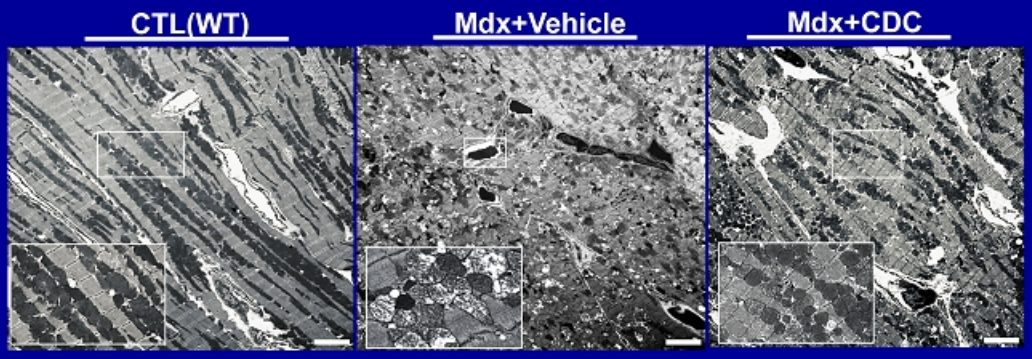
Physiological Effects of CDCs in mdx Model

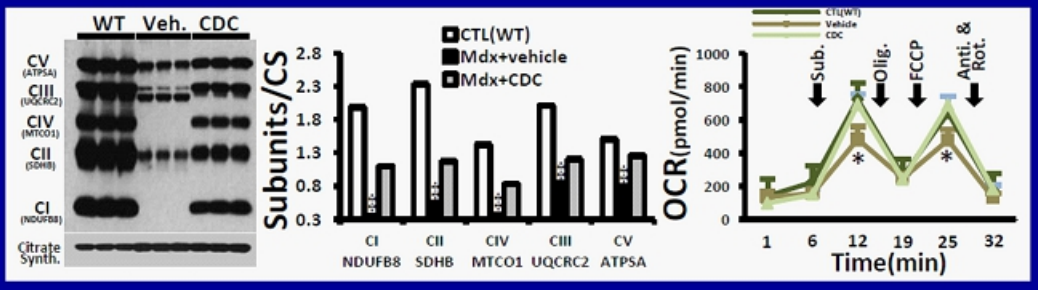


*CDCs have been the subject of >100 peer-reviewed papers since 2007

Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)30049-3).

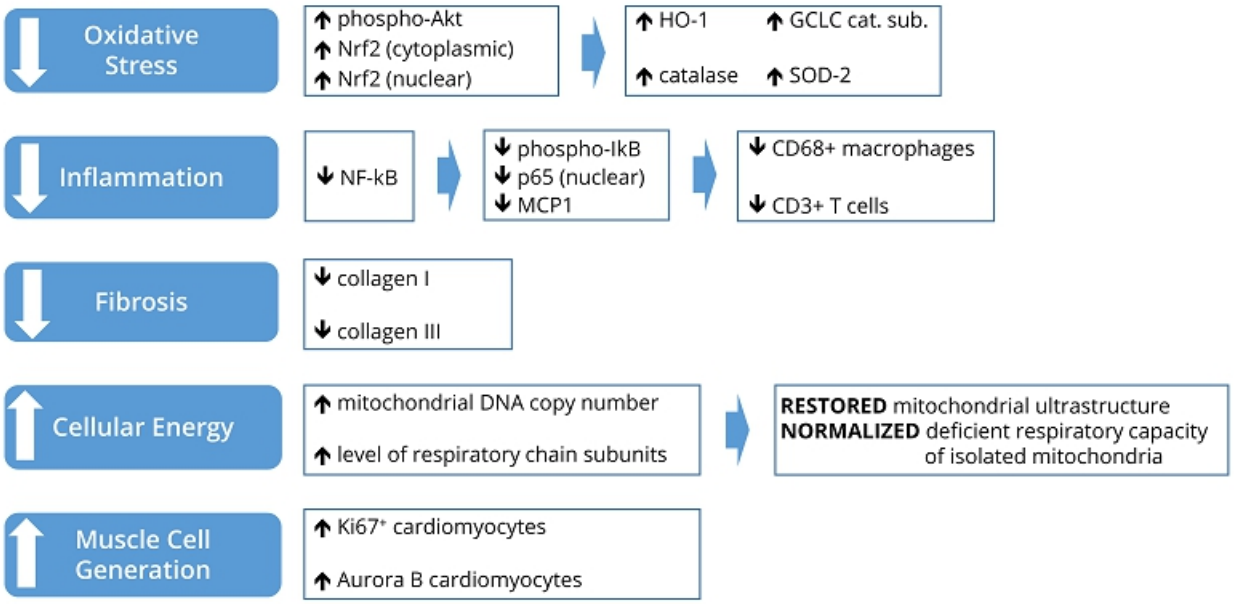
Restoration of mitochondrial integrity





Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)[illegible])

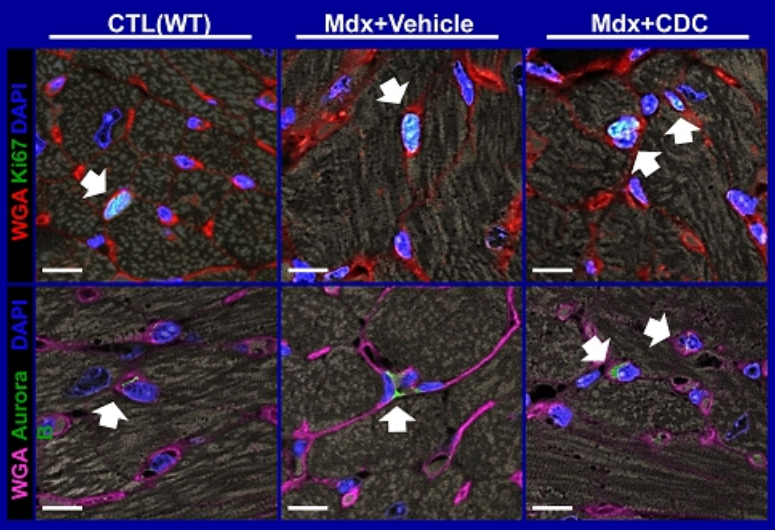
Physiological Effects of CDCs in mdx Model

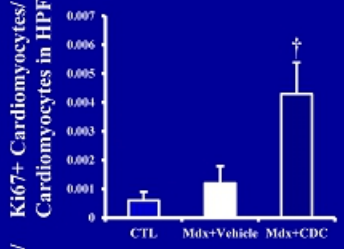


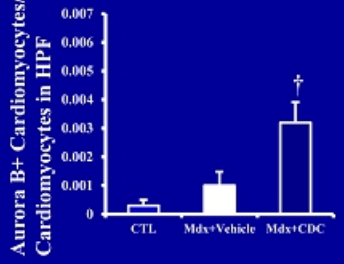
*CDCs have been the subject of >100 peer-reviewed papers since 2007

Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)30049-3).

Cardiomyogenesis

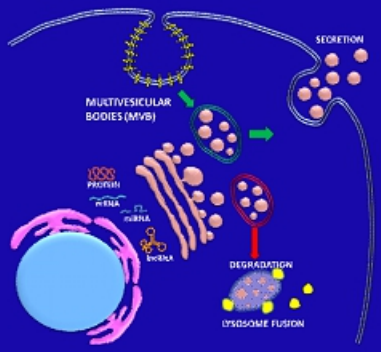






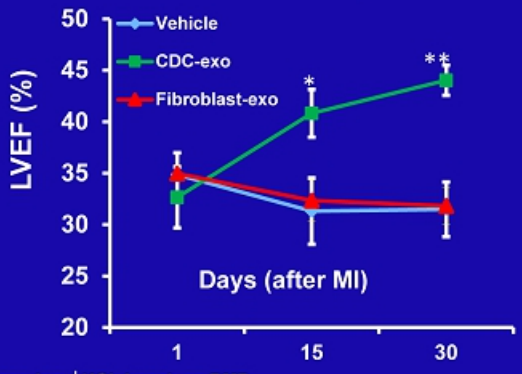
Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)

Exosomes: CDCs MoA Defined

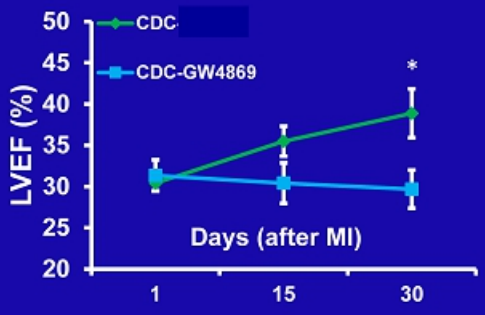


- 30-150 nm particles
- Present in all body fluids
- Released by nearly all cell types
- Loaded with miRs and other bioactive contents
- Payload very cell-specific

CDC exosomes ↑ EF



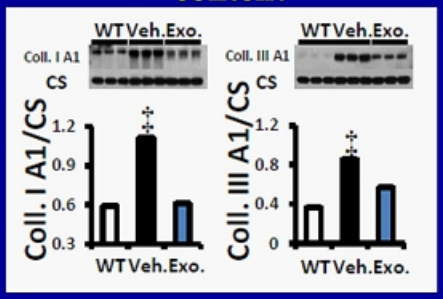
Blocking exosome biosynthesis abrogates CDC benefit



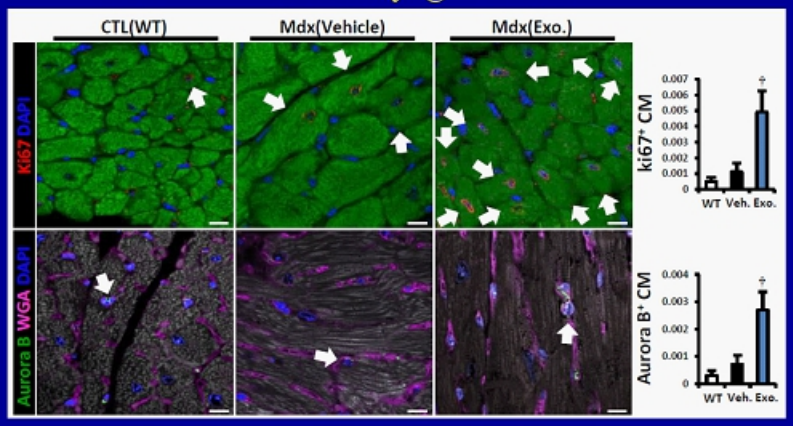
Ibrahim et al., *Stem Cell Reports* 2014

Intramyocardial exosomes recap effects of CDCs

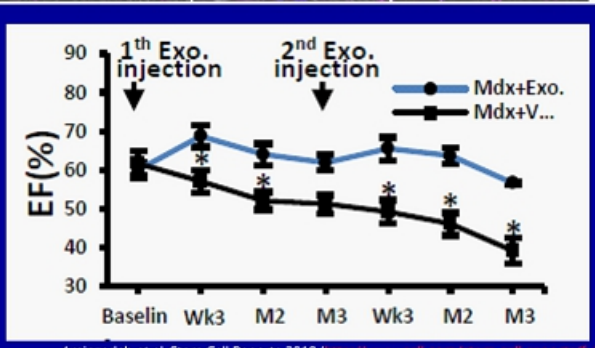
Collagen content



Cardiomyogenesis



Functional benefit on heart



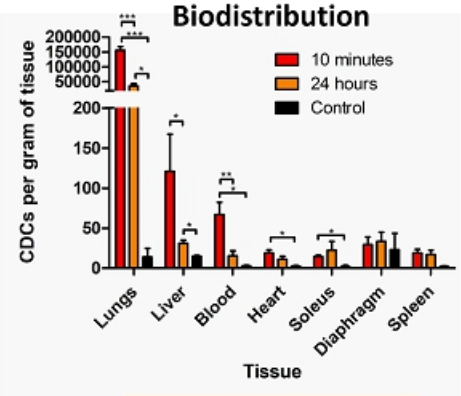
Aminzadeh et al, Stem Cell Reports 2018 (http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(18)300-

Intravenous CDC methods

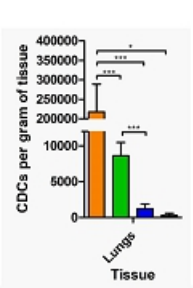
- Mouse model of DMD
  - 10-12 m/o *mdx* mice
  - Randomized to CDC vs vehicle
  - Followed for 3-26 weeks
  - EF, exercise capacity, isolated muscle function
- CDCs
  - From background mouse strain (C57BL/10)
  - 250k cells infused via jugular vein

Adapted from Cedars-Sinai Medical Center unpublished data

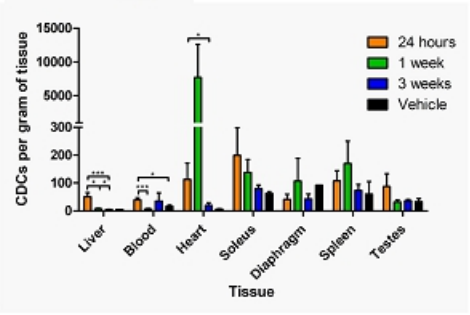
Biodistribution and Clearance of IV CAP-1002



Mouse model: WT mice
CDCs: Human, 150K
Route: Jugular vein

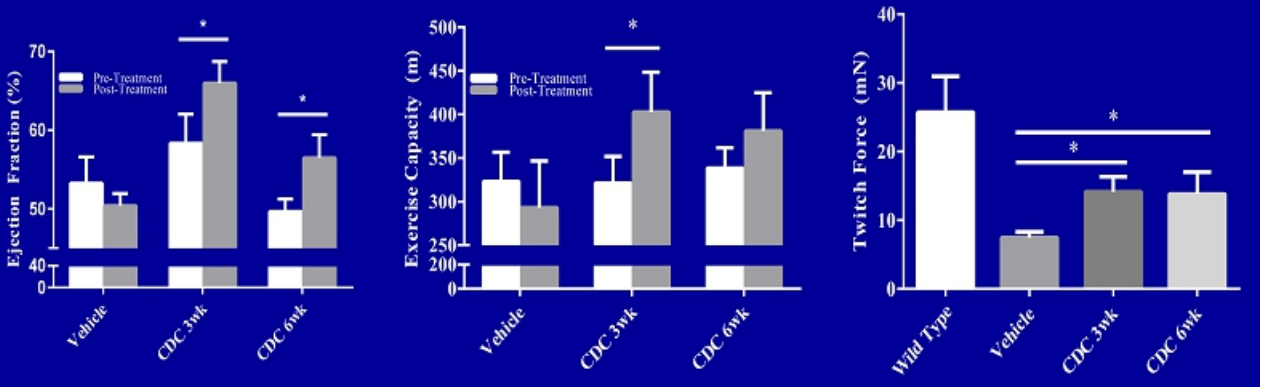


Mouse model: SCID mice
CDCs: Human, 150K
Route: Jugular vein

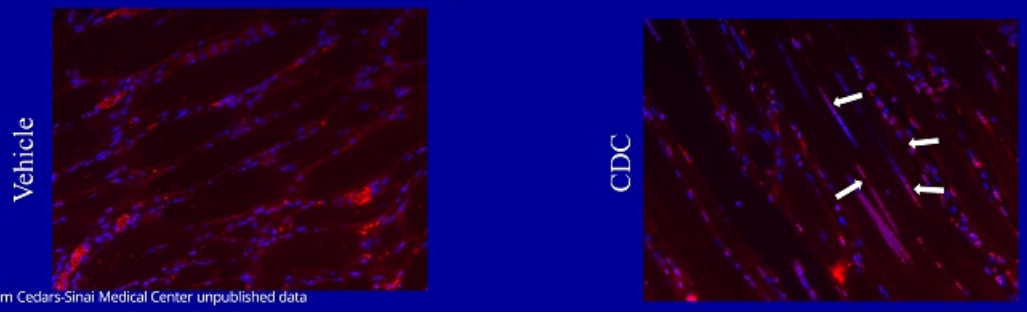


Capricor unpublished data

Cardiac, skeletal, and isolated muscle function after IV CDCs

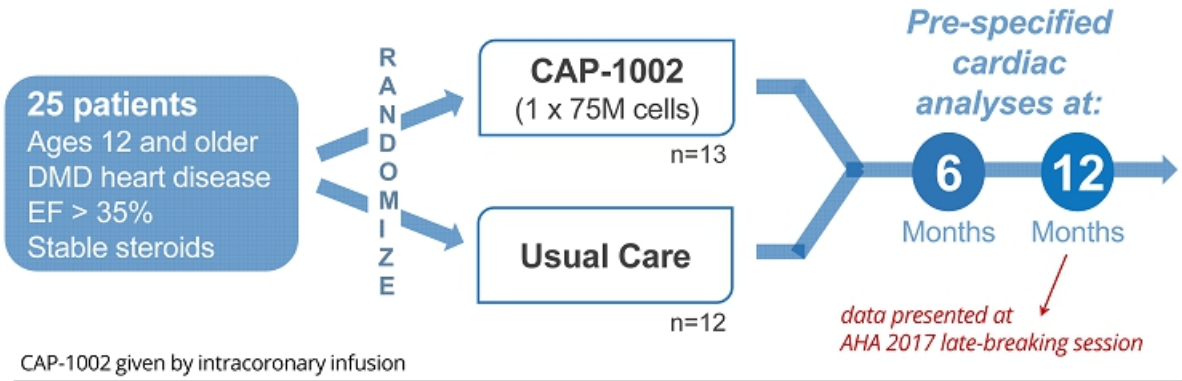


More fusion-competent myoblasts in soleus after IV CDCs



Adapted from Cedars-Sinai Medical Center unpublished data

Phase I / II HOPE-Duchenne Clinical Trial



CAP-1002 given by intracoronary infusion

- One-time, multi-vessel, intracoronary delivery of cells
- Safety trial with multiple exploratory efficacy endpoints
- Three U.S. sites: Cedars-Sinai Medical Center
  Cincinnati Children's
  University of Florida

https://clinicaltrials.gov/ct2/show/NCT02485938

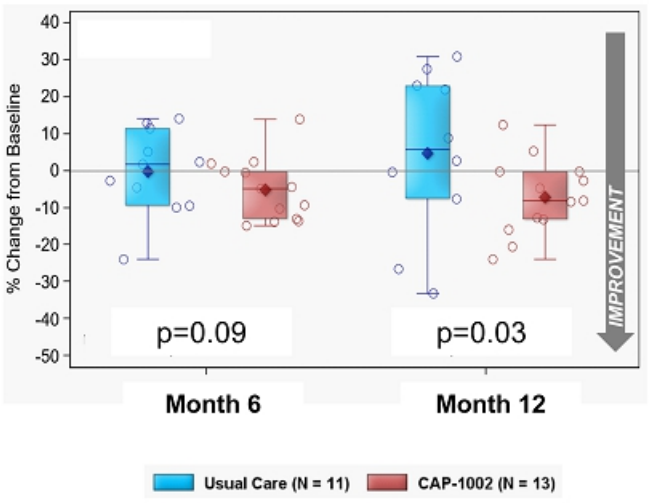
Baseline Characteristics

	Usual Care (n=12)	CAP-1002 (n=13)
Age, median years (range)	17.5 (12–20)	18 (14–25)
Wheelchair Use Always (%)	7 (58)	10 (77)
Cardiac Scar Size, mean % (SD)	21.4 (10.8)	17.6 (6.8)
LV Ejection Fraction, mean % (SD)	48.4 (7.5)	49.6 (6.7)
Intracoronary Dose, M cells (SD)	n/a	73.7 (3.6)

Patients were all male, were all receiving chronic treatment with systemic steroids, and were mostly Caucasian.

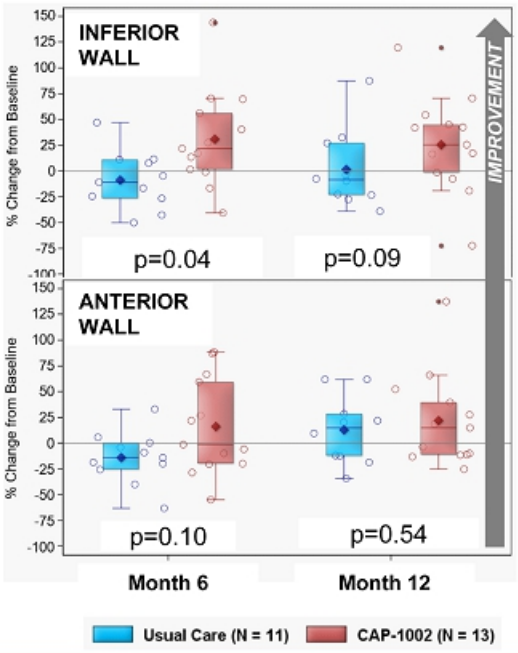
- HOPE population characterized by advanced disease; majority were non-ambulant
- Most DMD clinical development has been conducted in less sick patients

Heart Muscle: Reduced Myocardial Scarring



- Assessed by cardiac MRI with blinded analysis by core lab
- Scar increased in the Usual Care group, but decreased in the CAP-1002 group
  - 11.9% group difference in change score at Month 12 (p=0.03)
- Decreased scar is counter to the natural history of DMD

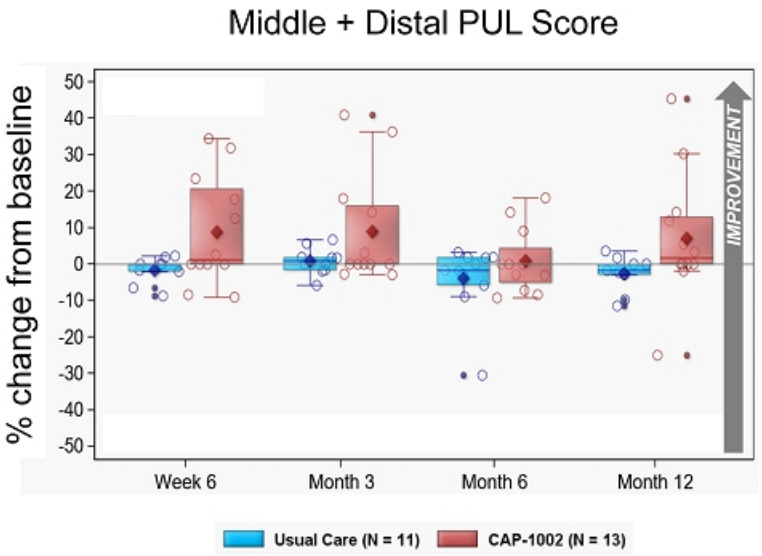
Heart Muscle: Increased Regional Systolic Wall Thickening



- Measurement of cardiac function by MRI allows focus on treated areas
- Magnitude of scar reduction is consistent with natural history of scar progression in DMD
  - Inferior → Anterior → Lateral → Septal
- Measure is important indicator of overall cardiac function in DMD

Skeletal Muscle: PUL Results Indicate Functional Benefit

- Performance of the Upper Limb (PUL) test is a validated instrument in DMD
  - Relates to patients' ability to perform common activities of daily living
- Trends towards improvement observed throughout follow-up



HOPE-2 Clinical Trial of CAP-1002 in DMD

— **Potential registration trial plan to initiate in 1Q 2018**

- Randomized, double-blind, placebo-controlled
- Target enrollment of 84 patients with advanced disease
- Peripheral intravenous delivery – supported by preclinical studies
- Repeat-dose design – potential to achieve sustained benefit
- Primary efficacy endpoint – difference in change in mid-PUL scores at Month 12
- Principal Investigator – Craig M. McDonald, M.D.

— **FDA willing to consider PUL as an efficacy endpoint for registration**

- Type B meeting held in June, following six-month HOPE data

— **Granted RMAT designation**

https://www.clinicaltrials.gov/ct2/show/study/NCT03406780

Emerging genetic therapies for DMD

Jeffrey S. Chamberlain, Ph.D.
McCaw Endowed Chair in Muscular Dystrophy
Director, Sen. Paul D. Wellstone Muscular Dystrophy Research Center
Depts. of Neurology, Medicine and Biochemistry
University of Washington
Seattle, WA USA

Disclosures: JSC is a member of the scientific advisory boards of Solid Biosciences, Ballard Biologics, AAVogen and Akashi Therapeutics

Gene Therapy –different types

- **Gene replacement therapy: deliver a new version of a gene to the target tissue (aka gene addition)**
- **Gene editing: directly modify a gene to fix or bypass a mutation**
  - **CRISPR/Cas9**
- **Gene knockdown: Suppress the activity of a mutant gene**
  - **Inhibitory RNA (siRNA, shRNA, etc)**
- **Transcript modification, e.g. 'exon skipping'**

- **Rationale bolstered by multiple recent successes with human gene therapy:**
  - **X-SCID, Hemophilia b, Liebers congenital amaurosis, Lipoprotein lipase deficiency (Glybera), Metachromatic Leukodystrophy, Wiskott-Aldrich Syndrome**
  - **Spinal muscular atrophy**
  - **CAR-T cell modification**
  - **Muscular dystrophy….**

Why gene therapy?

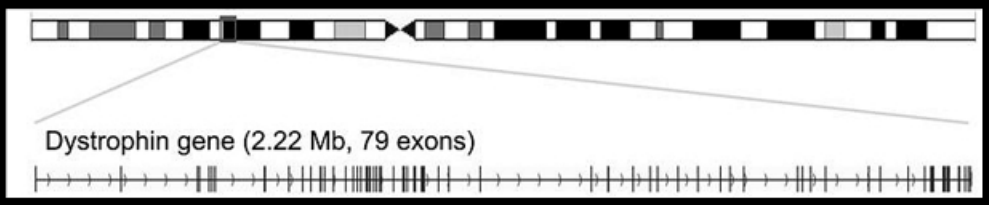
- **Fix the primary cause of genetic disorders**
- **Potential for a permanent treatment**
- **Genetic manipulation of stem cells**
- **Overcome genetic errors that lead to cancer**
- **Powerful approach to developing new vaccines**

Delivering gene therapy to the body

- **'Viral' Vectors: modified from viruses, no longer "virus"**
  - **Adeno-associated viral vectors (AAV) –best for non-dividing cells**
  - **Lentiviral vectors –best for dividing cells (e.g. stem cells)**
  - **Adenoviral vectors –mostly now used for vaccines, cancer**
- **Non-viral vectors: plasmids, anti-sense oligonucleotides; "nanoparticles"**
  - **Short acting , easier to manufacture, high safety**
  - **Transcript modification, gene editing**
- ***Ex vivo* gene therapy: Corrected, or normal, Stem Cells**
  - **Bring along therapeutic gene(s) or trophic factors**

Duchenne muscular dystrophy (DMD)

- Most common form of muscular dystrophy (>300,000 cases)
- Caused by mutations in the 2.2 MB *dystrophin* gene
- X-linked, recessive inheritance
- 1/3 of cases due to new mutation; thousands of independent mutations



Strategies for the development of DMD therapies

- **Viral vector delivery of genes to muscles**
  - **Dystrophin replacement**
  - **Delivery of a surrogate gene (*e.g.* Utrophin; GALGT2)**
  - **Transcript modification - bypass mutation**
  - **Gene editing (*e.g.* CRISPR/Cas9)**
- **Antisense oligonucleotide delivery (exon skipping)**
- **Stem cell transplantation (*ex vivo* gene therapy)**
- **Pharmacologic therapy - *palliative***

  -steroid hormones (prednisone); induce muscle hypertrophy (myostatin inhibitors); reduce inflammation/fibrosis (TGF-β inhibitors), enhance regeneration, stop codon suppression (aminoglycosides)
- **Combinatorial- *future***

Gene Therapy for DMD/BMD

- ***Goal:*** **Develop methods to *replace* or *repair* dystrophin gene**
- ***Pros:***
  - **Fixes the primary cause of the disease – lack of dystrophin**
  - **Should work for ALL patients**
- ***Cons:***
  - **Requires bodywide (systemic) gene delivery to muscle**
    - **AAV vectors?**
- **Potential:**
  - **DMD (severe) -no dystrophin protein made**
  - **BMD (mild) -smaller dystrophins made**

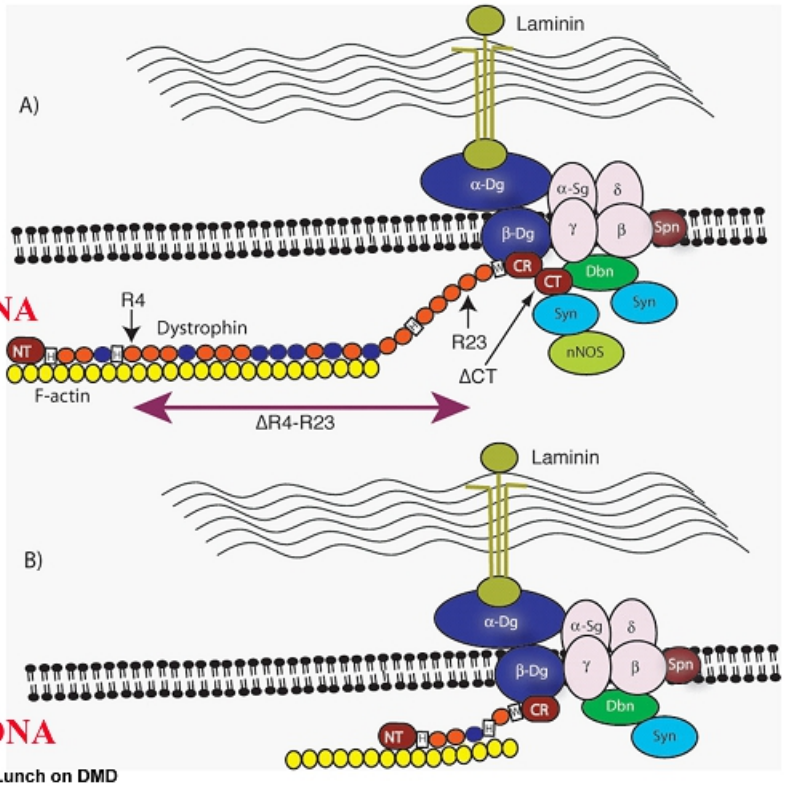
Challenges for gene therapy for DMD/BMD

- ***How can you deliver a new gene to muscles, bodywide, in a safe and effective manner?***
  - **Development of delivery VECTORS by manipulating viruses**
  - **Remove viral genes, replace with gene of interest (*e.g.* dystrophin)**

- ***Vectors derived from adeno-associated virus are promising***
  - **Some serotypes enable systemic gene delivery *via* the vasculature**
  - **AAV vectors have limited carrying capacity; dystrophin is huge gene**
  - **Produce smaller, synthetic versions of dystrophin that still work**

- ***Future/alternate goal: can the mutant gene be edited or repaired?***
  - **Gene editing with AAV-CRISPR/Cas9**

Assembly of the dystrophin-complex by micro-Dys



14 kb cDNA

3.7 kb cDNA

Adeno-associated viral (AAV) vectors

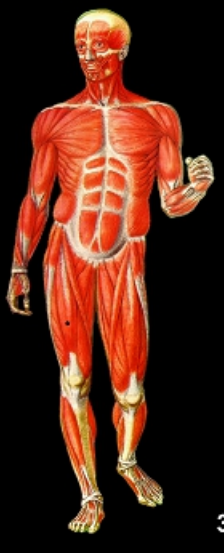
Non-integrating vectors, persist as episomes

***PROS*:**

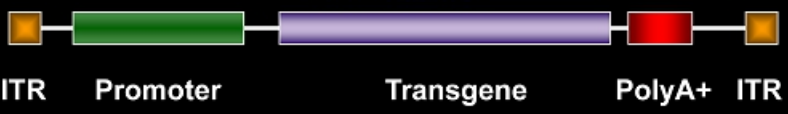
- **Numerous serotypes, many target muscle (AAV6, 8 & 9)**
- **Relatively easy to produce; scalable to bioreactor production**
- **Can be used for bodywide gene delivery, especially to muscles**

***CONS*:**

- **Small carrying capacity (~5 kb; Dys cDNA=14 kb)**
- **Generally poor results in stem cells**
- **Rapidly lost from dividing cells**



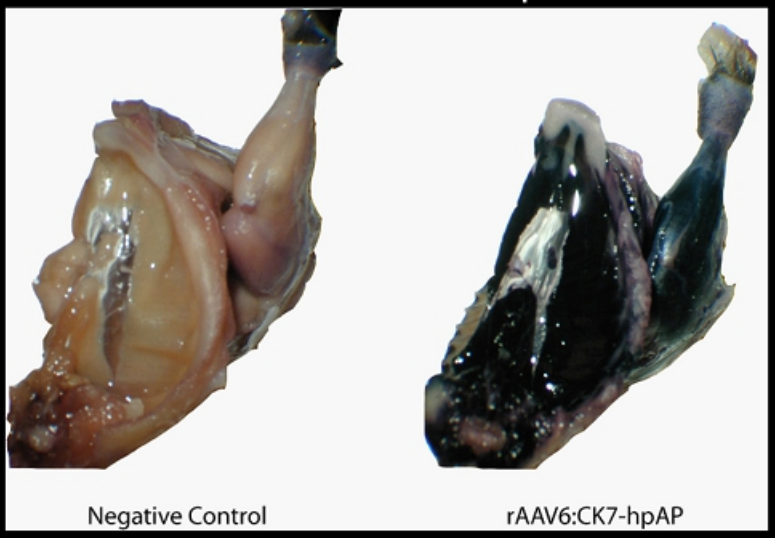
AAV vector:



Systemic gene transfer to muscle using AAV6

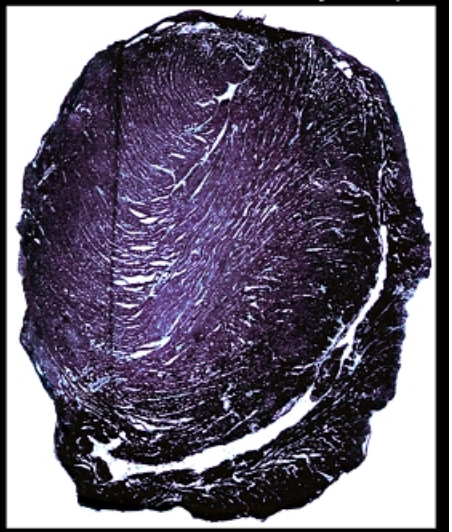
- **Single tail vein injection of AAV/alkaline phosphatase into adult mice**

Whole mounts stain - 2 mos pi



Negative Control rAAV6:CK7-hpAP

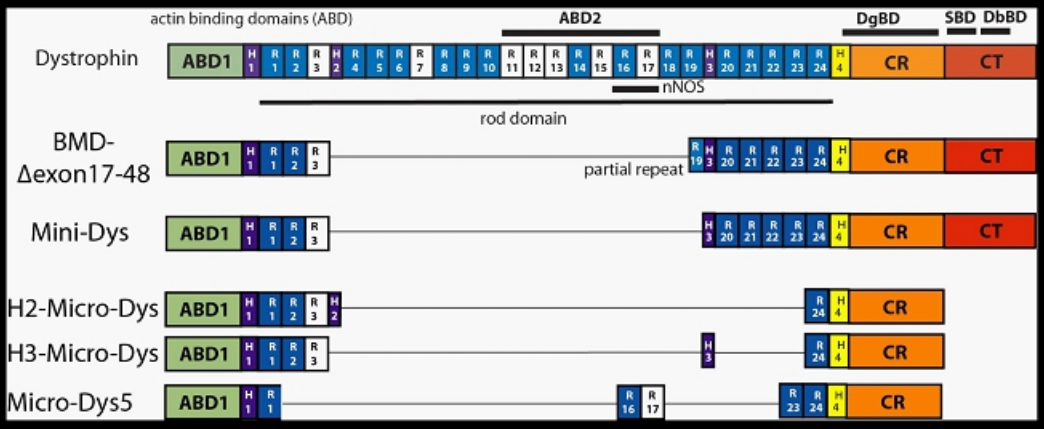
Histochemical stain - 2 years pi



AAV holds 5 kb; dystrophin gene = 2.2 MB

Gregorevic & Chamberlain, Nature Medicine, 2004

Development of micro-Dystrophins



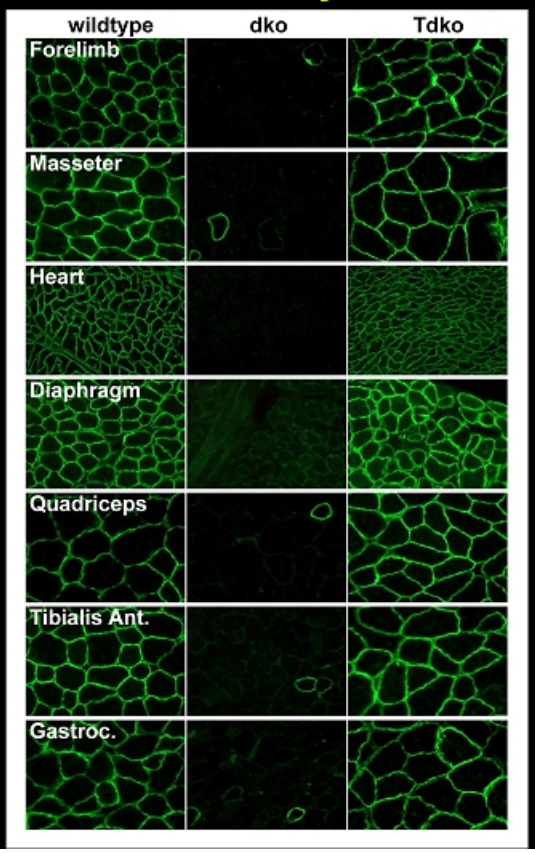
"mini"-Dystrophins modified from a very mildly affected BMD patient

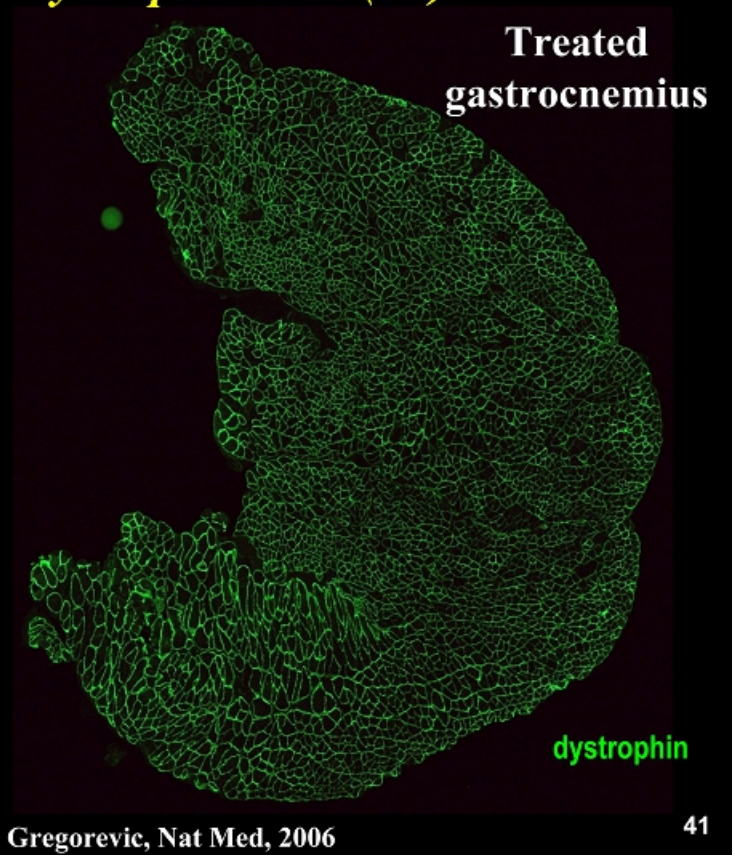
"Micro-dys" made by systematically removing additional protein domains

Many micro-dystrophins made by my lab and some others

"H2-microDys" and "micro-Dys5" entering clinical trials

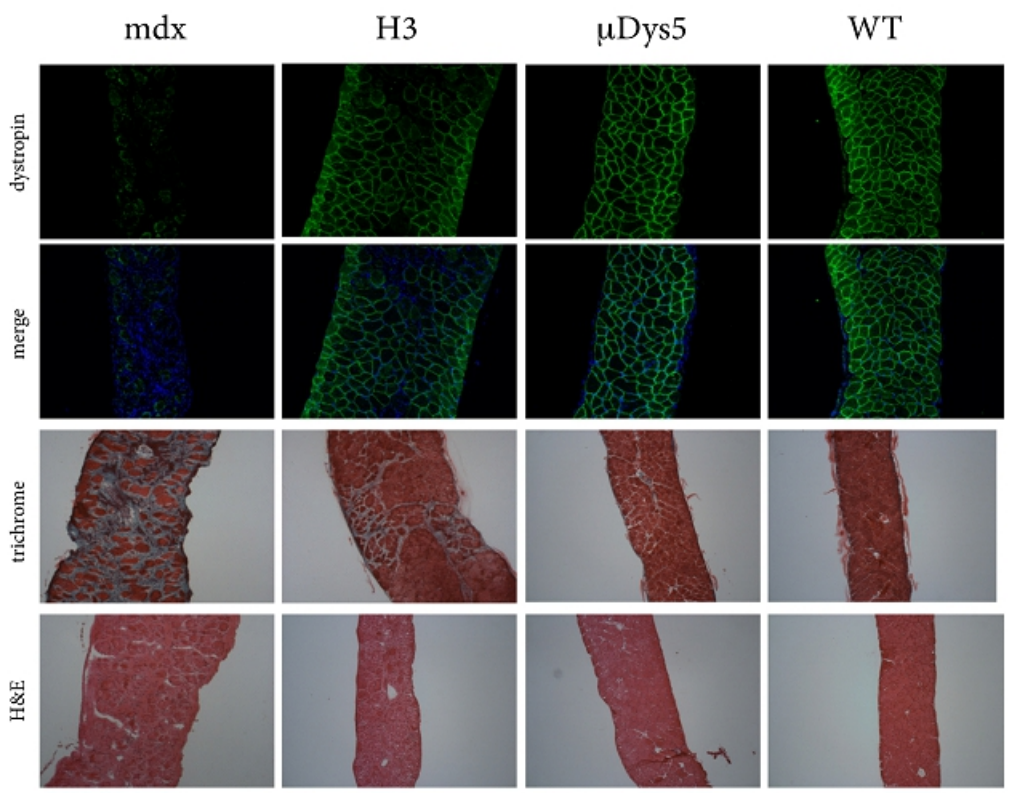
Expression of micro-Dystrophin one year after AAV infusion into dystrophic mice (IV)



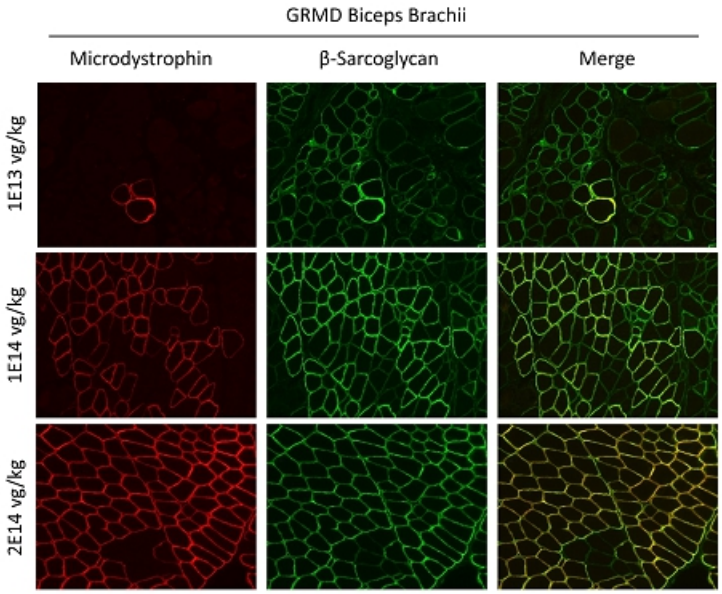


Gregorevic, Nat Med, 2006

MicroDys stably expressed 2 years after AAV infusion in mdx mice - diaphragm muscles

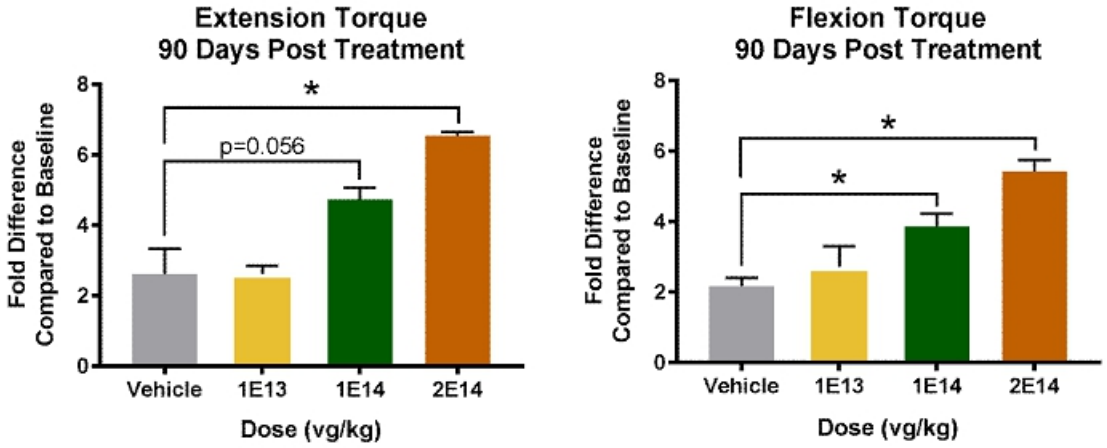


DGC expression in GRMD dogs following systemic SGT-001 infusion



Kornegay et al

SGT-001 (AAV-µDys) increases force in GRMD dogs following systemic delivery



Analysis of torque produced by extension and flexion of the tibiotarsal joint. *p<0.05

Kornegay et al

SOLID BIOSCIENCES

AAV-mediated gene therapy for DMD/BMD

- **Micro-dystrophins halt muscle wasting, protect from exercise-injury and improve strength**
- **Not all µDys are equivalent**
- **Efficient systemic delivery of AAV/µDys in dogs**
- **No reduction in µDys expression after at least 2 years**
- **High dose AAV9 delivery has been safely achieved in humans (e.g. SMA- Nationwide Children's)**
- **Clinical trials of AAV/µDys are beginning by several groups**

Clinical trials planned / in progress

- **Solid Biosciences - Ganot et al (Chamberlain uDys-3rd gen); AAV9**
- **Nationwide Children's – J Mendell et al (Sarepta) (Chamberlain uDys-1st gen); AAV-rh74**
- **Genethon – G Dickson (Sarepta) (Chamberlain uDys-1st gen); AAV8**
- **Pfizer– Samulski et al (Xiao uDys; Chamberlain/Hauschka promoter); AAV9**

Tentative plans: Systemic (intravascular) delivery of AAV-uDys

- **Solid Biosciences and Nationwide Children's are beginning trials**
- **Pfizer: Q2-Q3 2018??**
- **Genethon: 2019???**

Results:

- **Unclear on how long it will take to observe a functional benefit**

Gene therapy

- Difficulty of transitioning from academics to clinic
- Growing, large interest by Biotech and Venture Capitol communities
- American Society for Gene and Cell Therapy is the premier meeting

Future:

- Gene editing with CRISPR/Cas9? Safety/efficacy?
- New vectors?
- Scaling production
- Combinatorial therapies

Gene therapy options/alternatives?

- **Delivery/upregulation of Utrophin (Summit)**
  - **AAV/μUtrn: Chamberlain**
- **Overexpression of GALGT2 (NCH trial imminent)**
  - **Modifies dystroglycan to assemble a Utrophin-complex**
- **Stem cells: e.g. Capricor**
  - **Modulate muscle environment/enhance regeneration**
  - **Provide new myogenic stem cells to replace muscle loss?**

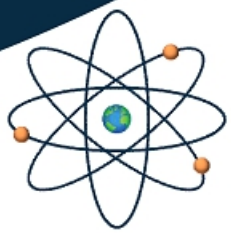
***Combinations*:**

- **Gene therapy + Stem cell therapy?**
- **Add anti-fibrotics and/or anti-inflamatories?**
- **Add enhancers of muscle mass**


Wellstone Muscular Dystrophy Research Center-Seattle
Chamberlain Lab:
Katrin Hollinger – 3rd gen µDys
Julian Ramos – 3rd gen µDys
Julie Crudele - µDys/immunology
James Allen – AAV
Christine Halbert – AAV
Matt Karolak – DGC
Maja Zavaljevski – DMD/FSHD/DM1
Darren Bisset - DMD/FSHD/DM1
Niclas Bengtsson – Cas9
John Hall – Sat cells/Cas9/FSHD
Aisha Mushtaq – DMD/DM1
Andrea Arnett – AAV
Glen Banks - µUtrn/ringbinden
Jane Seto - µDys/FKRP
U Washington:
Guy Odom-µUtrn
Steve Hauschka-MCK
Joel Chamberlain-FSHD
Supported by The National Institutes of Health (NIAMS/NHLBI)
The Muscular Dystrophy Association (USA)
LGMD2I Fund; Solid Biosciences
| Capricor, Inc. | KOL Lunch on DMD

OUTCOME MEASURES IN DMD CLINICAL AND TRIAL CONSIDERATIONS

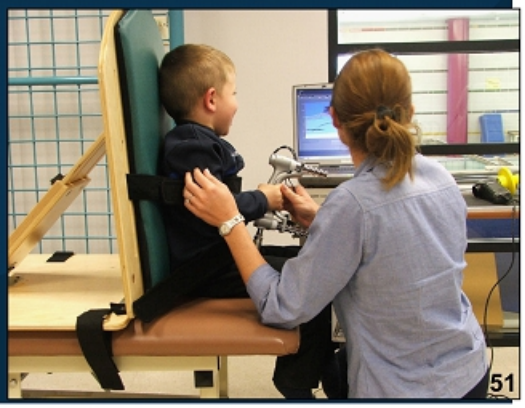
PRESENTED BY : MICHELLE EAGLE



Advancing
Trial
Outcome
Measures
International Ltd

OUTCOME MEASURES IN DMD

- Tools/assessments used to:
  - Evaluate the baseline status of a patient
  - Evaluate the effect of an intervention
  - Monitor disease progression
  - Inform clinical decision making regarding initiation/change of therapies
- Clinic or clinical trial context



WHAT MAKES A GOOD OUTCOME MEASURE?

- Reliable
  - Excellent inter-rater and intra-rater reliability
  - Low measurement error
- Valid
  - The degree to which an assessment measures what it intends to
- Sensitive
  - Responsive in the ability to detect meaningful, real changes

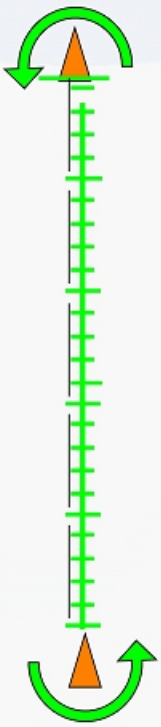
QUALITIES OF GOOD OUTCOME MEASURES

- Meaningful
  - Clinical meaningfulness
- Cost efficient
- Easy to administer
- Standardised

TREAT-NMD Neuromuscular Network

PROBLEMS

- Loss of function
- Weakness
- Contractures
- Immobility



ASSESSMENT

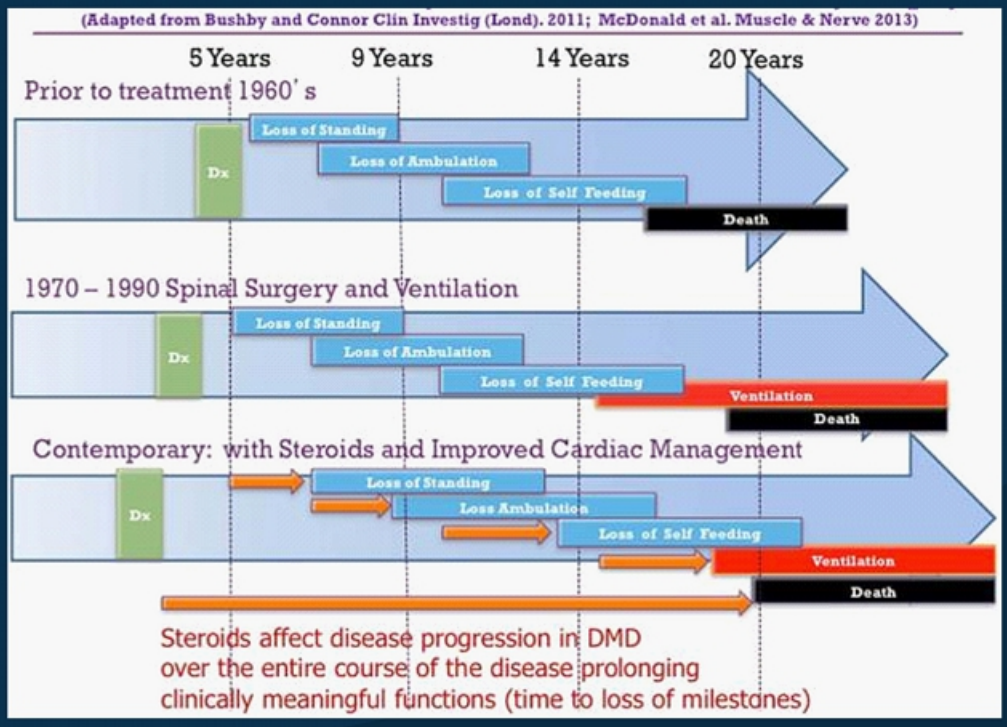
- Functional Scales – North Star, PUL
- EK Scale
- timed tests – 10 metre, rise from floor, 6 MWT
- muscle strength - MMT, myometry, QMT
- Range of movement
- Respiratory - FVC, MIP/MEP, PCF

CURRENT OUTCOME MEASURES USED IN DMD

- North Star Ambulatory Assessment
- PUL (Performance upper limb)
- Egen Klassification (EK)
- 9 Hole peg test
- 6MWT
- Timed functional tests
  - Timed up and go
  - Rise from floor
  - Climb/descend stairs
  - Run/walk 10 metres
- ACTIVE seated

- Pulmonary Function Tests FVC/PEF/PCF/MIP/MEP/SNIP
- Strength measures
  - Manual Muscle Testing
  - Quantitative Muscle Testing
  - myometry
  - Grip strength
- Patient reported OMs (PROM)
- QOL measures

PROGRESSION OF DISEASE OVER TIME



OM'S

- A single outcome is unlikely to cover the breadth of the disease from highly ambulant to wheelchair dependent with limited hand function
- Rates of change may vary for upper and lower limb function
- Careful balance between asking the impossible and the ultra easy
- Some OM have been developed that are specifically for ambulant and others for non-ambulant people, others are more general and can be used across all ages but tend to be less senstivie

PROGRESSIVE IMPROVEMENT IN UNDERSTANDING OM'S

- We understand more about the relationship between strength and function
- That the individual may not represent the population
- That OMs do not always correlate highly throughout the disease progression and that some OMs are more useful at different stages of disease
- Some OMs may be more relevant to measure function and others may be more sensitive to change and that the two are not necessarily the same but both may be required in a clinical trial
- That a tool box is required - with the right tool for the right job
- Don't put all your eggs in one basket!

DECISION FRAMEWORK FOR INCLUSION OF CLINICAL OUTCOME MEASURES IN PHASE II/III TRIALS

Outcome measure	Griffiths locomotor	Bayley III gross motor	North Star Amb. Ass. (NSAA)	Timed function tests	6MWT	Strength MMT	Strength quant.	Pulmonary function tests	Perf Upper Limb (PUL)	PROs-PODCI	PROs-PROM	Myotools
Clinical subgroups	0–8 years	1–42 mo.	3.5 years until non-amb	4 years until non-amb.	5 years until non-amb.	4 years to grade 2–	LE: 5–12 UE: 5–20+	7–20+ years	7–20+ years	3–21 years	7–20+ years	5+ years
Conceptual framework fits DMD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reliability	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Validation with other measures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	In progress	✓
Normative ranges	✓	✓	✓	✓	✓	✓	In progress	✓	In progress	✓	In progress	✓
Ongoing natural history studies	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Multicentre studies	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Responsiveness to treatment	?	?	✓	✓	✓	✓ or (-)	✓ or (-)	✓ If age ≥ 10	?	?	?	In progress
Clinical meaningfulness	?	?	✓	✓	✓	✓	?	✓	✓	✓	✓	In progress

The table shows the application of outcome measures relevant for DMD in relation to age and validation status (✓). To be validated (?).

Lynn *et al. Neuromuscul Dis* 2014;25:96–105

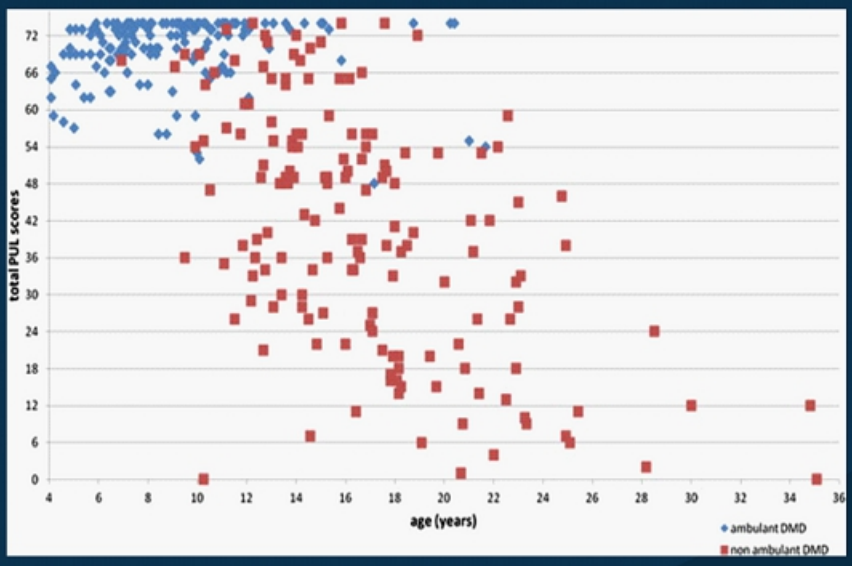
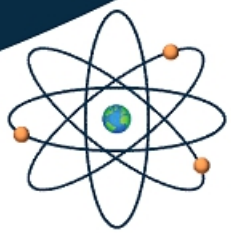


Fig. 2 Total PUL scores in ambulant (blue) and non ambulant (red) DMD patients plotted according to age.

Pane et al. 2014 http://dx.doi.org/10.1016/j.nmd.2013.11.014

AMBULATORY ASSESSMENTS

NSAA/ 6 MWT/ TIMED FUNCTION TESTS



Advancing
Trial
Outcome
Measures
International Ltd

LOSS OF AMBULATORY FUNCTION OCCURS IN A PREDICTABLE WAY

- Unable to jump, hop and run
- Gowers' sign with standing
- Loss of standing from the floor
- Loss of lie to sit
- Loss of stair climbing
- Loss of ability to stand from a chair
- Loss of ability to walk independently (10 meter walk/run; 6MWD)
- Loss of standing in place

North Star Ambulatory Assessment

•Developed taking into consideration all the functional milestones and activities that are clinically meaningful in DMD

•A 10-point change in the linearised scale is clinically meaningful, e.g.

90–80 = can no longer hop
50–40 = inability to rise independently from the floor
21–11 = loss of ability to stand still and upright

6MWD, 6-minute walk distance

North Star Ambulatory Assessment

Activity	Instructions to patient	Start position/test detail	Comments
1. Stand	Can you stand up tall for me for as long as you can and as still as you can	Feet should be close together and heels on the ground if possible. Arms by sides. NO shoes should be worn.	Best done on the floor rather than on a mat. Whichever is chosen maintain consistency through repeated testing sessions. Minimum count of 3 seconds to score 2
2. Walk	Can you walk from A to B (state to and where from) for me.	Walk without shoes/socks on. Should be enough of a distance to observe 'normal gait' for that subject	A value judgement needs to be made in scoring – if the patient generally toe walks but occasionally gets heels flat, or can on request but doesn't usually, they should score 1
3. Stand up from chair	Stand up from the chair keeping your arms folded if you can	Starting position 90º hips and knees, feet on floor/supported on a box step.	A size-appropriate chair or height adjustable plinth should be used. Arms should be kept crossed throughout the activity to score 2
4. Stand on one leg - Right	Can you stand on your right leg for as long as you can?	Minimum count of 3 seconds to score 2. NO shoes should be worn.	Best done on the floor rather than on a mat. Whichever is chosen maintain consistency through repeated testing sessions.
5. Stand on one leg - Left	Can you stand on your left leg for as long as you can?	Minimum count of 3 seconds to score 2. NO shoes should be worn.	Best done on the floor rather than on a mat. Whichever is chosen maintain consistency through repeated testing sessions.
6. Climb box step - right	Can you step onto the top of the box using your right leg first?	Stands facing the box step. Step should be approximately 15cm high	Support may be provided by the use of a height adjustable plinth, or, if not available a 'neutral' hand from the therapist.
7. Climb box step - left	Can you step onto the top of the box using your left leg first?	Stands facing the box step. Step should be approximately 15cm high	Support may be provided by the use of a height adjustable plinth, or, if not available a 'neutral' hand from the therapist.
8. Descend box step - Right	Can you step down from the box using your right leg first?	Stands on top of the box step facing forwards. Step should be approximately 15cm high	Support may be provided by the use of a height adjustable plinth, or, if not available a 'neutral' hand from the therapist.
9. Descend box step - Left	Can you step down from the box using your left leg first?	Stands on top of the box step facing forwards. Step should be approximately 15cm high	Support may be provided by the use of a height adjustable plinth, or, if not available a 'neutral' hand from the therapist.
10. Gets to sitting	Can you get from lying to sitting?	Starting position supine on a mat. No pillow should be used under head	If patient turns into prone or towards the floor to work their way into sitting 1 should be scored
11. Rise from floor	Get up from the floor using as little support as possible and as fast as you can (from supine)	Starting position supine with arms by sides, legs straight. No pillow to be used	Activity should be attempted without use of furniture in the first instance. Do not note time if a chair has to be used.
12. Lifts head	Lift your head to look at your toes keeping your arms folded	Supine on a mat. No pillow should be used.	Ask patient to keep arms crossed over chest during the activity to avoid self-assist. Also ask to look at toes to ensure neck is flexed – should be a chin to chest manoeuvre.
13. Stands on heels	Can you stand on your heels?	Standing on the floor. No shoes to be worn.	Watch for inversion. If substantial inversion but forefeet are still lifted – score 1. If only inversion with lateral border of foot still on the ground score 0.
14. Jump	How high can you jump?	Standing on the floor, feet fairly close together.	Want height, not forward movement. Small amount of forward movement acceptable
15. Hop right leg	Can you hop on your right leg?	Starting position standing on floor on right leg. No shoes should be worn.	Needs obvious floor clearance to score 2
16. Hop left leg	Can you hop on your left leg?	Starting position standing on floor on right leg. No shoes should be worn.	Needs obvious floor clearance to score 2
17. Run (10m)	Run as fast you can to……(give point)	A straight 10m walkway should be clearly marked in a quiet department or corridor. A stopwatch should be used to time the walk. Be consistent as to whether shoes are worn or not. Ensure safety of patient. They should self select speed after being asked to go 'as fast as they can'.	'Duchenne jog' - not a true run (there probably IS a double support phase), but more than a walk. Typically characterized by excessive use of arms, trunk rotation, substantial 'waddle'. No real 'push-off'

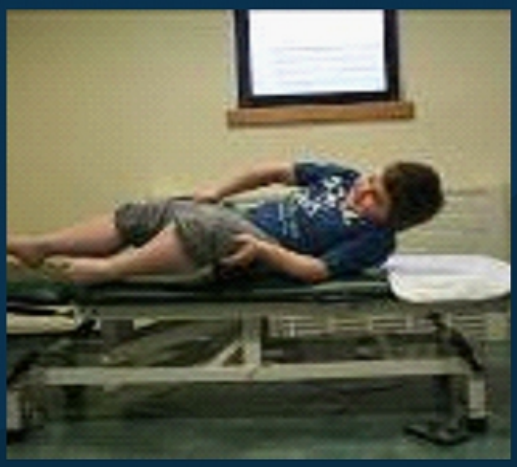
NORTH STAR AMBULATORY ASSESSMENT

Sit to stand

Descend step

Jump

Gets to sit



6MWT

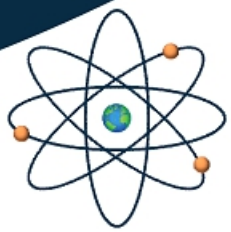
- Adapted/validated for DMD (McDonald 2010)
- Regulator approved
- Minimally clinically important difference considered 30 meters
- Correlates with:
  - Knee extension strength
  - 10 minutes continuous step activity
- Number of challenges conducting test, especially with younger and more cognitively impaired patients
  - Shorter fixed distance tests under development

6-MINUTE WALK TEST

- 6MWT: popular primary outcome measure
- Other primary outcome measures exist, including 4-stair climb
- E Mercuri showed that if the distance walked in 6 minutes is at least 330 metres at baseline, the risk of losing ambulation within 2 years is significantly reduced
  (Mazzone *et al. PLOS One* 2013;8:e52512)
- And that for every 30 metre incremental decrease in the baseline 6MWT, the percentage of patients who remain ambulatory over the following 2 years decreases substantially
- However, a $50 incentive can significantly improve the test result
  (Alfano *et al. Neuromuscul Dis* 2014;24:860)

6MWT, 6-minute walk test

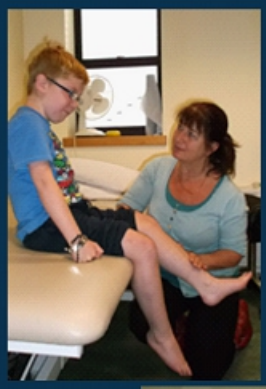
STRENGTH TESTING



Advancing
Trial
Outcome
Measures
International Ltd

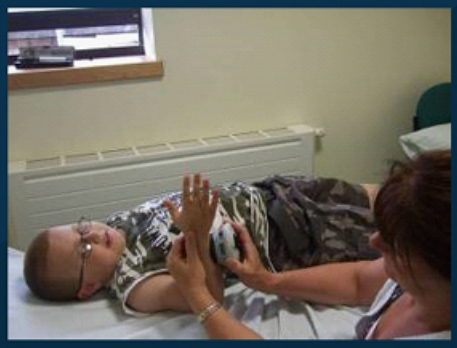
MANUAL MUSCLE TESTING (MMT)

- MRC scale
- Reliable in patients with NMD when conducted by experienced evaluators
- Issues with differentiating between higher grades:
  - Importance of practice and experience
- Cheap/easy to conduct



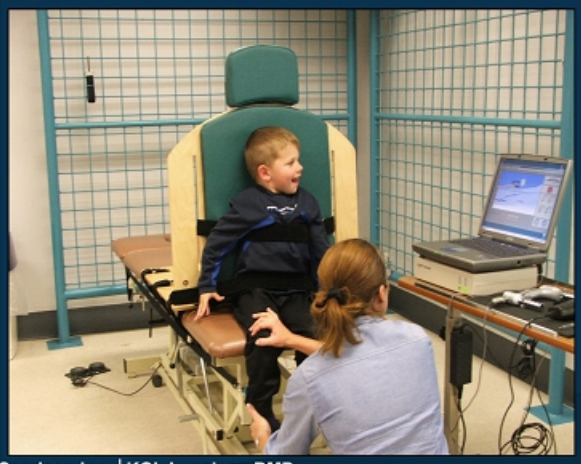
HAND HELD MYOMETRY

- Variety of myometers available:
  - Microfet
- Make test
- Explanation/demonstration/practice
- Key muscle groups
  - Standardised testing positions and myometer placement
- Best of 3"valid" efforts
  - Repeat if patient moves out of position or doesn't gives a submaximal effort
- Encouragement +++
  - As you would for any effort dependent test

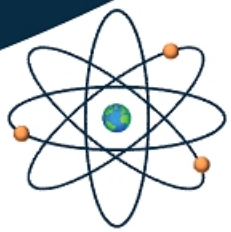


QUANTITATIVE MUSCLE TESTING SYSTEMS

CINRG CQMS



ASSESSMENTS FOR NON-AMBULANT



Advancing
Trial
Outcome
Measures
International Ltd

NON-AMBULATORY MILESTONES – EGEN KLASSIFIKATION SCALE

- The EK scale is a good clinical tool – each question can help to formulate requirements for treatment or adaptations
- Highly clinically meaningful but less sensitive to change over the short term

- Loss of ability to turn in bed
- Loss of head control
- Loss of trunk mobility
- Loss of ability to control wheelchair

EK, Egen Klassifikation

Need for a tool that could assess upper limb function across the lifespan

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY REVIEW

A critical review of functional assessment tools for upper limbs in Duchenne muscular dystrophy

ELENA S MAZZONE[1]* | GESSICA VASCO[1]* | CONCETTA PALERMO[1] | FLAVIANA BIANCO[1] | CARMEN GALLUCCIO[1] | VALERIA RICOTTI[2] | ANTONELLA D CASTRONOVO[1] | MARIA SOLE DI MAURO[1] | MARIKA PANE[1] | ANNA MAYHEW[3] | EUGENIO MERCURI[1,2]

1 Department of Paediatric Neurology, Catholic University, Rome, Italy. **2** Dubowitz Neuromuscular Centre, Institute of Child Health, London; **3** Institute of Genetic Medicine, Newcastle Upon Tyne, UK.

Correspondence to Dr Eugenio Mercuri at Child Neurology Unit, Policlinico Gemelli, Largo Gemelli, 8, 00168 Rome, Italy. E-mail: eumercuri@gmail.com
*The first two authors contributed equally to the study.

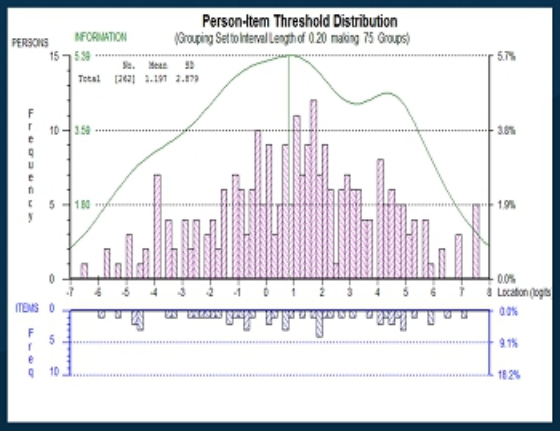
Developmental Medicine & Child Neurology
Volume 54, Issue 10, pages 879–885, October 2012

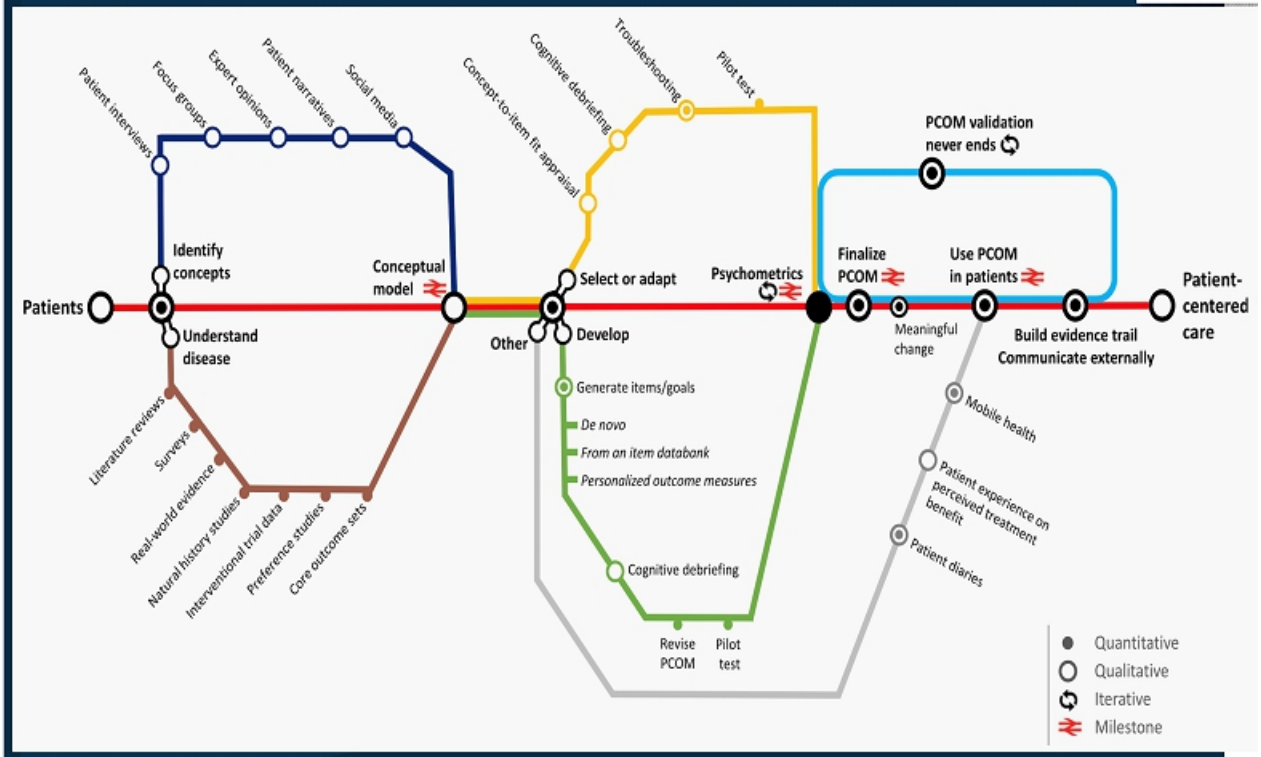
Prior to this publication in 2012 there were numerous workshops and discussions on existing measures

NON-AMBULATORY MILESTONES

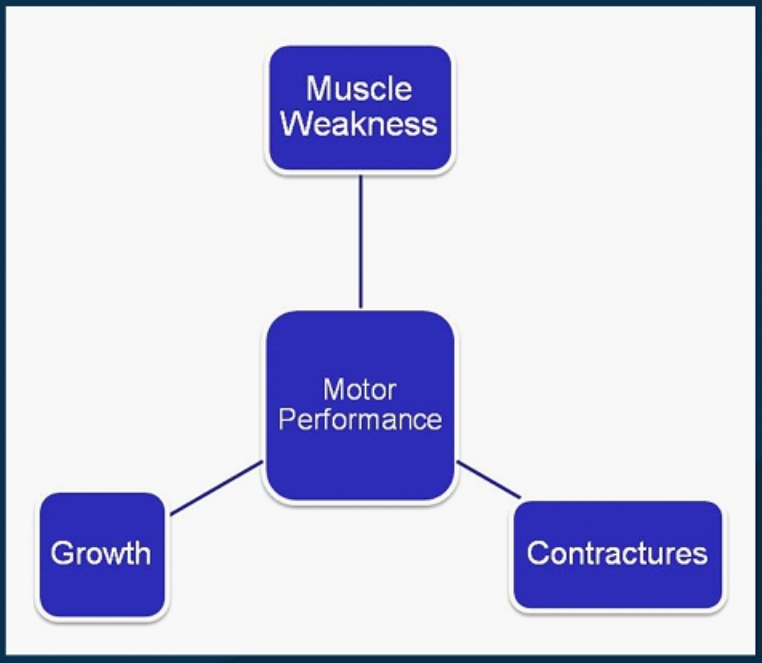
- Loss of ability to reach over head
- Loss of ability to reach the scalp
- Loss of ability to self-feed without adaptations (hand to mouth)
- Loss of ability to place hands to table top
- Loss of ability to use a computer (distal hand function)

- Performance of Upper Limb
- Developed using Rasch Analysis and clinical sensibility

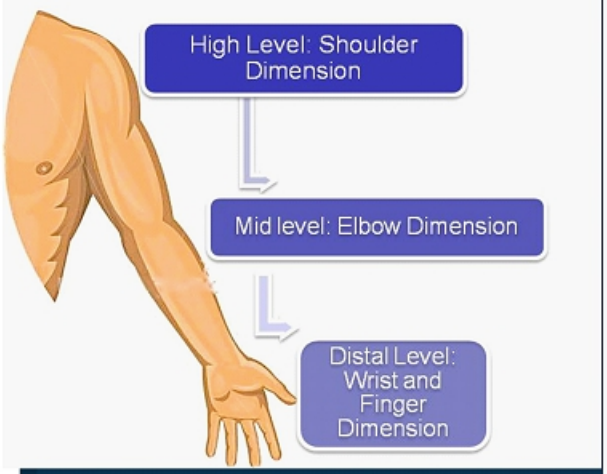


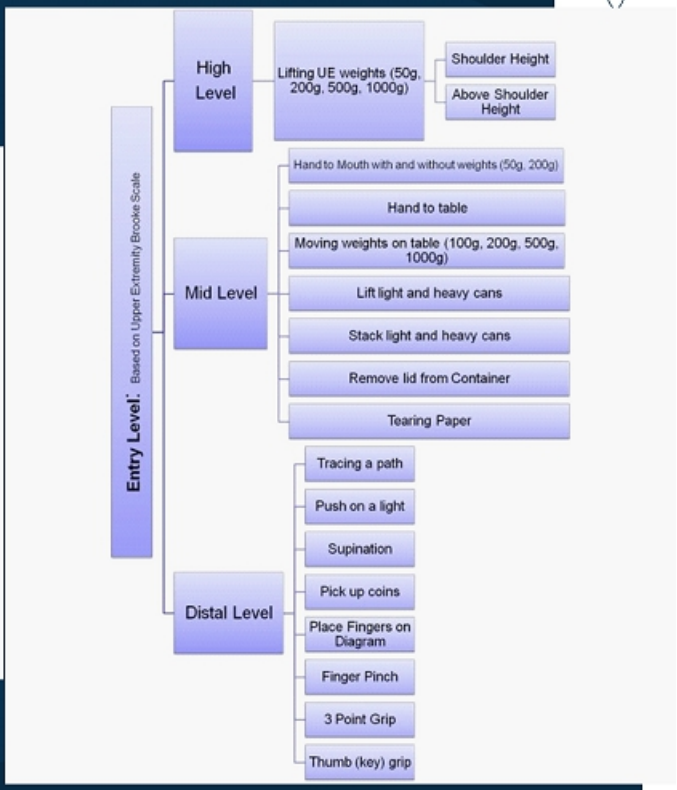

Patient interviews
Focus groups
Expert opinions
Patient narratives
Social media
Concept-to-item fit appraisal
Cognitive debriefing
Troubleshooting
Pilot test
PCOM validation never ends
Identify concepts
Conceptual model
Select or adapt
Psychometrics
Finalize PCOM
Use PCOM in patients
Patient-centered care
Patients
Understand disease
Other
Develop
Meaningful change
Build evidence trail
Communicate externally
Literature reviews
Surveys
Real-world evidence
Natural history studies
Interventional trial data
Preference studies
Core outcome sets
Generate items/goals
De novo
From an item databank
Personalized outcome measures
Cognitive debriefing
Revise PCOM
Pilot test
Mobile health
Patient experience on perceived treatment benefit
Patient diaries
Quantitative
Qualitative
Iterative
Milestone

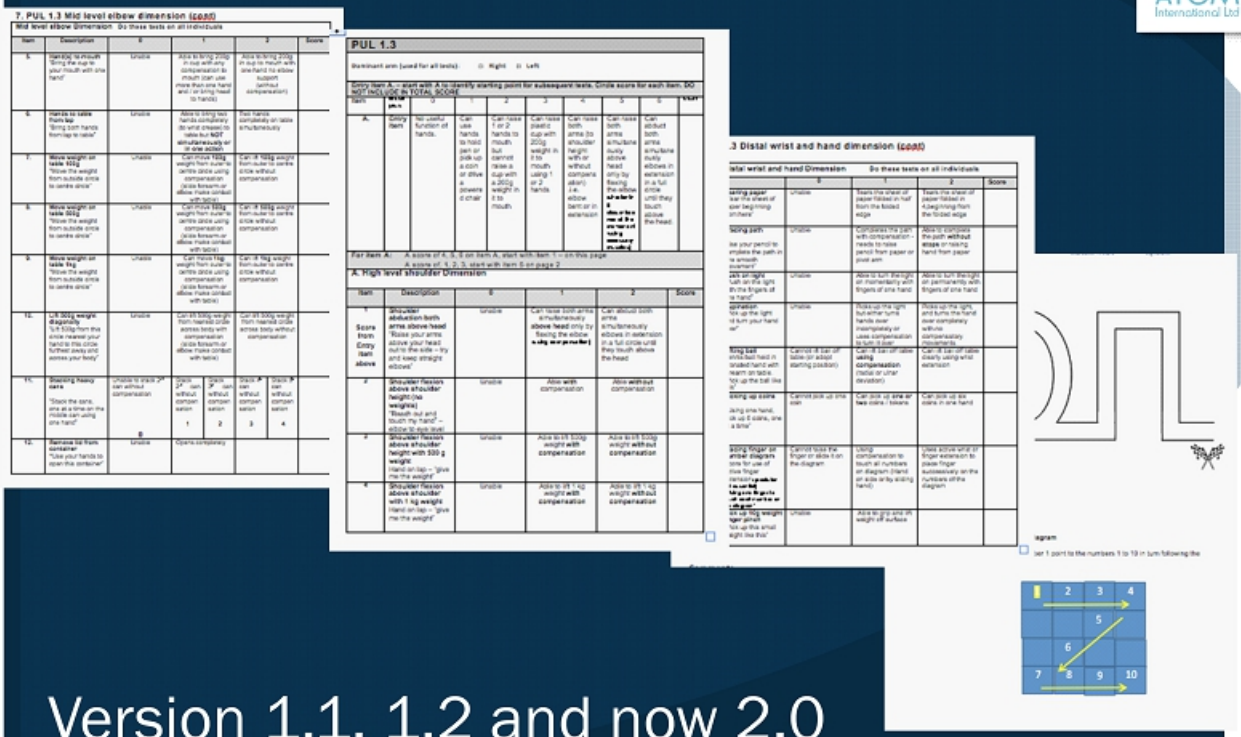
CONCEPTUAL FRAMEWORK



DIMENSIONS+ ITEMS







Version 1.1, 1.2 and now 2.0

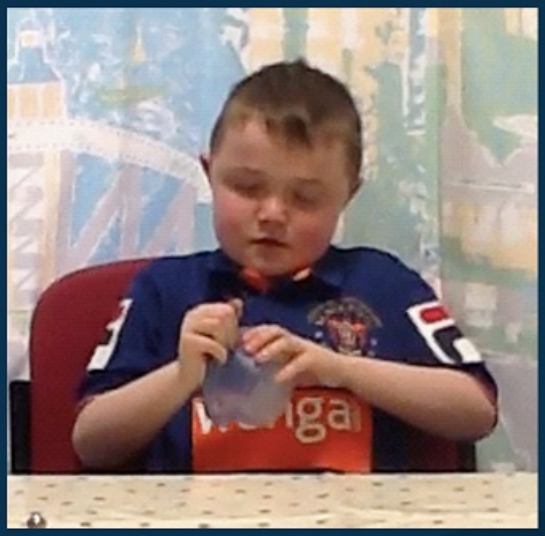
PUL ITEMS

Shoulder domain

mid level- domain

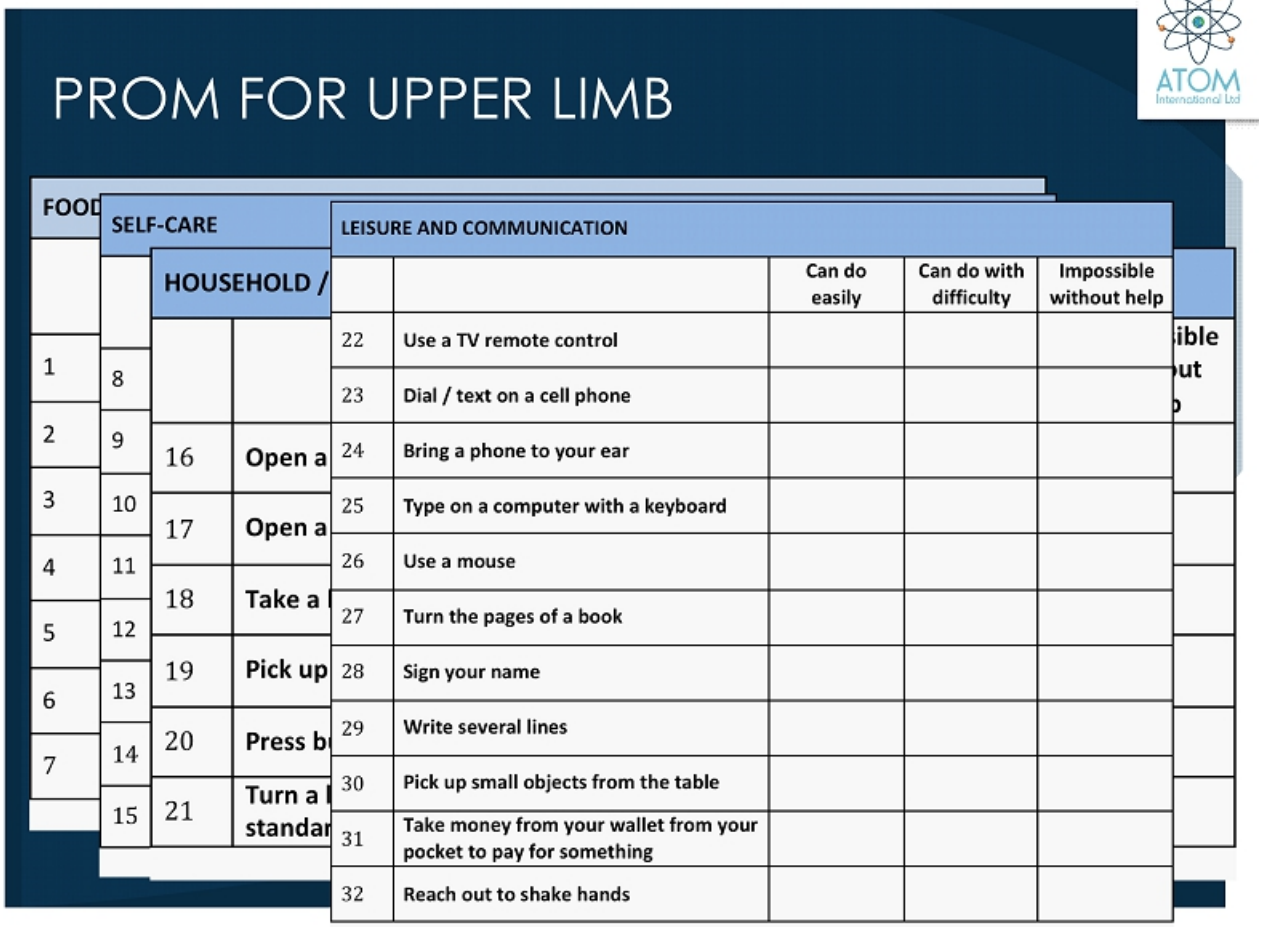
PUL ITEMS

Bilateral activity



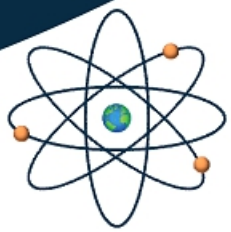
Distal domain

PROM FOR UPPER LIMB



FOOD	SELF-CARE		LEISURE AND COMMUNICATION			
		HOUSEHOLD /			Can do easily	Can do with difficulty	Impossible without help
1	8		22	Use a TV remote control			
2	9	16	23	Dial / text on a cell phone			
3	10	17	24	Bring a phone to your ear			
4	11	18	25	Type on a computer with a keyboard			
5	12	19	26	Use a mouse			
6	13	20	27	Turn the pages of a book			
7	14	21	28	Sign your name			
	15		29	Write several lines			
			30	Pick up small objects from the table			
			31	Take money from your wallet from your pocket to pay for something			
			32	Reach out to shake hands			

RESPIRATORY FUNCTION TESTS

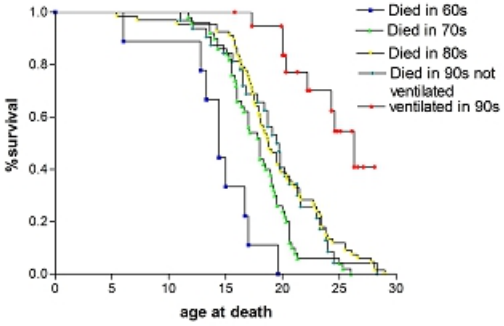


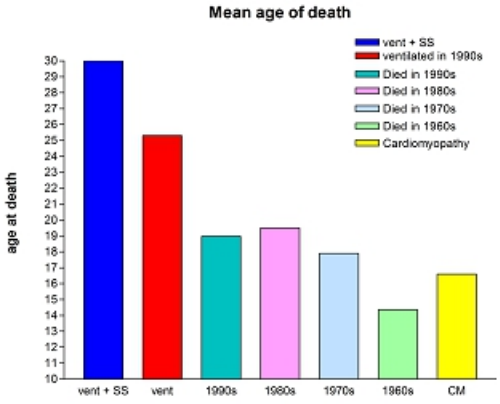
Advancing
Trial
Outcome
Measures
International Ltd

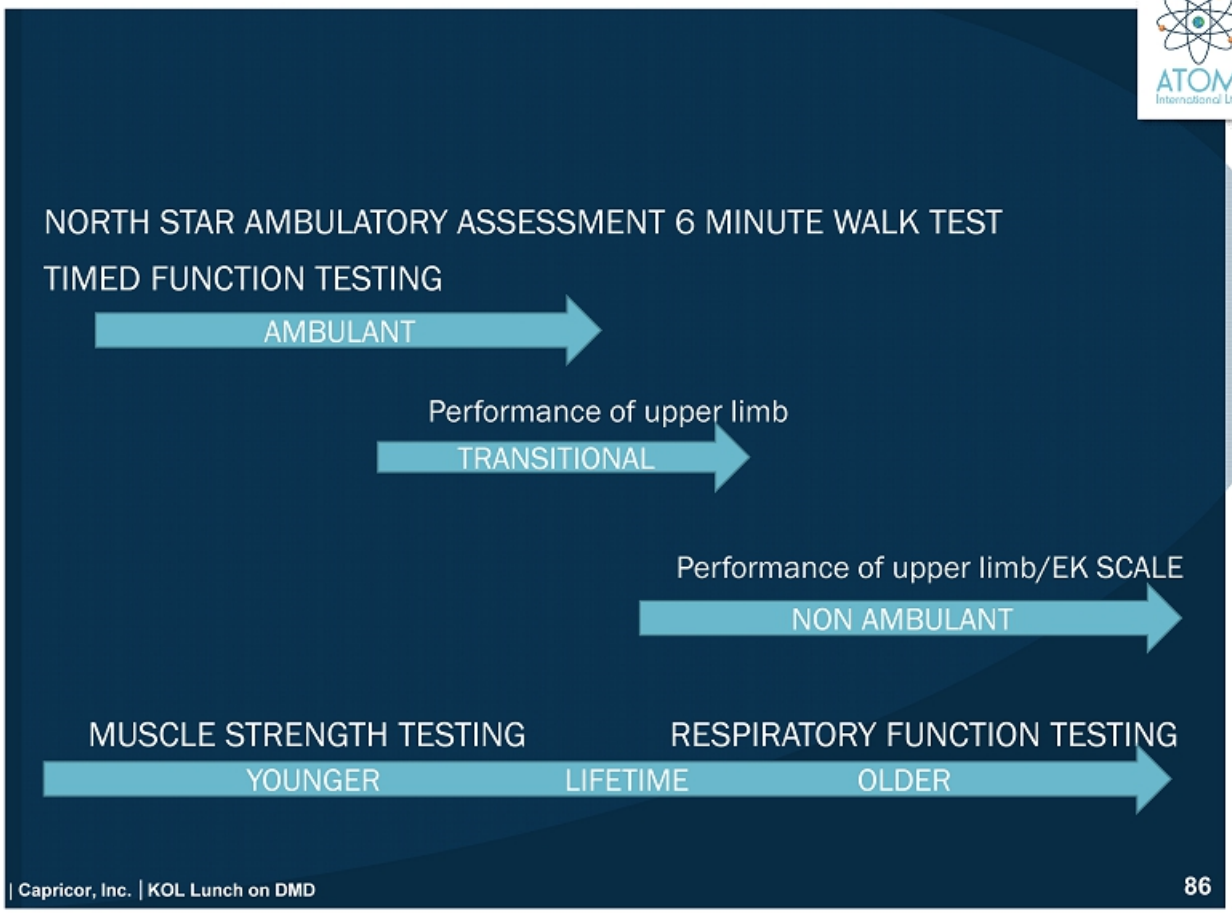
RESPIRATORY FUNCTION

- Respiratory function (RF) and survival are strongly associated
- Most frequently, both in clinics and in trials, forced vital capacity is measured
- Milestones include time to ventilation and death
- Other commonly used measures are maximal inspiratory pressure, maximal expiratory pressure, and maximal sniff nasal inspiratory pressure, Peak cough flow, peak expiratory flow
- Measurement in non-ambulant boys is particularly relevant but improving RF in ambulant boys is a goal for therapy

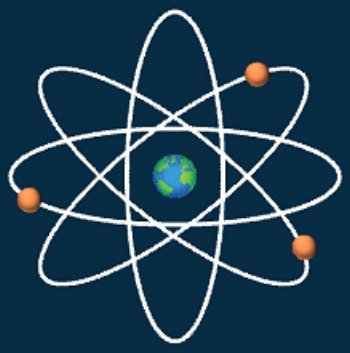
Survival in Duchenne muscular dystrophy: 1967–2002






NORTH STAR AMBULATORY ASSESSMENT 6 MINUTE WALK TEST
TIMED FUNCTION TESTING
AMBULANT
Performance of upper limb
TRANSITIONAL
Performance of upper limb/EK SCALE
NON AMBULANT
MUSCLE STRENGTH TESTING
RESPIRATORY FUNCTION TESTING
YOUNGER
LIFETIME
OLDER

Thank you



Advancing
Trial
Outcome
Measures
International Ltd

Duchenne Muscular Dystrophy: Overview, Natural History, and Unmet Need

Craig McDonald, MD Professor of PM&R and Pediatrics
Study Chair CINRG Duchenne Natural History Study
University of California Davis Medical Center
UCDAVIS CHILDREN'S HOSPITAL Sacr
Neuromuscular Research Center Discovering Creates Hope

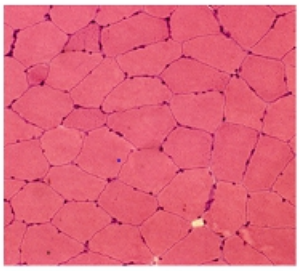
Disclosures

- **Consulting work on Duchenne muscular dystrophy clinical trials for**
  - Capricor Therapeutics, Inc.
  - Catabasis Pharmaceuticals, Inc.
  - PTC Therapeutics
  - Sarepta
  - Prosensa
  - Pfizer
  - Eli Lilly
  - Bristol Myers Squib
  - Italfarmaco
  - Mitobridge
  - Cardero Therapeutics

Duchenne Muscular Dystrophy Is a Devastating Progressive Disease with Significant Unmet Need

- **Rare recessive x-linked disorder caused by mutation in the *DMD* gene**
- **Leads to dystrophin deficiency in muscle tissue and subsequently chronic activation of NF-kB**
- **Progressive disease that leads to devastating deteriorating muscle strength and early death**
- **Only supportive treatments are available**
  - Physical therapy
  - Orthopedic Surgery for contractures and scoliosis
  - Assisted ventilation
  - Heart failure management (e.g., afterload reduction)
  - Off-label / labeled use of corticosteroids
  - Eteplirsen in the US for exon-51 mutations
  - Ataluren in the EU for nonsense mutations

Disease Progression Is Characterized by Muscle Damage and Replacement of Muscle Fibers with Fat Infiltration and Sclerosis, Resulting in Loss of Function



Normal muscle tissue

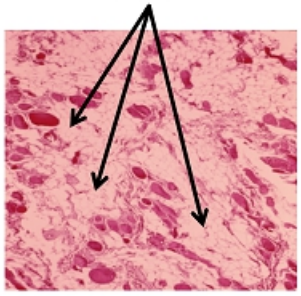
Lack of dystrophin cause shearing of the sarcolemma and activation of NF-kB, increasing cellular damage and muscle fiber loss

Progressive loss of muscle fibers and replacement of functional muscle units by fat infiltration and sclerosis

Loss of function; walking capacity preserved in spite of significant loss of muscle strength due to

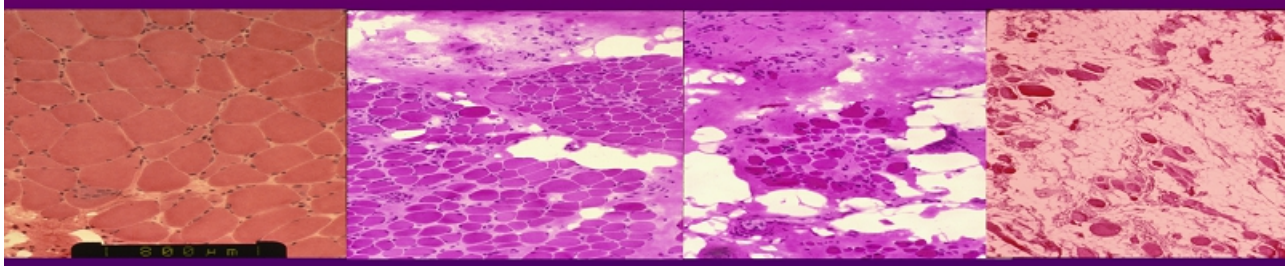
- Reserve capacity in muscle function
- Biomechanical compensations

Fat infiltration, sclerotic changes and loss of muscle fibers

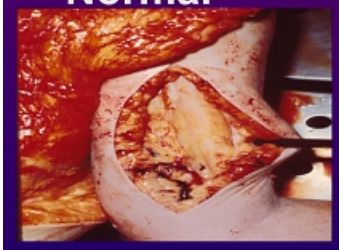


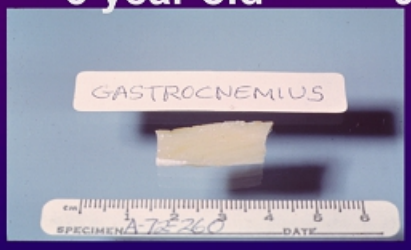
Muscle tissue 19 year old DMD patient Post-Mortem

Loss of Muscle Fiber in DMD:



Normal 3 year old 9 year old Post-





19 year old (Post-Mortem in Year 1990)

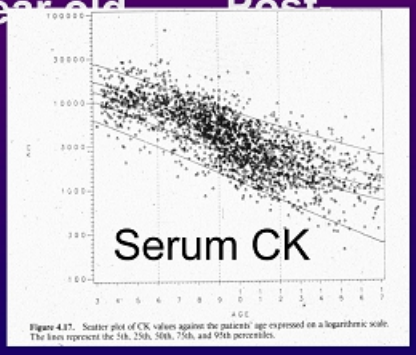
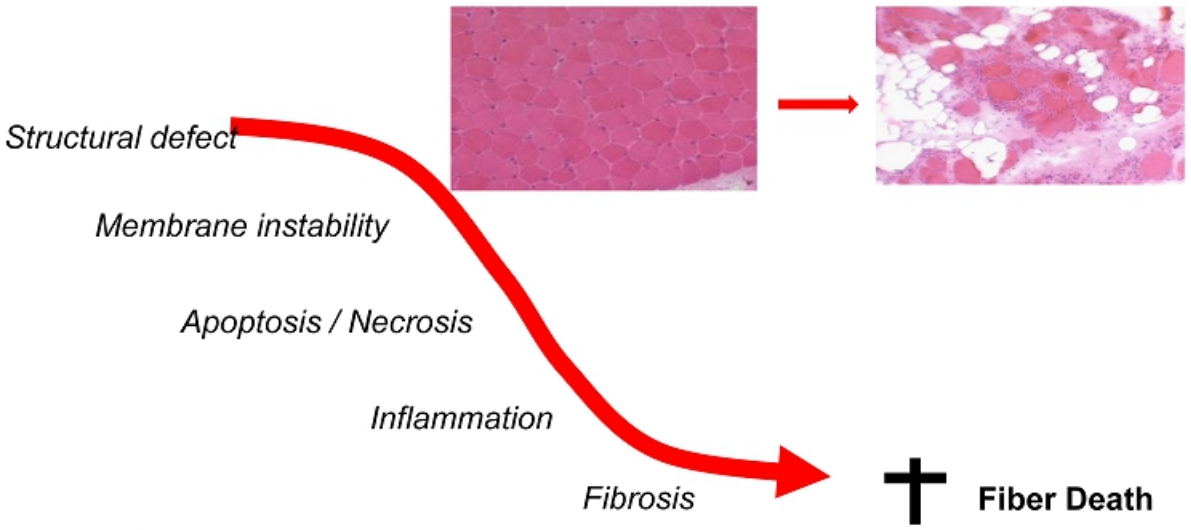


Figure 4.17. Scatter plot of CK values against the patients' age expressed on a logarithmic scale. The lines represent the 5th, 25th, 50th, 75th, and 95th percentiles.

DMD pathomechanism

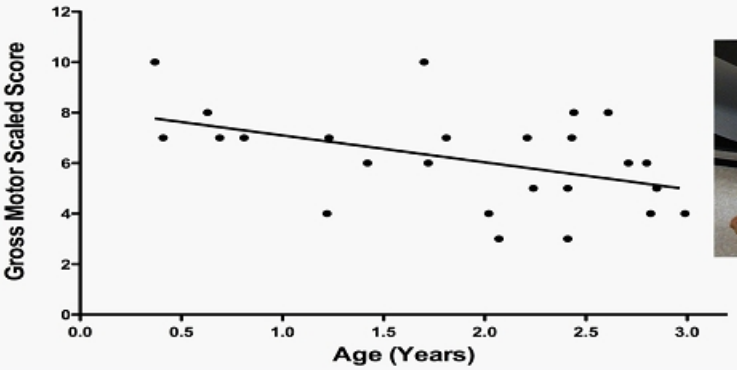


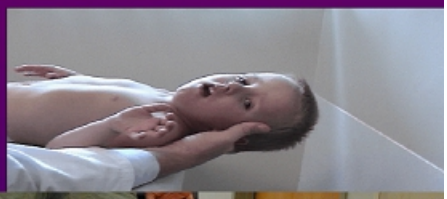
Adapted from
Engvall & Wewer (2003) FASEB 17:1579

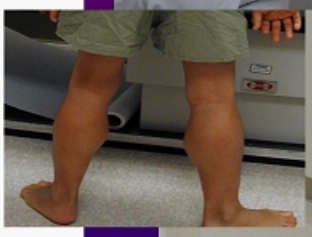
Motor and Cognitive Assessment of Infants and Young Boys with Duchenne Muscular Dystrophy:

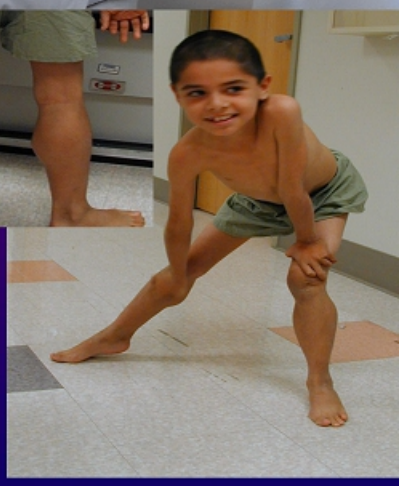
Results from the Muscular Dystrophy Association DMD Clinical Research Network. Connolly et al.
(n=25; 1.8±0.8 years)

Figure 2A. Bayley-III Gross Motor Scaled Scores versus Age



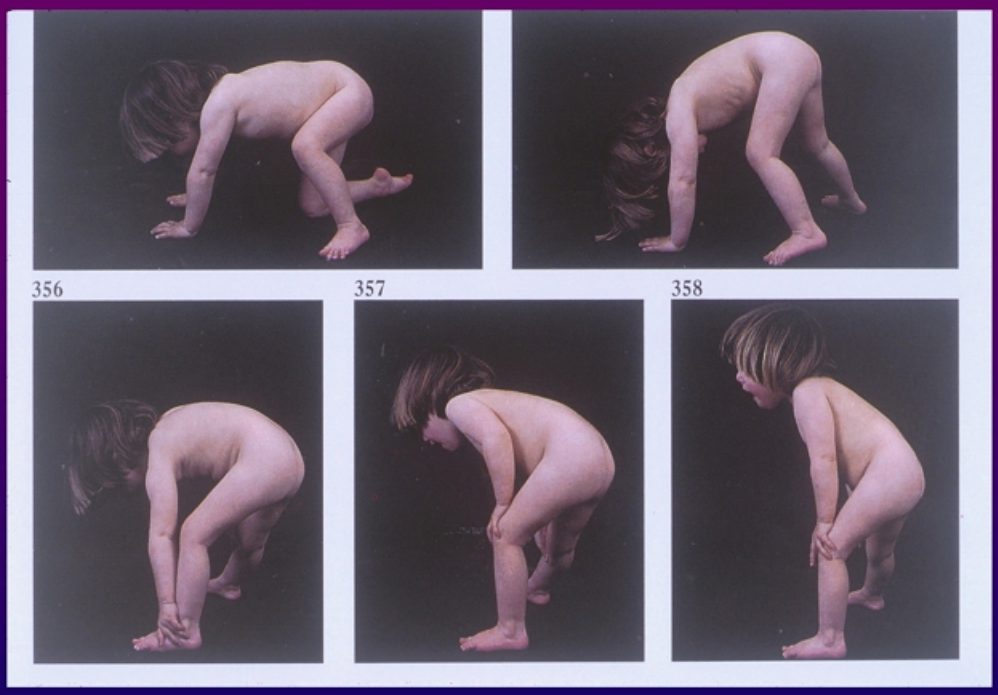






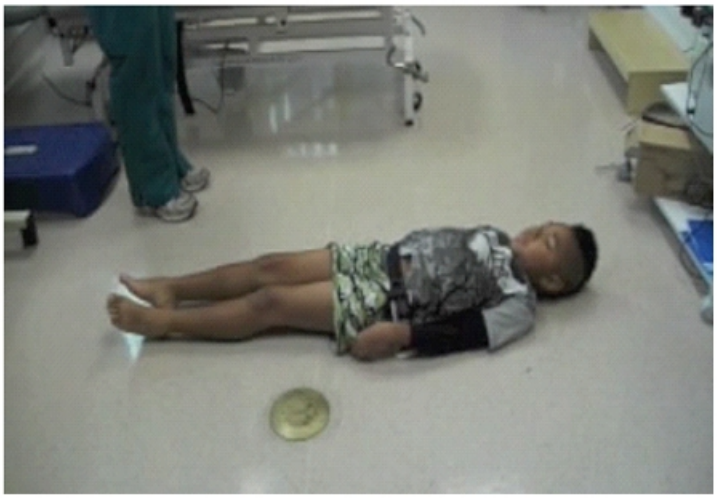
- Neck Flexion Weakness one of earliest clinical signs

- 2 years, 10 months


356
357
358

Early Gower's Sign (2 yr 10 mo)

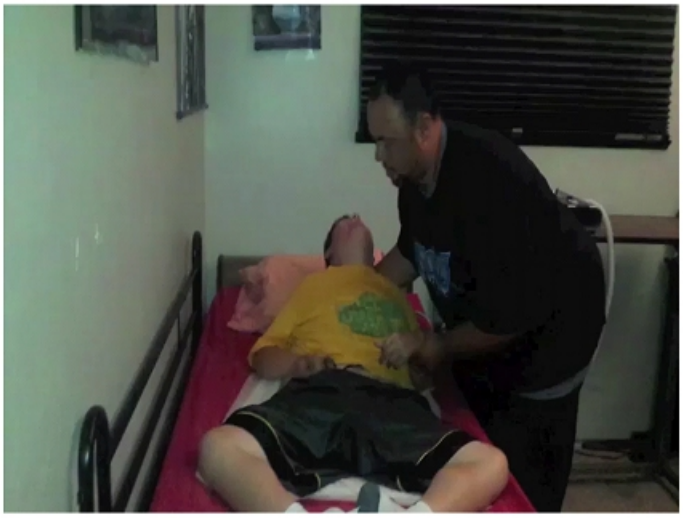
9 Year Old Boy: Baseline Assessment
Rise From Floor 7 Sec; 6MWD 414 Meters



Case Study: 9 Year Old Boy: Assessment in 2007
Rise From Floor 13 Sec; 6MWD 330 Meters

DMD Patient
Age 9.5
10-meter Walk/Run = 6.5 s
6MWD = 330 Meters

Case Study: Burden of Disease

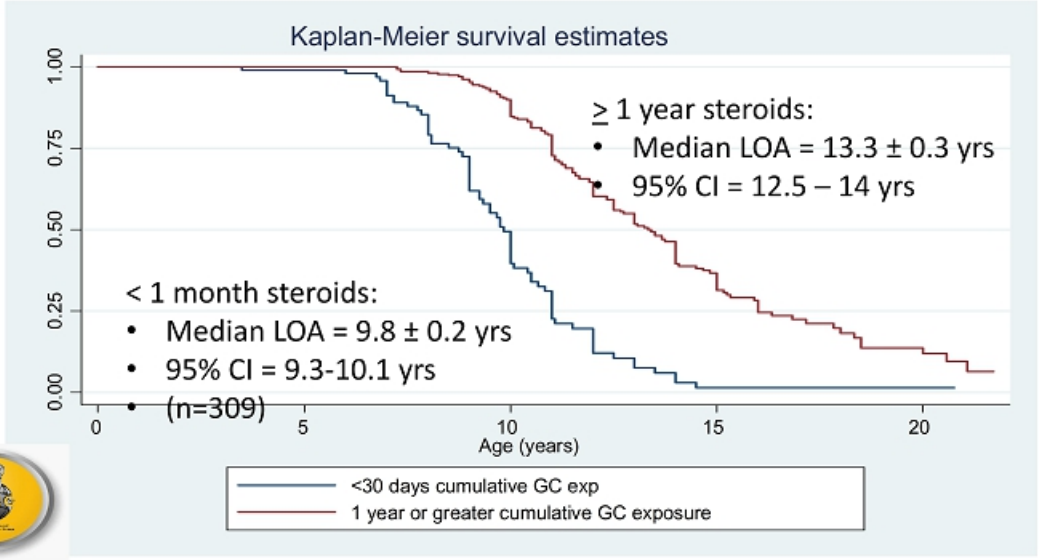


Same Young man
aged 17
Assessment 2015

Contemporary Treatments that have Affected the Natural History of Disease Progression and Survival in DMD

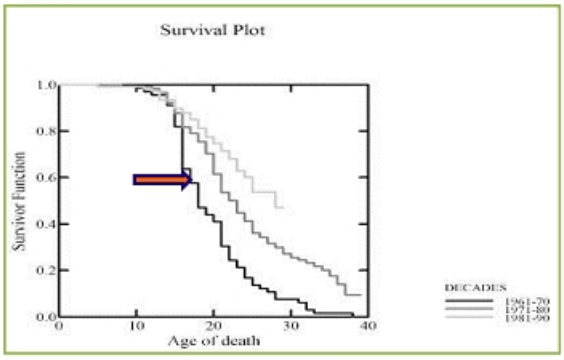
1. **Glucocorticoids**
2. **Management of spine deformity**
   - Glucocorticoids
   - Timely spine surgery for curves >30 to 40 degrees
3. **Pulmonary management**
   - Airway clearance strategies/mechanical cough assistance
   - Noninvasive ventilation
4. **Cardiac management**
   - Early afterload reduction (e.g., ACE inhibitors)
   - Recognition and management of heart failure

CINRG Data: Loss of Ambulation
(all mutation subtypes and steroid use, N = 309)



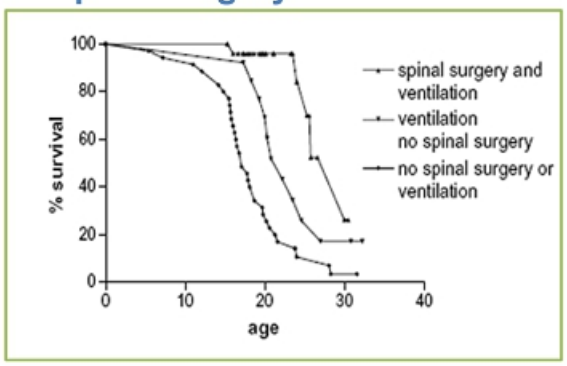
There Has Been a Changing Natural History in DMD Over the Last 4 Decades Affecting *Survival*

1960s
No Treatment



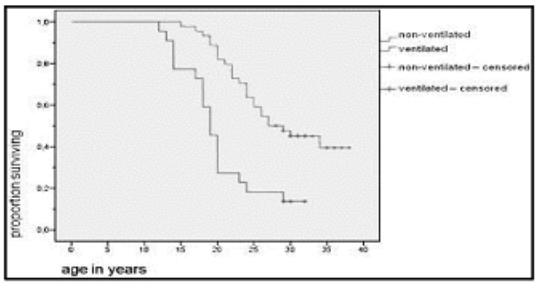
Passamano, et al. *Acta Myol.* 2012;31(2):121-125.

1970-1990
Spine Surgery & Ventilation



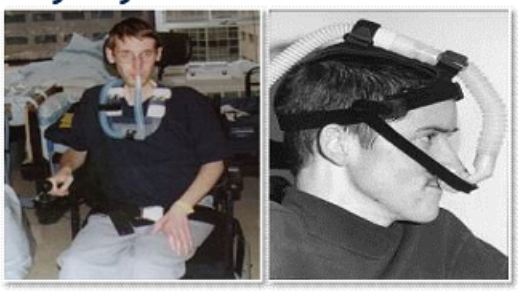
Eagle, et al. *Neuromuscul Disord.* 2007;17(6):470-475.

DMD Survival Affected Primarily by Ventilation



Rall and Grimm: Acta Myol. 2012 Oct;31(2):117-20.

- **Ventilation was recognized as a main intervention affecting survival**
- Ventilated median survival = 27.0 yr
- Without ventilation = 19.0 yr

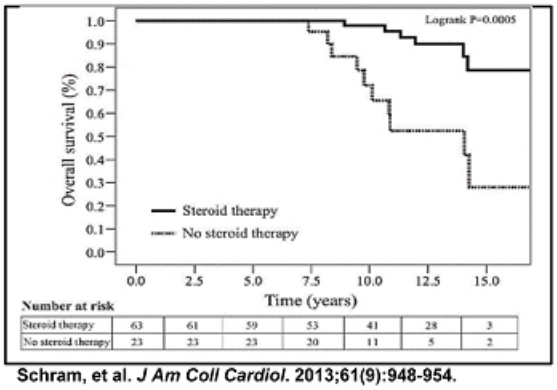


Passamano, et al. *Acta Myol.* 2012;31(2):121-125.

- **Ventilation was recognized as a main intervention affecting survival**
- Ventilated mean survival = 27.9 yr (range, 23 - 38.6 yr)
- Without ventilation = 17.7 yr (range, 11.6-27.5 yr)

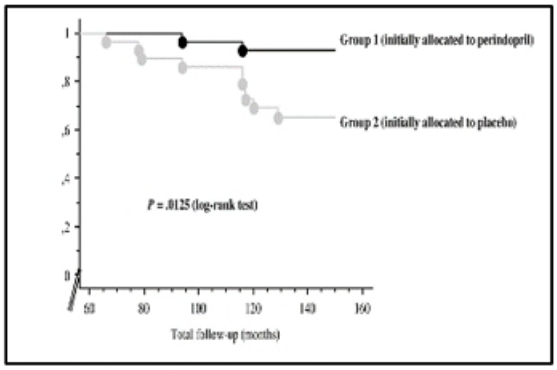
There Has Been a Changing Natural History in DMD Over the Last 4 Decades Affecting *Survival*

1980s – Present
Glucocorticoids/Steroids



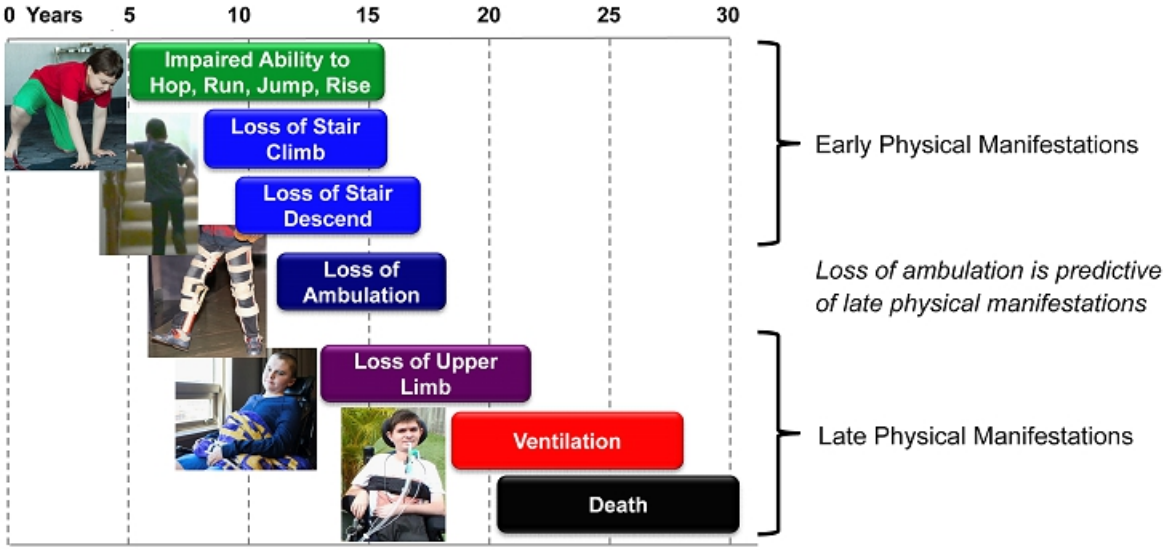
Schram, et al. *J Am Coll Cardiol.* 2013;61(9):948-954.

2000 - Present
Afterload Reduction With ACE Inhibitors

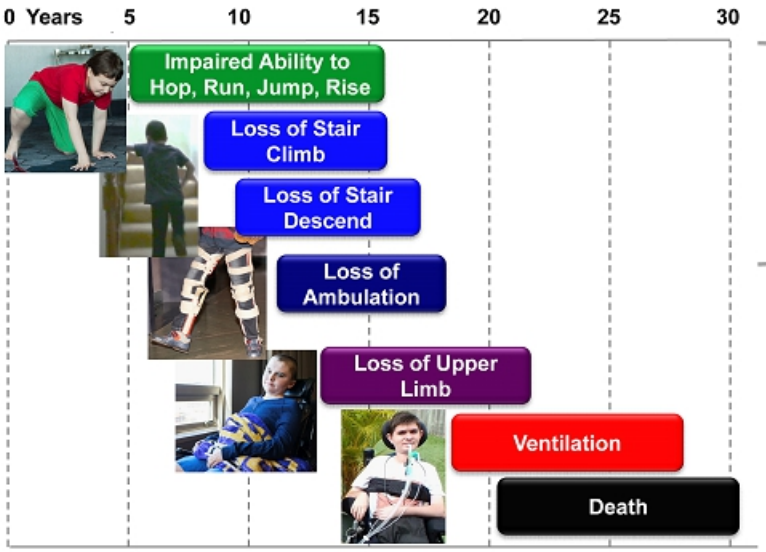


Duboc D, et al. *Am Heart J.* 2007;154(3):596-602.

DMD Progression is Sequential, Non-Linear and Irreversible



Measuring DMD Progression Requires Use of Multiple Outcome Measures



Endpoint Measures

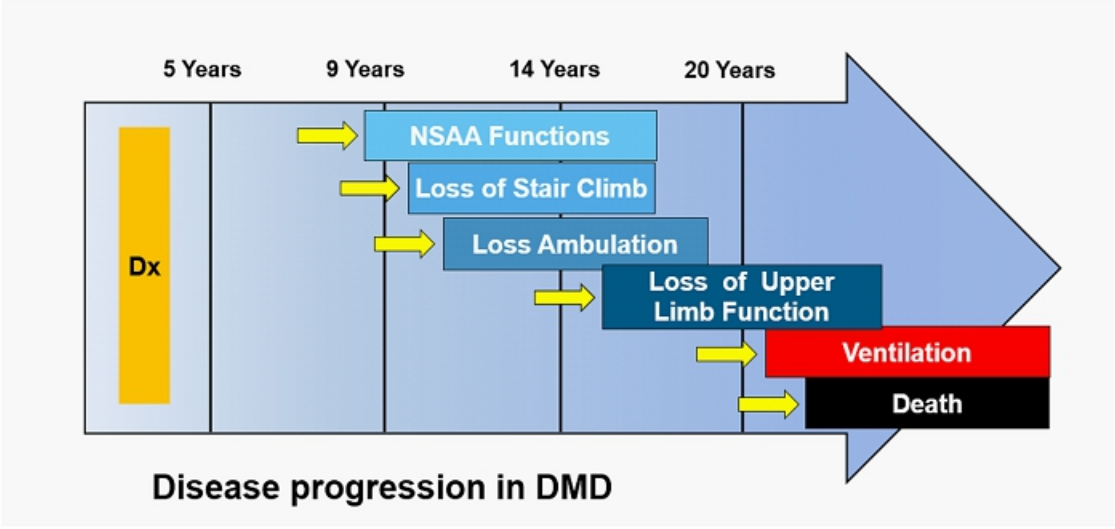
Muscle Function
- 6-minute walk test
- 4-stair climb
- 4-stair descend
- 10m walk / run

Disease Progression
- North Star Ambulatory Assessment (NSAA)
- Loss of Ambulation

Upper limb Impairment
- Brooke / EK Scales
- Performance of Upper Limb (PUL)

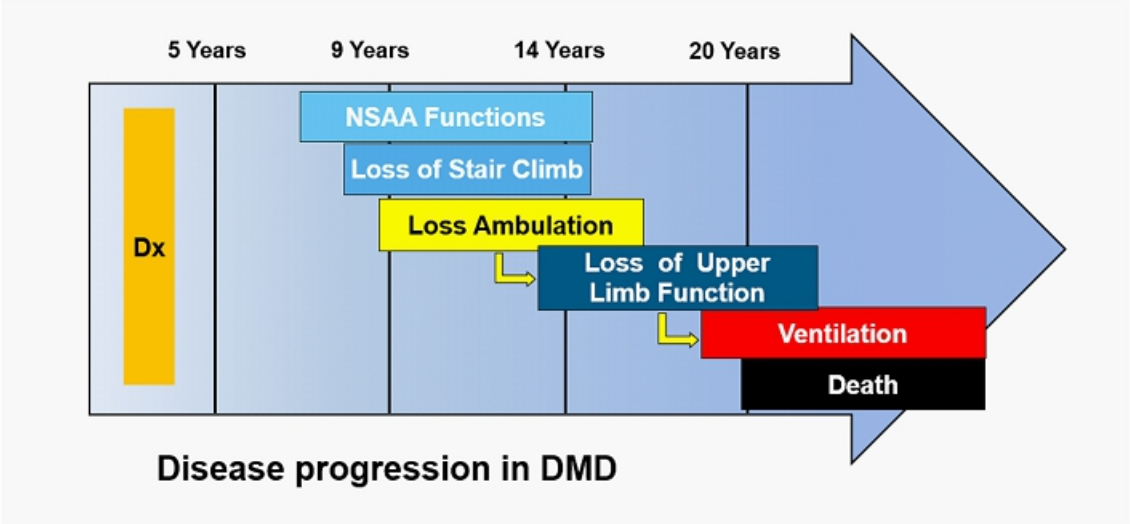
Pulmonary Function
- Forced vital capacity

Ataluren Preserves 6MWD, TFTs, NSAA and Predicts for Overall Delay in Disease Progression



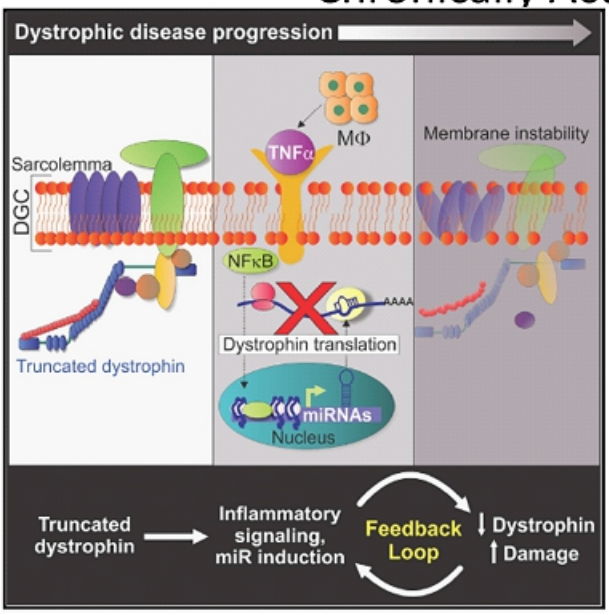
Adapted from Bushby, Connor. Clin Investig (Lond), 2011; McDonald, et al. Muscle Nerve. 2013

Loss of Ambulation Predicts for Subsequent Progression Milestones



Adapted from Bushby, Connor. Clin Investig (Lond), 2011; McDonald, et al. Muscle Nerve, 2013.

Glucocorticoids target NF-κB which is Chronically Activated in DMD



- miRNAs in muscle microenvironments cause variable dystrophin in muscular dystrophy
- miRNAs are elevated in dystrophic myofibers and increase with disease severity
- Inflammatory cytokines induce miRNAs, and antiinflammatories block their expression
- miRNAs provide a precision medicine target in dystrophy and exon skipping

THE LANCET

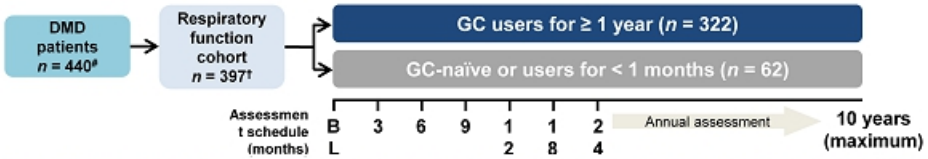
Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study

conform with journal style (with study descriptor after colon). Changes OK?]

*Craig M McDonald, Erik K Henricson, Richard T Abresch, Tina Duong, Nanette C Joyce, Fengming Hu, Paula R Clemens, Eric P Hoffman, Avital Cnaan, Heather Gordish-Dressman, and the CINRG Investigators**

CINRG-Duchenne Natural History Study: Prospective multicenter longitudinal observational study in DMD

The **largest natural history study conducted to date in DMD**[1-3]



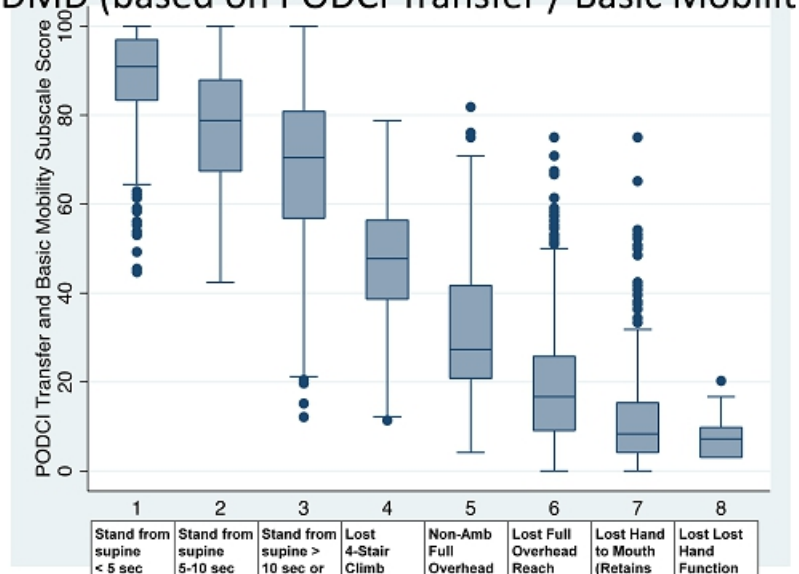
Key eligibility criteria : Clinical picture consistent with typical DMD, family history, and molecular diagnostic characterization of DMD-associated dystrophinopathy[1]

Patient demographics: Mean age at BL: 10.7; at last study visit:15.3 (total cohort)[1]

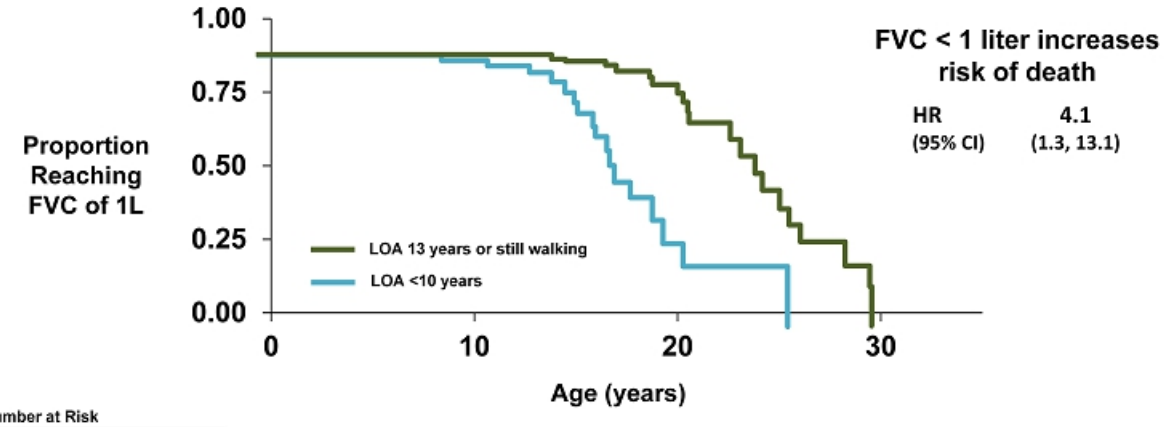
Assessments: Anthropometrics, functional assessments (e.g. Brooke's score, NSAA), timed functional tests (e.g. 6MWT, quantitative muscle strength), **pulmonary function (e.g. FVC, PEF)**, patient-reported outcomes/health-related QoL[2]

An initial cohort of patients was recruited between 2006 and 2009 (n = 340) and a second cohort of 4 – 8 year olds between 2012 and 2015; †Patients who provided at least one FVC assessment at age 7 or later
6MWT: 6-minute walk test; BL: Baseline; DMD: Duchenne muscular dystrophy; FVC: Forced vital capacity; GC: Glucocorticoid; NSAA: North Star ambulatory assessment; PEF: Peak expiratory flow; QoL: Quality of life
1. McDonald C, et al. Lancet, 2017; 2. McDonald C et al. Muscle Nerve 2013;48:32–54; 3. http://www.cinrgresearch.org/duchenne-natural-history// (Accessed May 2017).

8 Milestones that are clinically meaningful in DMD (based on PODCI Transfer / Basic Mobility)



Age at Loss of Ambulation Predicts Age at Onset of 1 liter FVC (CINRG Data)



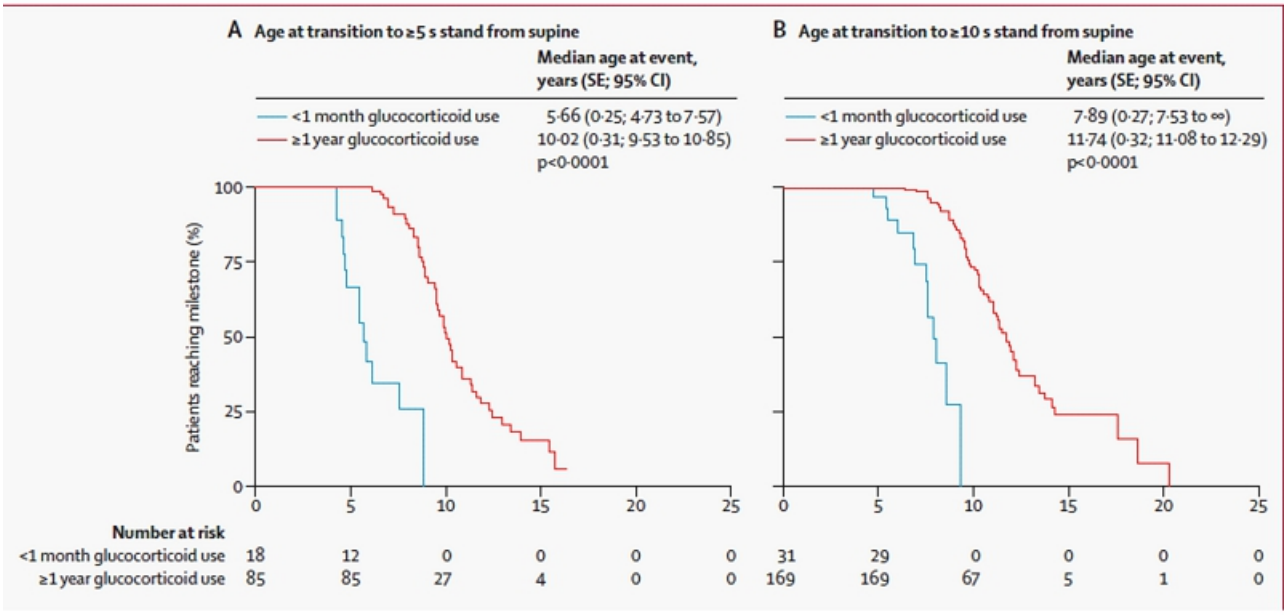
FVC < 1 liter increases risk of death

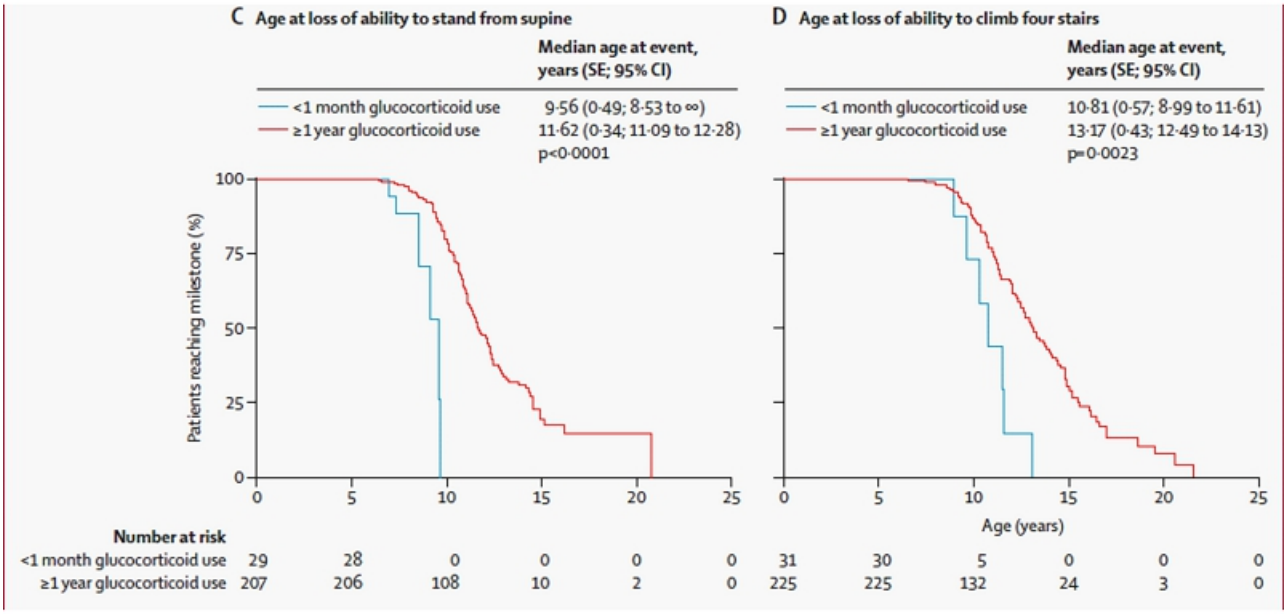
HR	4.1
(95% CI)	(1.3, 13.1)

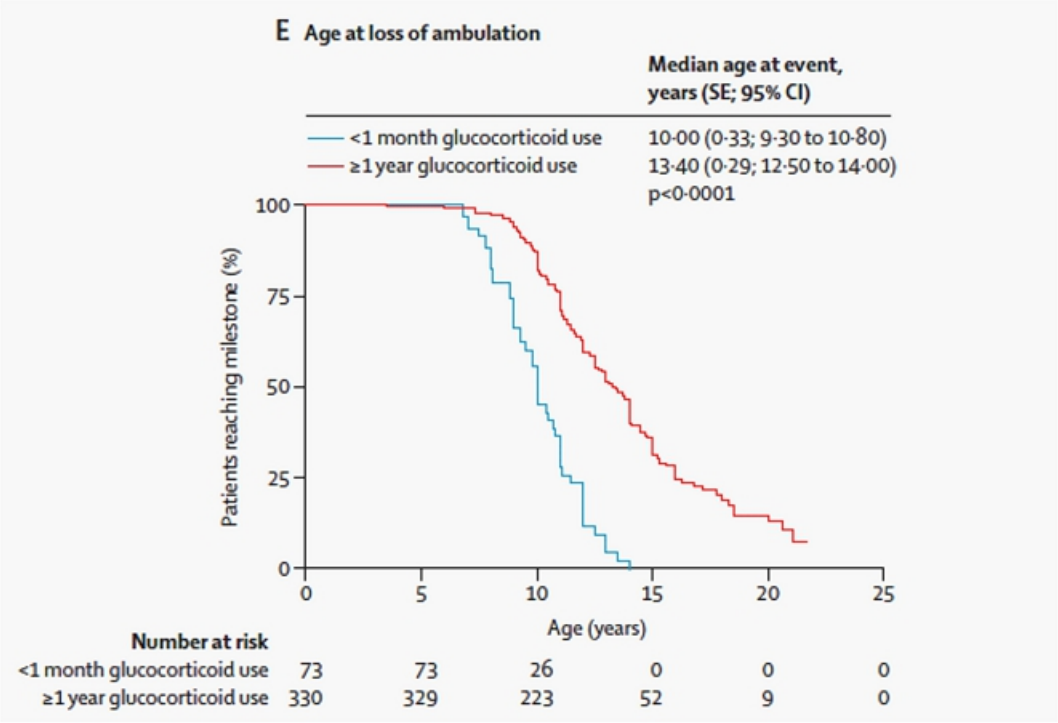
Number at Risk								
LOA <10 years	53	53	46	22	3	1	0	0
LOA 13 years or still walking	208	208	132	71	27	7	0	0

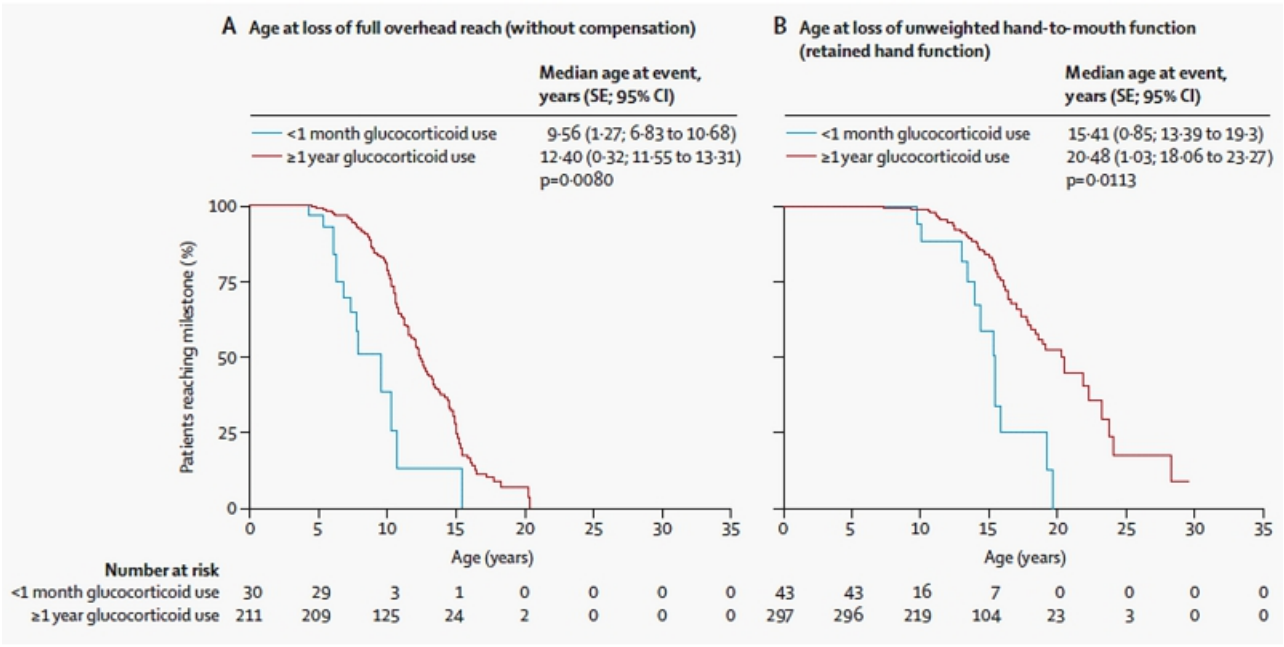
Ambulatory patients age 9-18 at study entry

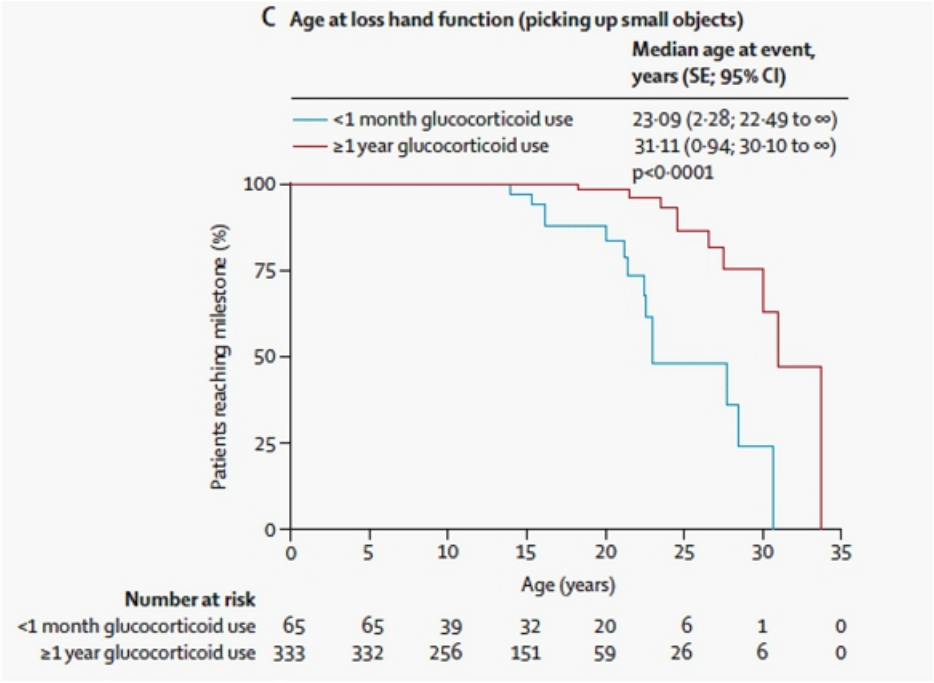
McDonald et al. Lancet, 2018


A Age at transition to ≥5 s stand from supine
Median age at event, years (SE; 95% CI)
<1 month glucocorticoid use 5·66 (0·25; 4·73 to 7·57)
≥1 year glucocorticoid use 10·02 (0·31; 9·53 to 10·85)
p<0·0001
B Age at transition to ≥10 s stand from supine
Median age at event, years (SE; 95% CI)
<1 month glucocorticoid use 7·89 (0·27; 7·53 to ∞)
≥1 year glucocorticoid use 11·74 (0·32; 11·08 to 12·29)
p<0·0001
Patients reaching milestone (%)
100
75
50
25
0
0 5 10 15 20 25
Number at risk
<1 month glucocorticoid use 18 12 0 0 0 0 31 29 0 0 0 0
≥1 year glucocorticoid use 85 85 27 4 0 0 169 169 67 5 1 0

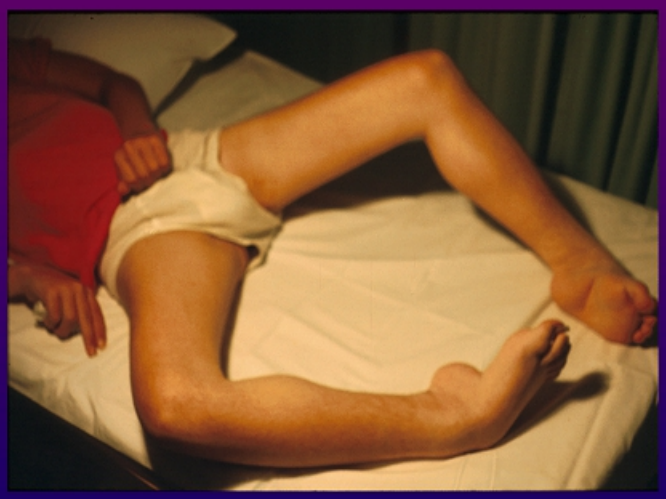

C Age at loss of ability to stand from supine
Median age at event, years (SE; 95% CI)
<1 month glucocorticoid use 9·56 (0·49; 8·53 to ∞)
≥1 year glucocorticoid use 11·62 (0·34; 11·09 to 12·28)
p<0·0001
Patients reaching milestone (%)
100
75
50
25
0
0 5 10 15 20 25
D Age at loss of ability to climb four stairs
Median age at event, years (SE; 95% CI)
<1 month glucocorticoid use 10·81 (0·57; 8·99 to 11·61)
≥1 year glucocorticoid use 13·17 (0·43; 12·49 to 14·13)
p=0·0023
0 5 10 15 20 25
Age (years)
Number at risk
<1 month glucocorticoid use 29 28 0 0 0 0 31 30 5 0 0 0
≥1 year glucocorticoid use 207 206 108 10 2 0 225 225 132 24 3 0


E Age at loss of ambulation
Median age at event, years (SE; 95% CI)
<1 month glucocorticoid use
10·00 (0·33; 9·30 to 10·80)
≥1 year glucocorticoid use
13·40 (0·29; 12·50 to 14·00)
p<0·0001
Patients reaching milestone (%)
100
75
50
25
0
0
5
10
15
20
25
Age (years)
Number at risk
<1 month glucocorticoid use 73 73 26 0 0 0
≥1 year glucocorticoid use 330 329 223 52 9 0

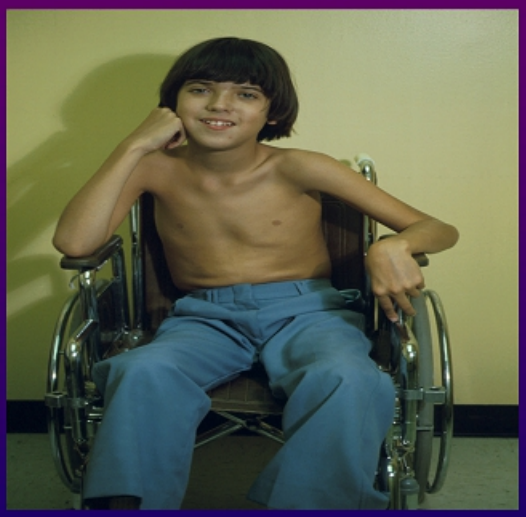

A Age at loss of full overhead reach (without compensation)
Median age at event, years (SE; 95% CI)
<1 month glucocorticoid use 9·56 (1·27; 6·83 to 10·68)
≥1 year glucocorticoid use 12·40 (0·32; 11·55 to 13·31)
p=0·0080
Patients reaching milestone (%)
100
75
50
25
0
0 5 10 15 20 25 30 35
Age (years)
B Age at loss of unweighted hand-to-mouth function (retained hand function)
Median age at event, years (SE; 95% CI)
<1 month glucocorticoid use 15·41 (0·85; 13·39 to 19·3)
≥1 year glucocorticoid use 20·48 (1·03; 18·06 to 23·27)
p=0·0113
0 5 10 15 20 25 30 35
Age (years)
Number at risk
<1 month glucocorticoid use 30 29 3 1 0 0 0 0 43 43 16 7 0 0 0 0
≥1 year glucocorticoid use 211 209 125 24 2 0 0 0 297 296 219 104 23 3 0 0


C Age at loss hand function (picking up small objects)
Median age at event, years (SE; 95% CI)
<1 month glucocorticoid use
23·09 (2·28; 22·49 to ∞)
≥1 year glucocorticoid use
31·11 (0·94; 30·10 to ∞)
p<0·0001
Patients reaching milestone (%)
100
75
50
25
0
0
5
10
15
20
25
30
35
Age (years)
Number at risk
<1 month glucocorticoid use 65 65 39 32 20 6 1 0
≥1 year glucocorticoid use 333 332 256 151 59 26 6 0

Static positioning leads to contractures in DMD



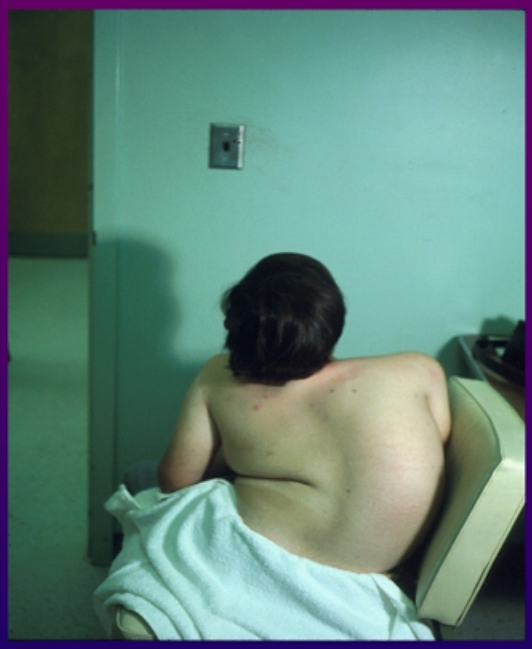
Static positioning leads to contractures in DMD



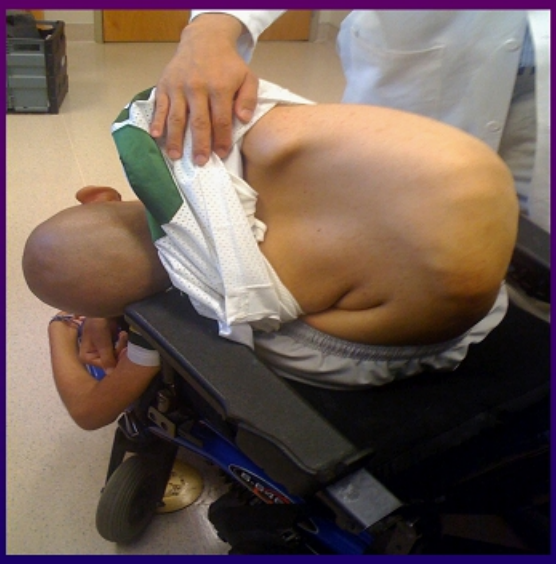
Scoliosis in DMD

Without steroids
80-90% require fusion

With steroids
20-30% require fusion



Quality of Life Implications for Untreated Spine Deformity

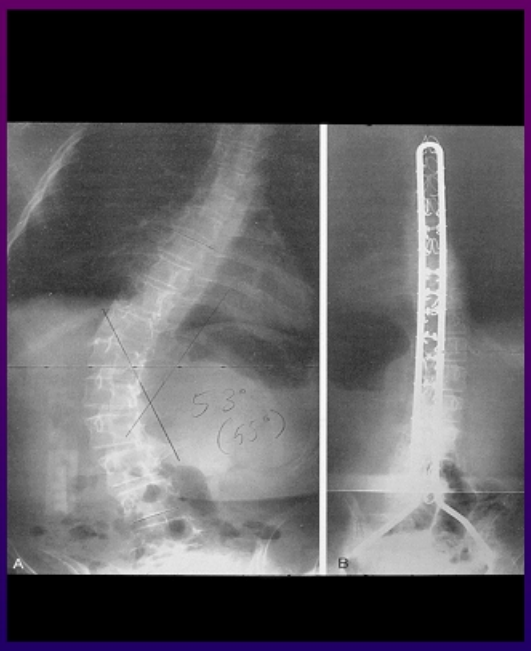


Spinal Fusion / instrumentation

Curve severity
20-40 degrees
optimal

FVC > 40% predicted
optimal

<30%FVC possible



Cardiomyopathy in DMD

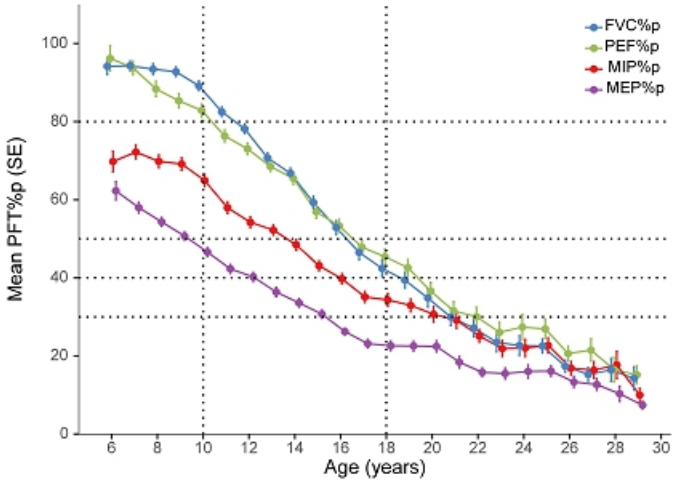
- Clinically significant cardiomyopathy rare before age 10; MRI changes common
- Fibrosis posterior wall left ventricle
- Myocardium exhibits abnormal contractility
- Arrythmias

- Treatment: Early ACE Inhibitors; Evidence Class Ia
  - enalapril, lisinopril, perindopril
- ? ARBs (Losartan)
- ? Beta Blockers (metoprolol, carvedilol)
- ? Aldosterone receptor antagonists (Spironolactone, eplerenone)
- ? Diuretics (Furosemide, Thiazides)

GI / Nutrition Issues

- Weight Gain around time of WC
- Late stage cachexia (need for G-tube/PEG)
- Gut hypomotility / gastroparesis
- Respiratory issues and GI procedures

Progression in pulmonary function loss by age

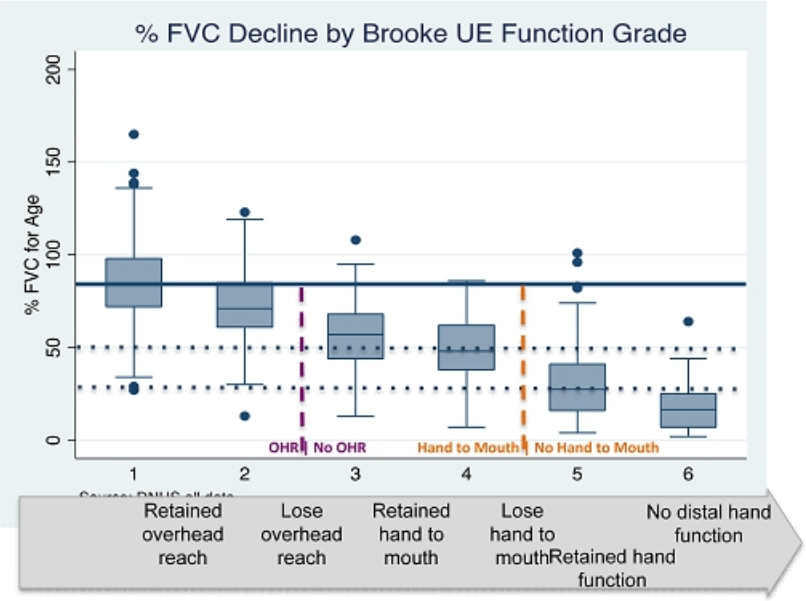


Source: CINRG DNHS.

Brooke upper extremity functional grade

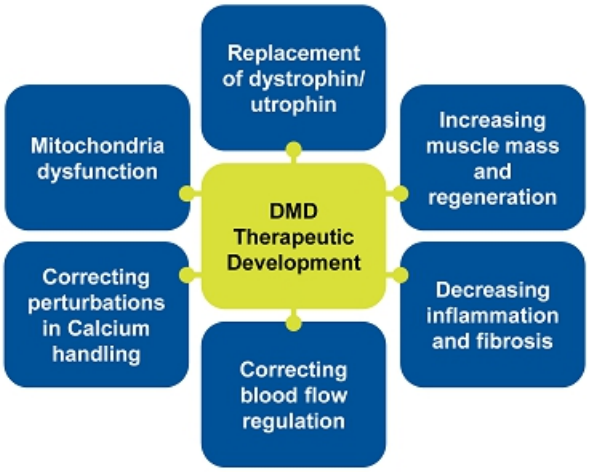
1	2	3	4	5	6
					
Starting with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head.	**Can raise arms above head** only be flexing the elbow or using accessory muscles.	**Cannot raise arms above head** but can raise an 8oz. glass of water to mouth.	**Can raise hands to mouth** but cannot raise an 8oz. glass of water to mouth.	**Cannot raise hands to mouth** but can use hands to hold a pen or pick up small objects from a table.	Cannot raise hands to mouth and has no functional use of hands.

%FVC decline by Brooke upper extremity functional grade

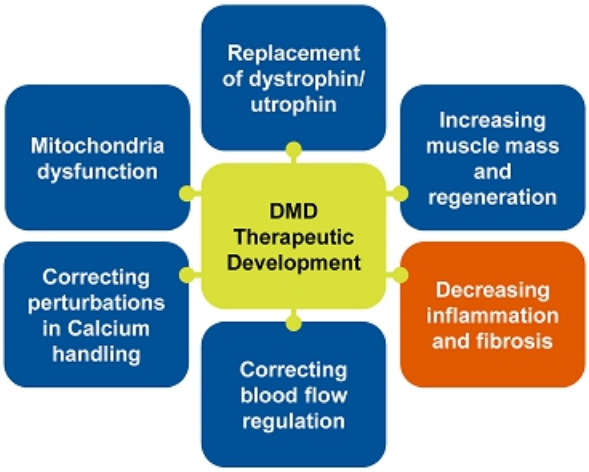


DHNS all data.

Development of State-of-the-Art Combination Therapies for Duchenne Muscular Dystrophy

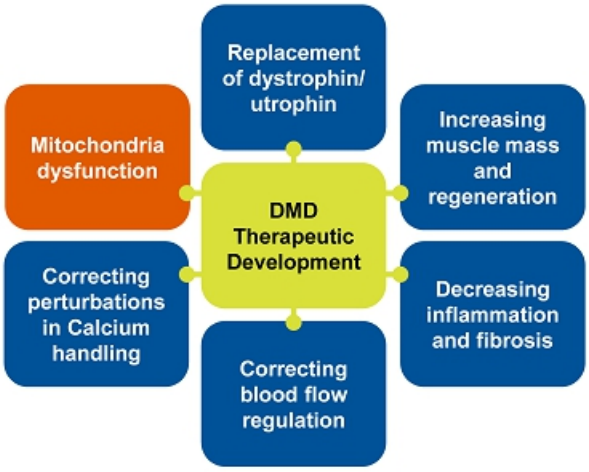


- Six main categories for therapeutic targets for DMD
- One addresses primary genetic defect; rest address downstream aspects of the pathogenesis
- Targeting any single pathway may be an approvable mono-therapy
- Future treatment paradigm may involve targeting multiple pathways to have greater patient impact



- **NF-κB Is Chronically Activated in DMD**
- Prednisone / Prednisolone
- Deflazacort (Emflaza, PTC)

- Current Trials:
- Vamorolone (ReveraGen)
  - Dissociative steroids (decreased Aes)
- Edasalonexent (Catabasis)
  - covalently linked salicylic acid (ASA) and docosahexaenoic acid (DHA),
  - synergistically leverages the ability of both compounds to intracellularly inhibit activated NF-κB



- **Therapeutics targeting mitochondrial health**
- Idebenone (Santhera)
- PPARδ agonist (Astellas)
- (+)-epicatechin (Cardero)

- ? CAP-1002

Summary

1. DMD natural history is changing, with significant preservation of motor, cardiac and pulmonary function, leading to increased survival over the past three decades
2. Cannot apply a single primary endpoint across the ambulatory or non-ambulatory spectrum of disease
3. Glucocorticoid use confers significant functional benefits but is limited by side effects in a significant proportion of the population
4. Progression of pulmonary impairment to critical thresholds is associated with increase in mortality
5. There is an area of high unmet need for patients both on and off steroids and in the in the 2nd decade for treatment of upper limb and pulmonary function loss
6. Emerging cell-based therapies and gene therapies offer exciting possibilities to significant impact DMD

Acknowledgements
CINRG Investigators

Cooperative International Neuromuscular Research Group

School of Medicine · UC Davis

Children's National Medical Center

NIDRR — National Institute on Disability and Rehabilitation Research

NICHD

SEN. PAUL D. WELLSTONE MD COOPERATIVE RESEARCH CENTER

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE

NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases
NATIONAL INSTITUTES OF HEALTH

Congressionally Directed Medical Research Programs
CDMRP

National Institute of Neurological Disorders and Stroke
National Institutes of Health

BRAVE Program

Benefit - Risk Assessment Valuation & Evidence

Understanding Patient and Caregiver Preferences

Ryan Fischer, SVP Community Engagement

Parent Project Muscular Dystrophy — JOIN THE FIGHT. END DUCHENNE.

Presented By: Pat Furlong

Why Collect Patient Preference Information (PPI)?

What can be learned?

Discovery ▶ Development ▶ Delivery

- Identify unmet medical needs
- Provide insight into symptom priorities
- Identify target treat profile
- Inform endpoint development
- Inform development of PRO's
- Understand risk tolerance, tolerance for uncertainty, and benefit preferences of patients and caregivers
- Understand preferences of sub-populations and subgroups

Stated Preference Methods

- Methods for collecting and analyzing data about what people think and feel
  - Special types of surveys that provide numbers to explain how important **'good'** things are in comparison to **'bad'** things.
  - How much **'bad'** will people accept for the **'good'**?

Pilot Preference Study

Community Engaged, Patient Centric Approach

Collaborator: Johns Hopkins School of Public Health (Dr. John Bridges)

Research Objectives:

- To understand meaningful preferences of caregivers for emerging Duchenne therapies
- Demonstrate a process by which a patient advocacy organization might develop scientific evidence on treatment preferences

Respondents: 119 Caregivers

Method: Best Worst Scaling

Attributes and Levels

- **Effect on muscle function**
  (none, slows, stops)
- **Gain in expected lifespan**
  (none, 2, 5 years)
- **Post-approval information**
  (none, 1, 2 years)
- **Nausea**
  (none, loss of appetite, loss of appetite and occasional vomiting)
- **Risk of bleeds**
  (none, risk of bleeding gums and increased bruising, risk of hemorrhagic stroke)
- **Risk of heart arrhythmia**
  (none, risk of harmless heart arrhythmia, risk of dangerous heart arrhythmia and sudden death)

Example Task

Best	Treatment	Worst
○	Slows the progression of weakness	○
○	2 year gain in expected lifespan	○
○	1 year of post-approval drug information available	○
○	Causes loss of appetite	○
○	Increased risk of bleeding gums and increased bruising	○
○	Increased risk of harmless heart arrhythmia	○

Choose the best thing in this treatment and the worst thing

Results – what we learned

- **Caregivers are willing to accept considerable risk in order to achieve stopping or slowing the progression of Duchenne (non curative)**
- Caregivers were willing to **trade off on longer lifespan** choosing **quality of life over quantity for benefit**
- Caregivers **prioritized the protection of muscle function** over all other attributes.
- There was **limits to their risk tolerance**, they would not accept a treatment with 2 serious risks.
- Caregivers **marginally valued post market data**

Study 2 – Pulmonary Treatment for Duchenne

Study Sponsor: Santhera

Collaborator: Johns Hopkins School of Public Health
(Dr. John Bridges)

Research Objectives:

Aimed to evaluate

- The degree to which pulmonary outcomes represent meaningful benefit
- Acceptable risk, harms, burden given the pulmonary benefit
- Degree to which preferences differed between caregivers and patients

Respondents: 96 caregivers, 59 patients

Method: Best Worst Scaling/Conjoint Analysis

Second Study on Lung Benefits

Most important to treat		Least important to treat
O	Frequent waking at night	O
O	Headaches	O
O	Feeling tired	O
O	Weaker ability to cough	O
O	Constipation	O

Best		Worst
O	Cough strength: **Maintained for 10 years**	O
O	Lung infections during your life: **Half as many**	O
O	Your chance for diarrhea: **1 in 2 (50%)**	O
O	How often you need a blood test: **2 times a year**	O

Would you choose this treatment?

☐ Yes ☐ No

Results – what we learned

- Patients and caregivers **prioritized pulmonary and cardiac benefit** among non skeletal treatment targets
- Patients and caregivers were **willing to accept risk and burden** in order to achieve pulmonary benefits.
- There was **little difference between** the preferences of **patients and caregivers**
- **Maintaining cough strength and less lung infections** represent meaningful benefits
- A drug profile similar to **Idebenone** presents a **favorable choice for a treatment**

Study 4: Treatment Preferences for Duchenne: A global study (2018)

Funding Support: Pfizer, Everylife Foundation

Collaborator: Johns Hopkins School of Public Health (Dr. John Bridges)
6 participating countries and patient group lead:

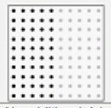
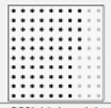
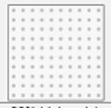
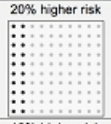
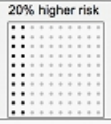
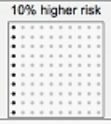
USA – *PPMD*
UK – *Duchenne UK*
Canada – *Jesse's Journey*
Netherlands – *Duchenne Parent Project Netherlands*
Belgium – *Duchenne Parent Project Belgium*
Australia – *Save our Sons*

Research Objective: To learn about how patient and caregivers evaluate risks and benefits and how they may differ internationally. Explore unmet needs.

Respondent goal: 60 each country, 20 patients 40 caregivers (360 total)
Method: Discreet Choice Experiment
Wave 1 potential for Wave 2

Experiments

- Treatment Preferences (DCE)

	Drug A	Drug B
Is there muscle benefit?	Small improvement	Large improvement
How many people would benefit?	50% 	75% 
What is the risk of kidney damage?	No additional risk 	20% higher risk 
What is the extra fracture risk?	20% higher risk 	10% higher risk 
In your opinion, which is the better drug?	☐	☐

Unmet Needs Prioritizations

- Research outcomes
- Care standards
- Trial eligibility
- Clinical trials
- No placebo
- Compassionate use
- Social initiatives

Unmet needs A	Unmet needs B
Clinical trials	Care standards
Social initiatives	No placebo
Compassionate use	
I think unmet needs A should be prioritized ☐	I think unmet needs B should be prioritized ☐

Familiarity with Drug Development clinical trials, and reimbursement

	Very much	Somewhat	A little bit	Not at all	Does not exist in my country
How familiar are you with drug discovery and pre-clinical research in your country?	☐	☐	☐	☐	☐
How familiar are you with clinical studies in your country?	☐	☐	☐	☐	☐
How familiar are you with the regulatory approval process in your country?	☐	☐	☐	☐	☐
How familiar are you with how insurance and reimbursement coverage decisions are made in your country?	☐	☐	☐	☐	☐
How familiar are you with opportunities for patient involvement in drug development and regulatory approval in your country?	☐	☐	☐	☐	☐
How familiar are you with who controls pricing for drugs in your country?	☐	☐	☐	☐	☐
How familiar are you with how the drug development and regulatory approval process in your country compares to other countries?	☐	☐	☐	☐	☐

Timeline

- **Stakeholder engagement**
  Sept 2017-January 2018
- **Survey Development**
  Dec 2017-February 2018
- **Survey Implementation**
  March 2018-May 2018
- Pote**ntial Wave 2**
  June 2018-Oct 2018 (Europe)
- **Publications**
- Oct 2018

Study 5:
Duchenne Gene Transfer Preference Study & Educational Initiative

Qualitative Interviews → Stated Preference Survey → Educational Initiative

Sponsors: Pfizer and Solid Biosciences

Collaborator: RTI International (Holly Peay, PhD)

Research Objective: Explore preferences and risk tolerance about emerging gene therapy technologies

Methods: Semi structured interviews, Threshold, BW Scaling

Qualitative Results – What we learned

Benefits	**Respondents highly valued potential benefits** to skeletal muscle, cardiac, and pulmonary function • *Muscle*: **differently valued** for quality of life impacts **based on progression** • *Cardiac/pulmonary*: greater relative importance with progression
Risks	**More than half tolerant of 1% risk of death**, with evidence of **increased risk tolerance in adults and at later stages**
Limitations (Caveats)	**Most were concerned about limitations** (possible one-time, time-limited benefit; loss of future trial eligibility) • **Optimistic** about scientific advances • Described a **'right time'** for use of gene therapy

Development of Survey (Quantitative data)

Anticipated recruitment numbers –150 parents and 50 adults with Duchenne

Inclusion Criteria

- Adults with Duchenne muscular dystrophy (must be at least 18 years old)
- The parent of a person with Duchenne muscular dystrophy, or a guardian (current or past) of a person with Duchenne. Must be at least 18 years old.

Aims of Study

- **Threshold experiment:** Determine maximum acceptable risk (directed toward an approved therapy)
- **Best-Worst Scaling experiment:** Assess priorities regarding factors influencing clinical trial decision making

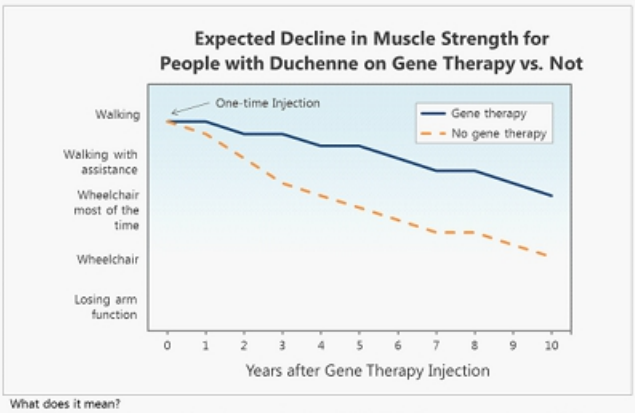
Participants are required to view a 2 minute whiteboard video about Gene Therapy before taking survey

Threshold Experiment
(approved therapy)

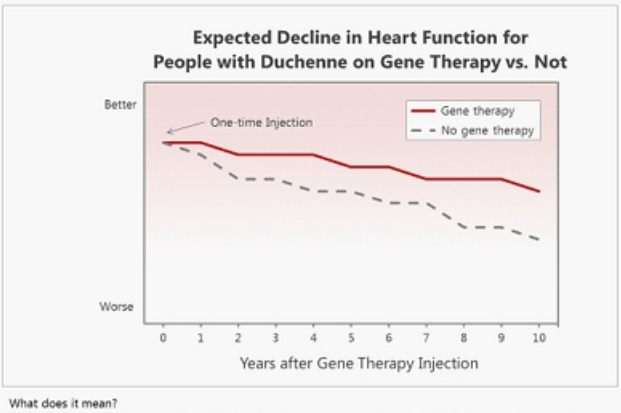
- **Imagine that your child's doctor offers your child gene therapy for Duchenne.**
  The doctor shows you these two graphs.

  They show the average benefit experienced by 2,000 people who used gene therapy.

  The solid lines show how using gene therapy has helped their muscle strength and heart function compared to people who don't use gene therapy. The doctor cannot tell you how long the benefit will last. It won't last forever, but should last for 10 years.



What does it mean?
This graph compares the expected muscle progression of people with DMD that are on gene therapy (solid line) compared to people with DMD that are not on gene therapy (dashed line). After a single IV infusion of the gene therapy drug (arrow), people on gene therapy are expected to have greater stability in muscle strength compared to people without gene therapy for an estimated 10 years after the infusion.



What does it mean?
This graph compares the decline in cardiac function of people on gene therapy (solid line) compared to people not on gene therapy (dashed line). After a single IV infusion (arrow), people on gene therapy maintained function longer compared to people without gene therapy for 10 years after the treatment.

Risk Numbers:

1/2000

10/2000

20/2000

200/2000

Would you choose gene therapy?

	Yes	No
I would choose gene therapy for my child right now	○	○
I would choose have chosen gene therapy for my child when he was a newborn	○	○
I would choose gene therapy for my child in the last year that he could walk well	○	○
I would choose gene therapy for my child in the last year that he could lift his arms to his mouth	○	○

Best Worst Experiment (clinical trial)

Clinical Trial Attributes

- Chance of improved muscle function
- Chance of improved heart function
- Chance of improved lung function
- Benefit lasts 10 years
- Trial uses placebo group
- Lowest dose may be too low for benefit
- Not eligible for future trials
- No later use of gene therapies or gene editing (CRISPR)
- Two muscle biopsies
- Chance of long hospitalization
- Chance of death

Task Example

Which is **most important to your decision about** whether to join the trial? What is **least important to your decision?**

Most important to my decision		Least important to my decision
○	Two muscle biopsies required	○
○	Benefit lasts 10 years	○
○	Chance of improved lung function	○
○	Lowest dose may be too low for benefit	○
○	Chance of death	○

Timeline

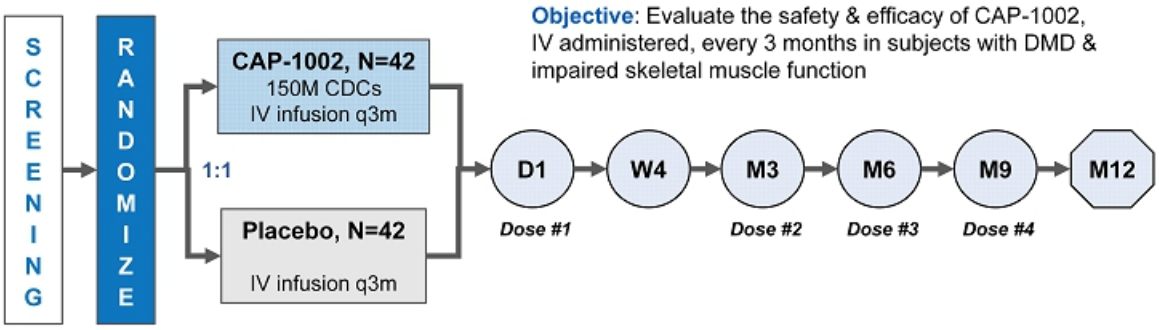
- **Qualitative study** - *completed*
- **Draft survey** - *completed*
- **Recruitment** – *January 2018– March 2018*
- **Analysis** – *early spring*
- **Report** - *late spring*

Thank you!

HOPE-2 Trial Design

Presented By: Deborah Ascheim M.D.

HOPE-2 Trial



- Randomized, double-blind, placebo-controlled trial
- N ≤ 84
- Total of 4 doses of IV CAP-1002 or placebo; 12-month follow-up
- Open-label extension for patients randomized to placebo (pending DSMB recommendation)

Endpoints

Primary

- Upper-limb function at Month 12 by mid-level PUL
- Pre-specified safety events

Secondary

- Upper-limb function (mid-level PUL) at Months 3, 6, & 9
- Cardiac function by MRI
- Incidence and severity of AEs

Exploratory

- Elbow, grip, & pinch strength
- PUL (all levels)
- Cardiac structure & function
- Pulmonary function testing
- NSAA
- Biomarkers
- Quality of life
- Resource utilization

HOPE-2 Considerations

- Ambulatory and non-ambulatory boys and young men with compromised upper limb function considered for enrollment
- Later stage disease➡ few competitors
- We believe CAP-1002 is complementary to other disease modifying therapies (dystrophin modulating Rxs)

For more information, visit capricor.com or clinicaltrials.gov (NCT03406780)

Collaborators

- HOPE-1 trial patients
- Patient advocacy group partners

DMD Advisory Board

- Barry Byrne, MD, PhD
- Michelle Eagle, PhD
- Richard Finkel, MD
- Pat Furlong
- Kan Hor, MD
- John Jefferies, MD
- Oscar Henry Mayer, MD
- Craig McDonald, MD
- Eugenio Mercuri, MD, PhD
- Francesco Muntoni, MD
- Michael Taylor, MD PhD
- Ron Victor, MD
- Thomas Voit, MD

Thank you

Q&A