The “ESSENCE” Clinical Trial: Protocol Design and Challenges

Perry Shieh, M.D., Ph.D.
Associate Professor of Neurology
Neuromuscular Program
UCLA Medical Center

Relevant Disclosures

Have served as a Consultant on an Ad Hoc Advisory Board for Sarepta Therapeutics

Serve as a site-Investigator for clinical trials sponsored by Sarepta Therapeutics, including the ESSENCE clinical trial, which is the subject of this meeting

Travel for today's meeting supported by the FDA

Outline

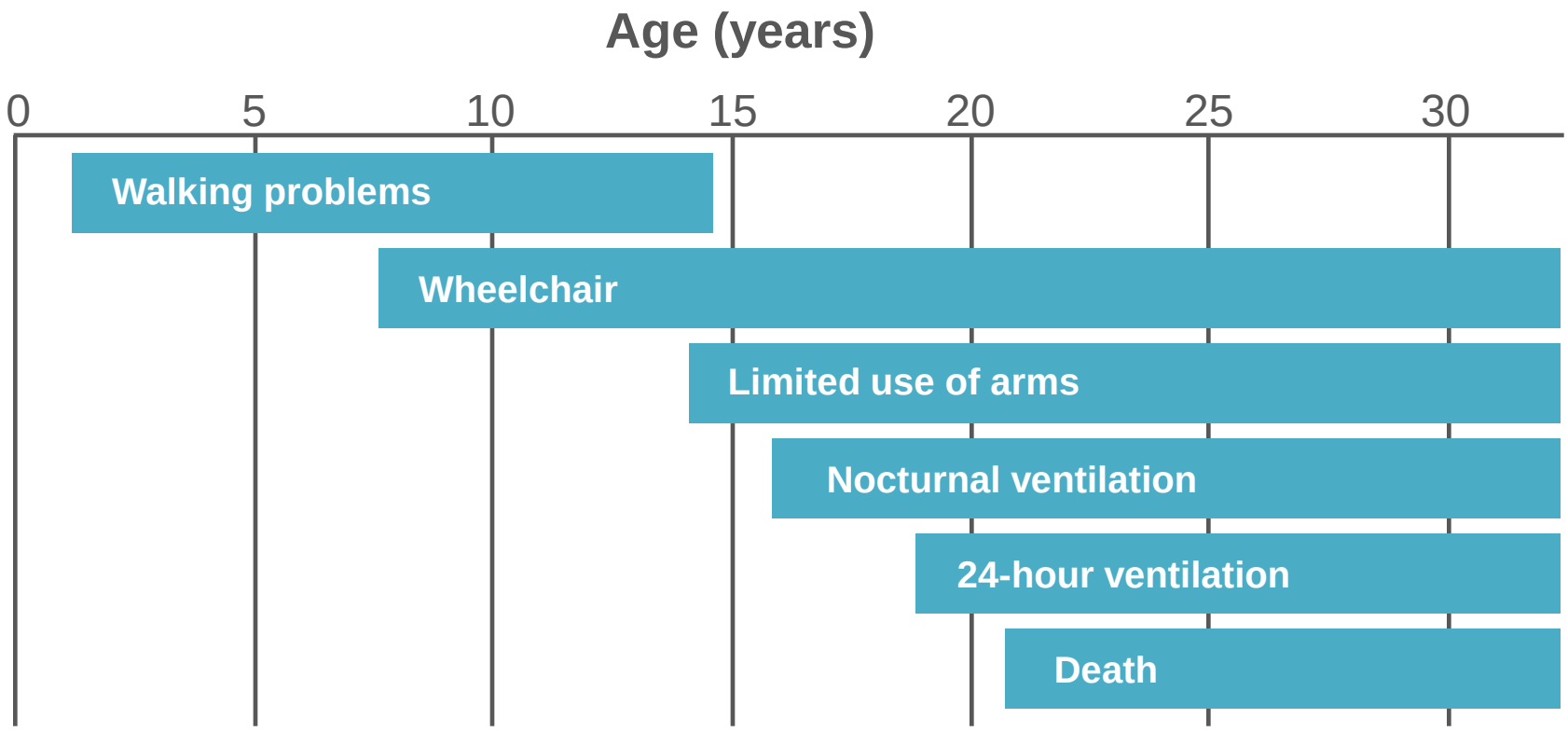
- Background of Duchenne Muscular Dystrophy
- SRP-4045 and SRP-4053: Rationale for Exon Skipping
- Highlights of the ESSENCE Protocol
- Challenges in implementing the ESSENCE Protocol

Background

Duchenne Muscular Dystrophy

- DMD is a disease of boys who have a mutation in a gene called dystrophin
- Because of their inability to make the dystrophin protein, their muscles degenerate

DMD: Progression of Disease



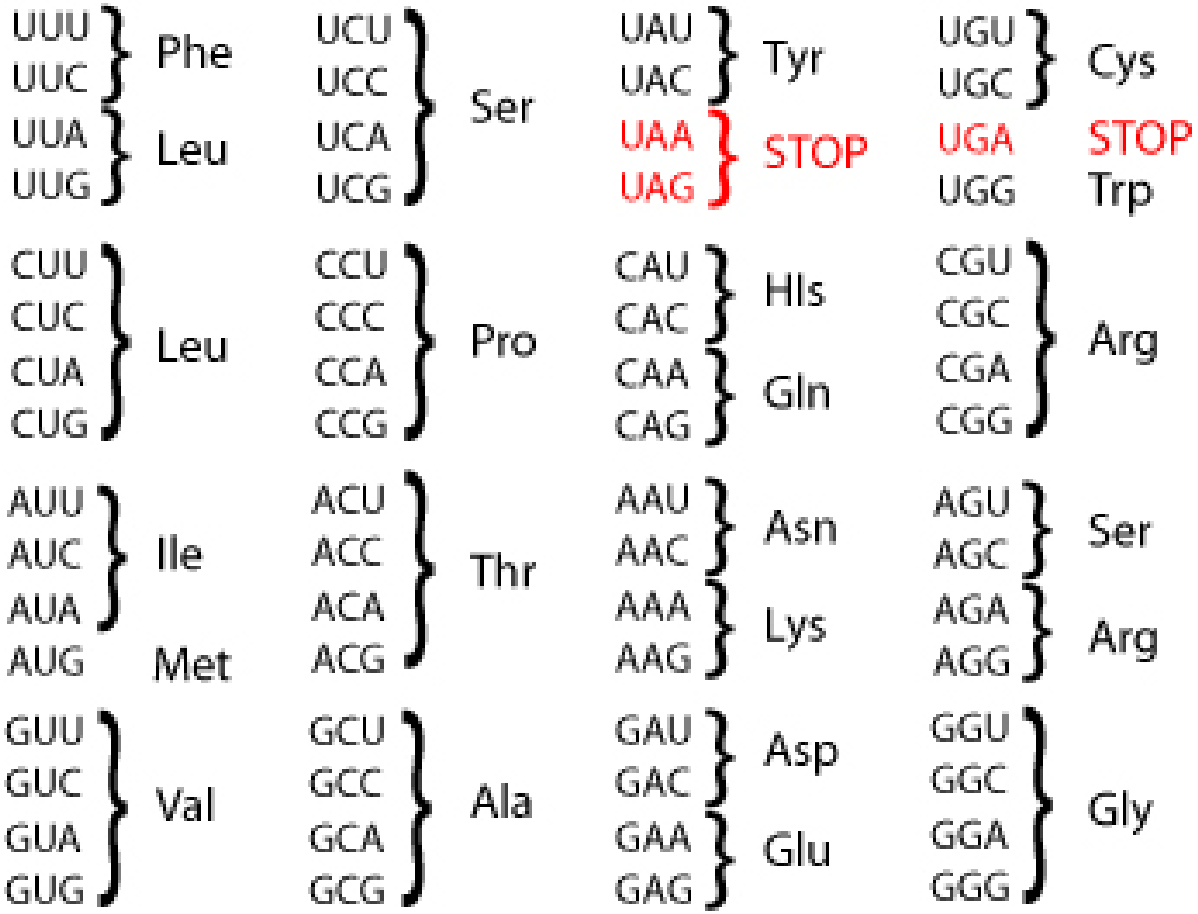
Predicting Severity of Disease: The Reading Frame Rule

- Becker Muscular dystrophy is also caused by mutations in dystrophin, but is characterized by a milder course than Duchenne Muscular Dystrophy
- Monaco AP, et al., proposed the reading frame hypothesis[1] that predicts the severity of disease
- Aartsma-Rus A, et al., found (in a database of 4700 patients) that the rule holds true in 91% of patients[2]

1. Monaco AP, et al. *Genomics*. 1988;2:90-95.
2. Aartsma-Rus A, et al. *Muscle Nerve*. 2006;34:135-144.

Codons and the reading frame

- Each 3-letter codon encode an amino acid



The Reading Frame

1 2 3 1 2 3 1 2 3 1 2 3 1 2 3

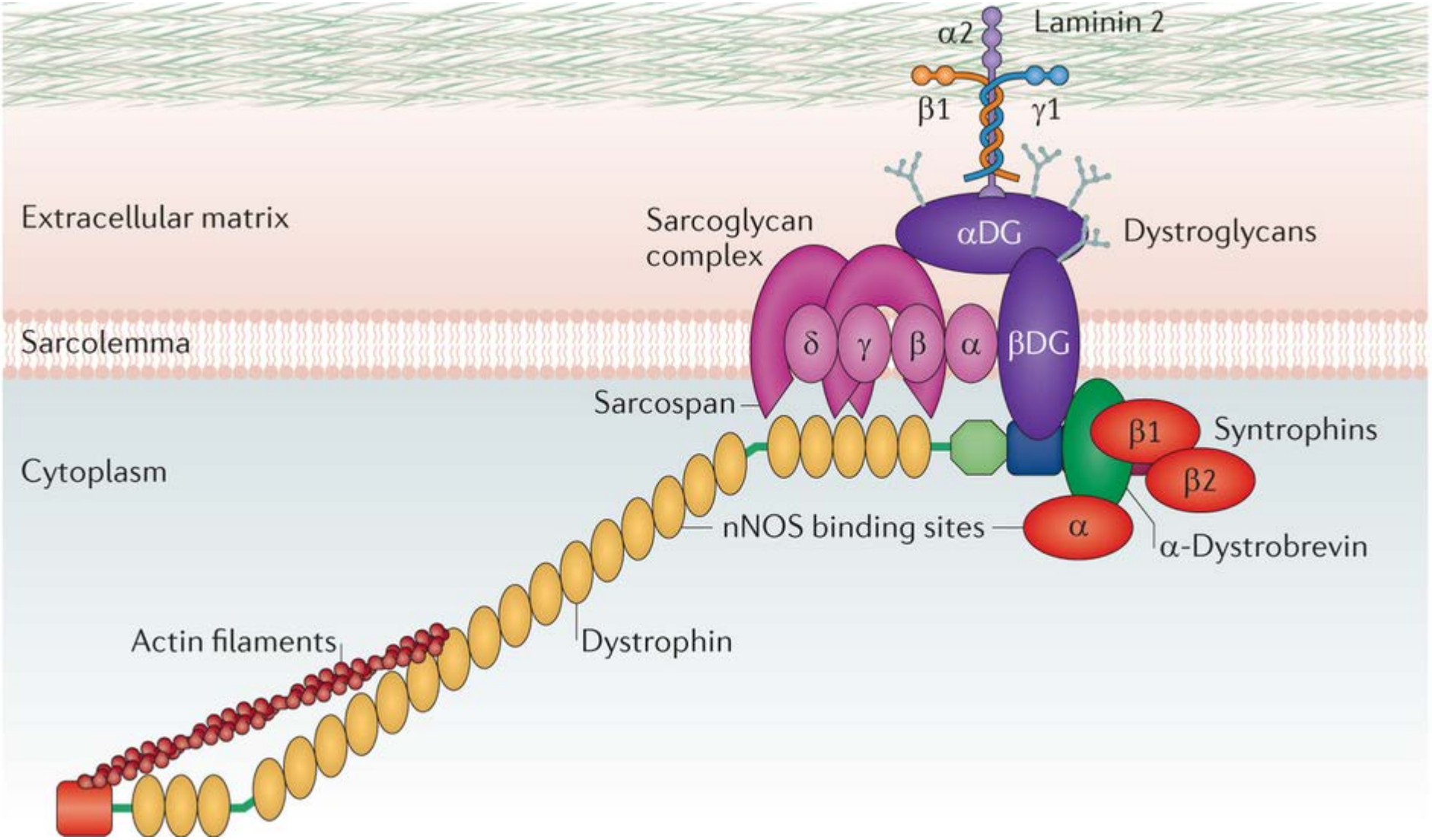
DADPETTHEFATDOG

DAD PET THE FAT DOG

ADP ETT HEF ATD OG

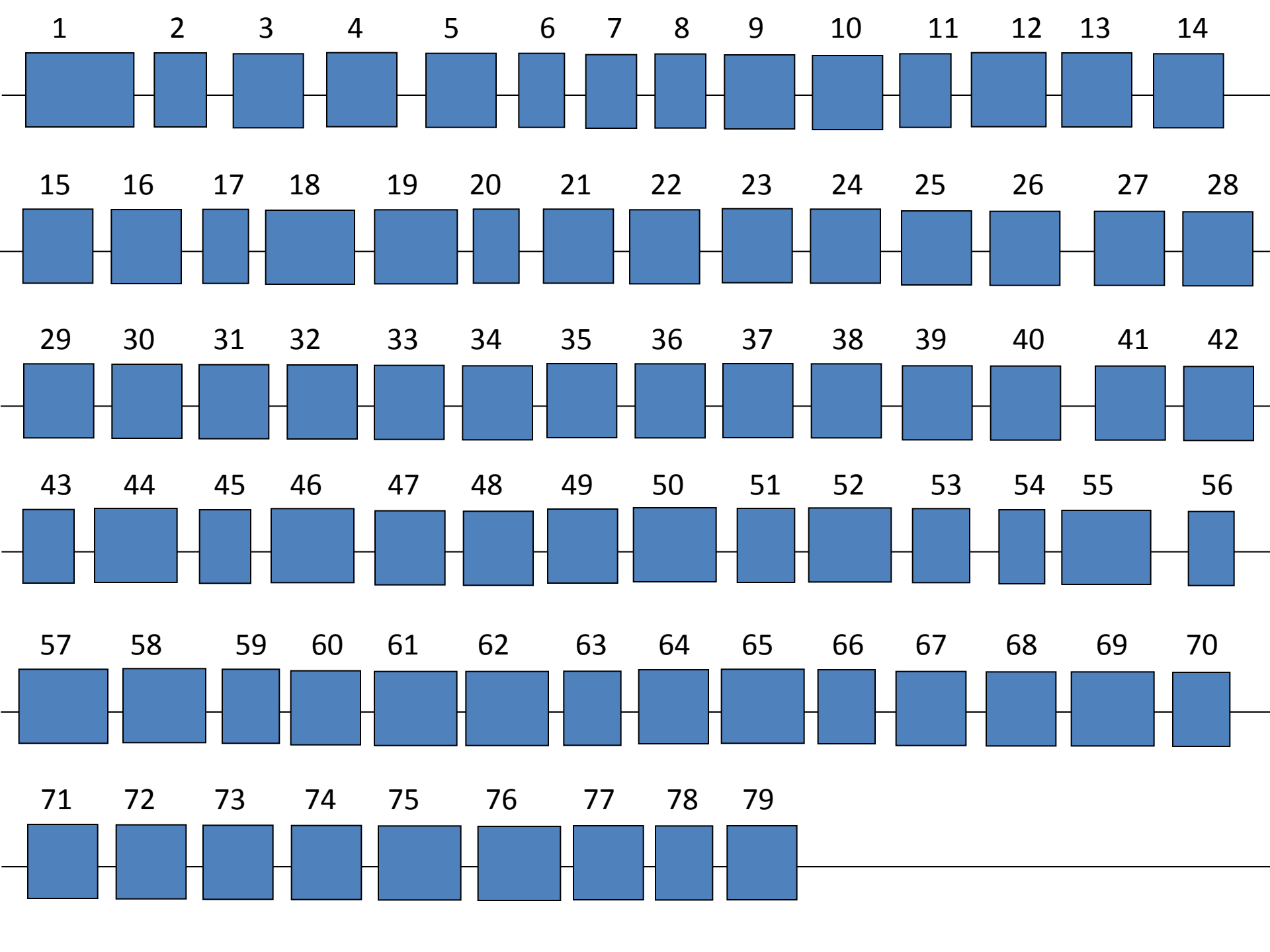
DPE TTH EFA TDO G

The Role of Dystrophin



nNOS, neuronal nitric oxide synthase.

Fairclough RJ, et al. *Nat Rev Genet*. 2013;14:373-378.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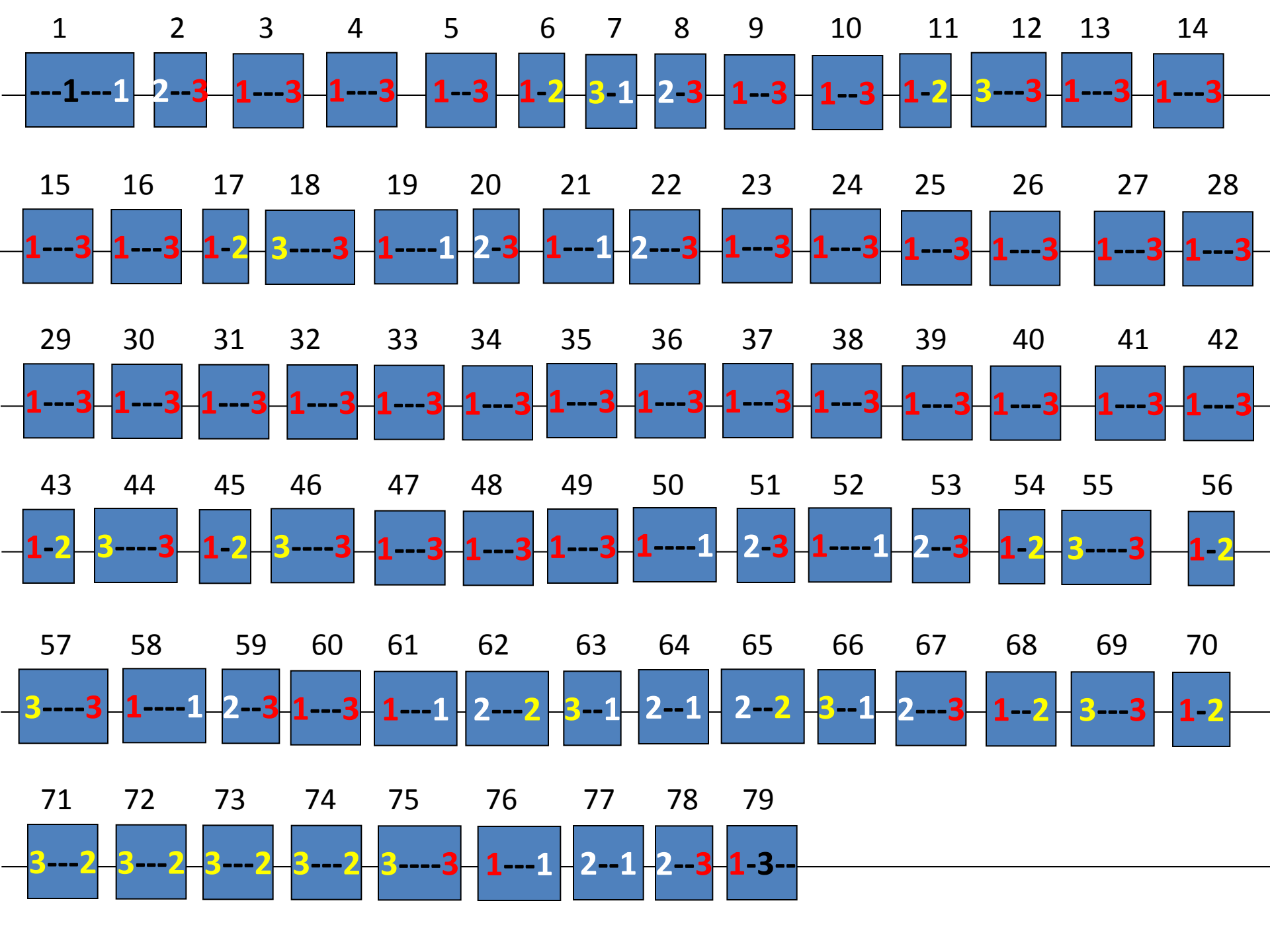
57 58 59 60 61 62 63 64 65 66 67 68 69 70
71 72 73 74 75 76 77 78 79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Mutations in Dystrophin (cont'd)

Mutations may be:

- Large deletions: 68%
- Large duplications: 11%
- Small deletions/duplications
- Single-nucleotide substitutions

} 7%

- Nonsense mutations: 10%
- Splice-site mutations: <1%
- Intronic mutations: 3%

Bladen CL, et al. *Hum Mutat*. 2015;36:395-402.


1 2 3 4 5 6 7 8 9 10 11 12 13 14
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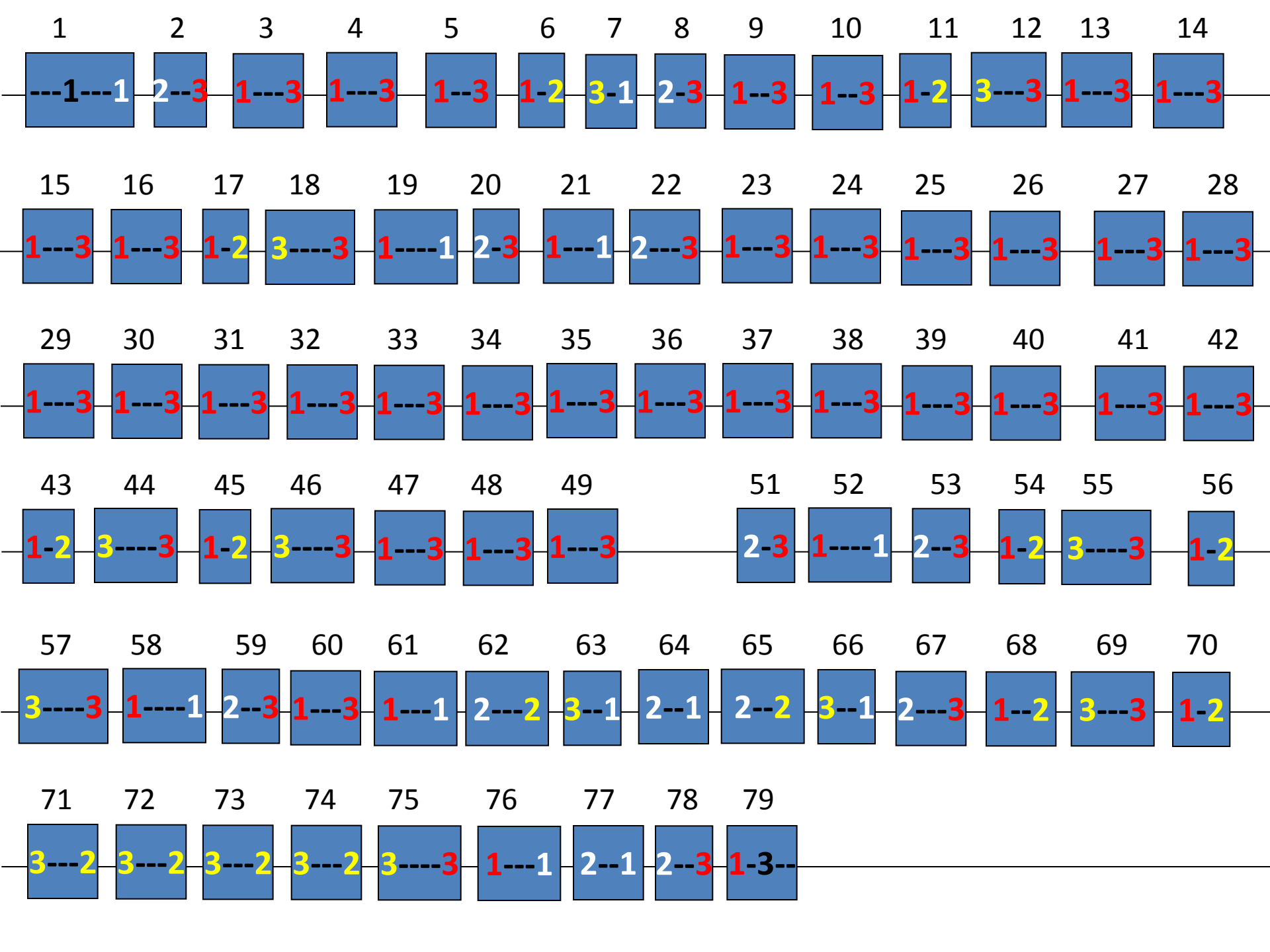
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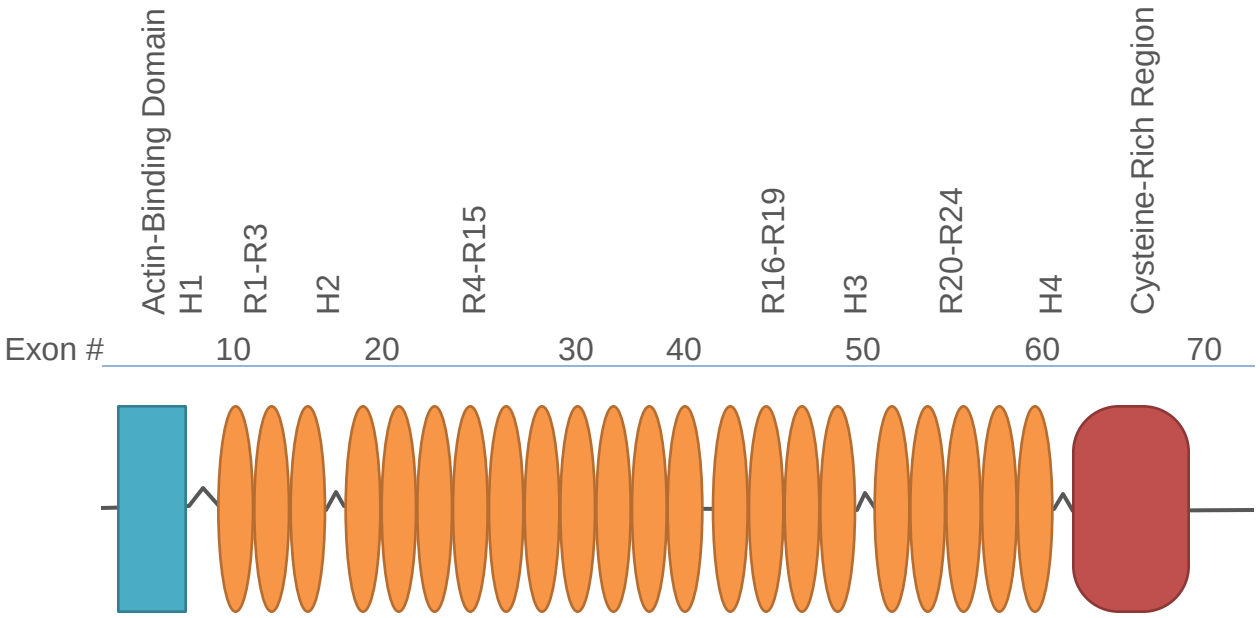
DMD Versus BMD

Mutations that have a more severe phenotype (DMD) generally:

- **Disrupt** the reading frame
- **Remove critical regions** of the dystrophin protein

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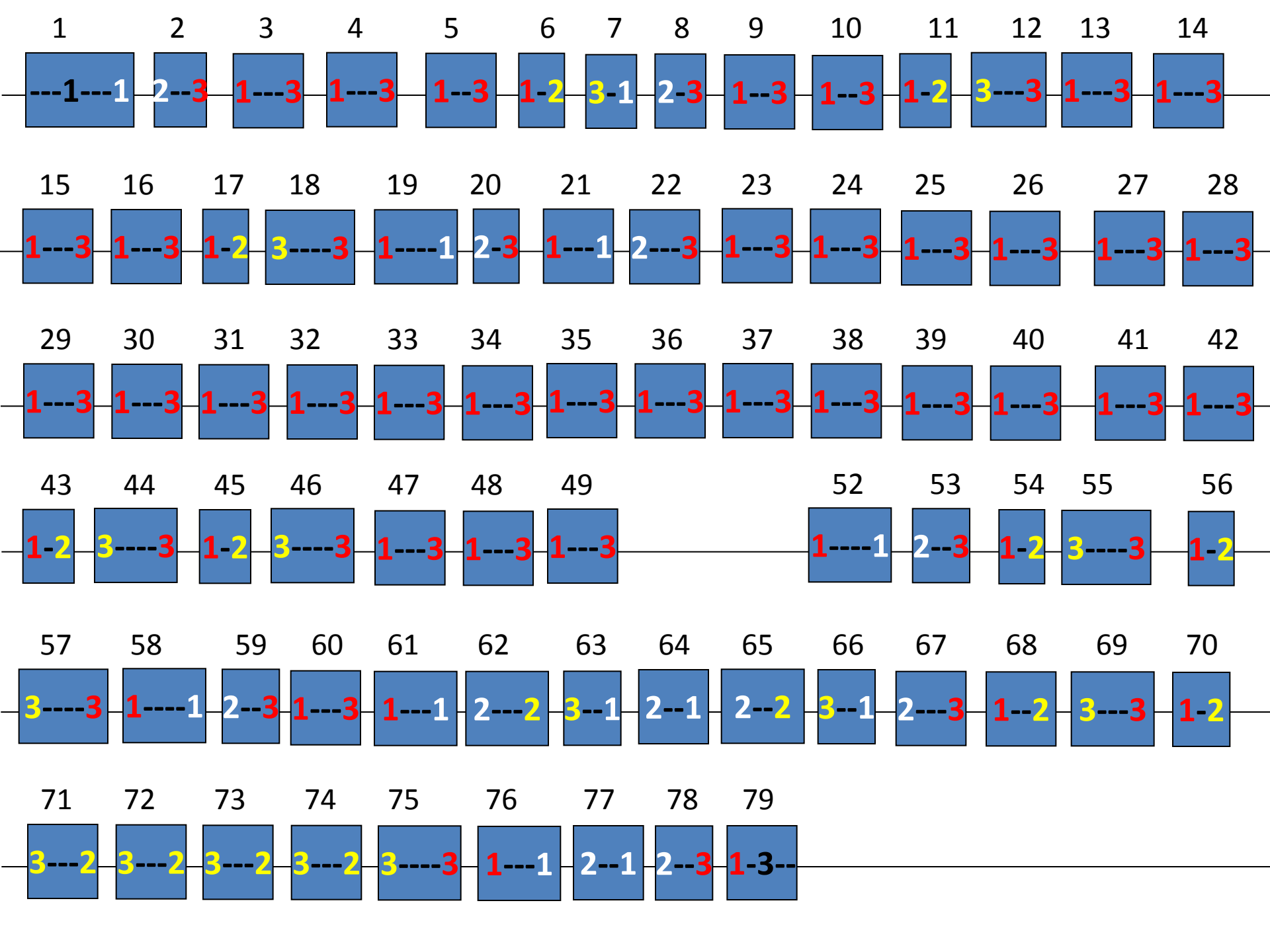
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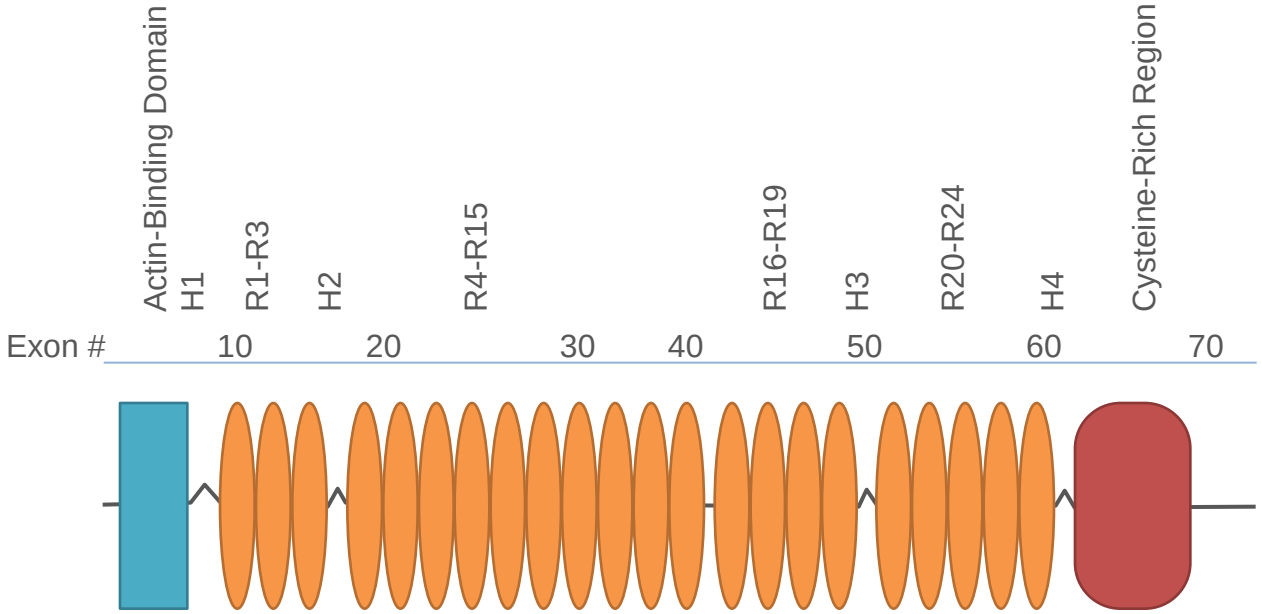
DMD Versus BMD

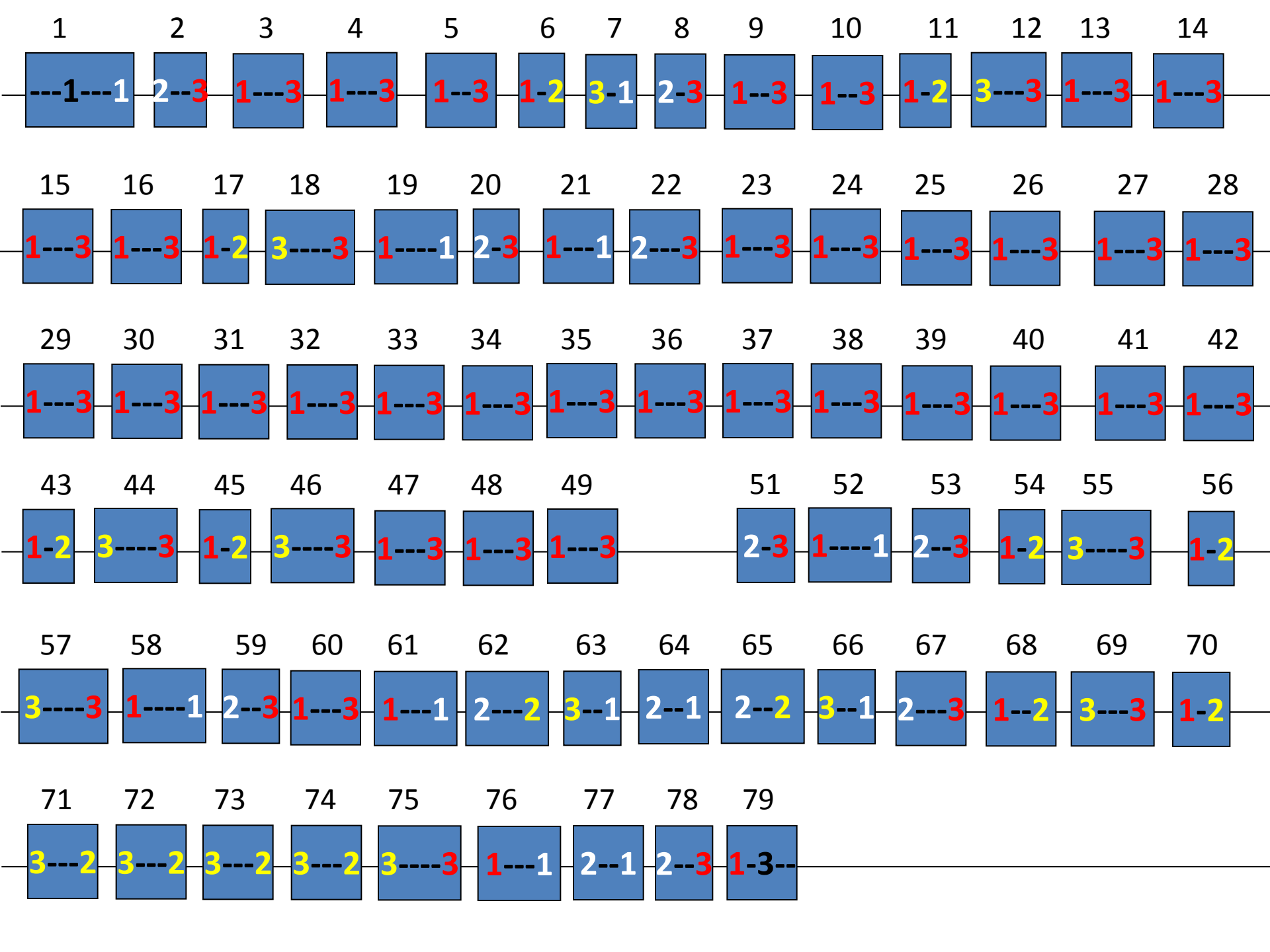
Mutations that **preserve** the reading frame (especially mutations in the central rod domain) generally have a milder phenotype (BMD)



Exon Skipping

Exon skipping is a treatment strategy designed to restore the reading frame.

Eteplirsen: Morpholino anti-sense oligonucleotides directed against critical splicing sequences within exon 51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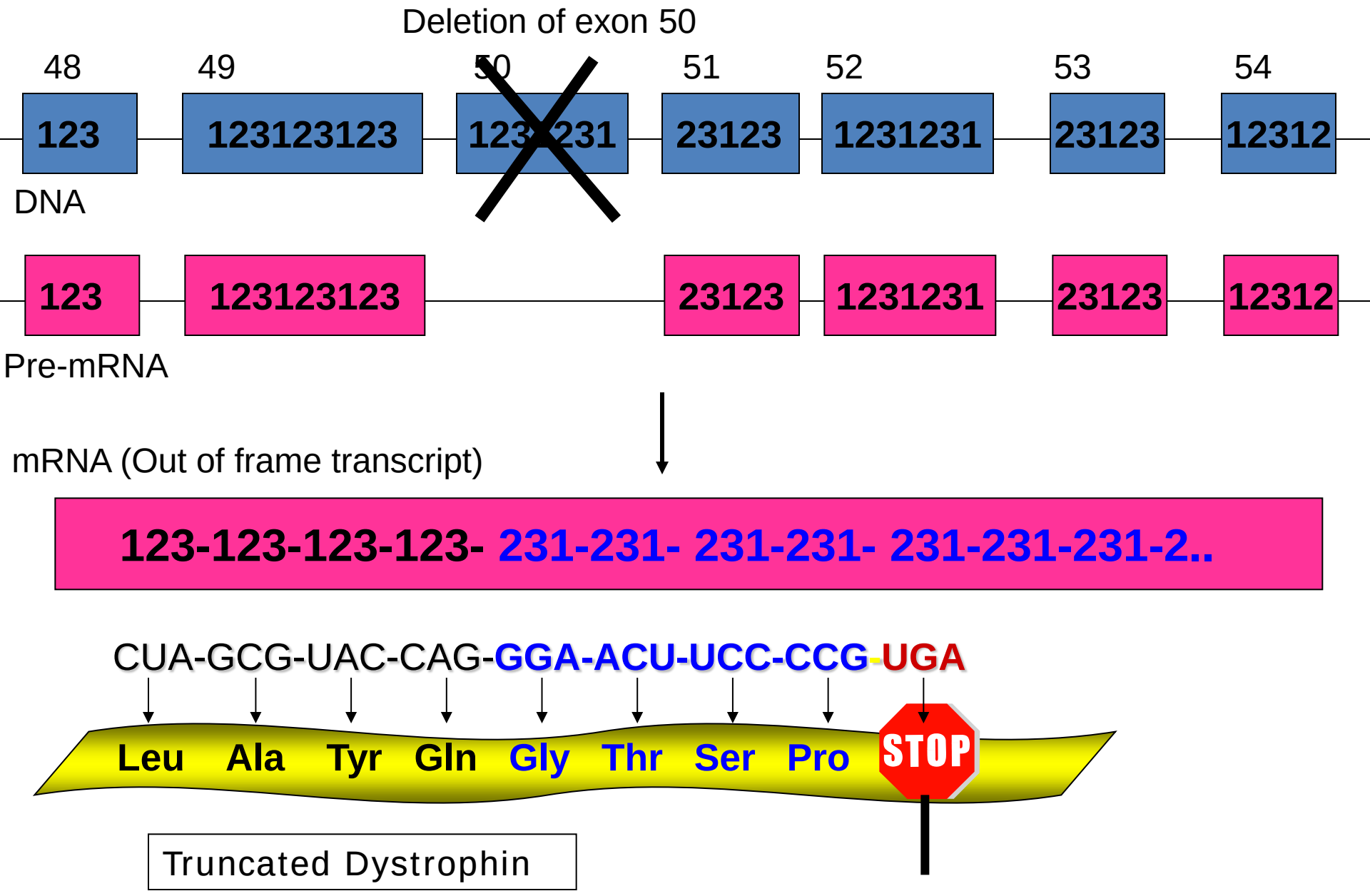
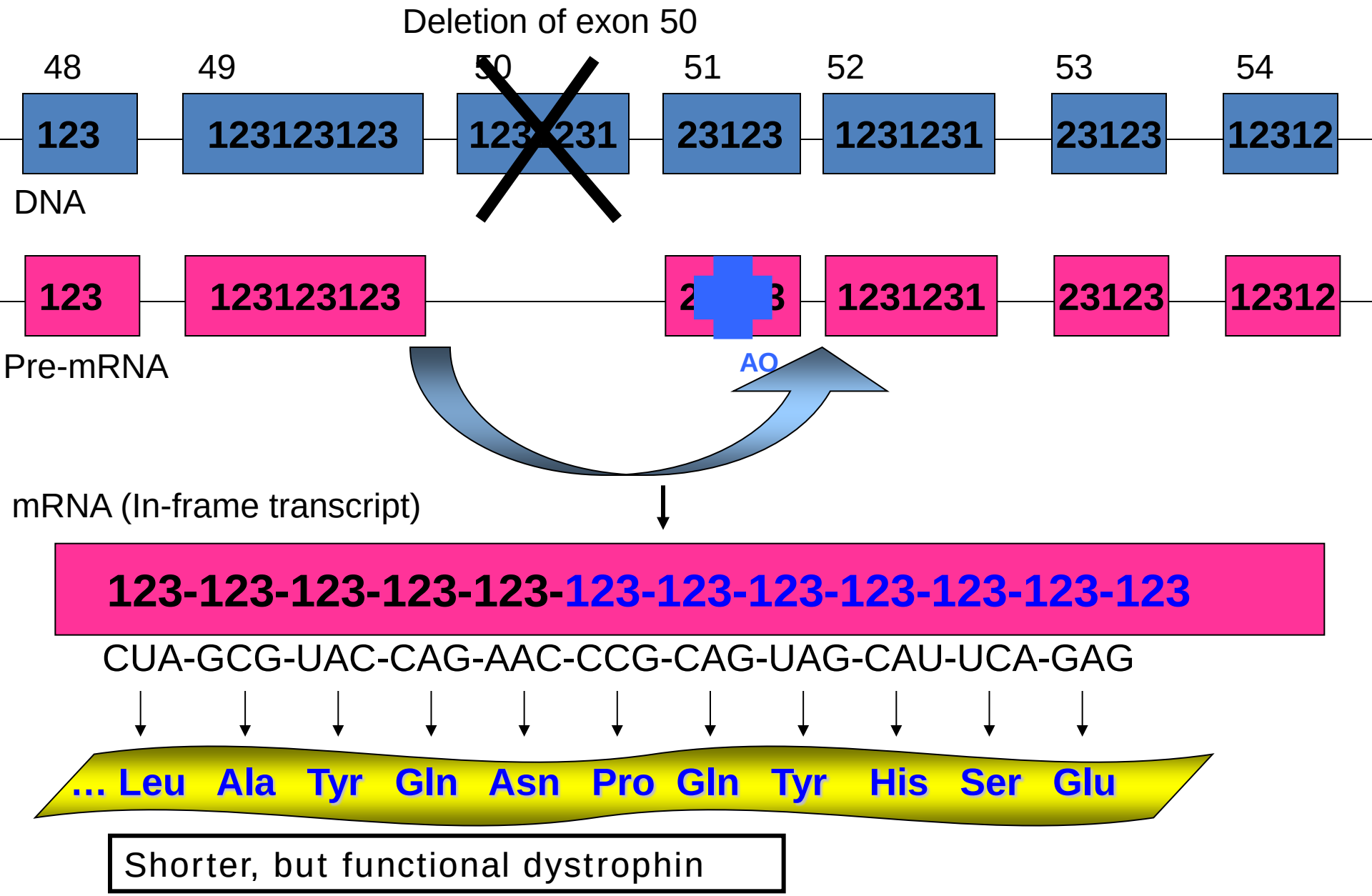
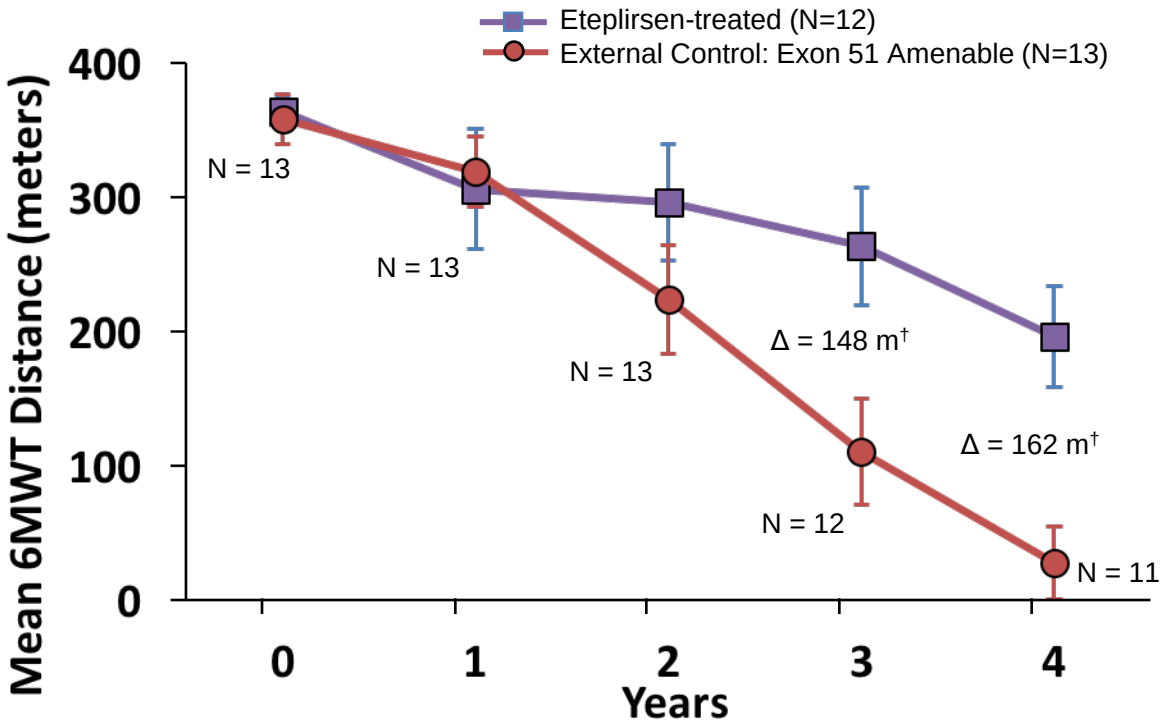
Out-of-frame deletions → DMD



Exon Skipping



6MWT data from eteplirsen treated patients vs. external control cohort



†Difference in mean change from baseline, Day 1 values used for eteplirsen
Patients who lost ambulation contributed a score of 0 to the mean
Individual time points missing: ECM2 Year 4, ECG3 Year 3 & 4

ESSENCE: Protocol Highlights

Study of patients with genotypes that are amenable to exon 45 and exon 53 skipping

- SRP-4045
- SRP-4053

Similar to eteplirsen, these investigational products are designed to block sequences within these respective exons that are required for splicing

ESSENCE: Protocol Highlights

The protocol combines all of the lessons learned from previous clinical trials on exon skipping:

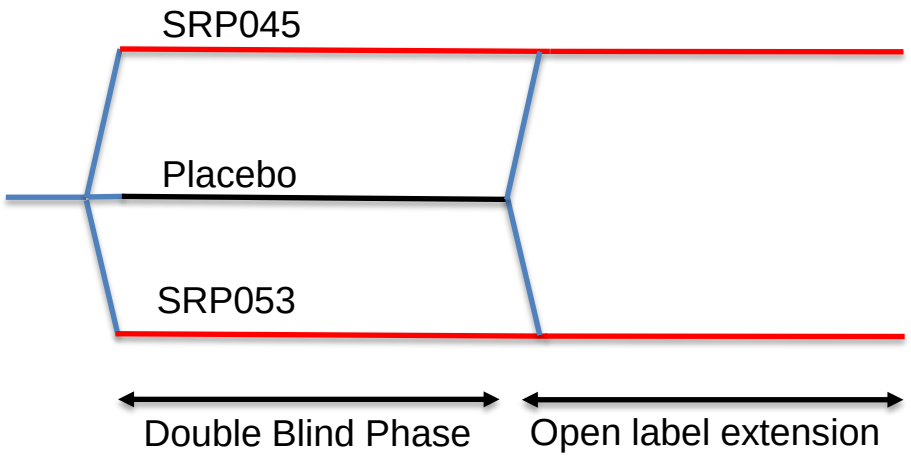
- Double blind, placebo controlled design
- Adequate power (n = ~99 subjects), combining two different exon skipping investigational products: SRP-4045 and SRP-4053
- 2 year double-blind period was based on guidance provided by FDA[1]

[1]"Duchenne Muscular Dystrophy and related Dystrophinopathies: Developing Drugs for Treatment. Guidance for Industry." https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM450229.pdf

ESSENCE: Protocol Highlights

4 year study

- 2 year double-blind phase
- 2 year open label phase



ESSENCE: The Protocol

Operational Details

- Randomized 2:1 - active vs. placebo
- Weekly IV infusion of investigational product
- Open muscle biopsy at baseline and at week 48

- At present time, no implantable IV access device is allowed at U.S. sites

ESSENCE: The Protocol

Key Outcome measures

- Primary Outcome: 6 minute walk distance at 48 weeks (interim) and 96 weeks (final) vs. baseline
- Secondary Outcome: Dystrophin quantification (Western Blot of muscle tissue) 48 weeks vs. baseline

Protocol Challenges

- Screening began August 2016
- First patient randomized September 28, 2016
- The most common complaint has been the difficulty of IV access

- Methods used to mitigate IV access problems:
  - Lidocaine Cream prior to placement of IV access
  - Infrared Vein finder

Concerns

- Among patients with difficult IV access: Psychological and physical suffering of patients and psychological suffering of family members
- Among patient with adequate IV access: Potential progressive worsening of IV access with repeated attempts during the course of the clinical trial
- Among patient with behavior issues, autism or OCD (which are common among DMD patients) – IV access can be a struggle, even among patients who should have good IV access

Alternatives to peripherally placed IV

Table 1 Types of Central Venous Catheter (CVC).[10,18,34,36,112,113,116,127]

Catheter type	Features	Uses	Duration of use	Infection risk
Peripherally inserted CVC (PICC lines)	Inserted peripherally into basilic, cephalic or brachial veins and enter superior vena cava (SVC)	Blood sampling Fluid, blood product and total parenteral nutrition (TPN) administration Medication (such as inotropes, antibiotics, chemotherapy)	4 weeks–6 months	Similar, or lower rates of infection to non-tunnelled CVCs[18,113,114]
Non-tunnelled CVC	Percutaneously inserted into subclavian, internal jugular or femoral vein	Blood sampling Fluid and blood product and TPN administration Medication Haemodialysis	7–10 days	Highest risk of infection[18]
Tunnelled CVC (Hickman, Broviac, Grohong)	Surgically or radiologically implanted into subclavian, internal jugular or femoral vein	Blood sampling Blood product and TPN administration Medication including antibiotics and chemotherapy Haemodialysis	Months – years	Tunnelling reduces rate of infection compared to non-tunnelled CVCs[10,127]
Totally implantable venous-access port (TIVAP)	Tunnelled beneath the skin with subcutaenous port accessed with a needle. Implanted by surgical/radiological placement into subclavian or internal jugular vein	Infrequent access on long term basis such as for antibiotics (such as for patients with cystic fibrosis), chemotherapy	Months – years	Lowest risk of infection[10,113,116]

CVC – central venous catheter, PICC – peripherally inserted central venous catheter, SVC – superior vena cava, TPN – total parenteral nutrition, TIVAP – totally implantable venous-access port.

Chesshyre et al, J Infect. 2015 Jun;71 Suppl 1:S59-75.

Proposed alternative: Port-a-Cath

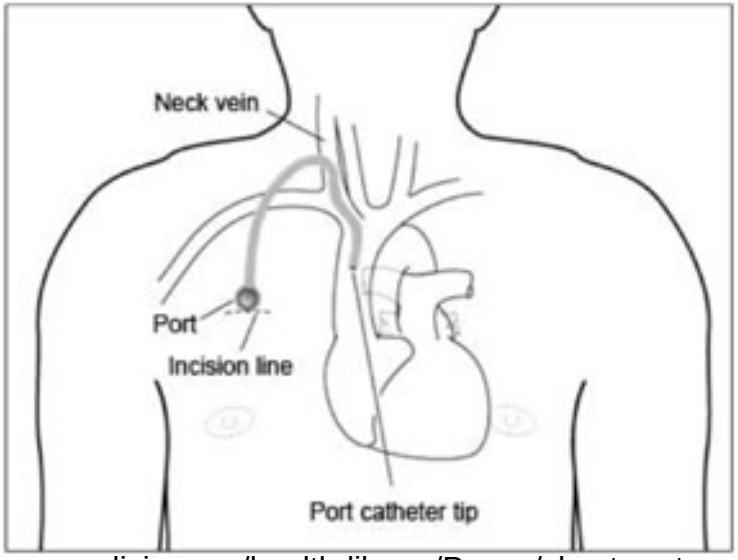
- Port-a-Cath placement has been used among many of our patients who have required frequent IV access.
- It has been used in other clinical trials, including previous Sarepta Exon Skipping clinical trials, to facilitate IV access.

Port-a-Cath

http://www.bardpv.com/portfolio/titanium-low-profile/#prettyPhoto

Experience with Port-a-Cath

- Port-placement requires a surgical procedure under anesthesia with laryngeal mask airway or endotracheal tube.
- The port is placed under the skin of the chest
- The catheter tunneled under the skin to the entry point of the jugular or subclavian vein
- The tip of the catheter is most commonly placed in the junction of SVC-right atrium



http://www.uwmedicine.org/health-library/Pages/chest-port.aspx

Experience with ports

- Our Nurses at UCLA have experience with using port-a-caths for clinical care and for clinical trials
- They are easy to use and do not typically create significant discomfort to our patients.
- Port-a-caths can be used instead of phlebotomy for routine laboratory work as well

Risks of port-a-cath

The procedure of placing the port-a-cath carries the risk of:

- Surgical complications
  - e.g. hematoma
- Procedural sedation

Patients with Port-a-caths are at risk for:

- Infection
- Thrombosis

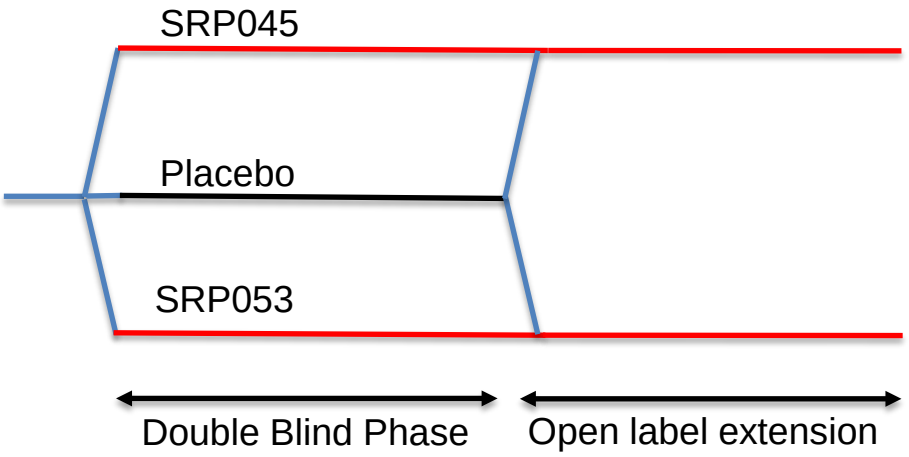
[1]Fu et al, J Surg Res. 2016 Oct;205(2):419-25

Risks of port-a-cath: comments

- For subjects that are enrolled in the future, UCLA and the other surgical centers identified in the ESSENCE study can perform muscle biopsies and port-a-cath procedures during the same surgical encounter, minimizing the risk of procedural sedation

Alternative Risk-Benefit Analysis

- Using component analysis, it has been the opinion of the FDA and several IRBs that the ESSENCE protocol fell within 21 CFR 50.53 (45 CFR 46.406)
- However, this does not account for the prospect of benefit of the open label extension



Alternative Risk-Benefit Analysis

- Research subjects that are randomized to active treatment – there is a prospect of direct benefit of 4 years of treatment
- Research subjects that are randomized to placebo – prospect of direct benefit of two years of treatment
- Since the risks of the port lie mostly with the surgical procedure of placing the port, essentially a fixed risk with different degrees of benefit.

Conclusions

- This ESSENCE study is designed to establish the efficacy of an promising investigational medication in a severe pediatric disease with an unmet need.
- The study is well designed and based on currently accepted recommendations and standards
- The enrollment interest of this study speaks to the importance of this study to patients and their families

Additional Comment

- If one considers the study over the course of 4 years (including the open label extension), the study may be considered to have a prospect of direct benefit to the research subjects

21 CFR 50.54

- The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
- The clinical investigation will be conducted in accordance with sound ethical principles
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 21 CFR 50.55.

Thank you for your attention

Perry Shieh, MD, PhD
Neuromuscular Program
Department of Neurology