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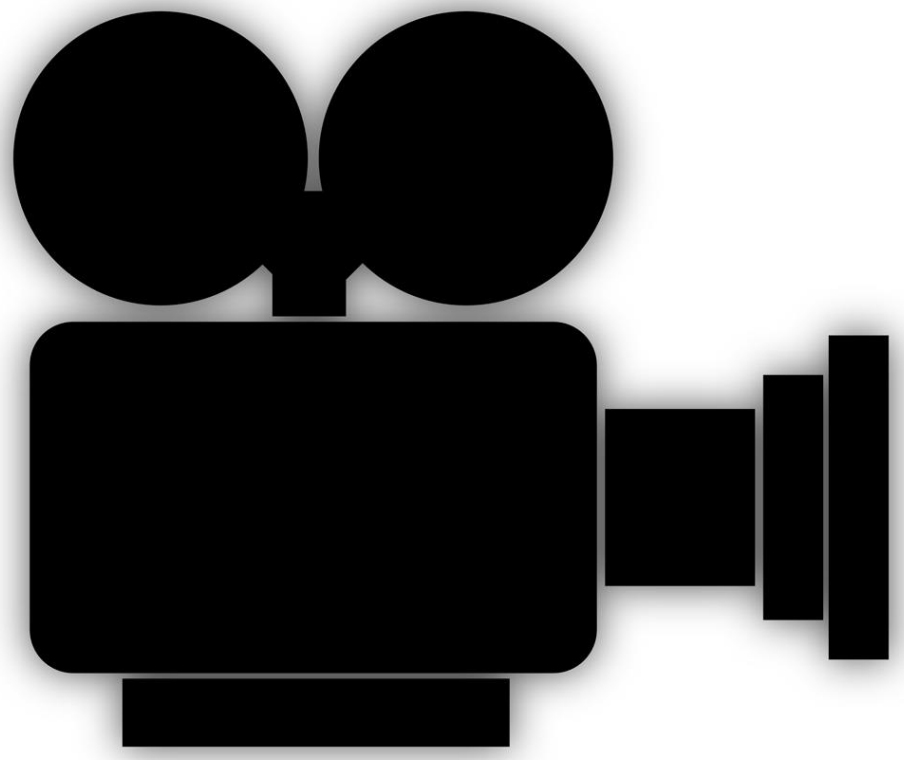
AMERICAN SOCIETY of GENE & CELL THERAPY

Understanding the Gene Therapy Process and Aftercare

For sound, stream audio through your speakers.
If you are having trouble accessing sound, please send a message using the chat box in the lower left hand corner.

Alone we are rare. Together we are strong.®

This webinar is being recorded.



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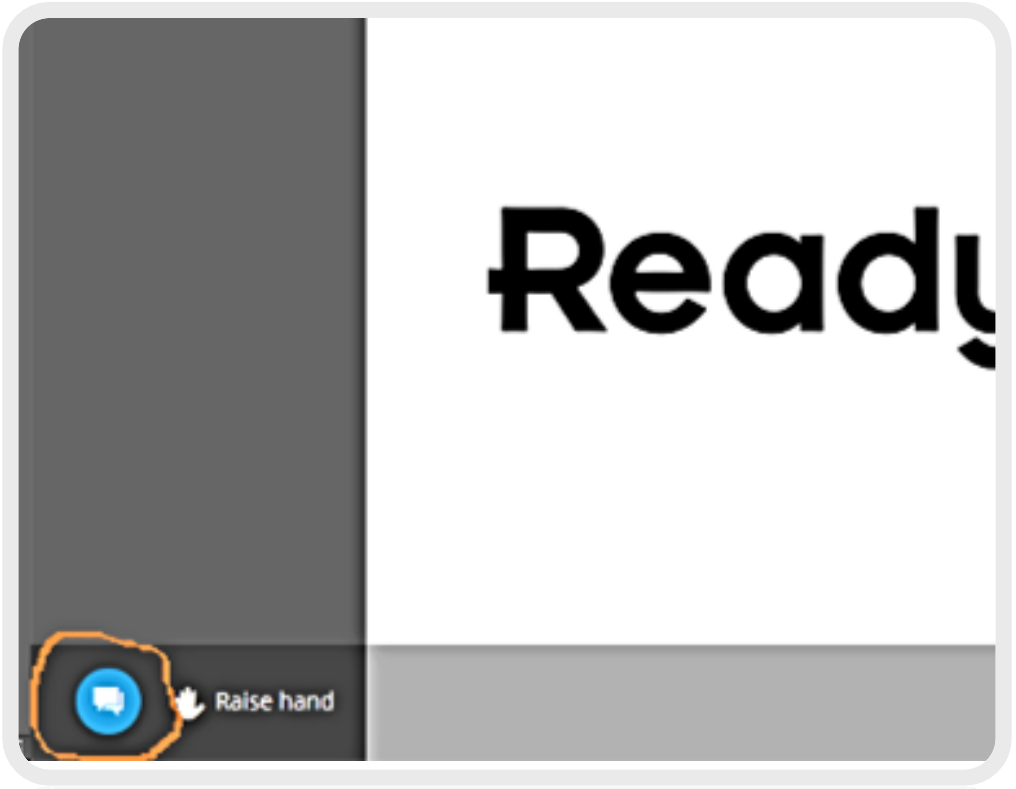
Question and Answer Session

Submit your questions using the chat function. It can be found at the **lower left hand corner** of the window.



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NORD, an independent nonprofit, is leading the fight to improve the lives of **rare disease patients and families.**

We do this by supporting patients and organizations, accelerating research, providing education, disseminating information and driving public policy.

Notes & Updates

Learn more
https://rarediseases.org/living-rare-forum/

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Gene Therapy Webinar Series

Understanding the Gene Therapy Process and Aftercare is the fourth webinar in an exciting five-part series on gene therapy from NORD in collaboration with the American Society for Gene and Cell Therapy (ASGCT.) Mark your calendar for the final webinar of the series:

- **Life After Gene Therapy -** Wednesday, December 18

Dates subject to change

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Speakers

Barry Byrne, MD, PhD
Director
UF Powell Gene Therapy Center

Jerry Mendell, MD
Principal Investigator
Center for Gene Therapy,
The Research Institute of Nationwide Children's

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Gene Therapy Clinical Trial Participation

Barry J. Byrne, MD, PhD
Powell Gene Therapy Center
University of Florida, College Medicine

Disclosures

Chief Medical Advisor – Muscular Dystrophy Association
Member of Pfizer Rare Disease Therapeutic Area Advisory Board
Inventor of AAV technology related to neuromuscular disease and AAV production technology owned by the University of Florida.

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How to be prepared for a gene therapy study?

Homework…

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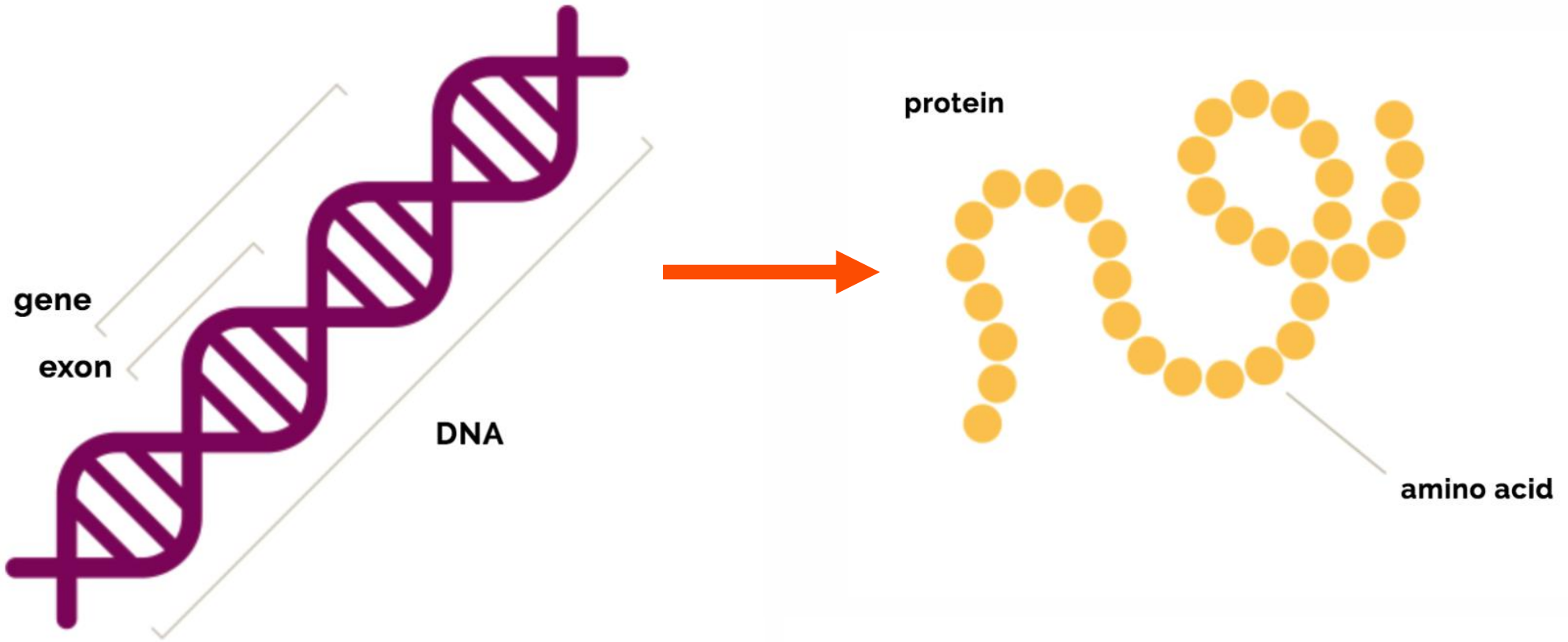
DNA Provides the Instructions for Proteins



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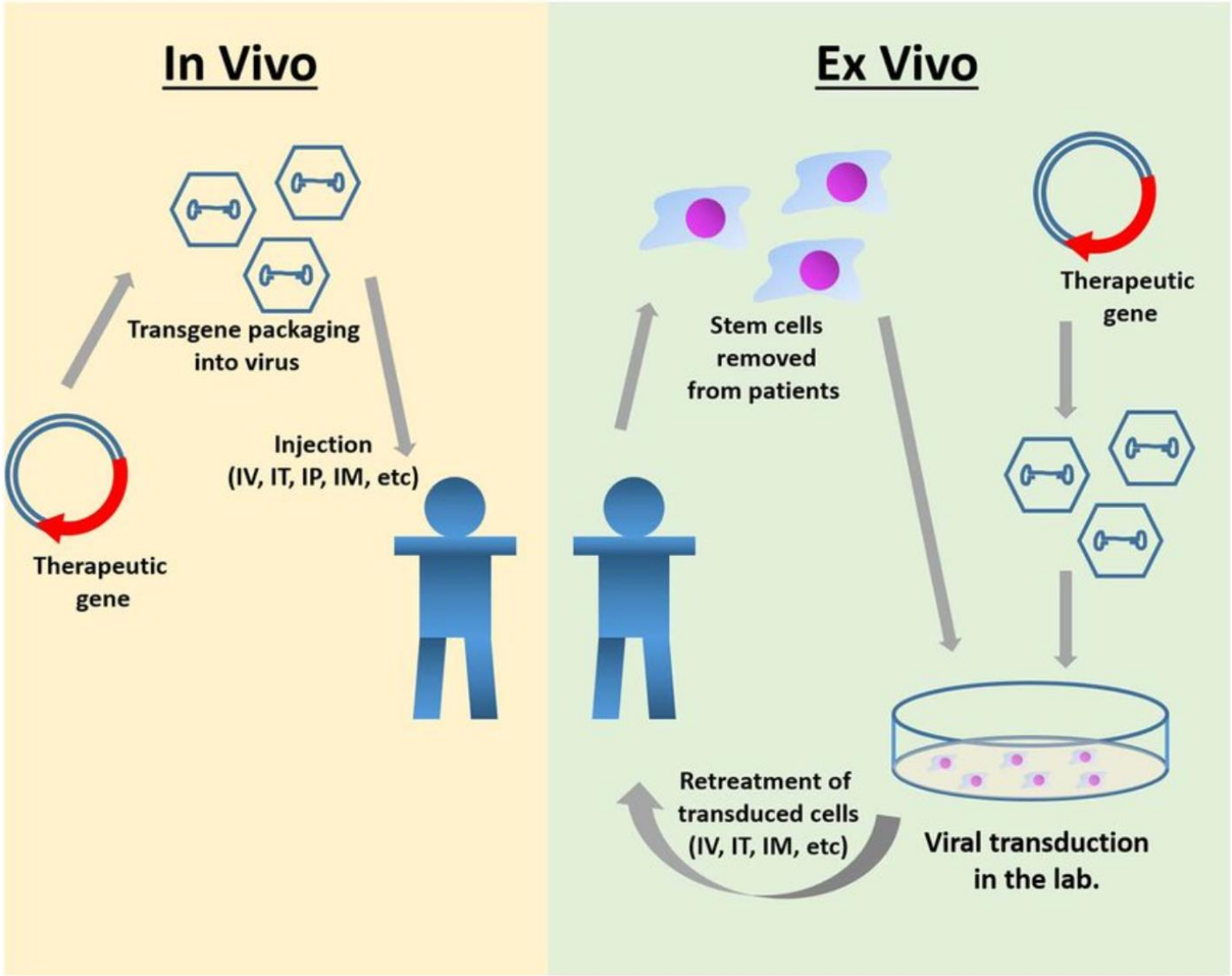
Gene Therapy Delivery Systems



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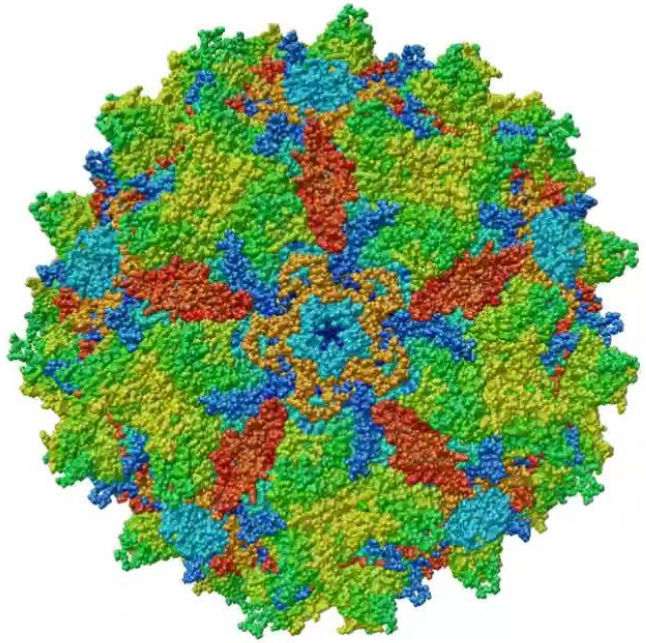
Adeno-Associated Virus (AAV) Vectors



Courtesy of M. Agbandje-McKenna
University of Florida

- Inherently non-pathogenic, unique nature of high-dose therapy
- Many serotypes provide wide range of tissue tropism
- Persists long-term without integration
- Risk vs Benefit in favor of therapeutic benefit

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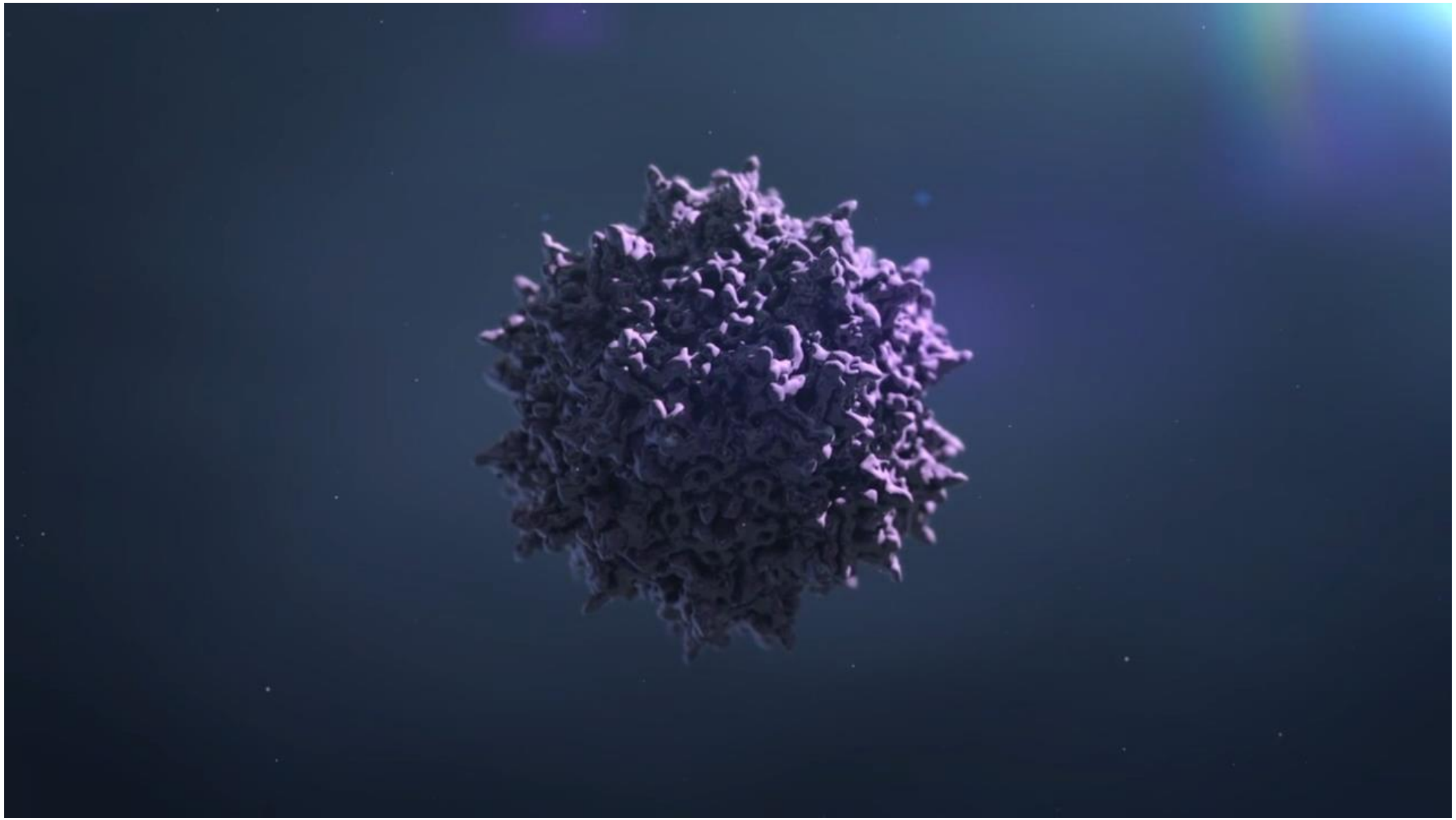

Participation in Gene Therapy Clinical Studies

Screening

1) Informed consent
    - Unique nature of gene therapy
    - Clinical features
2) Meet functional criteria
3) Age criteria

Baseline

1) Baseline evaluation
2) Timed function tests
3) Laboratory studies
4) Study schedule established

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Participation in Gene Therapy Studies

- What preparations or screenings take place?
- Is there genetic counseling?
- Are there any pre-treatments before receiving gene therapy?
- How frequently do the patient and family interact with different members of the treatment team?
- Do they travel long distances?
- How long to they stay?


Who is on the team?

Clinical Study Team

- **Principal Investigator** – responsible for overall study conduct
- **Co-investigators** – other specialists
- **Study Coordinator** – responsible as the manger of all study events
- **Clinical evaluator** – physical therapy
- **Travel coordinator** – manages logistics for patient travel and lodging
- **Study monitor** – external person to review all study data

The Role of Patient Organizations

Patient organizations play many roles in supporting patients and families during their gene therapy journey.

- Data collection to enhance disease understanding and accelerate effective therapies and drug development
- Connect patients treatment centers and specialists
- Connect patients to clinical trials
- Connect patients and caregivers to support programs

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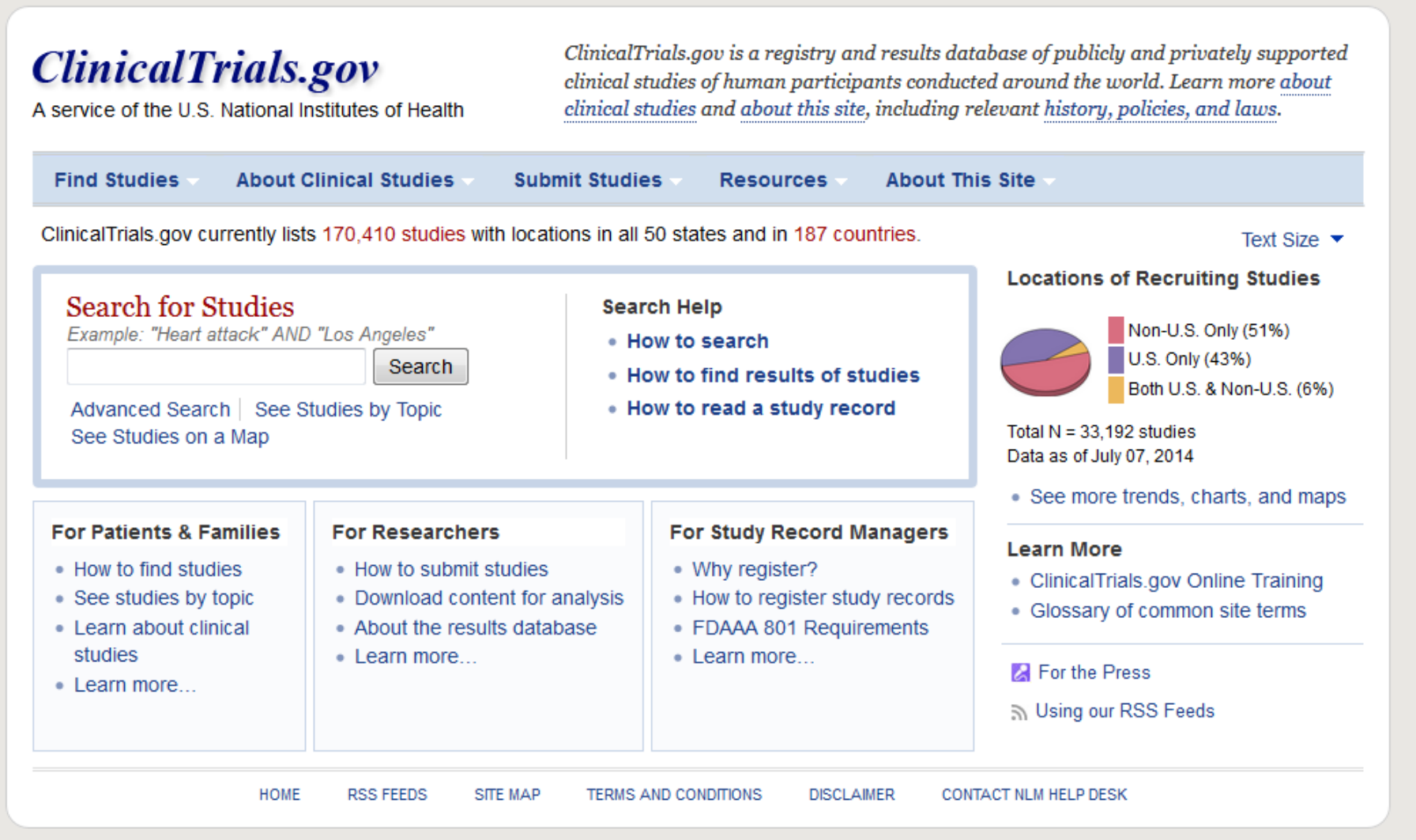

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http://www.ClinicalTrials.gov

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For those with medical conditions…

- Finding a trial in which to participate
- Finding an expanded access drug
- Finding a center of research for a given condition/intervention

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For those seeking study results…

- Linkage to PubMed
- Summary results in database
- Results for all pre-specified outcome measures
- Standardized format facilitating comparisons

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ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 315,240 research studies in all 50 states and in 209 countries.

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.

Find a study (all fields optional)

Status

- ○ Recruiting and not yet recruiting studies
- ● All studies

Condition or disease (For example: breast cancer)

Other terms (For example: NCT number, drug name, investigator name)

Country

Search | Advanced Search

Help | Studies by Topic | Studies on Map | Glossary

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List | By Topic | On Map | Search Details

Terms and Synonyms Searched:

Terms Synonyms	Search Results*	Entire Database**
Duchenne Muscular Dystrophy	43 studies	260 studies
Muscular dystrophy, Duchenne	42 studies	249 studies
Becker muscular dystrophy	5 studies	46 studies
Muscular Dystrophy	43 studies	443 studies
Dystrophy	43 studies	850 studies
Muscular	43 studies	7,513 studies
Muscle	7 studies	4,789 studies
musculus	--	2 studies
Duchenne	43 studies	262 studies

-- No studies found

* Number of studies in the search results containing the term or synonym

** Number of studies in the entire database containing the term or synonym

- [ ] Completed
- [ ] Withdrawn
- [ ] Unknown status†

Expanded Access ⓘ : ⊞

Eligibility Criteria ⊟

Age ⓘ :

years OR

Age Group ⓘ:

- [ ] Child (birth–17)
- [ ] Adult (18–64)
- [ ] Older Adult (65+)

Sex ⓘ :

- (•) All
- ( ) Female
- ( ) Male

- [ ] Accepts Healthy Volunteers ⓘ

Study Type ⊞

Study Results ⊞

Study Phase ⊞

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
2	☐	Recruiting	Microdystrophin **Gene Transfer** Study in Adolescents and Children With DMD	• **Duchenne Muscular Dystrophy**	• Genetic: SGT-001	• University of Florida Gainesville, Florida, United States • University of Massachusetts Medical School-Worcester Worcester, Massachusetts, United States
3	☐	Recruiting	A Randomized, Double-blind, Placebo-controlled Study of SRP-9001 for **Duchenne Muscular Dystrophy** (DMD)	• **Muscular Dystrophy, Duchenne**	• Drug: SRP-9001 • Drug: Placebo	• David Geffen School of Medicine at UCLA Los Angeles, California, United States • Nationwide Children's Hospital Columbus, Ohio, United States
4	☐	Recruiting	Endomysial Fibrosis, **Muscular** Inflammatory Response and Calcium Homeostasis Dysfunction in **Duchenne Muscular Dystrophy**	• **Duchenne Muscular** Distrophy (DMD)	• Other: Muscle biopsy	• UH Bordeaux Bordeaux, France • UH Lille Lille, France • Montpellier University Hospital Montpellier, France • (and 4 more...)

What are the critical inclusion/exclusion criteria for clinical trials?

Example: Participation in Clinical Studies for Duchenne Muscular Dystrophy

Included

1) Must have Duchenne
   - Defined by mutation
   - Clinical features
2) Meet functional criteria
3) Age criteria

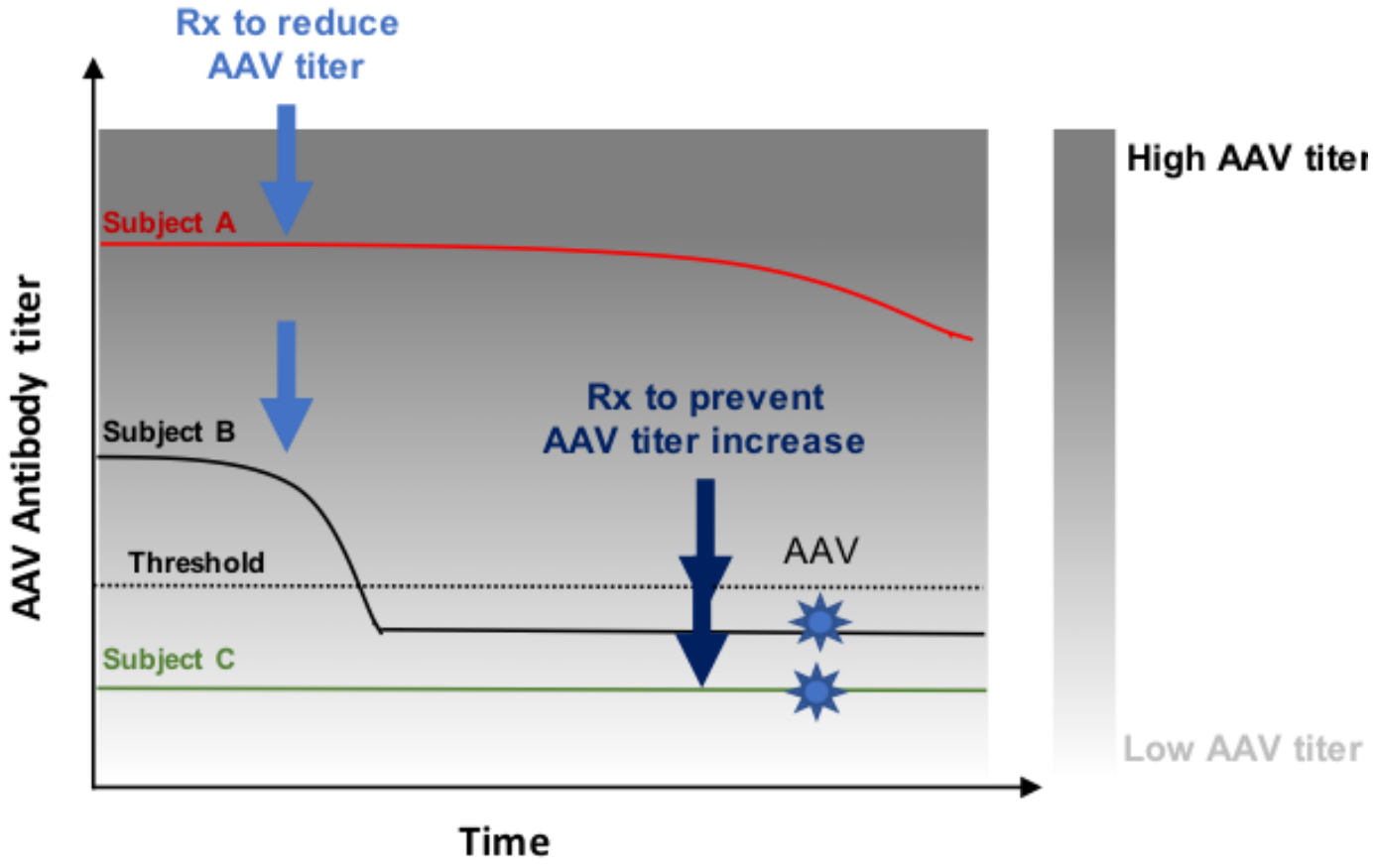
Excluded

1) Ambulatory / functional status
2) Drug therapy – eg, steroids
3) Other study participation
4) AAV exposure status

What are AAV antibodies and why do they matter?

- About **50-60%** of individuals may have prior AAV exposure.
- Preimmunity of AAV is an exclusion criteria for most of studies.

1) Is the threshold used in clinical trials appropriate?
2) What is the most effective immunomodulation regimen to decrease levels of preexisting AAV immunity?
3) What level of preexisting antibody precludes treatment?



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Is receiving gene therapy durable for the life-span?

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Is receiving gene therapy durable for the life-span?

MAYBE… but probably NOT!

Early exposure = Less durable

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Take Home

- Viral vectors can be made in sufficient quantity and quality for registration studies – commercial supply is an ongoing challenge.
- Prevention is required to block antibodies to AAV
- Early exposure = Less durable
  BUT … Primary immune response to AAV can be blocked

Take Home

- Pre-existing antibodies can be treated to allow for AAV gene therapy.
- Gene therapy is associated with side-effects/risk that must be justified with long-term benefit.

Gene delivery to patients at the bedside

Jerry Mendell, MD
Principal Investigator
Center for Gene Therapy,
The Research Institute of Nationwide Children's

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Madilyn Yang (far left) has been battling a rare breathing disorder since birth called Central Congenital Hypoventilation Syndrome (CCHS) or Ondine's Curse.

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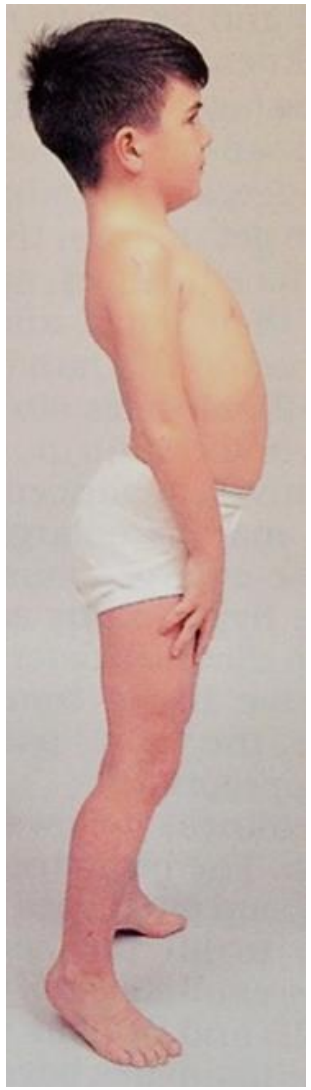
Gene delivery to patients at the bedside

Alone we are rare. Together we are strong.®

Gene Therapy for Muscular Dystrophy



- Duchenne Muscular Dystrophy
- Most Common Form of Childhood Muscular Dystrophy
- Currently in Clinical Trial

DMD is an example to show how gene therapy is done.

Similar methods are applied to other diseases

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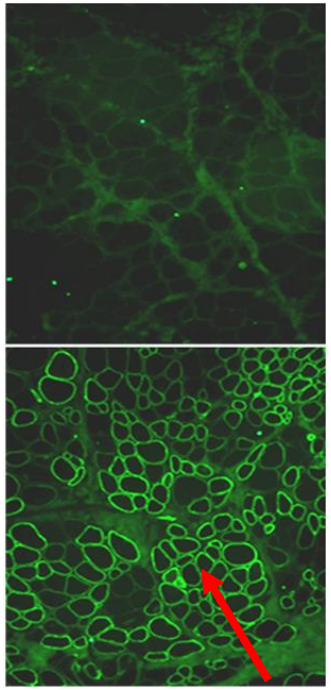
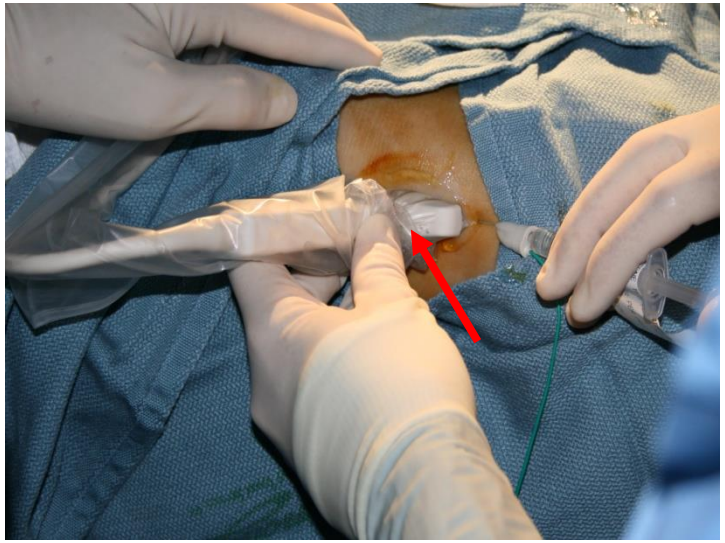
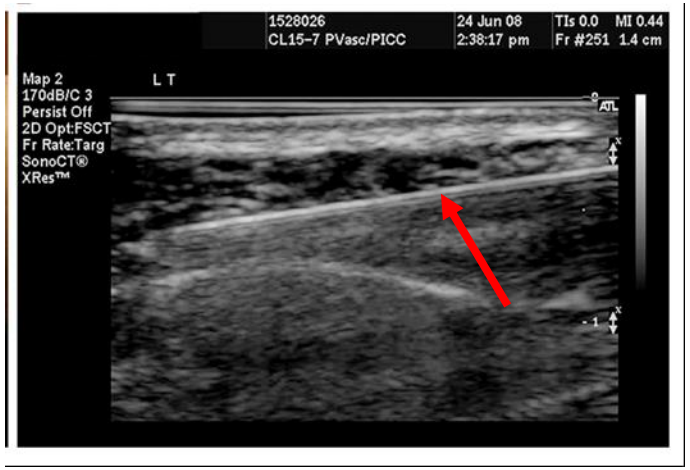
Gene Delivery Was Limited by Technology in our First Gene Therapy Trials



Excellent Gene Expression



Ultrasound guided Gene Delivery (sound waves into muscle)



Gene injected directly into muscle through an inserted needle

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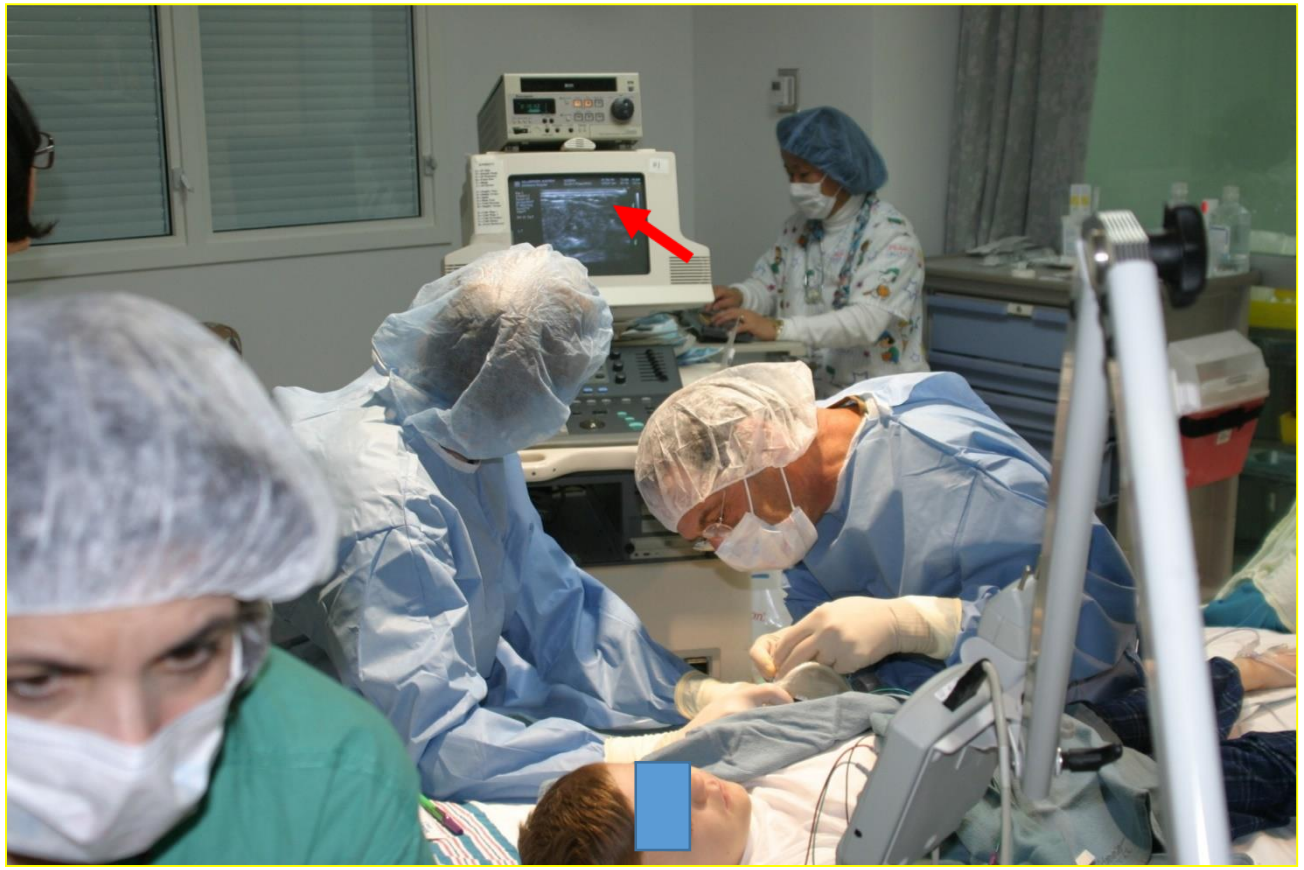
Gene Therapy for Muscular Dystrophy

March 28, 2006



Needle inserted with help of Radiologist controlling needle placement with sound waves to muscle

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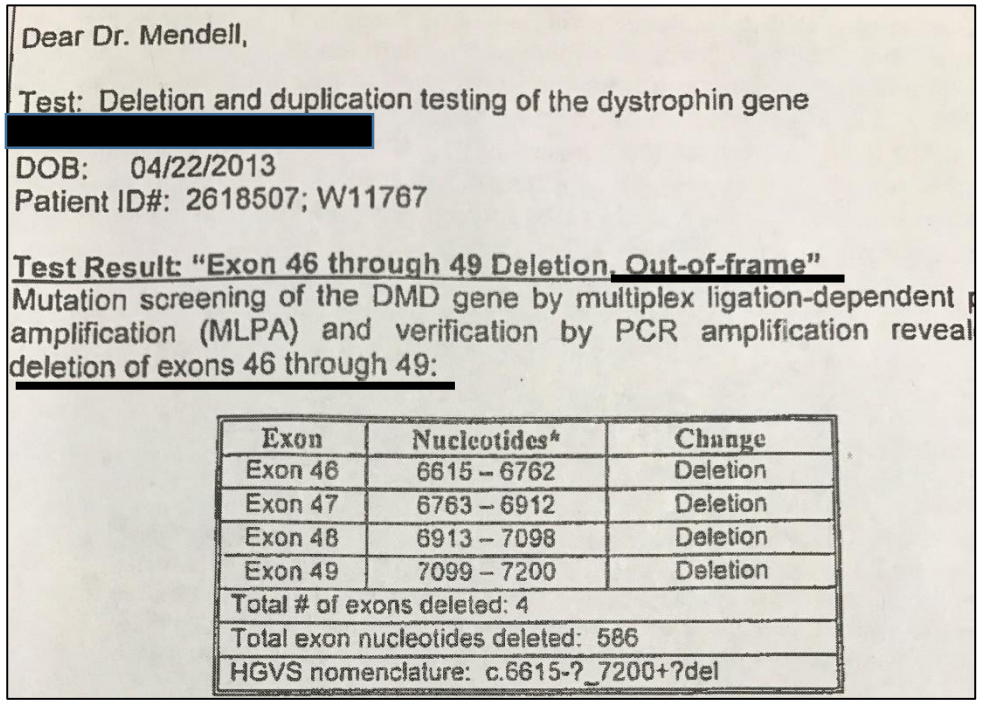
Technology Improved: Gene Delivery through the circulation to reach all muscles



Dear Dr. Mendell,

Test: Deletion and duplication testing of the dystrophin gene

[redacted]

DOB: 04/22/2013
Patient ID#: 2618507; W11767

Test Result: "Exon 46 through 49 Deletion, Out-of-frame"
Mutation screening of the DMD gene by multiplex ligation-dependent p
amplification (MLPA) and verification by PCR amplification reveal
deletion of exons 46 through 49:

Exon	Nucleotides*	Change
Exon 46	6615 – 6762	Deletion
Exon 47	6763 – 6912	Deletion
Exon 48	6913 – 7098	Deletion
Exon 49	7099 – 7200	Deletion
Total # of exons deleted: 4		
Total exon nucleotides deleted: 586		
HGVS nomenclature: c.6615-?_7200+?del		

Critical Steps before Clinical Trial

- Confirm the DMD Gene Mutation (or gene mutation for any clinical trial)
- Check for antibodies to AAV

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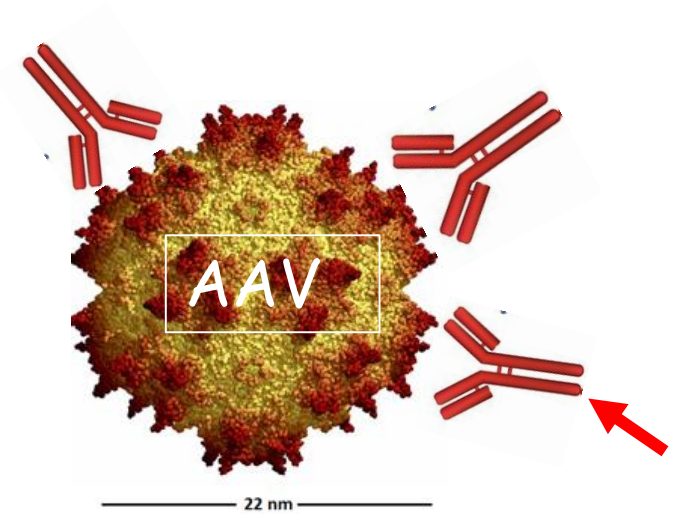
Making Sure No Antibody to AAV



Antibody

- Antibody could bind to AAV and block entry to target organ
- Requires a blood test to measure antibodies
- Takes about 4-7 days for lab result
- Must be done for any clinical gene therapy trial

Blood Tests Screened for risk factors for gene delivery

GENERAL CHEMISTRY		
SODIUM		140
POTASSIUM		3.1 ↓
CHLORIDE		108 ↑
CARBON DIOXIDE		27
BUN		15
CREATININE	*	<0.15 ↓
GLUCOSE	*	80
CALCIUM		9.4
MAGNESIUM		
PHOSPHORUS		
TOTAL PROTEIN		6.2
ALBUMIN		3.8
ALT	*	396 ↑
AST	*	222 ↑
ALKALINE PHOSPHATASE		87 ↓
BILIRUBIN, TOTAL		0.1
BILIRUBIN TOTAL (T...		<0.1 ↓
INDIRECT BILIRUBIN		0.0 ↓
DIRECT BILIRUBIN		0.1
GGT	*	12
AMYLASE		59

- Check for blood tests that could indicate a complication especially liver, kidney, diabetes
- Patient must be in good health except for genetic disease and done for any gene therapy trial

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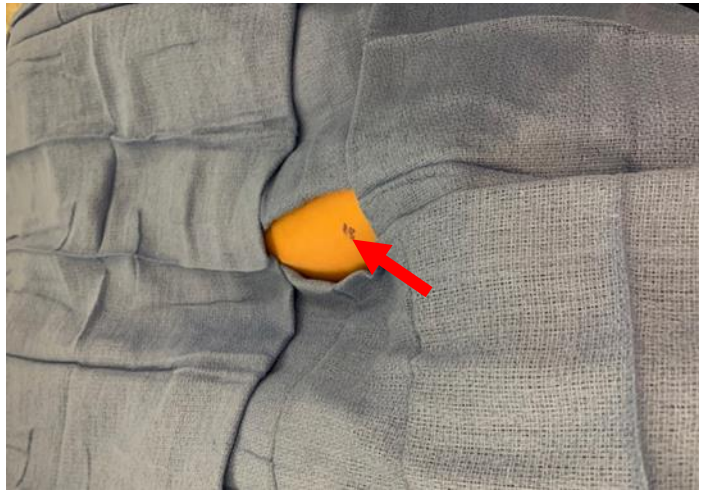
Muscle Biopsy Pre-Treatment

Prepares for comparison post gene delivery

Patient put to sleep



Muscle biopsy for muscle disease

Other gene therapy trials include other tests:
MRI heart, liver, kidney, or brain conditions

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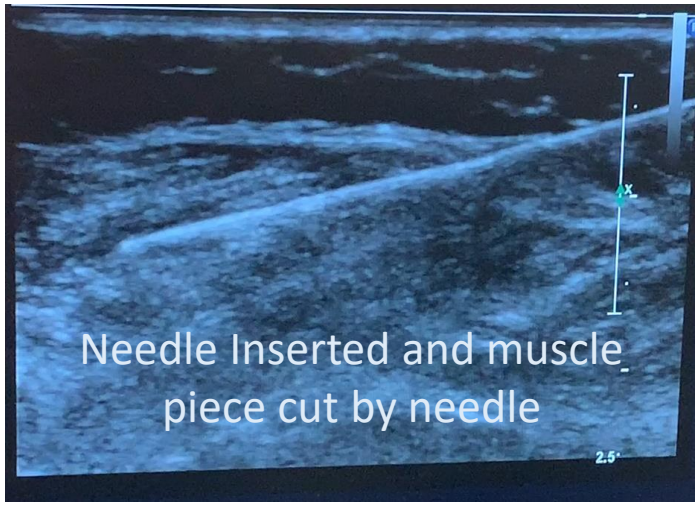
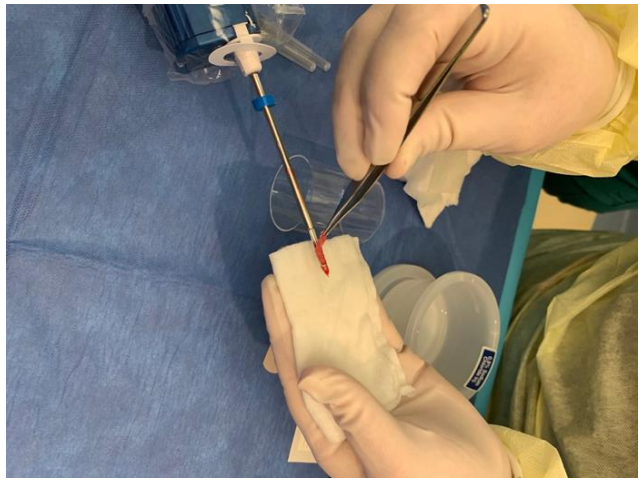
Muscle Biopsy Pre-Treatment

Same Procedure Done Post Gene Delivery





Needle Removed and
muscle sent to lab

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Gene Deliver through the circulation

Parents with Child During Delivery

Family together and excited

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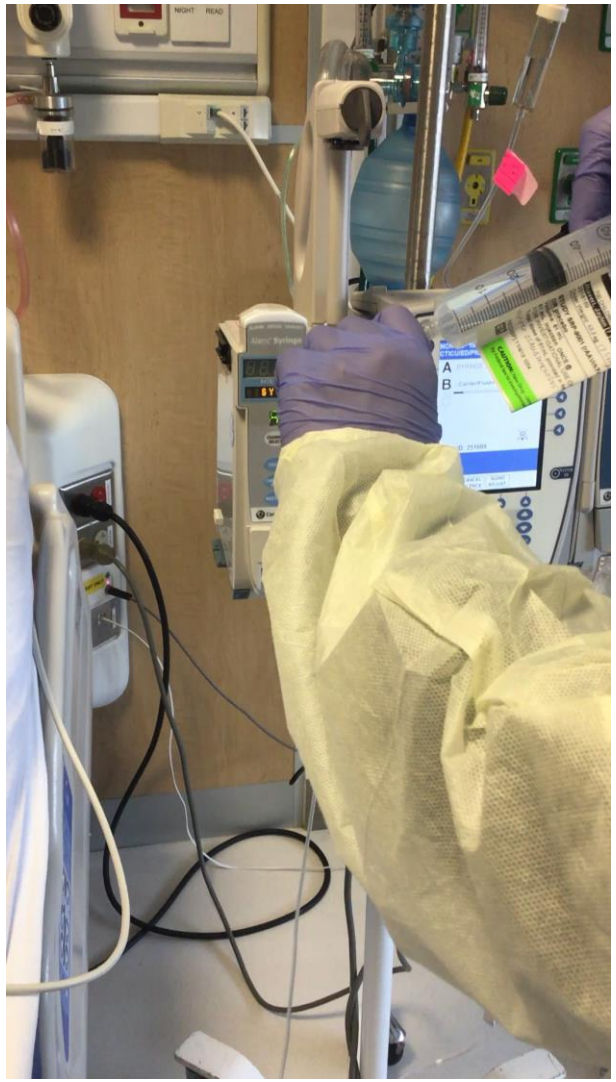
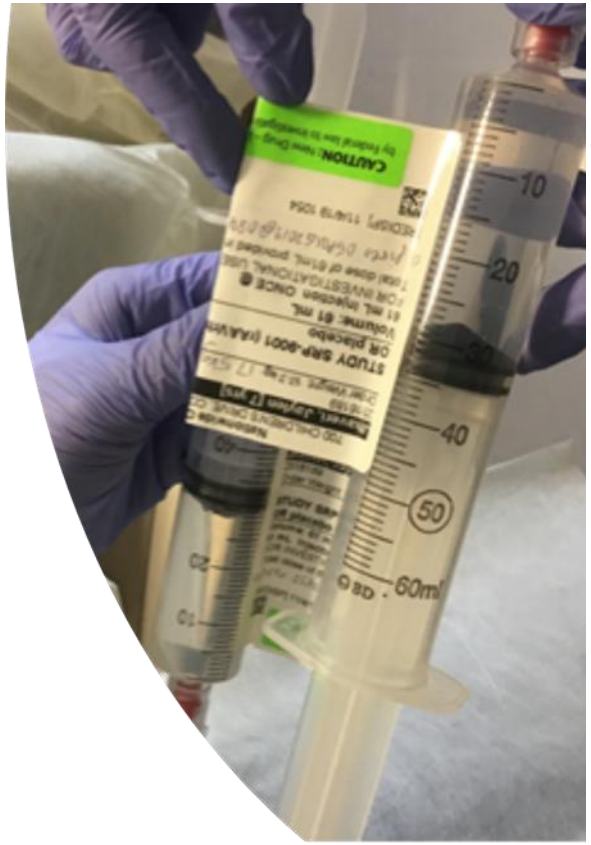
Gene from Pharmacy Loaded for Delivery in infusion pump





Procedure for gene delivery the same for other gene therapies

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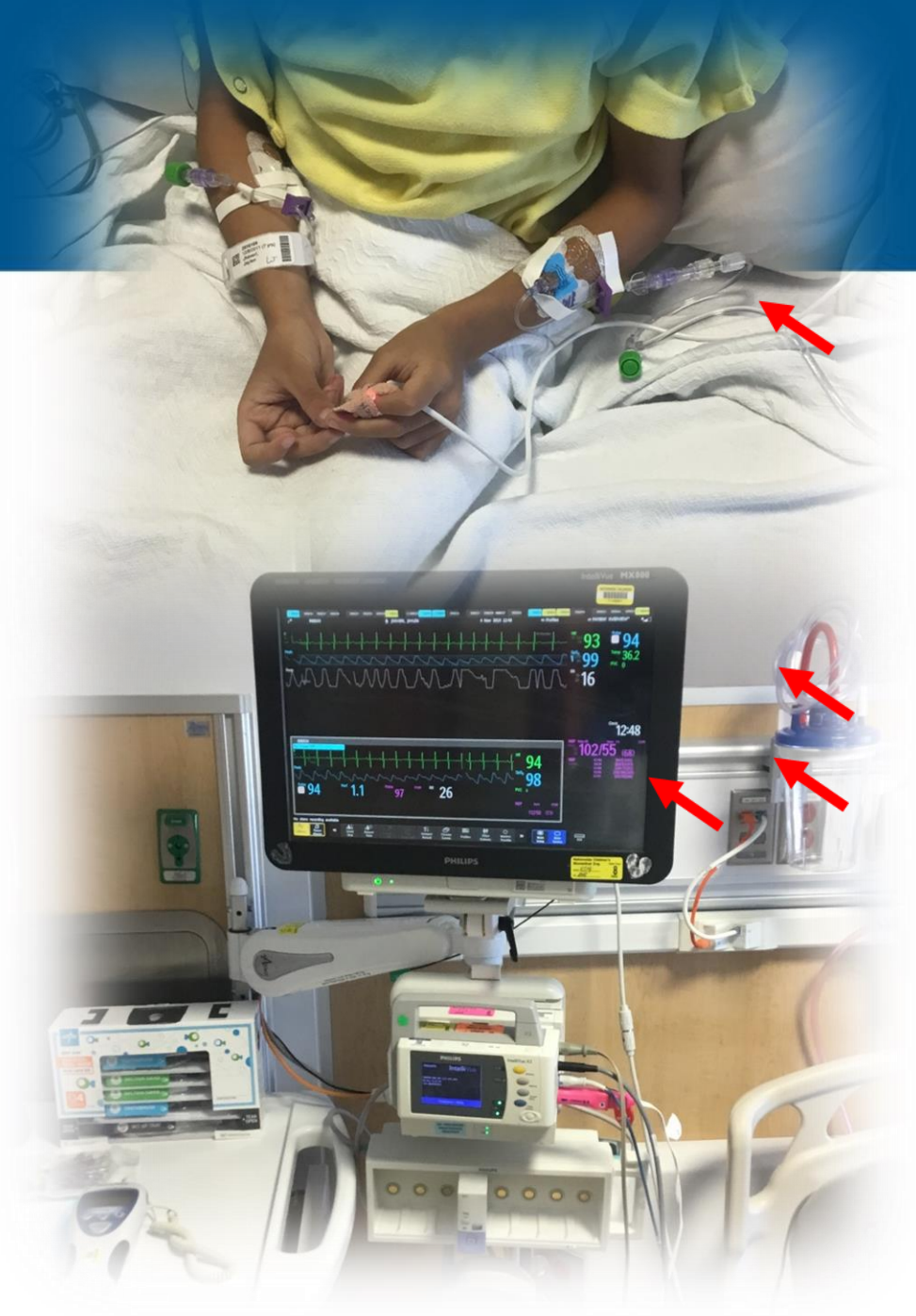
Careful Monitoring during Gene Delivery

Heart Rate

Blood Pressure

EKG



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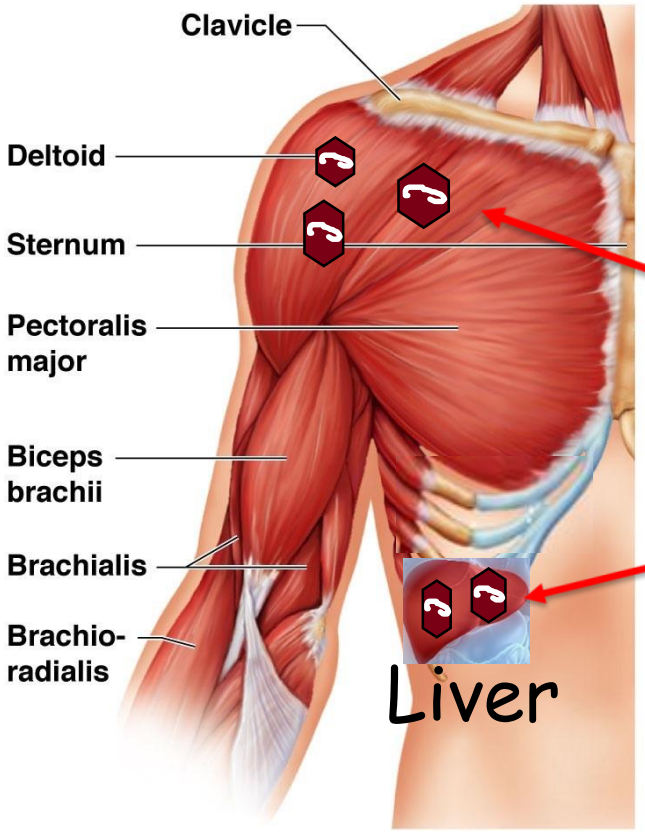
AAV Delivered to Muscle and Liver (and elsewhere)



Gene Delivery for other trials exactly the same except the target will be other organ

Prednisone is used to suppress Liver inflammation from AAV

May be Nausea and Vomiting after Gene Delivery

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Frequent Blood Tests for Side Effect

Blood taken every 2 weeks for 3 months

Abnormal liver tests

GENERAL CHEMISTRY		
SODIUM	140	141
POTASSIUM	3.1	4.2
CHLORIDE	108	102
CARBON DIOXIDE	27	26
BUN	15	15
CREATININE	<0.15	0.19
GLUCOSE	80	95
CALCIUM	9.4	9.9
MAGNESIUM		
PHOSPHORUS		
TOTAL PROTEIN	6.2	7.9
ALBUMIN	3.8	4.6
ALT	396	637
AST	222	599
ALKALINE PHOSPHATASE	87	148
BILIRUBIN, TOTAL	0.1	
BILIRUBIN TOTAL (T...	<0.1	0.7
INDIRECT BILIRUBIN	0.0	
DIRECT BILIRUBIN	0.1	
GGT	12	871
AMYLASE	59	
CK	8,906	
LDH	1,567	

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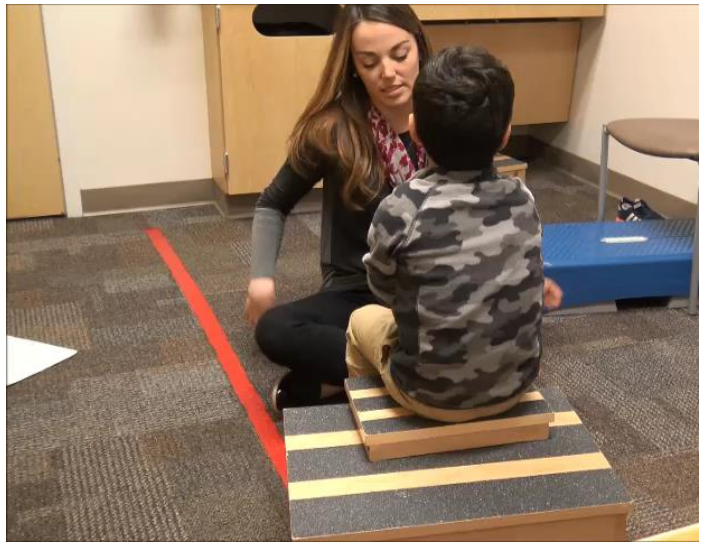
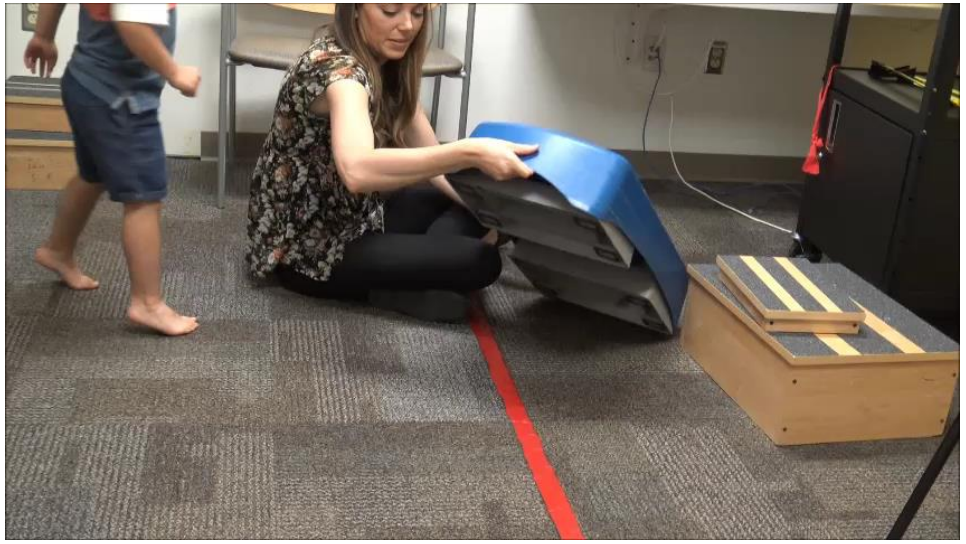
Testing to see if there is benefit
Examples of NSAA



Also Timed Tests:
- 100m walk/run
- Climbing Stairs
- Time to Rise



North Star Ambulatory Assessment
17 measures

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Positive Results for Gene Therapy
Example in Spinal Muscular Atrophy

Gene Therapy at 2 months
now sitting at 6 months later

SMA Infants never learn to sit
Now all following gene therapy are able to sit

Patient consent was granted for the use of these images.

Looking Good
4 years after Gene Therapy
day 28 following birth

“Bye Mom”
Off to School!

Thanks to all Patients and Families

Clinical Trials are works in progress with
collaboration between
patients, families, and Gene Therapy Centers

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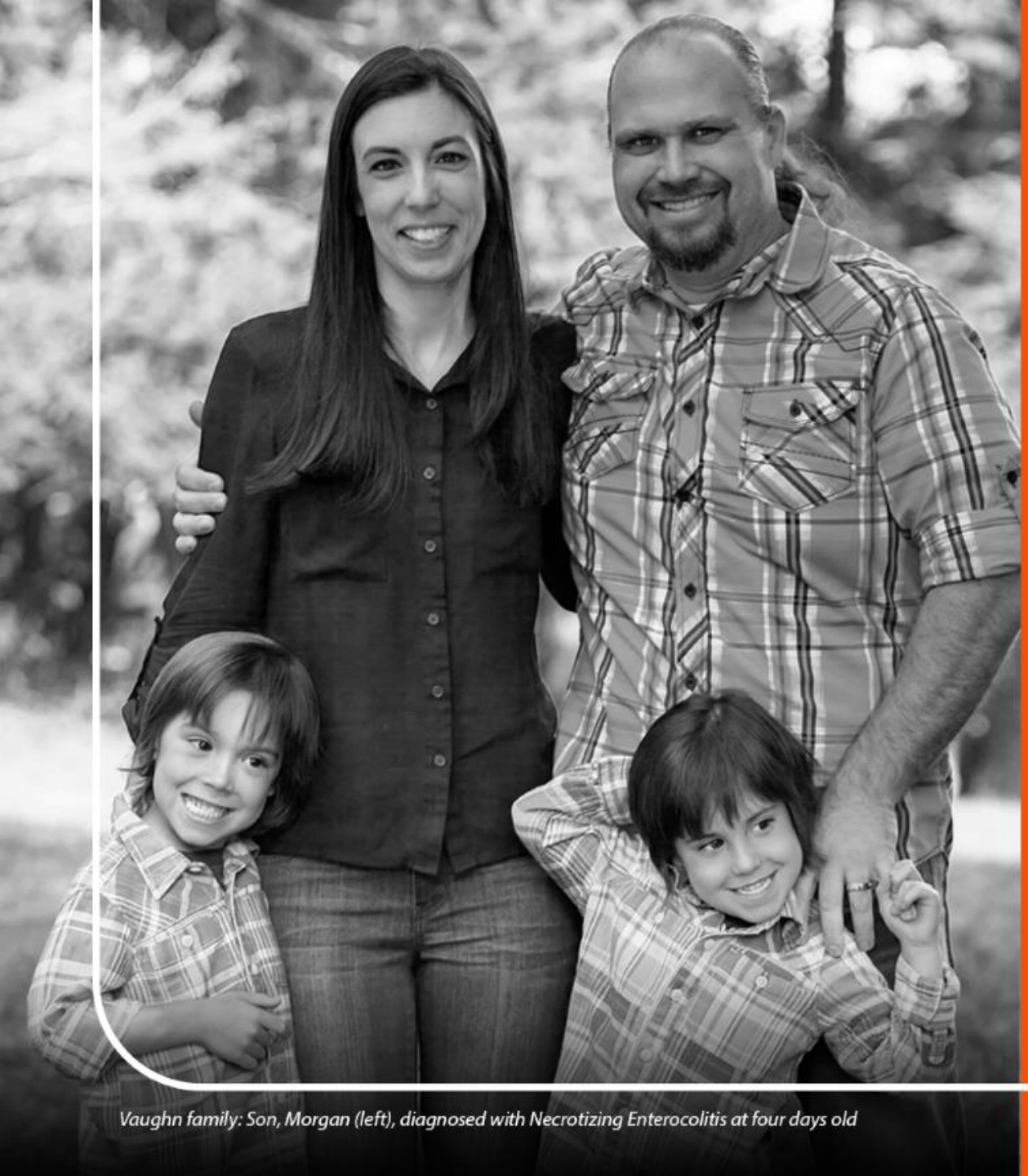

Vaughn family: Son, Morgan (left), diagnosed with Necrotizing Enterocolitis at four days old

Question and Answer Session

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Resources for Patients and Caregivers

Clinical Trials

Clinicaltrials.gov or asgct.org/clincialtrials

National Institutes of Health

https://ghr.nlm.nih.gov/primer/therapy/genetherapy

Food and Drug Administration

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

ASGCT

https://www.asgct.org/education/gene-therapy-basics

NORD

https://rarediseases.org/video-topic/research-science/#watch-39678

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Questions?

Submit your questions in the chat box.

Dr. Mendell and Dr. Byrne will answer them in the order in which they came in and based on relevance to the discussion.

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