Disclosures/CME

• No relevant financial relationships
• All patients and parents have given me permission to discuss their cases and use their images
Objectives
1) Community/Relationships
2) Take chances
3) Read the Book!
4) Share your experience

Outline

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>The Denger Family</td>
</tr>
<tr>
<td>2014</td>
<td>Letter to Rich Peterson</td>
</tr>
<tr>
<td>2015</td>
<td>Physician Leadership Development Fellowship</td>
</tr>
</tbody>
</table>

If life were easy and not so fast...I wouldn’t think about the past...
Just a few old guys who set the stage...

Community! Relationships!

Provider Leadership Development Fellowship

Building Leadership Capacity

The Provider Leadership Development Fellowship (PLDF) program was designed to help emerging provider leaders from across the MaineHealth system develop their leadership skills, knowledge and capacity. The core content of the PLDF program is a series of one-day learning sessions, each focusing on a different, essential leadership skill or competency. Each learning session is led by an experienced MaineHealth provider leader and features local, regional or national experts.

Meet the Faculty

Facility members are recognized for their leadership skills and strong interest in developing leadership capacity in other physicians.

+ How can I be nominated?
+ What is expected of PLDF program participants?
+ What are the program goals?
+ What are the program benefits?
2015

• Caroline Chaloner
• Pediatric PT
• 5 different specialized neuromuscular evaluations

Duchenne

- X-linked genetic disorder
- Dystrophinopathy
- Chronic, progressive
  - Cardiopulmonary systems eventually affected
- Very elevated CK level
  - Molecular genetic testing → Exon deletions, duplications
- Steroids to prolong ambulation
- Supportive therapy otherwise, life expectancy late 20’s/early 30’s
- Gene therapies now exist
Exon skipping therapy

WHAT IS THE DIFFERENCE BETWEEN IN-FRAME VS OUT-OF-FRAME ERRORS?

If you or your child have a deletion mutation, you have probably heard the terms in-frame and out-of-frame. Sometimes this is referred to as the reading frame rule.

In-Frame

A deletion is in-frame if the reading frame of the gene is preserved and not disrupted, so a dystrophin protein can be made. The protein may be shorter than normal, but it is still functional. In-frame deletions typically result in Becker muscular dystrophy, which usually has a more mild presentation compared to Duchenne because there is some dystrophin protein present in the cells.

Out-of-Frame

A deletion is out-of-frame if the reading frame is completely disrupted, so that no dystrophin protein can be made. Out-of-frame deletions typically result in Duchenne muscular dystrophy, which usually has a more severe presentation compared to Becker because there is no dystrophin protein present in the cells.

It is important to remember that this reading frame rule is not always perfect. There are some out-of-frame deletions that cause Becker, and some in-frame deletions that cause Duchenne. Sometimes a child’s diagnosis will be “intermediate or unclear” until the child grows older and their progression can be observed. Please speak with your doctor or genetic counselor if you have questions.

Eteplirsen for the treatment of Duchenne muscular dystrophy
Eteplirsen for the treatment of Duchenne muscular dystrophy

CHANGE FROM BASELINE (METERS)


Approving a Problematic Muscular Dystrophy Drug

Implications for FDA Policy

One partial solution could be the adoption of novel regulatory models, such as limited approval with intensive collection of new clinical evidence, before a drug becomes universally available. As a further step, drugs that have not yet shown clinical outcome benefits could be made available at just the cost of production, or most profits could be kept in escrow, until adequate trials are completed.

Patients with DMD need better treatments, and drugs like eteplirsen might one day fill that role. For now, though, the drug has provided a worrisome model for the next generation of molecularly targeted therapies: demonstrate a slight difference in a laboratory test, activate the patient community, win approval, and charge high prices, while relying on limited regulatory follow-up.
December 2016

• Patrick Denger
• My first prescription of a genetic therapy – eteplirsen!
• Lots of uncertainty
• Take Chances!

Spinal Muscular Atrophy

• AR disorder, deletion or mutation of exon 7 of SMN1 gene on 5q
  • 95% of individuals have homozygous deletion
• Affected individuals have variable copy numbers of SMN2
  • SMN2 a paralog of SMN1, producing low but essential levels of SMN protein
  • The more copies, the milder the disease
• 1:54 carrier frequency
• Incidence of 1:10,000-11,000 births, prevalence of ~1-2:100,000
• Historically the leading monogenic cause of death in infancy
Spinal Muscular Atrophy

- **Type 1**
  - < 6 months of life, most severe form
  - Accounts for 60% of cases
  - Generally 2 copies of SMN2
- **Type 2**
  - > 6 months of life, sit but never learn to walk
  - Accounts for 30% of cases
  - Generally 3 copies of SMN2
- **Type 3 or 4**
  - Accounts for remaining 10% of cases
  - Generally 4 or more copies of SMN2

SMA Treatments – Nusinersen - 2017

- **Anti-Sense Oligonucleotide (ASO)**
  - Modifies pre-mRNA splicing to promote exon 7 inclusion in SMN2 mRNA transcripts
  - *SMN Up-Regulating Therapy*
  - More full length SMN protein produced
  - Intrathecal injection
    - 4 loading doses in first 60 days
    - One dose every 4 months thereafter
Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

![Graph A: Event-free Survival](image)

**Event-free Survival (%)**
- Hazard ratio for death or permanent assisted ventilation, 0.33 (95% CI. 0.32–0.89)
- **P=0.005**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Week</th>
<th>Nusinersen</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>80</td>
<td>69</td>
<td>56</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>39</td>
<td>31</td>
</tr>
</tbody>
</table>

![Graph B: Overall Survival](image)

**Overall Survival (%)**
- Hazard ratio for death, 0.37 (95% CI. 0.18–0.77)
- **P=0.004**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Week</th>
<th>Nusinersen</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>80</td>
<td>69</td>
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</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>39</td>
<td>31</td>
</tr>
</tbody>
</table>

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Research Report

Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening

![Algorithm Diagram](image)

Table 1: Summary of motor milestone achievements of infants receiving nusinersen in ENDEAR versus NURTURE clinical trials

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Total number of infants achieving milestone, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head control (full)</td>
<td>ENDEAR* (Symptomatic patients; N = 73)</td>
</tr>
<tr>
<td></td>
<td>NURTURE† (Pre-symptomatic patients; N = 13)</td>
</tr>
<tr>
<td>Sitting (independent; stable, pivot)</td>
<td>16773 (22)</td>
</tr>
<tr>
<td>Standing (stands with support, unaided)</td>
<td>6773 (8)</td>
</tr>
<tr>
<td>Walking (cruising, walking)</td>
<td>0773 (0)</td>
</tr>
</tbody>
</table>

*SMN Up-Regulating Therapy
†SMN survival motor neuron

Fig. 1. SMA Newborn Screening Treatment Schematic for SMN-Up-Regulating Therapy. SMA = spinal muscular atrophy; SMN = survival motor neuron.
November 2017
Local filmmaker honors brother with movie

"Brothers," co-produced by Mike Norton and Reggie Groff, will be shown in Westbrook on Nov. 15.

Maine Filmmaker Showcase: BROTHERS - MFA

This is a film about a family who have faced incredible adversity but continue to push forward. It centers around Mike, an artist and filmmaker, wheelchair bound with Muscular Dystrophy and only the use of two fingers, who is grappling with the recent loss of his brother and baby cousin. Mike’s younger brother, TJ, the athletic, charismatic and cross potential powerlifter, took his own life after years of deepening schizophrenia. We learn what it takes to be a parent and a brother with overwhelmed grief and yet we see how love and creativity give the family the strength to carry on.
2019 Follow-up

Original ambulation measurements

Cardiopulmonary measurements

Fall 2018

- Meet Ronan
- Outpatient diagnosis
- PICU
- MGH for zolgensma
- Followed by nusinersen
Kathryn J. Swoboda, MD

Dr. Swoboda received her medical degree at The Northwestern Feinberg School of Medicine. She completed her neurology residency at the Harvard Longwood Neurology Program at the Brigham and Women’s Hospital, and additional subspecialty training in Clinical Genetics and Neuromuscular disease/Neurophysiology at Boston Children’s Hospital and the Lahey-Hitchcock Clinic. Dr. Swoboda’s research and clinical activities are dedicated to the diagnosis and treatment of neurologic disorders, especially neuromuscular diseases, movement disorders, and neurodegenerative disorders with childhood-onset.

Questions being addressed in the lab

<table>
<thead>
<tr>
<th>Questions</th>
<th>Projects</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do non-neural, systemic tissues contribute to Spinal Muscular Atrophy (SMA) pathology?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What clinical, genetic, and molecular tools can predict the age of onset, disease severity and course of pathogenesis for rare neuromuscular diseases?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What tissues, proteins, and molecular pathways can be targets of potential novel or co-adjuvant therapeutics for children and adults with neuromuscular diseases?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The U.S. Food and Drug Administration today approved Zolgensma (onasemnogene abeparvovec-xioi), the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and a leading genetic cause of infant mortality.

For Immediate Release: May 24, 2019
Expanding exponentially, like some recursive virus....

- Zolgensma approved in 2019
- AAV-9 gene transfer
  - Using adeno associated virus as a vector to deliver genetic material
  - Does not integrate into the patient genome
  - Low immunogenicity
  - Delivery of a fully functional SMN gene into motor neurons
  - AAV-9 capsid shell crosses BBB
  - Contains human SMN transgene
  - Introduced as a self-complementary double stranded molecule
    - Enables rapid onset of transcription and protein synthesis
  - Continuous promoter
Ronan making gains!!
2020 s/p zolgensma and ongoing nusinersen

Risdiplam – 2020!

The U.S. Food and Drug Administration today approved Evrysdi (risdiplam) to treat patients two months of age and older with spinal muscular atrophy (SMA), a rare and often fatal genetic disease affecting muscle strength and movement. This is the second drug and the first oral drug approved to treat this disease.

“Evrysdi is the first drug for this disease that can be taken orally, providing an important treatment option for patients with SMA, following the approval of the first treatment for this devastating disease less than four years ago,” said Billy Dunn, M.D., director of the Office of Neuroscience in the FDA’s Center for Drug Evaluation and Research.
Risdiplam

- Modifies the splicing of SMN2 mRNA to include exon 7
- Resulting in an increase in the concentration of the functional SMN protein
- Similar to nusinersen, upregulates functional SMN protein
- Only oral drug, given daily

Risdiplam SMA 1 Motor Function Improvement

<table>
<thead>
<tr>
<th>CHOP-INTEND Score at Baseline</th>
<th>Median CHOP-INTEND Score (range)</th>
<th>Median Change in Score from Baseline (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (N=43)</td>
<td>22.0 (8.0 to 37.0)</td>
<td>20.0 (-2.0 to 45.0)</td>
</tr>
<tr>
<td>Month 12 (N=38)</td>
<td>42.0 (13.0 to 57.0)</td>
<td></td>
</tr>
</tbody>
</table>

Threshold for response (≥4-point increase)
Overall baseline demographics were balanced between risdiplam and placebo/risdiplam groups

<table>
<thead>
<tr>
<th>Age at screening, years, median (range)</th>
<th>Risdiplam (n=120)</th>
<th>Placebo/risdiplam* (n=40)</th>
<th>Total (N=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–11</td>
<td>9 (2–25)</td>
<td>9 (2–24)</td>
<td>9 (2–25)</td>
</tr>
<tr>
<td>12–17</td>
<td>37 (36.9)</td>
<td>18 (30.0)</td>
<td>55 (30.0)</td>
</tr>
<tr>
<td>18–25</td>
<td>14 (11.7)</td>
<td>9 (11.3)</td>
<td>22 (12.2)</td>
</tr>
<tr>
<td>Age group, years, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>61 (50.8)</td>
<td>30 (50.0)</td>
<td>91 (50.8)</td>
</tr>
<tr>
<td>Male</td>
<td>59 (49.2)</td>
<td>30 (50.0)</td>
<td>89 (49.2)</td>
</tr>
<tr>
<td>SMA type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>64 (70.0)</td>
<td>44 (73.3)</td>
<td>128 (71.1)</td>
</tr>
<tr>
<td>3</td>
<td>36 (30.0)</td>
<td>16 (26.7)</td>
<td>52 (28.9)</td>
</tr>
<tr>
<td>SAMG2 copy number, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (2.5)</td>
<td>1 (1.7)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>3</td>
<td>107 (89.2)</td>
<td>51 (85.6)</td>
<td>158 (87.8)</td>
</tr>
<tr>
<td>4</td>
<td>10 (8.3)</td>
<td>8 (13.3)</td>
<td>18 (10)</td>
</tr>
</tbody>
</table>

*All infants (N=41)
April 2021 – Maine initiates Newborn Screen

- NBS assay:
  - PCR to detect presence of SMN1 in blood spot
  - Can identify SMN1 exon 7 deletions in all SMA patients while all unaffected patients showed presence of exon 7
  - Inexpensive, can be multiplexed to SCID assay
  - Pilots 100% PPV
  - Ongoing study of a 2nd PCR test to identify both homozygous and heterozygous SMN1 Exon 7 deletions and SMN2 copy number
What about >4 copies SMN??

<table>
<thead>
<tr>
<th>Test or Outcome Measure</th>
<th>Level of Change/Results Which Would Prompt Initiation of Treatment</th>
<th>Appropriate Age of Patient for Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMG/neuromuscular</td>
<td>Any active or chronic neurogenic change</td>
<td>All</td>
</tr>
<tr>
<td>CMAP</td>
<td>Below normative values for an age-matched child</td>
<td>All</td>
</tr>
<tr>
<td>Myoneurology</td>
<td>Decrease in extent of muscle contraction</td>
<td>≥4 years</td>
</tr>
<tr>
<td>Physical Exam/Reflexes</td>
<td>Any of the following: loss of reflexes, failure to meet or regression in ability to perform movements, proximal weakness, and weakness in trunk, righting, or rotation</td>
<td>≥4 years</td>
</tr>
<tr>
<td>CHOP INTEND</td>
<td>Failure to gain motor functions with age in keeping with normal development or a drop in total score from previous assessment</td>
<td>Infants</td>
</tr>
<tr>
<td>HINE</td>
<td>Failure to gain motor functions with age in keeping with normal development or a drop in total score from previous assessment</td>
<td>Infants</td>
</tr>
<tr>
<td>Hammerstein Functional</td>
<td>A failure to gain motor functions with age in keeping with normal development or a drop in total score from previous assessment</td>
<td>≥2 years</td>
</tr>
<tr>
<td>Motor Scale – Expanded</td>
<td>A failure to gain motor functions with age in keeping with normal development or a drop in total score from previous assessment</td>
<td>≥5 years</td>
</tr>
<tr>
<td>6MWT</td>
<td>A failure to gain motor functions with age in keeping with normal development or a drop in total score from previous assessment</td>
<td>Infants/Toddlers (Recommended 1 to 42 months)</td>
</tr>
</tbody>
</table>

CHOP INTEND: Children's Hospital of Philadelphia Infants Test of Neuromuscular Disorders; CMAP = compound muscle action potential; EMG = electromyography; HINE = Hammerstein Infant Neurological Exam; SMN2 = spinal motor neuron 2; 6MWT = six-minute walk test.
Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy

Alex R. Mentor, MD, PhD, 1, 2, 3, 4 * Tarish A. Ali-Ahmed, MD, 5 Beth J. Lohman, MD, 5 Mark A. McCullough, MD, 6 Linda H. Lenan, PT, PhD, 7, 8 Lindsay M. Altman, PT, DPT 7, 8 Nicholas P. Rosset, PT, DPT, 7, 8 John A. Assmann, PT, DPT, 7, 8 Jennifer R. Davis, MD, 7, 8 Hayley S. Scharf, PhD, 7, 8 Matthew H. Heffernan, MD, 8 and Richard L. Miller, MD, 1, 2, 3, 4

Greatest Development Milestones Achieved During the START Long-term Follow-up Study

Milestones are shown for the 16 patients in the therapeutic-dose cohort who received dosing early and had low baseline motor function (blue quadrant), those who received dosing early and had high motor function (orange quadrant), and those who received dosing late (gray quadrant). Values in parentheses are the age at which the milestone was achieved (in months). Patients were grouped according to baseline motor function (Children’s Hospital of Philadelphia Infant Test of Neuromuscular Development scores: <20 points [low] or ≥20 points [high]) and age at dosing (<3 months [early] or ≥3 months [late]). This figure was adapted with Akron permission from Leman et al.22
Ronan 2021 after changing to risdiplam

2021 Follow-up

Comparison of Long-term Ambulatory Function in Patients with Duchenne Muscular Dystrophy Treated with Eteplirsen and Matched Natural History Controls

A

B
Sarepta and New Exon Skipping Therapies

FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation

FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation

But if you ever need the names of those you couldn’t save....
With your past and your future precisely divided....

- AAV therapy?
- Stem cell therapy?
- Good old prednisone?
3 active trials now!

• Micro-Dystrophin Clinical Trials
  • Using AAV to deliver miniaturized dystrophin gene
  • Based upon clinical observations of mild Becker patients who are missing very large portions of the DMD gene
  • Open label/safety muscle biopsy study show increased micro-dystrophin expression and clinical improvement
Stem cell-based therapies for Duchenne muscular dystrophy

Congshuan Sun, Carlo Serra, Gabsang Lee, Kathryn Wagner

Departments of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, 21205, USA.

TWICE-WEEKLY GLUCOCORTICOSTEROIDS IN INFANTS AND YOUNG BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

Anne M. Connolly, MD, PhD, Craig M. Zaidman, MD, PAUL T. COLLIER, MD, PHD, MARY M. CRADOCK, PHD, KEVIN M. FLAMING, MD, RN, L. L. KUHN, MD, RICHARD S. FINKEL, MD, CRAIG M. McDIARMID, MD, SUSAN T. JOHNSON, MD, PAUL YANG, MD, S. L. BERNARDI, MD, CATHERINE A. SIENER, PT, PhD, JULIANE A. BERNARDI, MD, PAUL YANG, MD, S. L. BERNARDI, MD, CATHERINE A. SIENER, PT, PhD, and FOR THE MD ANDR DIABOLIC CLINICAL RESEARCH NETWORK

Current standard of care suggests early use of daily or twice-weekly corticosteroids for children starting before “substantial physical decline” without specifying an exact age. Controlled studies have never been performed in children younger than 4 years. This work suggests a different approach for this very young population. An additional limitation is that this study was not dose finding, and therefore it is possible that a lower dose might be equally efficacious. Because the effect was most profound in the most delayed children, twice-weekly GC appears to provide a safe approach for early treatment as long as weight is carefully monitored.
Summary of agents

• Duchenne:
• Current FDA approval:
  • Prednisone, deflazacort
  • 3 different exon skipping therapies accounting for ~29% of all mutations
• Future: AAV microdystrophin therapy, earlier intervention with twice weekly hormonal therapy

Summary of agents

• SMA:
• Current FDA approval:
  • Nusinersen/Spiranza, mRNA splicing modifier to upregulate SMN production, intrathecal only every 4 months, approved for all SMA types
  • Risdiplam/Evrysdi, mRNA splicing modifier to upregulate SMN production, daily oral therapy, approved for all SMA types
  • Onasemnogene Abeparvovev/Zolgensma, AAV-9 therapy to deliver fully functional SMN gene into motor neurons
Conclusions

• Community/Relationships!
• Take Chances!
• Read the book!
• Share your experience!
• Build it with your patients and your colleagues. You can’t get it done on your own.
• Get inspired by your patients and families – it’s ok to be uncomfortable and the only one doing something
• The great and knowledgeable Icculus
• The good and the bad, we all learn from each other