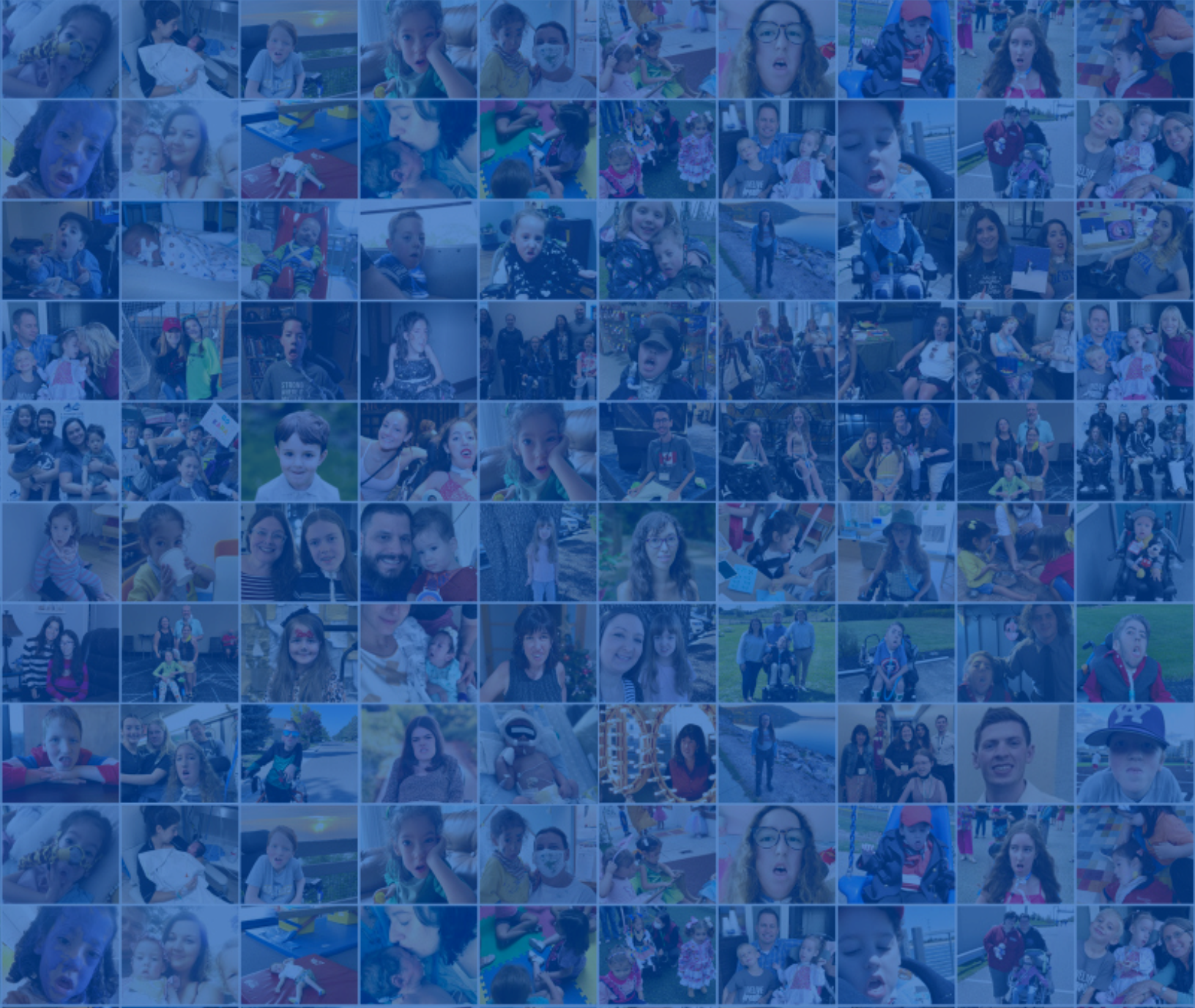
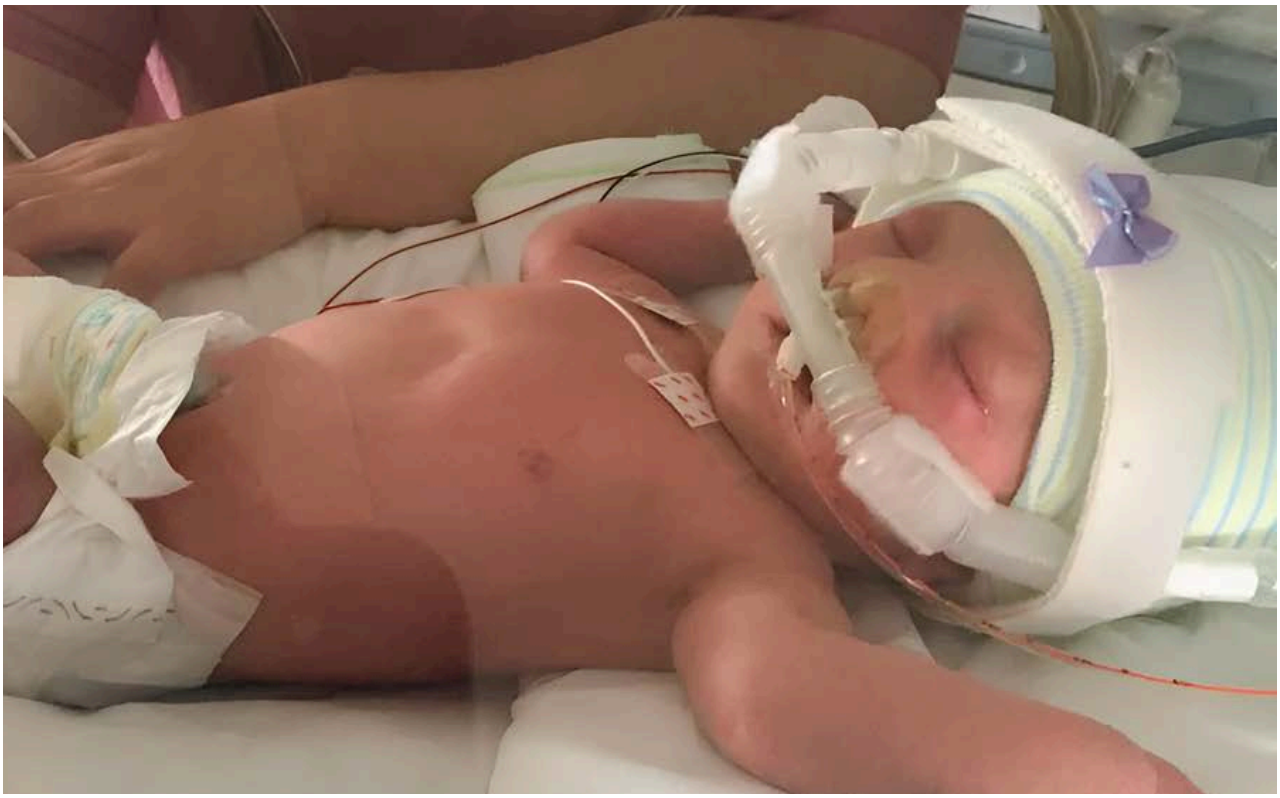


HELP US FIND TREATMENTS FOR NEMALINE MYOPATHY

A FOUNDATION BUILDING STRENGTH FOR NEMALINE MYOPATHY

Since 2008, AFBS has successfully brought together families affected by Nemaline Myopathy, top researchers, and industry partners to create connections, support NM patients, and advance research.

OUR MISSION



Our mission is to find treatments for the rare muscle disease Nemaline Myopathy.

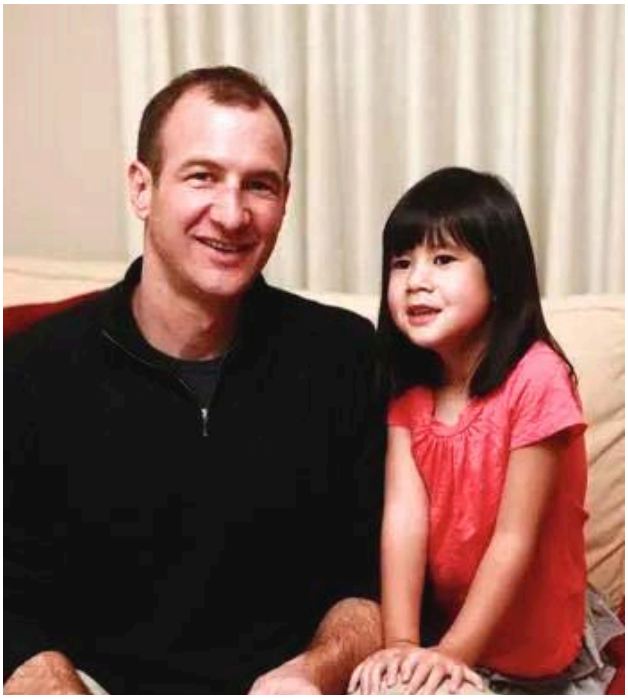
We work to address issues for our NM families from all angles, including advancing research, providing information about care, offering family support groups and ways to connect, and creating opportunities for in-person interaction and education at conferences and events.

OUR STORY

Marc and Dana Guillet founded **A Foundation Building Strength** in 2008, after the birth of their third child, Ava.

At birth, Ava had some obvious problems. Her hands and feet were mal-positioned and her cry was very weak. Her muscles were low tone or "floppy." Three weeks later, while in the neonatal intensive care unit, Marc and Dana were still learning how to care for their child that had no diagnosis.

Ava could not swallow milk on her own and on occasion would stop breathing in her sleep. Ava left the hospital with a tube passing from her nose to her stomach for feeding and a suction machine to manage her saliva which she could not swallow.



At 7 months, Ava had a feeding tube placed directly through her stomach wall and a muscle biopsy confirming a diagnosis of Nemaline Myopathy. There were no organizations dedicated to funding research for Nemaline Myopathy.

"Ava has gained incredible strength over the years, but our desire to help the entire Nemaline Myopathy community has created the world's leading non-profit organization dedicated solely to finding treatment, providing the NM community with information, support and raising awareness and advocacy for the rare disease."

- Marc Guillet

NEMALINE MYOPATHY

NM IS A RARE MEDICAL CONDITION THAT CAUSES MUSCLE WEAKNESS & VARIES IN SEVERITY FROM MILD SYMPTOMS TO PREMATURE MORTALITY.

Weak Body Muscles: People with NM may need wheelchairs or other physical support to get around.

Weak Face & Throat Muscles: Individuals with NM may have trouble speaking or swallowing.

Weak Breathing Muscles: People with NM may need the help of breathing machines.

NM doesn't affect brain development or cognitive functions like learning and thinking.

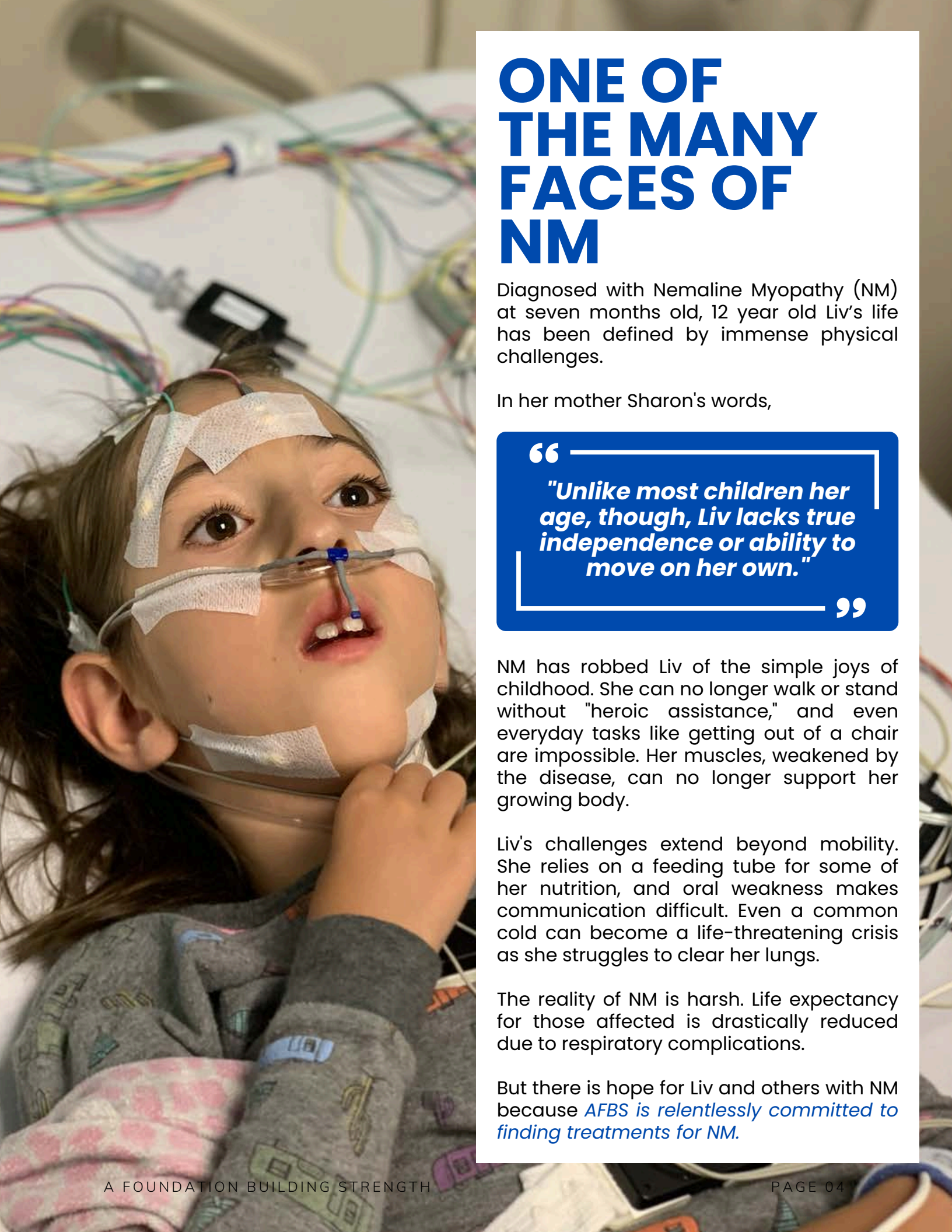
DID YOU KNOW?

NEMALINE MYOPATHY AFFECTS AN ESTIMATED **1 IN 50,000** PEOPLE. CURRENTLY NO TREATMENTS EXIST.

NM

CAN BE CAUSED BY MUTATIONS IN ONE OF 12 KNOWN GENES. MOST CASES ARE CAUSED BY MUTATIONS FOUND IN THE NEB GENE (50%) AND ACTA1 GENE (15-25%).

LEARN MORE ABOUT NM:



ONE OF THE MANY FACES OF NM

Diagnosed with Nemaline Myopathy (NM) at seven months old, 12 year old Liv's life has been defined by immense physical challenges.

In her mother Sharon's words,

> ***"Unlike most children her age, though, Liv lacks true independence or ability to move on her own."***

NM has robbed Liv of the simple joys of childhood. She can no longer walk or stand without "heroic assistance," and even everyday tasks like getting out of a chair are impossible. Her muscles, weakened by the disease, can no longer support her growing body.

Liv's challenges extend beyond mobility. She relies on a feeding tube for some of her nutrition, and oral weakness makes communication difficult. Even a common cold can become a life-threatening crisis as she struggles to clear her lungs.

The reality of NM is harsh. Life expectancy for those affected is drastically reduced due to respiratory complications.

But there is hope for Liv and others with NM because *AFBS is relentlessly committed to finding treatments for NM.*

OUR CHALLENGE

Currently there are no treatments or cure for Nemaline Myopathy (NM).

NM is a rare condition with a spectrum of severity requiring continuous disease management. The burden of care can be significant.

NM is a clinically and genetically heterogeneous disease, with a wide range of clinical phenotypes and an association with mutations in at least 12 known genes (ACTA1, NEB, TPM3, TPM2, TNNT1, TNNT3, CFL2, KBTBD13, KLHL40, KLHL41, LMOD3, MYPN, MYO18B). This necessitates varying approaches to studying, understanding, and treating the disease.

OUR PLAN

THE ROAD TO TREATMENT:

With philanthropic partnerships, AFBS can advance our work to find treatments for NM

01.

UNDERSTANDING NEMALINE MYOPATHY:

- We now understand genetic causes and inheritance
- We have a more comprehensive understanding of symptoms and how NM affects the body.
- Identified and characterized mutations in 12 genes that cause NM

02.

DEVELOPING THE RESEARCH ESSENTIALS:

- Developed and are utilizing mouse and zebrafish animal models
- Created patient derived cell lines and induced pluripotent stem cells
- Biomarker Identification
- Launched first NM Tissue Biobank
- Launched first NM patient-led registry
- Fully funding 3 year North American and Brazil study and partnering in UK

03.

THERAPEUTIC DEVELOPMENT

- Drug Screening: Exploring compounds for potential therapies
- Gene Therapy: Established and novel gene replacement strategies
- Gene Editing: Exploring cutting-edge technologies such as CRISPR/Cas9 to correct genetic mutations
- RNA Based Therepeutics: Exploring RNA Inhibitors and antisense oligonucleotides

04.

COLLABORATIVE RESEARCH

- AFBS Scientific Advisory Board: Established a collaborative network of researchers, clinicians, patient community and AFBS
- Scientific Conferences: Bring together world renowned researchers & affected individuals
- Data Sharing: Promoting open-access to data to accelerate research progress

05.

PATIENT SUPPORT

- Awareness: Increasing public and medical community awareness about NM (AFBS website, awareness resources, and social media)
- Support: Developing resources and support for patients and families (Congenital Myopathy Care Guide, NM Resource Kit, Consensus Statement on Standard of Care for Congenital Myopathies, and support groups)

06.

CLINICAL TRANSLATION

- Conducting preclinical trials in animal models to evaluate safety and efficacy of promising treatments
- Clinical Trials: Design and implement clinical trials for the most promising therapies, ensuring patient safety
- Regulatory Approval: Work with regulatory bodies to navigate the approval process for new treatments

IN PROGRESS

07.

LONG TERM GOALS

- Treatments: Our aim is to develop treatments for Nemaline Myopathy and improve the quality of life for those with NM through better management, supportive therapies, and disease modifying treatments.

A FOUNDATION BUILDING STRENGTH FOR NEMALINE MYOPATHY

OUR TEAM

Our **Board of Directors** is comprised of parents with affected children, as well as adults with NM. Our dedicated staff powers our mission and vision.

Marc Guillet
Founder & President | Board of Directors

Lyn Baier
Board Member

Sam Lipsick
Board Member

Matt and Kelly Lloyd
Board Members

Guilherme and Leticia Machado
Board Members

Boris and Sharon Shimanovsky
Board Members

Jen Tozer
Executive Director

Dr. Gus Dziewczapolski
Scientific Director

Stacy Cossette, MS
Program Director

The **Scientific Advisory Board** members bring a diverse background of expertise, leading the direction of Nemaline Myopathy research in the areas of ***clinical trial readiness, gene therapies, small molecules, industry engagement, data management, disease management, and patient engagement.***

Dr. Alan Beggs, Co-Lead
Boston Children's Hospital

Dr. Gina Ravenscroft, Co-Lead
Harry Perkins Institue

Dr. Lindsay Alfano
Nationwide Children's Hospital & Ohio State University, Clinical Trialist

Dr. A. Reghan Foley
National Institutes of Health, Pediatric Neuromuscular Specialist and Clinical Trialist

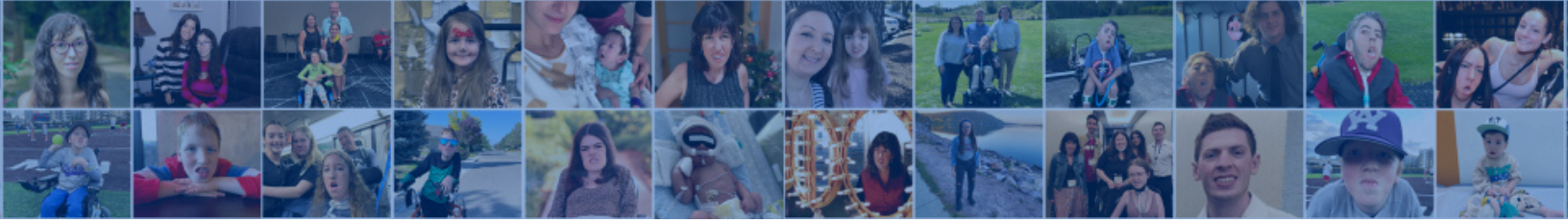
Adrian Gomez
Ramboll, Sustainability Leader

Lucinda Lee
University of North Carolina

Dr. Coen Ottenheijm
YUMC, Molecular Muscle Physiologist

Wayne Sackett
Estuary Biotherapeutics, Biotech Industry Leader

Dr. Nicol Voermans
Radboud University, Adult Neuromuscular Specialist and Clinical Trialist



OUR IMPACT

RESEARCH

- **Initiated the launch of the first ever NM Natural History Study** designed to chart the natural course of NM during childhood, giving researchers deeper insight into NM and readying the community for clinical trials.
- **Funded 42 research studies*** throughout the United States and across the globe resulting in a deeper understanding of NM, promoting international collaboration, and developing new methods/approaches to potential treatments for the disorder.
- **Development of accurate zebrafish and mouse models for various forms of NM**, which is the first step to bring research to clinical trials.
- **Developed induced pluripotent stem cell lines** from NM patients
- **Funded the first CRISPR/Cas9 Gene Editing project** of an NM gene (NEB)
- **Developed a lab grown 3D Muscle Model** from NM patient stem cells paving the way for testing potential therapies in a dish, including gene editing, protein correction, and boosting healthy actin production.
- **Established the first ever NM BioBank** for muscle tissue samples

COMMUNITY SUPPORT

- **Held biennial scientific family conferences**, convening patients, families, researchers, clinicians, and industry partners
- **Helped launch and develop an online patient registry (CMDIR)**, providing researchers with de-identified, aggregate access to a database of information provided by patients/families
- **Endorsed and distributed "The Care of Congenital Myopathy: A Guide for Families",** a comprehensive and valuable resource for those with Nemaline Myopathy. The guide represents the expertise and experience of medical professionals and families from all around the world.
- **Hosted webinars and online community meet ups,** connecting individuals and families affected by NM with each other and subject matter experts.
- **Provide ongoing personal support for genetic testing,** guiding families through the process of genetic confirmation testing.
- **Developed the Nemaline Myopathy Resource Kit,** providing helpful information and resources for affected individuals and their families.
- **Launched first Nemaline Myopathy Awareness Month & NM Awareness Day**

**For the latest updates on current AFBS Funded Research Projects, please see Appendix.*

OUR PRIORITIES

Together, we will advance our efforts towards finding treatments and improving the lives of those living with NM in the following ways:

CONDUCT THE FIRST NATURAL HISTORY STUDY FOR NM

- Crucial in our path to clinical trial readiness
- Coordinated and harmonized with European and Brazilian counterparts
- 6 Care Centers in North America:
  -Stanford Medicine
  -Boston Children's Hospital
  -NIH
  -St. Jude's Children's Hospital
  -UT Southwestern
  -SickKids Toronto

3 YEAR INVESTMENT: $1 MILLION

GROW OUR INTERNATIONAL REGISTRY, GENETIC CONFIRMATIONS AND TISSUE BIOBANK

- Continue to expand the CMDIR (Congenital Muscle Disease International Registry)
- Connect affected individuals to no cost genetic testing
- Continue to build the valuable specimen collection at Begg's Lab NM Biobank, allowing researchers to study the genetic & molecular underpinnings of this condition

3 YEAR INVESTMENT: $450K

EXPAND CLINICAL RESEARCH DISCOVERIES

- Maintain 6 active preclinical research studies
- Invest in groundbreaking research to advance toward clinical trials

3 YEAR INVESTMENT: $1.7 MILLION

CONFERENCES & WEBINARS

Bring together affected individuals and families and subject matter experts for education and connection.

3 YEAR INVESTMENT: $350K

YOUR GIFT WILL MAKE A TRANSFORMATIONAL DIFFERENCE.

A Foundation Building Strength has a dedicated expert care team, community-centered programming, engagement with stakeholders, and clear strategic goals. While our community has rallied to raise $6+ million in funding for international research, lessening the effects of NM and finding pathways to a cure, we have much more work to do to achieve our vision.

This can only be possible with the help of philanthropic partners like yourself to achieve our $3.5 million fundraising goal over the next three years.

TO MAKE INVESTMENTS/DONATIONS TO AFBS, PLEASE CONTACT JEN TOZER: JTOZER@BUILDINGSTRENGTH.ORG

RESEARCH APPENDIX

Thanks to your ongoing support of **A Foundation Building Strength**, we're making enormous strides towards our goal of finding treatments and therapies for Nemaline Myopathy. From promising gene therapy to cutting edge robotics, this year we've seen exciting developments from several of the research initiatives you have so generously helped to fund:

DEVELOPMENT OF GENE THERAPY FOR ACTA1 BASED NEMALINE MYOPATHY

Dr. Afrooz Rashnonejad's team at **Nationwide Children's Hospital** has shown significant early success in developing a gene therapy for ACTA1-related Nemaline Myopathy (NEM3). Their approach involves a "therapeutic genetic construct" that silences the faulty ACTA1 gene and a method to deliver a healthy copy of the gene into muscle cells. Initial tests showed a decrease in harmful protein clumps and successful disease mimicked in lab models. The next steps involve testing the therapy in live mice to determine the safest and most effective approach. This research offers promising potential for a future treatment of NEM3.

SOFT ROBOTIC GARMENTS FOR ASSISTING LOWER-LIMB FUNCTION FOR CHILDREN WITH NEMALINE MYOPATHY

AFBS is funding a promising exosuit research project led by **Dr. Jonathan Realmuto** at the **University of California, Riverside.** This soft robotic garment is designed to improve mobility for people with Nemaline Myopathy (NM) by assisting with daily activities like standing up and sitting down. The exosuit prioritizes comfort for extended wear and utilizes cutting-edge technology. The research is in its evaluation stage, where participants like Liv from the NM community are helping refine the prototype for a precise fit.

IDENTIFYING AND CORRECTING THE PATHOLOGICAL DRIVERS OF NEMALINE MYOPATHY IN STEM CELL-DERIVED ENGINEERED SKELETAL MUSCLE TISSUES

Dr. David Mack's research at the **University of Washington** is developing a human stem cell model of Nemaline Myopathy (NM) to test potential therapies. This model uses stem cells from NM patients with mutations in the ACTA1 gene to create 3D muscle tissues that mimic the disease. Early results show the model successfully replicates muscle weakness and the characteristic protein clumps seen in NM patients. If validated, this model will be used to test gene editing, small molecule drugs, and other interventions aimed at treating NM.

DEVELOPING THERAPIES FOR NEMALINE MYOPATHY

Dr. Vandana Gupta's team at **Brigham and Women's Hospital** is developing treatments for rare forms of Nemaline Myopathy caused by Kelch gene mutations (KLHL40, KLHL41). They are exploring two avenues: (a) gene replacement therapy to deliver a healthy copy of the gene and (b) repurposing existing FDA-approved drugs that improve muscle function in zebrafish models. Early results from gene replacement therapy in mice with severe NM showed improvement in lifespan and muscle function, warranting further study. Additionally, the team identified 16 promising drug candidates from a screen of hundreds of FDA-approved drugs in zebrafish with NM, paving the way for further investigation of their therapeutic potential.

EXPLORING THE POTENTIAL OF MAVACAMTEN AS A TREATMENT FOR NEMALINE MYOPATHY

Researchers at the **University of Copenhagen** led by **Drs. Julien Ochala and Jenni Laitila** discovered abnormal myosin head conformation in muscle fibers of NM patients with NEB mutations. This abnormality leads to excessive energy consumption (ATP). They tested Mavacamten, a recently FDA-approved drug targeting myosin, and successfully normalized energy use in isolated muscle fibers. However, in a mouse model of NEB-deficient NM, a four-week Mavacamten treatment did not improve muscle energy levels. This suggests a need for further studies exploring higher drug doses or longer treatment durations. Though the in vivo results weren't what they hoped for, their data will be published to benefit future research in this area.

NEMALINE MYOPATHY BIOBANKING PROGRAM

Under the leadership of **Dr. Alan Beggs** at **Beggs Lab, Boston Children's Hospital and Harvard University**, the AFBS funded Nemaline Myopathy Biobanking Program stands as the world's premier repository for NM tissue samples. This initiative, aimed at aiding research while alleviating financial burdens on patients, collects NM tissue donations from individuals of all ages and genetic subtypes. By expanding an extensive registry and clinical database, including DNA and tissue banking, and collaborating with AFBS to ensure comprehensive genetic testing, we're advancing scientific understanding, facilitating new therapies, and fostering global collaboration in the field of NM.

NEMALINE MYOPATHY NATURAL HISTORY STUDY

With an initial research review approval underway and a collaborative effort spanning across North America, Brazil and Europe, including renowned institutions **Stanford Medicine, Boston Children's Hospital, NIH, St. Jude's Children's Hospital, UT Southwestern** and **SickKids Toronto,** the first prospective natural history study for NM aims to provide invaluable insights that will pave the way for effective interventions and improved patient outcomes. This crucial three-year investment marks a significant step towards clinical trial readiness, highlighting our commitment to understanding and ultimately finding treatments for NM.

WE CANNOT DO THIS WORK ALONE.

Help us find treatments for Nemaline Myopathy.

A FOUNDATION BUILDING STRENGTH FOR NEMALINE MYOPATHY

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