UNITED MSD FOUNDATION

MULTIPLE SULFATASE DEFICIENCY

Research Strategy

Roadmap

Michał Ryczek,
age 3
(Poland)

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Note: Each featured child's story may be viewed on our website by clicking the hyperlink underlining their name.

Overview

This roadmap collects the knowledge, thoughts, ideas, and opinions of key stakeholders in the effort to develop treatments for Multiple Sulfatase Deficiency (MSD).

It is meant to serve as a guide to the United MSD Foundation (UMSDF) and allied organizations worldwide in setting priorities for funding and other support to further research toward solutions for MSD patients.

In 2023, the United MSD Foundation crafted a set of strategic priorities for research, detailed below.

This Research Strategy Map presents the detailed plan for achieving the ultimate goal of the United MSD Foundation and their allied organizations: ***to cure Multiple Sulfatase Deficiency.***

Priorities

- **Help usher the start of AAV9 gene therapy clinical trials**
- **Complete Prospective Natural History Study**
- **Launch and fully utilize the Patient Registry**
- **Create a Research Strategy Map (this document)**
- **Create more opportunities for dialogue and collaboration between researchers**
- **Engage Brazilian MSD community**

In addition to the above stated research priorities, interviews with the researchers and families of patients have suggested further activities aimed toward therapy development. These will be presented as potential backup programs to the gene therapy program, because achieving the goal of curing this disease cannot be confined to a single project or a single therapeutic option. The strategic priorities also include non-research functions of the UMSDF: supporting families with resources and community, and growing global awareness of MSD. Some of those activities overlap with the research effort and will be touched on briefly.

Description of Disease

Multiple Sulfatase Deficiency (MSD) is a rare, inherited neurodegenerative disorder that either prevents children from reaching development milestones, like walking and speaking, or causes rapid regression of these skills shortly after they are acquired. Progressive loss of brain function leads to declining motor, verbal, and autonomic abilities. The median life expectancy is approximately 13 years, and there is no treatment or cure.

In cells, a group of 17 sulfatase enzymes are responsible for the degradation of sulfatase esters, preventing the accumulation of substrates that would disrupt cellular processes. Their activity depends on the formylglycine-generating enzyme (FGE), encoded by the *sulfatase-modifying factor 1* (*SUMF1*) gene, which activates all sulfatases. MSD arises when both copies of *SUMF1* carry pathogenic variants, impairing FGE activity. Disease severity varies depending on the residual FGE activity which is dependent on the specific *SUMF1* variants.

Loss of an individual sulfatase enzyme causes one of several lysosomal storage diseases (LSDs), such as Sanfilippo syndrome, Hunter syndrome, or metachromatic leukodystrophy. Because all sulfatases require FGE, MSD represents a combined deficiency. However, as FGE activity is typically reduced rather than absent, only a subset of sulfatases show measurable deficiency in most patients. Consequently, MSD presents with overlapping features of multiple LSDs, particularly those with neurological involvement, and requires distinct clinical management and therapeutic approaches (Schlotawa, et al., 2020).

Diagnosis is based on clinical presentation such as developmental delay, hypotonia, abnormal neurologic exam findings, scoliosis, or cutaneous abnormalities, followed by biochemical confirmation of reduced sulfatase activity and genetic sequencing to identify biallelic pathogenic loss-of-function variants in *SUMF1*. The prognosis is strongly influenced by age at symptom onset. Infants with early presentation generally have the most severe course, with a median survival of 8.2 years, whereas patients without symptoms at birth have a median survival of 15.3 years (Schlotawa, et al., 2020b).

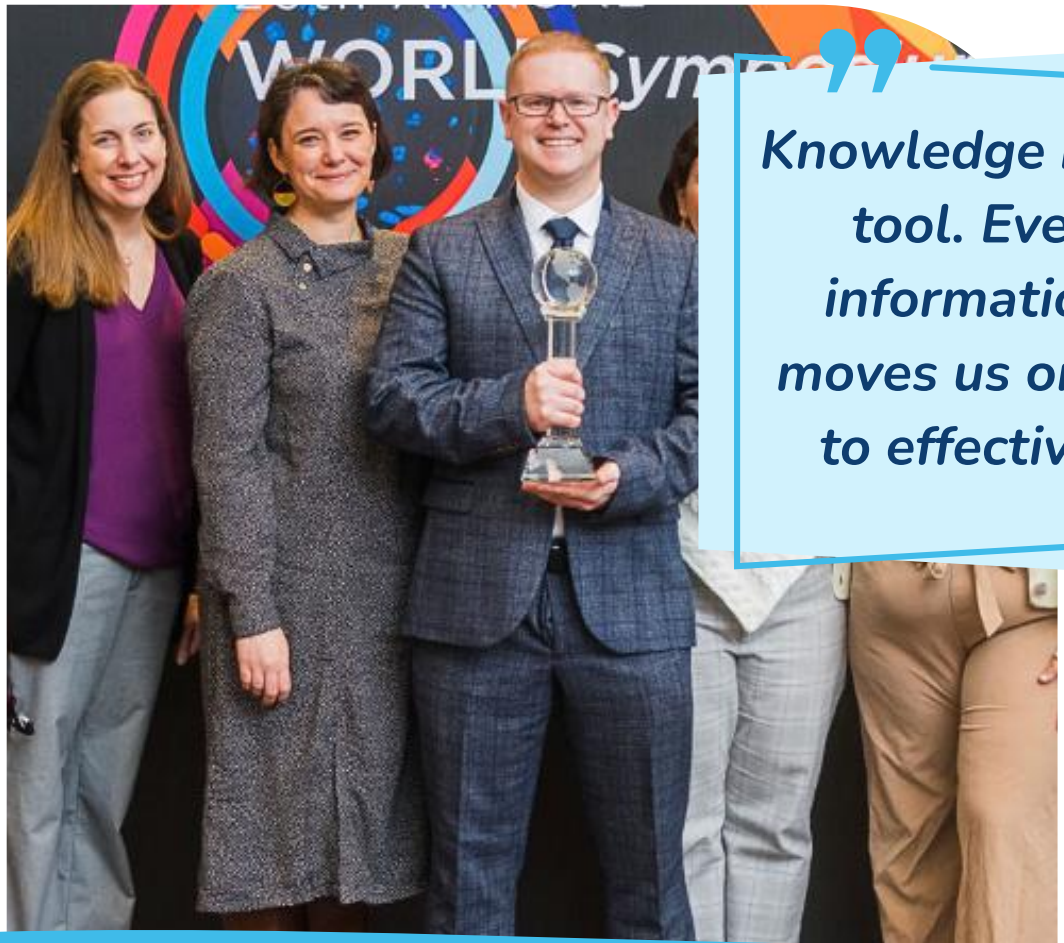
"MSD is a complex disease because it combines symptoms of single sulfatase deficiencies. It is a progressive, systemic, neurodegenerative disorder of early childhood."

-Schlotawa et al., 2020

Natural History Background

Natural history studies, including one supported by the United MSD Foundation (Adang, J Inherit Metab Dis, 2020), demonstrate that MSD is a relentlessly progressive neurologic disorder. Disease progression has been characterized by using clinical function scales for gross motor ability, expressive language, and feeding. Most affected children initially appear healthy, but caregivers soon observe delays in development, hypotonia, or orthopedic complications such as scoliosis. While many patients achieve early milestones, these abilities regress as sulfatide accumulation damages the brain. Loss of swallowing function often necessitates placement of a feeding tube. Respiratory complications, frequently due to aspiration, require ventilatory support, while gastrointestinal symptoms such as constipation are common.

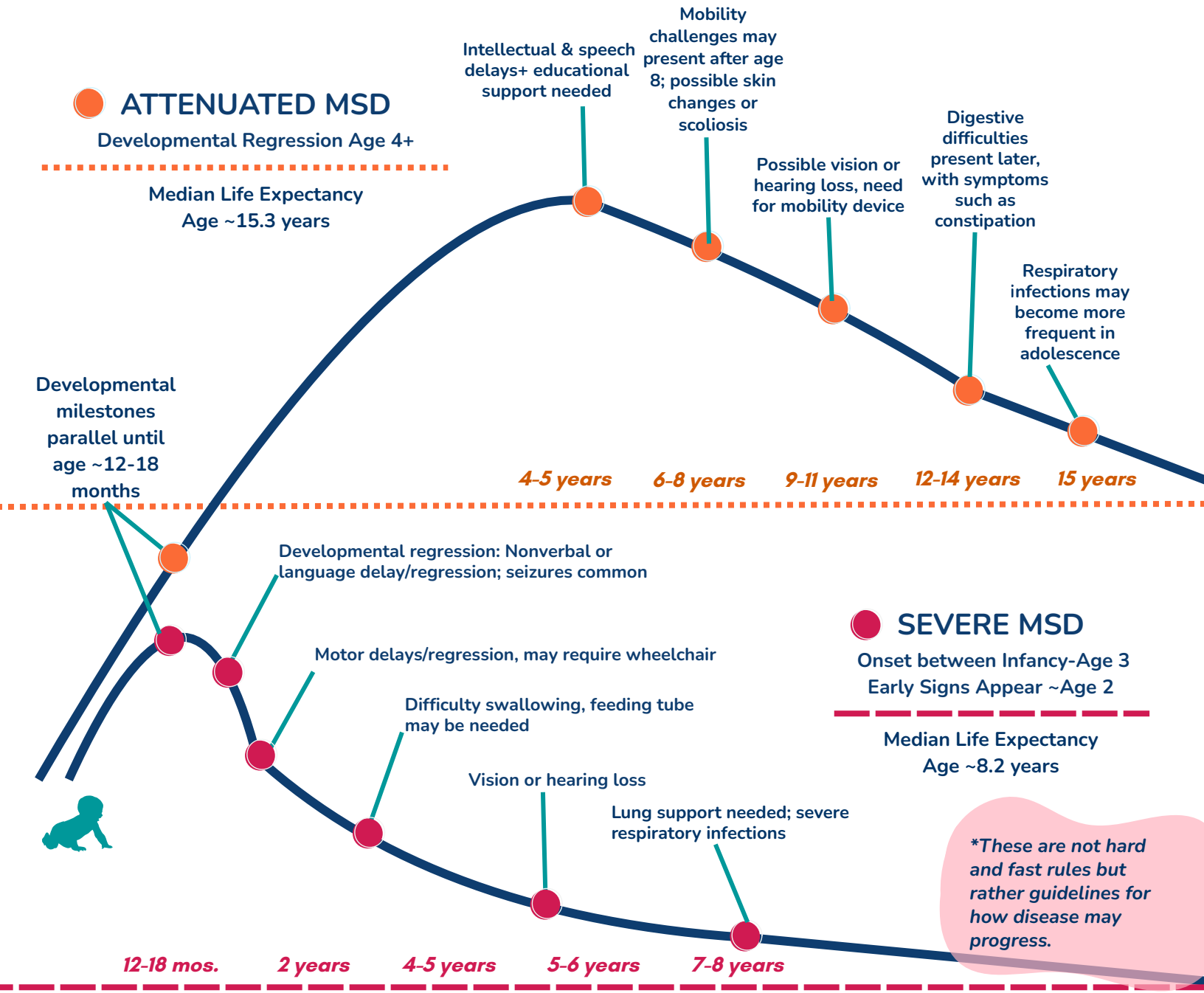
Cognitive decline is marked by loss of expressive language. Some children, particularly those with less severe variants, may achieve limited speech, but many never progress beyond single words, or fail to develop language altogether (Adang, 2020).



Knowledge is our greatest tool. Every piece of information collected moves us one step closer to effective therapies.

-Alan Finglas (Ireland), accepting the 2024 WORLDSymposium Patient Advocate Leader (PAL) Award

MSD Disease Progression*



*These are not hard and fast rules but rather guidelines for how disease may progress.

Biochemical studies of FGE variants reveal that all patients surviving beyond the neonatal period retain some residual enzyme activity. Most pathogenic variants destabilize the protein, reducing its half-life and decreasing cellular FGE levels. This mechanistic insight not only explains phenotypic variability but also highlights potential therapeutic avenues beyond gene replacement, such as strategies to stabilize or enhance residual FGE function (Schlotawa, et al., 2008).

Intellectual disability is manifested at this age by a loss of language function. While some MSD patients, particularly the less severe group, attain the ability to speak words or simple sentences, many do not progress beyond speaking single words or do not learn to speak at all (Adang, 2020).

A detailed understanding of the biochemistry of FGE and the effect of pathogenic variants on enzyme function and stability has allowed scientists to predict, to some degree, the likelihood that a given variant will result in a severe or less severe disease. All patients that survive past the neonatal period have at least one variant that retains some FGE activity. Most of these variants that retain activity decrease the half-life of the protein, meaning there is less FGE in the patient's cells at any given time. This understanding of the biochemistry of the enzyme creates avenues for the development of therapeutics beyond gene replacement (Schlotawa, 2008).

MSD **Angel Ivet Melus Perez, at age 3 (Spain)**

Research Landscape

For an ultra-rare disease, MSD has been the focus of a significant research effort. Much of the biochemical characterization of FGE has been performed at the Universities of Bielefeld and Göttingen in Germany, and the Telethon Institute of Genetics and Medicine (TIGEM) in Italy. The development of mouse models at the TIGEM and Jackson Laboratories (Setembre, et al., 2007; Sorrentino et al., 2023) that show symptoms similar to those of patients enables not only the development of therapeutics but also a greater understanding of the role of FGE in different tissues and cells in the body during development and beyond.

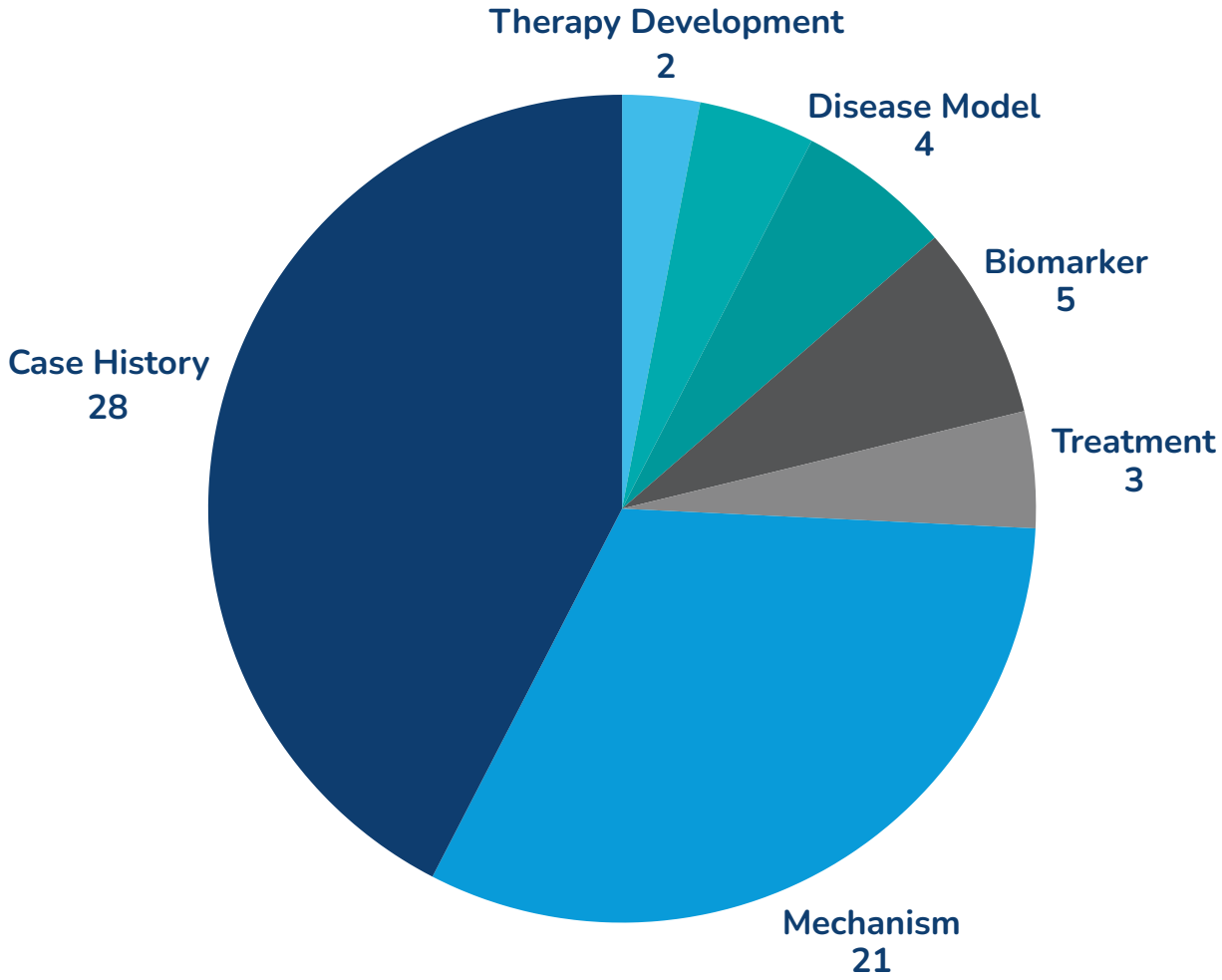
In the 21 years since the genetic cause of MSD was discovered by researchers at TIGEM and Göttingen (Dierks, 2003; Cosma, 2003), researchers worldwide have generated 67 research publications on MSD. The largest category of publications consists of case histories detailing descriptions of one or a few patients.

> ***Doctors and providers tell me all of these fancy scientific terms, but all I see is my son slowly dying. ...MSD has taken so much from us, but there is one thing it cannot touch: our love. ...In a world where there is no cure for MSD yet, let endless love be our cure for now.***

-Valerie Daniels, Mother of Max,
age 14 (center, U.S.)

Research Landscape, cont'd

These case histories are the raw materials for broader retrospective natural history studies that find commonalities among patients and attempt to make disease course predictions based on categories of disease presentation. The second largest category consists of descriptions of the mechanism by which *SUMF1* mutations lead to disease. These research studies enable scientists to develop new treatments for the disease. In addition, animal and cell-based models are essential for testing those new treatments. Biomarker studies help with clinical trial readiness (with further details discussed later in this document).



The research landscape reflects meaningful progress in understanding MSD, while also demonstrating that developing and testing new therapies remains an important priority.

Elijah Guzman, age 14 (U.S.)

Case Histories

In a 2020 publication, Schlotawa, et al. catalogued all of the publications describing MSD patients going back to 1965. They found 75 such publications, describing 145 patients with enough data to characterize their disease. The median age of survival was 13 years, with respiratory complications being the most frequently described cause of death. Most patients presented with developmental delay, dry skin, and bone development abnormalities.

The disease pathology could be detected in the brain by MRI, in the blood and skin cells by enzyme assays, and in the DNA by sequencing the *SUMF1* gene.

> ***I would ask the world to try to understand how beautiful and strong our children are, living with this horrible disease, that only gets worse with time.***
>
> -The Guzman Family

Anna Grace, age 20 (U.S.)

We now feel so blessed for all that the Foundation has done for MSD. Since Anna Grace's diagnosis, there is significantly more information for families and ongoing research to one day cure MSD.

-The Watson Family

FGE Biochemistry

FGE is the only enzyme in human cells capable of activating sulfatases. All of the known sulfatases require FGE modification to perform their vital function. FGE resides in a cellular compartment called the endoplasmic reticulum, which is the site of protein synthesis. When FGE activity is missing entirely, none of the 16 known sulfatases are active. To date, no patients have been described as having a complete loss of function of both *SUMF1* genes, suggesting that some FGE activity is required for humans to survive beyond birth.

The pathogenic variants in the *SUMF1* gene appear to produce an FGE enzyme that can still activate sulfatases but is less stable. This stability loss affects some sulfatases more than others, possibly due to the rate at which the sulfatases are synthesized. The vulnerability of sulfatases to FGE stability loss is reflected in both the decrease in the activity of these enzymes and the accumulation of their substrates (Adang, 2023). It also appears that sulfatase vulnerability to FGE stability loss is cell type-dependent, with induced pluripotent stem cells (iPSC) showing less sulfatase vulnerability than that of neurons (Pham, 2024).

The vulnerability of the different sulfatases to FGE stability loss affects not only the accumulation of the different substrates of those sulfatases, but also the manifestation of the disease. The clinical manifestations of MSD resemble those of two diseases caused by the loss of individual sulfatases: Mucopolysaccharidosis Type IIIA (MPS IIIA, or Sanfilippo type A) and Metachromatic Leukodystrophy (MLD). The genes affected in those two diseases are SGSH and ARSA, respectively. The SGSH and ARSA enzymes are the most vulnerable to FGE stability loss (Adang, 2023).

MSD Disease Models

Development of a therapeutic requires a way to test the intervention in some model of the disease. Typically, drug developers attempt to recreate the disease in mice because mice share biochemical and physiological features with those of humans. The tools available for mouse genetics allow several options for manipulation of genes. Other animal- and cell-based models may also prove useful, either to improve the throughput of an experiment or to allow different types of manipulation of the model.

Mice completely lacking *SUMF1* (*SUMF1* knockouts, or *SUMF1* -/-) were produced at TIGEM (Settembre, 2007). Most of these mice do not live past three months of age, but during that time they display many of the same features as those of MSD patients. A further refinement of this model, in which mice express a pathogenic variant of *SUMF1*, was generated by a UMSDF-funded collaboration between TIGEM and the Jackson Laboratories (Sorrentino, 2023). These mice live longer and thus allow longer-term experiments exploring therapeutic efficacy. In addition, expression of a pathogenic variant of *SUMF1* allows scientists to test therapeutics that stabilize these variant forms, which is not possible in the *SUMF1* knockout mice.

As with mice, genetic tools allow scientists to manipulate the genes of fruit flies and zebrafish with relative ease. Fruit fly models developed at Penn State show reduced lifespan and accumulation of heparan sulfate (Selleck, 2018). Three additional fruit fly models of MSD were created in collaboration with a company called Perlara, with funding from UMSDF and MSDAF, but are as yet uncharacterized (2025).

These fruit flies could be useful for testing multiple treatment variations that would be difficult to compare in the more expensive and long-lived mice. Zebrafish lacking the *SUMF1* gene, however, have a normal lifespan, but show skeletal abnormalities during development (Fleming, 2022). Further understanding of how these *SUMF1* knockout zebrafish survive may provide insights into alternative therapeutic interventions.

While animal models are valuable for testing therapies, they do not share the same genetic makeup as those of MSD patients. To model the interaction of human genes with pathogenic *SUMF1* variants, patient-derived cells are the preferred model system. These cells can be derived from samples taken from blood or skin. Once growing in the lab, they can be manipulated to become brain cells such as neurons or astrocytes. These cells have already been used to develop experimental treatments for MSD, such as tazarotene, which will be discussed later in this roadmap.

> ***These favorable safety results paved a clear path to move the gene therapy treatment towards a human trial through the Bespoke Gene Therapy Consortium.***
>
> *-Dr. Steven Gray*

Gaps in the Research Landscape

Unmet needs in MSD research identified by the key opinion leaders fall into two major categories:

1

- **Clinical Trial Readiness**
  - Diagnostic methods, such as newborn screening, that reduce the time to identify patients and allow earlier treatment that will likely prove more efficacious than later treatment
  - Biomarkers for disease severity and progression, which will enable accelerated clinical development
  - Natural history studies describing the course of disease progression, which will serve as a comparator group in a treatment study, and also enable development of outcome measures suitable for a registration trial and demonstration of the relevance of those outcome measures to patient well-being.

2

- **Therapeutic Development**
  - Advancement of two MSD clinical programs, including gene therapy, and repurposed tazarotene
  - Development of new therapeutics, including ex vivo gene therapy and discovery of small molecules that increase FGE activity

Clinical Trial Readiness

Prospective Natural History Study

The Children's Hospital of Philadelphia (CHOP) and the University of Göttingen are working together to address gaps identified in the meta-analysis and retrospective natural history study. The goal is to have patients seen twice in either the U.S. or Germany. The two visits, 12 months apart, will allow the researchers to monitor how the disease progresses. Researchers will measure patient function using Vineland 3 and CPChild and caregiver-reported quality of life using PedsQL GC and PedQL FIM. They will also collect radiological imaging (brain MRI) and collect biological fluids for biomarker analysis. Some of the analyses will be performed remotely to increase the number of patients enrolled, although some clinical measures will not be possible for the patients seen remotely.

Thus far, 19 patients have completed one evaluation using the Vineland 3 scale. It is already apparent from this first measurement that communication and motor skills may be limited by a "floor effect" wherein most patients exhibit the lowest possible score.

The CPCHILD scale allows for more separation between patients. Researchers are currently comparing the outcome in these functional scales with QoL measurements to determine the amount of functional change that corresponds to a meaningful difference to patients and caregivers.

A second assessment, planned as part of the natural history study, is intended to establish the rate of symptom change as well as changes in caregiver perceptions of quality of life. Patients treated in a gene therapy trial will be monitored by doctors for several years after treatment, and those outcomes will be compared with data from the natural history study to determine whether the therapy has had an effect.

Biomarkers

Given the ultra-rarity of MSD, it will be challenging and perhaps infeasible to show meaningful change in a clinical outcome measure in a reasonable amount of time since any clinical trial will enroll a limited number of participants who will be at different stages in their disease progression. Therefore, identification of biomarkers whose change would be reasonably likely to predict clinical benefit is a key goal for the MSD community.

Retrospective natural history studies (the largest assessing published information for 80 MSD patients) (Schlotawa, 2020) have established a correlation between the disease-causing *SUMF1* variants and clinical severity, a so-called genotype-phenotype correlation. As mentioned previously, it is clear from this retrospective natural history study, and biochemical characterization of patients across the MSD severity spectrum (Adang, 2024), that not all sulfatases are equally affected by loss of FGE.

A greater understanding of the relationship between FGE requirements for different sulfatases, the residual FGE activity for different MSD-causing variants, and the substrates and products for different sulfatases can form a basis for using biomarkers to assess disease severity and thus make prognostic assessments of patients.

Using biological samples and genotype information collected from the United MSD Foundation biobank and patient registry, Dr. Michael Gelb at the University of Washington, Dr. Marzia Pasquali at the ARUP, and Dr. Rebecca Ahrens-Nicklas of CHOP, along with their colleagues, were able to compare the activity of sulfatase enzymes in patients with different variants and their clinical features and measure the corresponding GAG-NREs. They found that the most affected sulfatases are ARSA (the sulfatase affected in MLD), GNS (loss of which causes MPS IIID), and SGSH (loss of which causes MPS IIIA).

Correspondingly, this result aligns with the clinical spectrum of MPS, because most MPS patients display primarily neurological symptoms, similar to those of MLD and MPS III, and the enzymes most affected by MPS variants are more essential for neuronal health.

By measuring GAG levels in urine in 13 MSD patients, a clear difference between control and patient samples was seen for those GAG species that are substrates for the enzymes most affected by FGE loss. This confirms the enzymes that are most sensitive to FGE loss and lays the foundation for the use of GAG-NREs measurements as biomarkers of disease severity.

This method will be further strengthened by including more patients with less severe disease, which makes correlation of GAG-NREs levels and disease severity possible. These data will also enable the development of GAG-NREs measurement as biomarkers of response to therapy (Adang, 2024).

Above: Researchers Dr. Laura Adang, Dr. Becca Ahrens-Nicklas, & Dr. Lars Schlotawa at the 2024 MSD International Conference

Patients with MSD are unable to break down long-chain sugar molecules called glycosaminoglycans (GAG). These GAG molecules build up in the body and can be detected in the cerebrospinal fluid (CSF), blood, and urine. Scientists at CHOP, the University of Washington, and other institutions measured urinary GAG levels in patients with MSD. Some patients with attenuated MSD had only slightly elevated GAG levels. As Adang, et al. (2024) demonstrated, urine GAG may be a useful biomarker for diagnosing patients and measuring treatment response.

This effort has received a significant boost with the announcement that Ultragenyx reached an agreement with the FDA that cerebrospinal fluid heparan sulfate (a species of GAG) is a reasonable surrogate endpoint that could support the company's application for accelerated approval for a treatment for MPS IIIA. This agreement will likely be extended to others seeking accelerated approval for MPS treatments on the basis of CSF GAG measurements, which may eventually be relevant to MSD, as well.

As demonstrated by Adang, et al. (2024) in "Biochemical Signatures of Disease Severity in Multiple Sulfatase Deficiency," levels of heparan sulfate were higher in the urine of patients with severe MSD than in those with a less severe, or attenuated, form of the disease. This study assessed GAGs in the urine of patients with MSD; therefore, further research to measure GAGs in cerebrospinal fluid (CSF) is warranted. Obtaining CSF samples from patients is not a trivial undertaking.

However, these samples would allow researchers to determine whether GAG measurements in CSF more specifically reflect sulfatase activity in the brain, the organ most severely affected by MSD.

A day-long symposium hosted by the Reagan-Udall Foundation held on February 21, 2024, made the case for the use of biomarkers in assessing the treatment efficacy for MPSs.

Outcome Measures

Left to right: Sarah Cortell Vandersypen, *The Zebra & The Bear* director Pat O'Connor, Dr. Steven Gray, and Amber Olsen

The success or failure of a clinical trial depends on much more than the activity of the drug. Clinical trials often fail to produce definitive results due to mismatch between the biology of the disease being measured and the primary outcome measure used. The primary outcome measure determines whether the treatment has produced a benefit for the patient. This is therefore the major factor in the decision to allow the drug to be given to patients in the future.

Previous clinical trials for neuronopathic LSDs have used clinical outcome scales such as Bayley Scales of Infant and Toddler Development, Gross Motor Function Measure (Fumagali, 2022), or a composite score comparing a patient's developmental stage to an age-match unaffected population, or Developmental Quotient. The Vineland Adaptive Behavior Scale, 3rd ed. (Vineland 3) is recommended as an outcome measure for clinical trials evaluating the effect of treatment in patients with MPS disorders of all ages (van der Lee, et al., 2020). This score shows a "floor effect" when administered to the patients in the current prospective natural history study being conducted at CHOP and the University of Göttingen.

While this guidance for clinical endpoints in neuronopathic MPS disorders is valuable, MSD is a different disease and may be best evaluated using an outcome measure unique to this patient population. The development of a new outcome measure requires repeated observations of patients in a natural history study. During this process it is vital to stay in close partnership with the FDA. In addition to the standard IND process during which the FDA interacts constructively with drug developers, government and private partnerships have created programs to facilitate new outcome measure development.

The CDER Center for Clinical Trial Innovation (C3TI) has created a Rare Disease Endpoint Advancement Pilot Program that offers continual guidance in this process specifically for rare diseases. (Critical Path Institute offers the Rare Disease COA resource.)

Newborn Screening

As with other developmental disorders, treatment for MSD would likely be most effective if given early in the disease course. Currently, this is difficult since the time it takes to diagnose patients from the first emergence of clinical signs may take several months, or even years. All babies born in the U.S., and in most of the developed countries of the world, have blood taken at birth to look for biomarkers of inborn errors of metabolism.

The purpose of this newborn screening (NBS) is to allow doctors to intervene in a disease as early as possible, before irreversible damage to the child has occurred. These dried blood samples would, if properly analyzed, identify MSD patients (Meikle, 2006; Hong, 2020; Adang, 2024). However, these tests are currently not being performed in any state or country. Because MSD bears a clinical and biochemical similarity to MLD, screening patients for MLD would likely identify MSD patients at birth.

The UMSDF supports this effort that will help the early identification of not only MLD patients, but possibly MSD patients as a secondary finding. NBS results that indicate a sulfatase deficiency are usually referred to a metabolic disease specialist for further diagnosis.

Therefore, in addition to NBS inclusion of the MLD test, an increase in overall awareness in the medical community for MSD will have a great impact on the early identification of MSD patients, shortening the diagnostic journey for MSD patients.

In a project funded by UMSDF, Dr. Michael Gelb has analyzed dried blood spots from symptomatic MSD patients. He has found that the samples contain markers for decreased activity of the enzymes ARSA (the loss of which causes MLD) and I2S (encoded by the IDS gene, which carries the pathogenic variants that cause MPS II).

For the next step in this project, Dr. Gelb must demonstrate that blood taken from newborns with disease-causing mutations in *SUMF1* would, like the samples from the older patients he has already tested, display ARSA and IDS functional loss. Obtaining such samples from newborns who were later diagnosed with MSD is a task made difficult by the rarity of MSD patients and the limited time in which most states store newborn blood samples.

We are forever thankful for those who paved this hard road before us. It means the world, knowing that there is hope for a cure.

The Hise Family (U.S.)

Mom Jessica at left, hugs Oliver, age 14

What Allies Can Do!

Natural History	• Encourage patients in the registry to enroll in the study. • Assist with travel to clinical sites.
Biomarkers	• Assist in the collection of biofluids, including CSF. • In the future, it may be advantageous to communicate with the FDA the advantages of using a treatment-responsive biomarker as a primary clinical trial endpoint.
Outcome Measures	Participate in discussion with the FDA to ensure patient-reported outcome measures are woven throughout every measurement in each trial.
Newborn Screening	Support the efforts of the MLD community to add MLD screening to the Recommended Universal Screening Panel, the state-approved screening panels, and international NBS programs.

Therapeutic Development

New Treatment Development

Several independent lines of research are aimed at developing treatments for MSD. The disorder is the result of loss of function of the *SUMF1* gene. Therefore, developing a gene replacement therapy is one major avenue for research. As with ultra-rare disease, creating a new treatment for MSD could be prohibitively expensive. To reduce the cost and time needed to develop a treatment, drug developers can find a drug that is already approved for a different disease and repurpose it for MSD. Such a project represents the second major avenue to developing MSD treatments.

Two other programs at an earlier stage of development will improve the chances of success and to give patients options for different kinds of treatment. These other treatments include ex vivo gene therapy and a drug designed to correct MSD function in patients. Experimental treatments have been developed for related diseases, and it is possible that if any of these treatments prove effective in treating those related diseases, they may also be helpful for treating MSD patients.

MSD Angel Jaxon Chavez with his, mom, Sophia Grise (U.S.)

AAV-Based Gene Therapy

Aim: Target cells most harmed by deficient FGE activity and deliver a functional copy of *SUMF1* to them.

Gene therapy based on the adeno-associated virus (AAV) platform is now an established therapeutic modality, with approved drugs to treat hemophilia, Duchenne muscular dystrophy, and retinal dystrophy. New treatments using AAV in the central nervous system include AAV9 encapsulated delivery of the gene SMN1 (Zolgensma) into the spinal cord for Spinal Muscular Atrophy and AAV2 encapsulated delivery of the DDC gene (Upstaza) into the brain for the treatment for aromatic L-amino acid decarboxylase deficiency.

Building on the success of approved gene therapies for other neurological diseases caused by missing or faulty genes, Dr. Steven Gray's laboratory at UT Southwestern developed a clinically relevant adeno-associated virus serotype 9 (AAV9) gene therapy designed to deliver a healthy copy of the *SUMF1* gene.

This gene provides the instructions for making formylglycine-generating enzyme (FGE), the enzyme required to activate all sulfatase enzymes.

In preclinical mouse studies conducted at the Jackson Laboratory (JAX), delivery of this vector in newborns resulted in increased survival and function (Presa, et al., 2025).

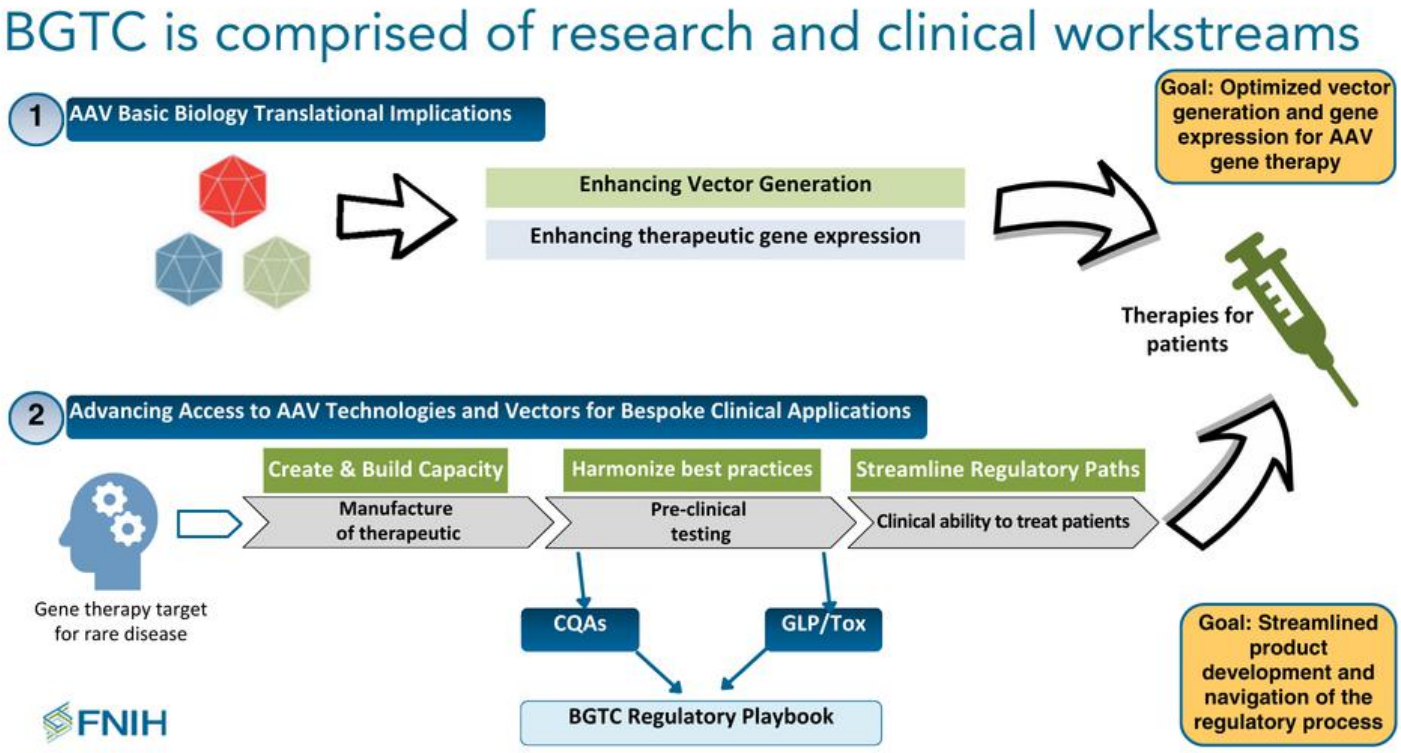
MSD Angel Jett Burke (U.S.), with his sister

These promising results provided critical proof of concept that replacing the defective *SUMF1* gene could address the underlying cause of MSD and help pave the way for the AAV9 clinical trial.

Moving from successful mouse studies to treating patients is a complex process. Before a clinical trial can begin, the gene therapy must undergo extensive safety testing, be manufactured to rigorous quality standards, and be carefully prepared for human use. UMSDF has played a critical role in supporting the early development of the AAV9-*SUMF1* gene therapy, yet continued funding and specialized expertise are essential to its clinical advancement. Inclusion in the BGTC MSD program has been a pivotal step in bringing this potential treatment to future MSD patients.

Bespoke Gene Therapy Consortium

The BGTC is a public/private partnership between government, industry partners, academic scientists, and patient advocacy groups. The overall goal of the BGTC is to improve the efficiency and quality of gene therapies based on AAV encapsulation for all diseases that would benefit from some form of gene therapy delivery to any tissue. To accomplish this, BGTC chose eight rare disease gene therapy programs to advance into early-stage clinical trials. It is expected that in advancing these eight therapies, lessons will be learned, to the benefit of all future gene therapy programs. One of the rare disease gene therapy programs that BGTC chose was the AAV9-*SUMF1* program developed by Dr. Steven Gray for the treatment of MSD.



The goals of BGTC include creating a common platform for the development of treatment for all of the estimated 10,000 rare diseases. Inclusion of the MSD program into the BGTC provides funding, expertise, and visibility to MSD research, regardless of the outcome of the clinical trial. While AAV9-*SUMF1* gene therapy has the potential to benefit some patients, the goal of a clinical trial is research. The outcome of these experiments can never be known until they are completed, and a possible outcome is the discovery that the treatment is not effective.

Being an advocate for our children is my full-time job. The benefit of this community is having a support system, so we know what research is out there, what physicians are available, and what we can do next– which is to push for a cure and try to make a difference.

-Tonya Goodin, mom of Grant & Grace (U.S.)

Repurposed Compound Tazarotene

Aim: Repurpose an approved drug that restores sulfatase activity in all the cells of the body

Developing a new treatment for a disease can cost hundreds of millions of dollars and take over a decade to complete. Much of the cost and time required can be saved by finding a new use for a drug that is already approved for treating another disease (Mele, 2024). Extensive testing in patients has shown that these drugs can be used safely to treat a condition, which is not true of most compounds that have been tested in clinical trials. If an approved drug is found that improves some aspect of a rare disease, a much lower cost and faster option is to repurpose that drug for use in the rare disease, by running a relatively small clinical trial in patients. This is the founding rationale for Remedi4All, a European project bringing together several partners to advance treatments for rare diseases.

In a study funded partially by UMSDF, scientists at the University of Göttingen tested a large array of approved drugs in cells that came from MSD patients. They measured the level of activity of the sulfatase enzyme ARSA, identifying four compounds for further investigation. Tazarotene and the related compound bexarotene increased ARSA activity and that of other sulfatases, suggesting an effect on a common pathway, most likely FGE. The compounds also reduce lysosomal pathology and GAG accumulation. The compounds tazarotene and bexarotene appear to function by increasing the stability of the FGE protein, which in MSD patients retains some residual activity (Schlotawa, et al., 2023).

Tazarotene is currently used as a topical treatment, or skin cream. To treat MSD patients, the drugs would need to be administered to the entire body, e.g., systemically. Tazarotene has been administered to psoriasis and cancer patients in this way in clinical trials and was well-tolerated. It is likely that systemic administration of tazarotene to MSD patients would also be well-tolerated, but a clinical study is necessary. No regulatory agency has ever approved orally-administered tazarotene, and no drug company has ever sold tazarotene in that form. Therefore, although tazarotene is an approved drug, a new form of the drug must be submitted for approval to regulatory agencies. This process could take considerable time and incur a large cost. Partnership with Remedi4All will facilitate the further development of oral tazarotene for MSD patients.

Future study of the mechanism behind the effect of tazarotene and bexarotene on FGE stability would be beneficial not only to understanding the activity of these drugs, but also may suggest other therapeutic interventions that would give patients options for treatment. Alisa DeGrave in Dr. Schlotawa's lab has shown that tazarotene induces a cell response related to endoplasmic reticulum stress. Because FGE resides in the endoplasmic reticulum, this mechanism may be relevant, and may indicate other methods of increasing the stability of FGE.

Ex vivo Gene Therapy

Aim: Replace the missing gene in the patient's own cells and allow those cells to take up residence in the patient's body.

The recent approval of Lenmeldy in the US-- also sold as Libmeldy in Europe-- for the treatment of MLD, suggests a high probability of success for a similar treatment for MSD. Because the symptoms of MLD and MSD are similar, it is likely that the replacement of the same cells that benefit MLD patients will benefit MSD patients. Promising early results for ex vivo gene therapy to treat MPS I (Gentner, et al., 2021) also support this approach. In this type of treatment, stem cells are extracted from a patient, genetically modified by replacing the missing gene (in this case *SUMF1*), and reintroduced. Because the patient is receiving their own stem cells, there is no danger of transplant rejection or graft versus host disease, as with other transplantation procedures. Patients would have to undergo a myeloablative conditioning treatment, which carries some medical risks.

In a mouse model of MSD, hematopoietic stem cells from *SUMF1* knockout mice were infected with virus containing the *SUMF1* gene. Implanted cells in these knockout mice-- including their glycosaminoglycan (GAG) levels, ARSA activity, and brain inflammation-- were measured. The transplanted stem cells appeared to restore function in the mice, suggesting that this is a potential avenue for treatment (Pham, et al., 2024).

Further study is needed to advance this concept into clinical studies. In particular, the genes transduced into the stem cells must be optimized. Patients may benefit from replacement of not only *SUMF1* but an increase in the level of ARSA or other sulfatases.

Mikhaiło, age 10, with his mother, Tetiana Melnichuk (Ukraine)

Pharmacological Chaperones

Aim: Find new chemical compounds that stabilize FGE and allow the enzyme to do its job in spite of disease-causing variants

A collaboration between Lars Schlotawa at the University of Gottingen, Matthias Baud at the University of Southampton, and Karthikeyan Radhakrishnan and Hartmut Niemann, at the University of Bielefeld, is searching for chemical compounds to stabilize FGE mutants and allow the enzyme to carry out its function in cells. Because most disease-causing variants in FGE affect protein stability rather than activity, stabilizing the protein will presumably increase the function in a patient's cells. The process to discover these compounds involves first identifying any chemical that can adhere to the protein surface, then seeking ways to connect compounds that adhere to different sites on the protein to produce better binders. The compounds that adhere well are expected to help maintain the proper structure of the protein despite a pathogenic variant's destabilizing effects. If such a chemical is discovered and shown to increase FGE activity in cells expressing the mutant FGE protein, the chemical "hits" would then be optimized to produce drug candidates, which would undergo further testing and optimization for clinical use. The MSD Action Foundation initiated this project, which would benefit from further funding.

What Can UMSDF & Allies Do to Help?

AAV9 Gene Therapy	• Maintain active participation in BGTC meetings • Connect with other gene therapy projects within BGTC and outside, to share lessons learned • Facilitate trial participation through registries
Oral Tazarotene	Facilitate trial participation through registries
Ex vivo Gene Therapy	Financial support for project
Pharmacological Chaperones	Financial support for project

Individual Treatment Studies

Aim: Follow up on results with single-patient studies of well-tolerated treatments

To date there have been two reported studies, both conducted in Iran, treating patients with MSD using compounds that could be described as nutraceuticals, nutritional supplements that are generally recognized as safe and that may have therapeutic potential.

Trehalose

The first study employed the use of disaccharide trehalose, a food additive that has been tested in neurodegenerative conditions, including Niemann-Pick disease, a lysosomal storage disease (Mobini, 2022). In one MSD patient carrying a homozygous *A177P* variant, trehalose was administered at a dose of 15 grams per week, by IV. Quality of life was assessed by a questionnaire called the TAPQOL, and the score increased from 67 at the beginning of the study to 80 at the end, indicating an improved health-related quality of life. There were no adverse events related to the administration of trehalose.

The US company Seelos Therapeutics is developing an IV formulation of trehalose for the treatment of neurodegenerative diseases such as ALS.

The company has reported that trehalose increases a cellular process called autophagy, which is a common element in neurological diseases. A recent paper shows that trehalose treatment reduces GAG levels in fibroblasts from MPS III patients (Rintz, 2023)

N-acetyl-L-leucine (NALL)

The second study (Saberi-Karimian, 2022), examining the potential of N-acetyl-L-leucine (NALL) in MSD, was performed in the same laboratory at Mashhad University in Iran. NALL is a modified amino acid found in food and as a naturally occurring metabolite. It has been investigated as a treatment for Niemann-Pick Disease Type C by IntraBio (Bremova, 2024). The drug has been approved and will be sold under the brand name Aqneursa. According to IntraBio, NALL corrects metabolic dysfunction and has been shown to normalize mitochondrial function (improving ATP production/reducing oxidative stress) and lysosomal function (resulting in a reduction of substrate accumulation). NPC patients taking NALL experienced a significant improvement as compared to placebo in the Clinical Impression of Change in Severity, a score that evaluates function in either an eight-meter walk test or a nine peg hole test (Bremova, 2024).

Individual Treatment Studies, cont'd

N-Acetyl-L-leucine (NALL) has been explored as a potential treatment for MSD. In one reported case, an individual showed improvements in movement and quality of life during treatment, and no treatment-related side effects were reported. Because these findings come from a single patient, additional research is needed to understand whether NALL is safe and effective for people with MSD.

The single MSD patient received three grams per day NALL (by an unknown route) over four weeks. The patient's function was assessed by a scale for ataxia (SARA), and quality of life was assessed by PedsQL. Both functional and QoL scores improved over the course of treatment. There were no adverse effects attributed to the treatment.

Given the positive results of trehalose and NALL treatment in lysosomal storage disease models and in patients, and the single patient trial results from the studies at Mashhad University, further study of these treatments may be warranted.

Allogeneic hematopoietic stem cell transplantation

Another study, here, investigates bone marrow transplantation as a possible treatment for MSD. Although there is a scientific rationale for this approach, there is currently insufficient evidence to determine whether it is effective for people with MSD.

Because bone marrow transplantation carries significant risks and there is limited evidence of benefit in MSD, it has not become a standard treatment and remains an area of ongoing research.

To date, two MSD patients at the University of Minnesota have undergone allogeneic hematopoietic stem cell transplantation.

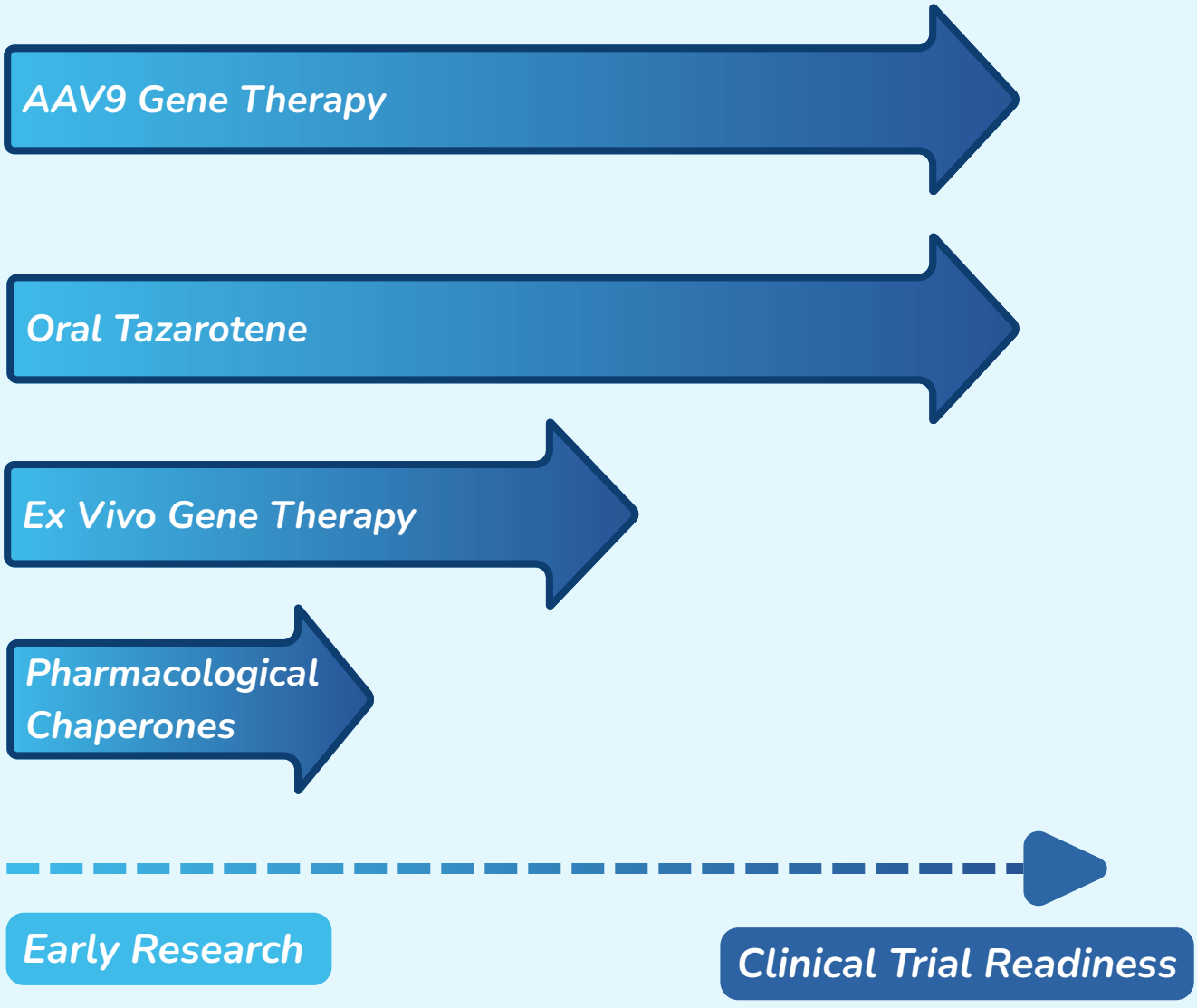
Allogeneic transplant has been used as a potential treatment, if risky, for inborn errors of metabolism (Boucher, 2015; Musolino, 2014; Gronvold, 2024).

Undergoing a bone marrow transplant carries with it a 10-15% mortality rate arising from a combination of disease progression, infection due to conditioning regimen and immune suppression, and the potential for the donor stem cells to mount an immune response against the patient (so-called graft versus host disease). The allogeneic transplant protocol in use at the University of Minnesota to treat LSDs is not disease-specific and can be adapted to treat other conditions where some benefit may outweigh the risks of the treatment.

Drug Development Pipeline

The drug development pipeline for MSD includes advanced programs and early-stage research. The development of any therapy will be enabled by ***biomarker development*** *and optimization of* ***physician- and patient-reported outcome measures.***

Progress to Clinical Trial Readiness



Current Stage of Development

The Foundation showed us the light at the end of the tunnel. They've not only helped connect us with so many other families, but they've also served as a beacon to help guide us through this journey. Their support has truly made us feel like we belong.

Ethan Duchon, age 10, with his family, including parents Melissa and Holden of StrEngthan (U.S.)

Moving MSD Research into the Future

Research initiatives extend natural history study to attenuated patients

Most patients evaluated in the retrospective natural history study and enrolled in the prospective natural history study, in progress, are categorized as late infantile onset, either severe or less severe. Patients with a variant that retains significant residual FGE activity have an attenuated form of the disease. These patients are often not diagnosed with MSD. Although they may be the patients who would receive the most clinical benefit from a therapeutic intervention, they may not get treated even if a therapy is approved.

Identifying and characterizing these attenuated patients is a top priority. They may be identified by sulfatase activity screening on dried blood spots taken at birth, engaging the larger pediatric neurology community, and reaching out to patient advocacy organizations representing conditions that may be a misdiagnosed attenuated MSD, such as autism.

The Scotting family (U.S.) Mom Stormi at left, Dad Tyler at right, with MSD Angel Baylor at center), held by CHOP doctors: Dr. Laura Adang (center left) and Dr. Rebecca Ahrens-Nicklas (center right).

Expand Patient Registry & Biobank

With two upcoming clinical trials evaluating treatments for MSD and more on the way, identifying patients, their genetic diagnosis, and their clinical presentation will be essential to ensure that these trials will be able to generate meaningful data and eventually deliver treatments to the patients they will most be able to help. This is accomplished by entering all diagnosed patients in a registry. UMSDF acts as an information hub to collect information from patients and deposit that information in a registry. This provides researchers access to anonymous patient data, thereby enabling and enhancing scientific studies. The registry can also be a conduit of information in the other direction, allowing UMSDF to forward information about upcoming research studies to the families of patients who wish to participate. The patient registry is constantly being updated with more patients, and participation helps all MSD patients by advancing progress toward treatments.

> ***Looking ahead, we hope for greater awareness, increased research, and, ultimately, better treatment options for multiple sulfatase deficiency.***

Until then, we continue our journey with love, patience, and an unyielding commitment to making Zeuri's life as fulfilling as possible.

-Zhang, father of Zeuri Zhang (China), age 16 at far right, pictured with his younger brother

Additional Research Initiatives

The biobank houses biological specimens (blood and urine) from MSD patients worldwide at a central location. These samples are then provided upon reasonable request to researchers interested in finding biomarkers or in understanding the disease mechanism. These samples can be collected from patients at their home by a mobile phlebotomy service. Development of a biomarker to measure disease progression and therapeutic efficacy would also benefit from more CSF samples, which are more difficult to collect. Any time a patient undergoes a procedure that would allow the collection of a small amount of CSF, caregivers should consider requesting an additional sample be frozen and sent to CHOP. As with the patient registry, participation in the biobank helps advance the development of therapies for all MSD patients.

Develop Additional Disease Models

Cell-based disease models of MSD can be incredibly valuable in characterizing the role of FGE in sulfatase activity, screening treatments, and validating new biomarker assays. To date, several cell-based models have been generated, including a mouse knockout fibroblast line, immortalized patient derived fibroblast lines, and patient-derived induced pluripotent stem cell (iPSC) lines (Schlotawa, 2023; Pham, 2024).

The patient-derived cell lines bear disease-causing *SUMF1* variants in addition to other genetic factors that may affect the disease severity. Obtaining multiple iPSC lines will allow researchers to further characterize the genotype-phenotype correlation and enable drug screening assays to ascertain the broad activity of compounds across mutation types. Typically, iPSC lines are obtained from patients' biological samples (blood or tissue). This effort therefore would proceed in parallel with the above-described work expanding the biobank.

Animal models are also important in understanding the disease mechanism and developing therapies. While cell models can be controlled more closely and used to test more compounds, they do not reflect the complete picture of sulfatase deficiency. Cells can generate active sulfatases for their neighbors through secretion and reuptake. In addition, different types of cells may be more susceptible to the lack of specific sulfatases, as seen in the cell line work of Pham, et al., 2024.

Additional Research Initiatives, cont'd

To get a complete picture of the effect of *SUMF1* variants, it is important to introduce disease-causing variants in animals that can be studied. There have already been zebrafish (Fleming, 2022), fruit fly (Selleck, 2018), and mouse (Settembre, 2007; Sorrentino, 2023) models of MSD developed, and these have proved useful in developing the gene therapy as well as the ex vivo gene therapy.

Further work could take advantage of several genetic tools available in mice. These include ways of tracking different lineages of cells during development, characterizing the ability of *SUMF1* positive cells to influence their *SUMF1* negative neighbors in different tissues, and examining the effect of different treatment timing on the development of symptoms.

It may also be helpful to develop mouse models with less severe forms of the disease to explore the resulting biomarker profile.

Mady Mancuello, age 4 (Argentina)

Understanding the Role of FGE in sulfatase activity

It is clear that while all sulfatases require FGE activity to reach full function, some sulfatases are not impacted by the reduced FGE activity in MSD patients. A greater understanding of how FGE variants affect the activity of the different sulfatases may provide deeper insight into disease biology. This will inform further therapeutic development not only for MSD but for other sulfatase deficiencies that may benefit from an increase in FGE activity above the level found in the cells of unaffected individuals.

There is currently no reliable method for measuring FGE activity directly. The activity is measured by introducing the gene-- with or without a sequence variant-- into cells lacking FGE, and measuring the activity of a vulnerable sulfatase like ARSA. Developing a new method to directly measure FGE activity would be helpful in characterizing new variants and in developing new treatments based on increasing the enzyme function.

Key Gaps in Knowledge	Action Needed
The mechanism of action of tazarotene increasing FGE stability is not yet known, which makes its use in combination therapies more uncertain.	Biochemical characterization of FGE in patient-derived iPSCs, further exploration of ER stress
We cannot predict which *SUMF1* variants can be stabilized by molecular chaperones, or what residual FGE activity will be produced by this stabilization in a cell context.	These questions will have to wait until the binding fragments are assembled into active compounds for testing.
The critical mass of functional FGE-producing cells to replace lost sulfatase function in different tissues	In vitro and in vivo studies on the effects of FGE expression on nearby FGE-deficient cells
The potential for deleterious effects of overexpression of FGE has not been fully explored, making it difficult to determine the optimal degree of overexpression of the gene.	Toxicology studies using different promoters or gene copy numbers to find dose-limiting toxicity of expression
Can any disease symptoms can be reversed? We still do not know if-- or at what point-- reversal may be possible.	Time-course studies in mice

If we band together as a rare disease community, we will have a lot more ability to make change for collective good.

-Jason Goodin, father of Grant and Grace Goodin

Facilitating Collaboration

Much of the knowledge of MSD has come first from the characterization of individual sulfatase deficiencies. Frequently, MSD researchers are also experts in other lysosomal storage diseases, staying up-to-date on the latest in lysosomal storage disease research from other labs. There are also parallels between MSD research and other rare, neurological conditions. For these reasons, it is important to keep the lines of communication open between the MSD community and other rare disease networks. UMSDF holds a bi-annual scientific conference, inviting researchers from around the world to present their data and learn from other scientists. In addition, UMSDF personnel attend conferences held by other rare disease organizations to share data and, where appropriate, establish research collaborations. This sharing of information is essential for all scientific research, but becomes especially important in ultra-rare diseases where information from a specific rare disease may contain some gaps due to the small size of the population.

The BGTC is not only a government-funded effort to develop treatments for specific rare diseases, it is also a tool for disseminating information about gene therapy development across the rare disease world. Frequent meetings with the BGTC community allow cross-fertilization of these programs, where lessons learned by one program can be internalized and used by another. The hope is that the consortium will result in a standard format for developing AAV gene therapies, wherein all rare disease patients may benefit from these lessons.

I was amazed to find resources, an active community, and even clinical trials on the horizon. There is real hope for treatments now. And while the journey is still heavy with shared grief, it is far less isolating knowing this community is working toward a cure.

-Mom Natalie Sheppard
with Remy Levine, age 5 (U.S.)

Charting the Path Ahead: The Journey Continues

As the United MSD Foundation enters its 10th year in 2026, we look back with immense gratitude and pride at the extraordinary strides our community has made in such a short time. From navigating the early unknowns of this disease to achieving major scientific breakthroughs, our collective determination has transformed the landscape of MSD research.

Yet, while we celebrate how far we have come, we know our work is far from finished. MSD research now sits at a pivotal, high-stakes threshold: where unprecedented hope meets an urgent, unmet need. To cross the finish line and bring life-changing treatments to our families, our immediate path forward focuses on several key priorities:

- **Pioneering Clinical Trials:** Advancing promising therapies such as AAV9-*SUMF1* and oral tazarotene as they prepare to enter clinical trials.
- **Refining Trial Readiness:** Strengthening clinical outcome measures, functional assessments, and biomarker tracking through continued participation in natural history studies to ensure future trials are set up for success.
- **Advancing Early Detection:** Expanding sample collection for our newborn screening test algorithm and partnering collaboratively with the MLD community to advocate for standardized screening protocols.
- **Elevating Existing Programs:** Providing robust, ongoing support for high-potential avenues, such as ex vivo gene therapy, which holds tremendous promise based on successes in similar conditions.
- **Exploring Next-Generation Science:** Continuing long-term translational research, including the development of pharmacological chaperones for FGE stabilization.

The progress outlined in this roadmap fills us with profound hope. Fueled by the resilience of our families, the passion of our scientists, and the dedication of our partners, we stand more united than ever. We will not slow down, and we will not stop, until effective treatments are a reality for every child and family facing MSD.

MSD Angel
Willow Cannan
(U.S.)

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Acknowledgments

This Research Strategy Roadmap is a testament to the power of collaboration and shared purpose. We extend our deepest gratitude to the scientists, clinicians, industry partners, and advocates who generously contributed their time and expertise to shape this vision. Thank you to the UMSDF Research Committee and Matt Jarpe for their work on this vital document. Most importantly, we express our profound appreciation to our MSD families. Your lived experiences, courage, and unwavering dedication are the heart of everything we do. It is your trust and hope that drive this research forward.

Interviews

Dr. Lars Schlotawa, interview, March 4, 2024

Dr. Steven Gray, interview, March 5, 2024

MSD Family Foundation meeting April 13, 2024 (MSD Action Foundation, Fundacion Cure MSD, Cura MSD, Grant Us Grace, and StrEngTHAN)

Dr. Kartik Radhakrishnan, interview, April 23, 2024

Dr. Andrew Shenkar, interview, April 25, 2024

Dr. Michael Gelb, interview May 7, 2024

Drs. Lars Schlotawa, Laura Adang, Rebecca Ahrens-Nicklas, interview May 15, 2024

Meetings

United MSD Foundation Research Committee meetings: Monthly

2024 International MSD Scientific & Family Conference, August 1-3, 2024

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