



Energy in Action

**MITOCHONDRIAL DISEASE EXTERNALLY-LED
PATIENT-FOCUSED DRUG DEVELOPMENT MEETING**

MARCH 29, 2019 | HYATTSVILLE, MD

VOICE OF THE PATIENT REPORT

MITOCHONDRIAL DISEASE:

ADULTS WITH MYOPATHY

CHILDREN WITH NEUROLOGIC SYMPTOMS

HOSTED BY UNITED MITOCHONDRIAL DISEASE FOUNDATION

IN COLLABORATION WITH MITOACTION AND MUSCULAR DYSTROPHY ASSOCIATION

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Voice of the Patient Report

“Mitochondrial Disease: Adults with Myopathy, Children with Neurologic Symptoms”

This report represents the summary report composed by the United Mitochondrial Disease Foundation (UMDF) as a result of an Externally-led Patient-Focused Drug Development meeting held on March 29, 2019 in Hyattsville, MD. This report reflects the host organization’s account of the perspectives of patients and caregivers who participated in the public meeting.

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- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
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A MESSAGE OF THANKS

On March 29, 2019, hundreds of mitochondrial disease patients, caregivers, advocates, healthcare providers, industry representatives, and government officials came together for an Externally-led Patient-Focused Drug Development (EI-PFDD) meeting to have our voices heard. On behalf of our patient community, their families and caregivers, thank you for your commitment and support!

The “Energy in Action” EI-PFDD meeting for mitochondrial disease aimed to set the groundwork for creating effective therapies for mitochondrial disease. This was truly a milestone for our community. It also served as a testament to the power of individual patient advocacy groups to come together to benefit our disease community. The meeting was the culmination of more than a year of planning and collaboration by the patient advocacy groups facilitating this meeting. We are thankful for the leadership of our friends at MitoAction and the Muscular Dystrophy Association, who helped us pull this tremendous meeting together.

We were grateful for the opportunity to amplify our collective voice for our distinguished guests from the U.S. Food and Drug Administration. Thank you for your time and support in bringing this meeting to fruition. Special thanks to Dr. Lucas Kempf, Acting Associate Director to the Rare Disease program in the Office of New Drugs, and Dr. Larissa Lapteva, Associate Director in the Division of Clinical Evaluation, Pharmacology, and Toxicology, Office of Tissues and Advanced Therapy, Center for Biologics Evaluation and Research, who provided great support and insightful commentary.

Many thanks also to James Valentine, for his dedication to rare disease communities and his outstanding facilitation of our meeting. We are also grateful to Dr. Michio Hirano and Dr. Amy Goldstein for their excellent clinical presentations on mitochondrial disease and their enduring commitment to our community.

Our patient families brought their voices to help us better understand their experiences, their struggles, and their hope. Courageous panelists put their energy in action and made a choice to share their perspective of certainty, amidst a path of often uncertainty. Our broader community came forward with a loud voice, through active participation in our meeting and our surveys. To our hundreds of participants, we are most grateful for your candor and your courage.

Because of all of you, we have a renewed sense of optimism that may lead us towards new and innovative therapies and treatments, and a world without mitochondrial disease.

Thank you for your tremendous support and commitment,



Brian Harman
President & CEO
The United Mitochondrial Disease Foundation

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EXECUTIVE SUMMARY

Mitochondrial disease is a family of serious, debilitating disorders that result from inherited genetic defects that affect primarily the mitochondrial oxidative phosphorylation system (OXPHOS) responsible for generating cellular energy. Primary inherited mitochondrial diseases encompass hundreds of individual genetic disorders that are heterogeneous and frequently multisystemic. Typically affected organs are those with a high energy demand, although virtually any organ or tissue can be involved. Variability in the presentation of mitochondrial disease in infants, young child and adults often complicates clinical diagnosis. Currently, there are no FDA-approved preventative or restorative agents for any mitochondrial disease or for these disorders as a whole. The leading approach to treatment of mitochondrial disease is management of symptoms and non-specific supportive care. Impact on the quality of life of patients and families is devastating and unpredictable, with lifelong and significant physical, emotional, social and financial implications.

The Externally-led Patient-Focused Drug Development (EI-PFDD) Initiative is part of FDA's commitments to more systematically obtain patients' perspectives on the burden of disease and impact of current treatments. An EI-PFDD meeting was held for mitochondrial disease in Hyattsville, Maryland on March 29, 2019. Through this meeting, FDA provided a forum where mitochondrial disease patients, families, and caregivers were able to share their unique insights on the impact of mitochondrial disease to their day-to-day lives. Perspectives on currently available treatment options and strategies for disease management, as well as expectations for the future treatments, were also shared.

The objective of the meeting was to increase FDA's understanding of how patients, families and caregivers experience and manage mitochondrial disease, and the factors that are considered when treatments are chosen. This may, in turn, help the FDA understand the appropriate benefit-risk balance for new treatment options, the severity of these conditions, and the urgency of unmet medical needs.

The voice of the mitochondrial disease patients was heard by focusing on two different subcategories of patients – adults with mitochondrial myopathy and pediatric patients with neurologic symptoms. These are very common manifestations of mitochondrial disease. While there are many other critical symptoms of mitochondrial disease, the meeting organizers believed that these focused discussions would allow a deeper understanding of the most common disease symptoms while also providing a window into the broader experiences of mitochondrial disease patients, as most patient suffers from a myriad of disorders that affect many body systems.

The voice of the mitochondrial disease patient was heard through courageous patient/caregiver testimonies, live polling of the broader audience, open discussions with the meeting attendees, and post-meeting surveys. Throughout the course of these activities, the voice of the mitochondrial disease patient was heard strongly and consistently, and the following key messages emerged:

General Conclusions on Mitochondrial Disease:

- **Mitochondrial disease is a complicated, diverse and unpredictable family of diseases with high unmet need**
 - Caused by hundreds of inherited genetic mutations, with new mutations continuing to be discovered
 - Widely diverse and unpredictable symptoms and manifestations with many subpopulations
 - Illnesses (e.g., viral or bacterial) often causes significant disease progression and regression
 - Symptoms are managed by many drugs and lifestyle modifications, but no drugs are approved that target the specific causes of disease

- Treatments are managed by trial-and-error and constant re-evaluation, and it is difficult to understand which drug and lifestyle interventions are providing benefit
- Many drug treatments for one symptom may cause worsening of other symptoms and must be discontinued or modified
- Prescription drugs, supplements, adaptive devices and other therapeutic interventions are expensive and often not covered by health insurance
- Patients have days that are better and worse, and it is often difficult to understand why
- Pediatric patients have difficulty transitioning into adult care within the healthcare system
- Drug development is challenging due to disease variability (even within-patient) and lack of well-defined clinical trial end points

Adults with Mitochondrial Myopathy

- **Adult patients with mitochondrial myopathy continuously deal with very difficult issues in their daily lives, the most important of which include:**
 - Muscle weakness
 - Chronic fatigue
 - Gastrointestinal problems
 - Pain
 - Exercise intolerance
 - Dysautonomia (autonomic nervous systems problems, dizziness, difficulty with temperature modulation, low blood sugar, blood pressure issues)
 - Sleep difficulties
 - Balance problems
 - Eye muscle problems
 - Cognitive issues (“brain fog”)
- **Specific activities of daily living that are most important to adult patients with mitochondrial myopathy but which they are unable to do include:**
 - Moving around independently and safely
 - Understandable communication with others
 - Walking and standing independently
 - Understanding conversation in noisy settings
 - Driving
 - Personal hygiene
 - Reading

- **The most concerning social, emotional or economic consequences for adult patients with mitochondrial myopathy include:**
 - Social isolation
 - Loss of hobbies or activities
 - Loss of independence
 - Loss of job or inability to get job
 - Financial difficulties
 - Frustration
 - Depression and/or anxiety
- **The current state of managing adult mitochondrial myopathy is summarized as follows:**
 - Rest, careful planning of activities, and inactivity
 - Diet management and trial-and error treatment with dietary supplements including a “mito-cocktail,” which is often personalized and prepared at a compounding pharmacy
 - Trial-and-error treatment with prescription medicines including pain medications, anti-depressants or anti-anxiety medications, heart medications and muscle relaxants
 - Modifications and accommodations at work, in school and at home
 - Stretching and exercise
 - Use of adaptive devices
 - C-PAP for sleep apnea
 - Immunotherapy, including IVIG, to help with prevention of illness
 - Overall, only 17% of participants believe their medications, therapies and lifestyle changes have significantly improved their quality of life
- **New treatments for adult mitochondrial myopathy should focus on the following unmet needs:**
 - Reduction in chronic fatigue and reduction in muscle weakness are most important
 - Reduction in pain, gastrointestinal problems and exercise intolerance are also desired
 - Gain in function (e.g., energy, strength, mobility, dexterity, cardiac function, speech) is highly desired
 - Slowing / stopping disease progression is very meaningful
 - Prolongation of life is important, but not the primary focus
- **Adults mitochondrial myopathy patients are most likely to use a new medication or participate in a clinical trial based on:**
 - Lack of serious side effects, which is most important
 - Cost
 - Burden of administration
 - Common side effects

Pediatric Patients with Neurologic Manifestations

- **Pediatric patients with neurologic manifestations of mitochondrial disease are highly disabled and progressive and their families continuously deal with very difficult issues in their daily lives, the most important of which include:**
 - Muscle weakness
 - Chronic fatigue
 - Gastrointestinal problems
 - Speech problems
 - Delayed milestones
 - Swallowing difficulties
 - Learning disability
 - Movement disorders
 - Seizures
 - Exercise intolerance
 - Pain

- **Specific activities of daily living that are most important to pediatric patients with neurologic manifestations but which they are unable to do include:**
 - Gross motor activities (moving independently, walking, standing, sports)
 - Communication
 - Fine motor activities
 - Going to school or work
 - Personal hygiene

- **The most concerning social, emotional or economic consequences for pediatric patients with neurologic manifestations of mitochondrial disease include:**
 - Frustration
 - Social isolation
 - Communication issues
 - Loss of independence
 - Modified school/work hours
 - Lack of hope for the future

- **The current state of managing pediatric patients with neurologic manifestations of mitochondrial disease is summarized as follows:**
 - Many types of prescription medications are used to manage a variety of symptoms. Seizure medications, anti-depressants or anti-anxiety medications, pain medications, and muscle relaxants are the most commonly used.
 - Diet management and nutritional modifications including the use of a G-tube, J-tube or TPN (Total Parenteral Nutrition), and trial-and error treatment with dietary supplements including a “mito-cocktail” (which is often personalized and prepared at a compounding pharmacy)
 - Modifications and accommodations
 - Physical therapy
 - Occupational therapy
 - Speech therapy
 - Use of adaptive devices
 - Infectious disease management and immunotherapy, including IVIG
 - Overall, only 23% of participants believe their medications, therapies and lifestyle changes have significantly improved their quality of life
- **New treatments for pediatric patients with neurologic manifestations of mitochondrial disease should focus on the following unmet needs:**
 - Reduction in fatigue and muscle weakness are most important
 - Improvement in gastrointestinal problems, speech, seizures, pain, movement disorders and swallowing difficulties are also desired
 - Gain in function (e.g. energy, strength, mobility, dexterity, cardiac function, speech) or slowing / stopping of disease progression (even without gain in function) are both highly desired
 - Prolongation of life is also very important
- **Caregivers and pediatric patients with neurologic manifestations of mitochondrial disease are most likely to use a new medication or participate in a clinical trial based on:**
 - Lack of serious side effects, which is most important
 - Burden of administration
 - Common side effects
 - Length of treatment
 - Cost and/or travel
 - Way treatment is administered

Dr. Philip Yeske, UMDF Science and Alliance Officer, reflected the overall key messages of the meeting, as summarized by clinical experts Drs. Hirano and Goldstein, as follows:

- The complexity of care needed for mitochondrial disease patients is reflected in the number of specialists needed to treat their disease
- From a patient experience perspective, there are good days and bad days, and these are unpredictable
- Fear of, and anxiety around, progression of disease caused by infection leading to a “mito crash” with months of recovery causes patients to live in isolation
- For adults living with mitochondrial myopathy, there is hope for therapies that will improve function
- For the pediatric population living with neurologic manifestations, slowing / stopping disease progression (particularly for cognitive ability) is critical, even without an improvement in function
- For teens transitioning to adulthood, there is a major gap in care that needs to be addressed by the mitochondrial disease community

This EI-PFDD meeting was a critical step forward for the mitochondrial disease community. The insights collected and reported on in detail in this “Voice of the Patient” report reflect important perspectives of people living with mitochondrial diseases and may help direct the FDA in partnership with pharmaceutical companies to develop the critical medicines that are desperately needed by this community. These insights will now be used to help develop a benefit-risk framework that the FDA may utilize in their regulatory decision making. Some preliminary recommendations for this benefit-risk framework can be found in this report.

“One of the things that struck me -- and this is probably well known to all of you -- is that sixteen symptoms per patient is the average. For drug developers, that could be a little bit daunting because they're sort of used to looking at the world through a little bit of narrow pinhole of symptoms; therefore, drug targets the symptom. So, when we talk about a syndrome, that's a much harder problem because everybody here has some different cluster of all those symptoms....The other very important thing that you talked about that needs to be appreciated is how heterogenic it is and how unpredictable it is. You have a sort of general vocabulary what a good day is, and that may be very individual for each of you but it's understandable by each one of you, which is also important for drug companies to understand how to make a metric that describes a good day.

- Lucas Kempf, MD, PLLC, Acting Associate Director, Rare Disease Program, Office of New Drugs, CDER, FDA

MITOCHONDRIAL DISEASE EXTERNALLY-LED PFDD MEETING DESIGN

The Food and Drug Administration (FDA) is tasked with assuring that drugs, vaccines, biological products and medical devices intended for human use are safe and effective. To more systematically obtain the patient perspective on specific diseases and their treatments, the FDA has conducted 25 disease-specific patient-focused drug development (PFDD) meetings and has welcomed patient organizations to conduct Externally-led PFDD (EI-PFDD) meetings. Background and guidance on EI-PFDD meetings can be found at the following link:

<https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings>

The United Mitochondrial Disease Foundation (UMDF) applied to the FDA and was granted approval to host, in partnership with patient organizations the Muscular Dystrophy Association and MitoAction, an EI-PFDD meeting focused on mitochondrial disease. This EI-PFDD meeting enables the mitochondrial disease community to share with key FDA officials and other stakeholders the burdens of the disease and perspective on future idealized treatments. This in turn may inform the FDA regarding the benefit-risk balance of treatment options, the severity of the disease, and the urgency of unmet medical needs.

The goals of this meeting were as follows:

- Provide broad mitochondrial disease patient perspective to the FDA by presenting testimony, discussing key topics and identifying treatment priorities.
- Capture patient-provided data that will help to inform the design of future clinical trials with respect to outcome measures that are meaningful to those affected by mitochondrial disease.

The EI-PFDD meeting included panelists that represent a spectrum of perspectives, including age, geographic region, affected adults and caregivers of pediatric patients. Importantly, the perspective of two distinct sub-populations of mitochondrial disease patients were explored and captured throughout the course of the meeting. These included adults with mitochondrial myopathy and pediatric patients with neurological manifestations of mitochondrial disease. The focus on these manifestations of mitochondrial disease allowed a deeper understanding of the most common disease symptoms while also providing a window into the broader experiences of mitochondrial disease patients, as most patient suffers from a myriad of disorders that affect many body systems.

The voice of the mitochondrial disease patient was heard through courageous patient/caregiver testimonies, live polling of the broader audience, open discussions with the meeting attendees, and post-meeting surveys. The EI-PFDD meeting was attended in-person by 125 people, and via a livestream webcast by 170 registrants. The post-meeting survey was completed by representatives (patients or caregivers) of 393 individual patients living with mitochondrial disease. 55% are adult mitochondrial myopathy patients, 12% are caregivers of an adult with and mitochondrial myopathy (or have lost a loved one), 30% are a parent/caregiver of a child who has a neurologic manifestation of mitochondrial disease (or have lost such a loved one), and 2% fit in none of these categories.

A recording of the entire Externally-led PFDD Meeting for mitochondrial disease can be viewed at the UMDF website. See Appendix 1 for the link to view the recording or read the associated transcript.

BACKGROUND ON MITOCHONDRIAL DISEASE

What is Mitochondrial Disease?

Mitochondrial disease is a family of serious, debilitating disorders that arise as a result of inherited genetic defects (“primary mitochondrial disease”). Primary mitochondrial diseases are caused by genetic defects in both nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) that affect primarily the mitochondrial oxidative phosphorylation system (OXPHOS) responsible for generating cellular energy. Primary inherited mitochondrial diseases encompass hundreds of individual genetic disorders that are heterogeneous and frequently multisystemic presenting with a complex array of phenotypes affecting anyone from birth to death. Typically affected organs are those with a high energy demand, including skeletal and cardiac muscle, endocrine organs, kidney, nonmucosal components of the intestinal tract, retina, and the central nervous system. However, virtually any organ or tissue can be involved. The prevalence of mitochondrial disease is still unclear due to the challenges in establishing a precise genetic diagnosis, and complexities in patient presentations. The prevalence of all pathogenic mutations in both nDNA and mtDNA is estimated to be at least 1:4000.

How is Mitochondrial Disease Diagnosed?

Variability in the presentation of mitochondrial disease in infants, young children and adults often complicates clinical diagnosis. Diagnostic challenges result from not only the variable and often nonspecific presentation of these disorders, but also from the absence of a reliable biomarkers specific for the screening or diagnosis of the disease. Advances in genomics have allowed for improved diagnosis. Multisystem disease manifestations often occur, leading to a need for comprehensive and multidisciplinary care.

Some of the more common mitochondrial disease diagnoses include Kearns-Sayre syndrome (KSS), Chronic Progressive External Ophthalmoplegia syndrome (CPEO), Myoclonus Epilepsy Ragged-Red Fibers (MERFF), Mitochondrial Encephalopathy, Lactic Acidosis & Stroke-Like Episodes (MELAS), Thymidine Kinase 2 Deficiency (TK2d), Myoneurogastrointestinal Disorder and Encephalopathy (MNGIE), POLG-Related Mitochondrial Diseases, Leigh syndrome, and Mitochondrial Enoyl CoA Reductase Protein-Associated Neurodegeneration (MEPAN).

The North American Mitochondrial Disease Consortium (NAMDC), a member of the NIH-funded Rare Disease Clinical Research Network (RDCRN), has a detailed clinical registry with over 1,200 patients enrolled. In an analysis of patients enrolled through May 1, 2016, the majority (61%) had onset in childhood (<12 years-old). Children living with mitochondrial disease are generally more severely affected than adults. Typically, the childhood-onset patients are afflicted by severe neurological dysfunction as part of a multi-organ disease that is often fatal in youth. The severity of childhood mitochondrial diseases exemplified by the most frequent pediatric form, Leigh syndrome, that usually begins between 3 months and 2 years of age and manifests as developmental regression or delay with neurodegeneration of basal ganglia and brainstem regions. Leigh syndrome has been linked to mutations in over 75 nDNA and mtDNA genes that have been associated with variable median survival spanning in most cases from infancy to childhood, and infrequently to early adulthood. Unfortunately, patients who survive into adulthood typically show severe cognitive impairment, movement disorders, seizures, and other debilitating neurological impairments.

What are the Symptoms of Mitochondrial Disease?

Mitochondrial disease has a severe impact on several bodily systems with neurological complications being the most prominent in the pediatric group and myopathic symptoms most common in the adult population. Most often, symptoms affect organs with the highest cellular metabolic demands leading to neurologic manifestations, myopathies, visual and hearing loss. It is often observed that children are more neurologically devastated and exhibit central and peripheral neurological abnormalities leading to developmental delays, regressions, seizures, abnormal brain imaging and neuropathies. The younger the disease presents, the more devastating the symptoms with shortened life span. Adults seem to develop more muscular involvement as they age, and symptoms can range from an isolated progressive ophthalmoplegia to severe proximal myopathy, leaving patients wheelchair-bound with minimal energy to perform simple day to day activities. 76% of NAMDC Registry subjects reported to have myopathy as one of their symptoms.

How is Mitochondrial Disease Currently Treated and Managed?

Currently, there are no FDA-approved preventative or restorative agents for any mitochondrial disease or for these disorders as a whole. The leading approach to treatment of mitochondrial disease is management of symptoms and non-specific supportive care. At what can be a significant financial burden to families, emphasis is given to optimal nutrition and hydration as well as enhancement OXPHOS function achieved through the use of high-dose dietary supplements despite the lack of scientific evidence of efficacy and anecdotal reports of safety. Exercise therapy is advocated given beneficial effects on mitochondrial biogenesis, but this remains difficult to follow by patients whose major complaints are muscle weakness and fatigue. Therefore, care is largely non-specific and supportive with little success in reducing the burden of the condition.

What Research is Currently Being Conducted to Develop New Therapies for Mitochondrial Disease?

Due to the variability in disease presentation and progression, clinical development in mitochondrial disease has been challenging. There are currently a number of natural history and biomarker studies ongoing which are intended to develop a better understanding of diagnostic markers and the disease course.

Stealth BioTherapeutics is currently enrolling a Phase 3 study called MMPOWER-3. This is a randomized double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of daily subcutaneous injections of elamipretide in patients with primary mitochondrial myopathy (PMM). Elamipretide is a small molecule peptide designed to penetrate the cellular and outer mitochondrial membrane and target cardiolipin, which is found exclusively in the inner mitochondrial membrane. The trial will primarily assess the change in distance walked during the six-minute walk test (6MWT) and patient-reported fatigue using a PMM-specific questionnaire, the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA). Secondly, the trial will evaluate changes in fatigue during activities using the PMMSA, quality of life, impact on the patient's most bothersome symptom on the PMMSA, and safety and tolerability of treatment with elamipretide.

Reata Pharmaceuticals is conducting a Phase 2 clinical trial (the MOTOR study) to evaluate the efficacy, safety, and pharmacodynamics of RTA 408 (omavaloxolone) in the treatment of adult patients with mitochondrial myopathy. In preclinical studies, RTA 408 was shown to target inflammatory, metabolic, and mitochondrial pathways by inducing Nrf2 and suppressing NF-κB. Unlike other drugs in development for the treatment of mitochondrial disease, RTA 408 directly affects mitochondrial function and energy production in muscle cells. Exercise capacity is utilized in MOTOR as the primary efficacy endpoint through measuring change in peak work during maximal exercise testing.

Mitochondrial replacement therapy (MRT) is another research area that is under active debate. MRT uses healthy mitochondria coming from a donor's egg whose nucleus has been removed and into which the mother's nucleus is transferred. *In vitro* fertilization (either before or after MRT) produces an embryo that contains nuclear DNA from the father and the mother with healthy mtDNA from the donor. This procedure gives women with mtDNA mutations a chance of having their own children who could be free of the mitochondrial disease.

MRT is not genetic manipulation, but rather a technological innovation and an expansion of *in vitro* fertilization, a clinically-approved technique used for four decades. The latest evidence from leading mitochondrial research institutions in the US and the UK indicate that mitochondrial replacement techniques are safe and effective in primates, although further research will be necessary to fully understand the long-term effects of MRT. Clinical studies using MRT are now ongoing in the UK, but are not currently allowed in the U.S., based on legislation that prohibits this. There is currently active discussion on the possibility of lifting the U.S. ban on this type of research.

SESSION 1: THE VOICE OF THE MITOCHONDRIAL DISEASE PATIENT – PERSPECTIVES FROM ADULTS WITH MITOCHONDRIAL MYOPATHY

In Session 1, the emphasis was on perspectives from adults with mitochondrial myopathy. The session was divided into two panels. In Panel #1, the focus was on symptoms and daily impacts of disease. In Panel #2, current and future approaches to treatment were discussed. Each panel included personal testimonies from patients and caregivers. This was followed by audience and remote polling and then a moderated group discussion with the broader audience in attendance at the meeting. Following the meeting, a post-meeting online survey (which included several open-ended questions) was administered to ensure the broadest and most complete participation possible. The polling results shown here are from the more robust post-meeting survey, which included 265 adult mitochondrial myopathy respondents.

The results of the patient voice activities from Session 1, Panels #1 and #2 are summarized below.

PANEL #1 – SYMPTOMS AND DAILY IMPACTS (Adults with Mitochondrial Myopathy)

Panel #1 Patient Testimonies:

The full testimonies from each patient can be found in Appendix 2. Here are some of the most impactful comments made by each.

Laura P -

*“The absolute worst part about mitochondrial disease is...whatever we are fighting that day. The **unpredictability of symptoms**, constant **demand to adapt to a new level of care/need**, and most importantly, as a family unit, **manage the needs of the entire family** while explaining to the world around us mitochondrial disease.*

*[My son’s] greatest quality of life altering symptom is **fatigue**. The inexplicable brown or blackouts where he has literally **no energy and partial to total brain fog**. Add to this life limiting is **heat/cold intolerance**. An otherwise intelligent, young man on the autism spectrum becomes dysfunctional- **slurring words, staring into space, and flapping his hands**- just to stay awake and cognizant of the world around him. Sadly, the world sees this and thinks he is mentally challenged rather than a college grad.”*

Devin S -

*“Every year brings a new challenge, a new norm to adapt to. In college it was **migraines** that hurt so much I used to cry out in pain in the middle of lectures. In grad school it was **dysautonomia** that caused me to pass out while doing my clinical rotations. I spent hours of undergrad pacing my dorm room unable to sit still from the **pain** I was in, and I spent hours of my master’s degree education in hospitals having **cardiology workups**. These examples are just a few highlights of how mito young adults live knowing that **we can never predict when our current norm will shift**. Because it always shifts – and then you’re figuring out if the latest symptom is life-threatening or just annoying.*

*On my best days I can **ignore the pain, rest in between every activity**, and mostly ignore my mito – I’m lucky that way. On the worst days I will be **crying in frustration** because going to the kitchen seems equivalent to climbing a mountain and just **trying to process what others are saying to me involves all of the energy and concentration that I have**.”*

Rachel S -

*“Listen to how my doctor recently described me for a research study: (Quote) “Rachel has... **very low exercise tolerance** which make it **impossible for her to do even basic housework, cooking, or cleaning** on most days...Her **cognitive function has also declined**...She **would like to be more active and involved... without becoming exhausted and in pain from minimal activities**. She is only 37 years old but many days she **functions like she is in her eighties**...”*

*No matter how much sleep I get, **my brain keeps right on feeling as sluggish and overwhelmed as the night before**, and life with such **relentless mental fatigue** is like having a brain that tops out at 20 miles per hour in a 65 mile-per-hour world. I can’t tell you how much I would love for my brain to keep up with loads of college-level reading, writing, and socializing as it once did, but for now I’m just **grateful for days when I have mental energy to compose a grocery list, check email, or read a chapter of a kid’s adventure book to my son**. These are simple abilities, but I don’t have them every day. And honestly, **most of the time even listening to music, making phone calls, or watching TV drain my mental energy** so much that I actively avoid them.”*

Debbie P -

*“My **balance/weakness continues to be unpredictable**. When I walk out the front door and fall into the bushes because my legs aren’t working right, I know that I really **need to concentrate on each step that I am taking** to make sure I pick my feet up all the way. I **always use some type of adaptive device, whether a cane, walker or wheelchair**. I am struggling with **losing my independence** and tripping even with the walker. My **memory / brain fog is worsening**, and it is frightening to me. My daughter was sick at school and I pulled up to her elementary school, parked, only to realize I was at the wrong school...because she is in HIGH SCHOOL! She had not been in that school for 5 years!*

*The **pain / fatigue / weakness / depression / anxiety is always present**, but the intensity is a moving target. What worries me most about mitochondrial disease is **how unpredictable it is and the unknown**. Will I be here in 5 years? Will we keep getting worse, will they find the gene causing what is happening?”*

Alyssa D -

*“The most crippling are **fatigue, pain, and dysautonomia**. The fatigue is almost impossible to describe because it seems other-worldly. It feels as though someone has taped cinder blocks to my eyelids some mornings and there is no way to keep them open. It can make it **impossible to chew** because I simply don’t have the energy to keep opening and closing my mouth. Sometimes it can even make walking feel as though I am trapped in 4 feet of quicksand. **Mito seems to reinvent the word fatigue**. The **symptoms vary** day to day and when I go to sleep at night I **never know what symptoms I’ll have the next day**.*

*I never knew how many types of pain there were until I started experiencing them first hand...These **different kinds of pain affect me on an almost everyday basis**, but the severity of the symptoms can alter from day to day. I’ve found that my **pain goes up after exerting myself**. I try to take breaks from some activities to prevent the crippling pain the next day. I **almost never have pain-free days**.*

***Dysautonomia** is like a drunk relative at a holiday party-----it doesn’t leave! It is the mis-regulation of the autonomic nervous system and for me causes **high heart rate, low blood pressure when changing position, dizziness, fainting, and tremors** to name a few. I experience these symptoms **every day, all day**. Dysautonomia can be **quite a hindrance to my quality of life** depending on the day.*

Panel #1 Polling Results:

Demographic Polling Questions:

Where do you currently reside?

Most of the participants are from US South (25%), US Northeast/New England (25%), Australia (20%), Europe (10%), and US Midwest (9%). 38% of participants live in a suburban area, 32% live in a city, and 30% live in a rural area.

How old is the patient now?

52% of the patients represented are >50 years old, 20% are 41-50 years old, 14% are 31-40 years old, 11% are 21-30 years old, and 3% are 18-20 years old.

At what age was the patient represented diagnosed with mitochondrial disease?

37% of the patients represented were diagnosed >40 years of age, 22% between 31-40 years of age, 17% between 21-30 years of age, 6% between 18-20 years of age, 4% between 11-17 years of age, and 7% between 0-10 years of age.

Symptoms and Daily Impacts Polling Questions (see appendix for full descriptions of possible answers):

What is the best description of the stage of disability for you or the person for whom you care?

This poll revealed that 39% have mild symptoms (able to walk and lead an independent life), 25% require a walker or other aid, 20% have significant symptoms (requiring some assistance for stability and walking), 7% are not able to walk without a wheelchair, 6% have severe disability (dependency on others), and 4% have minimal disability.

What is the best description of the patient's ability to carry out daily activities?

This poll showed that 22% are able to walk <100 feet on flat (unable to do stairs alone), 19% are able to walk <1/2 mile on flat, 16% are able to walk <1 mile on flat, 14% are able to walk <1/8 mile (1.5 city blocks) on flat, 13% have unlimited walking on flat (but are symptomatic on inclines or stairs), 11% are unable to walk (use a wheelchair exclusively), and 4% have no limitations.

Which mitochondrial disease symptoms most impact the patient's daily quality of life (select up to 5)?

The most common responses to this question included muscle weakness (78%), chronic fatigue (77%), gastrointestinal problems (52%), pain (52%), exercise intolerance (50%), dysautonomia (38%), sleep difficulties (36%), balance problems (36%), and eye muscle problems (33%).

What specific activities of daily life are most important to you that you (or the person for whom you care) are NOT able to do because of mitochondrial disease (select the top 3)?

The most common responses to this question included moving around independently and safely (43%), communication (speaking with others and being understood - 36%), walking and standing independently (34%), understanding conversation in noisy settings (33%), driving (31%), and personal hygiene (26%).

As a result of living with mitochondrial disease, which of the following social, emotional or economic consequences are most significant to you? (select up to 4)?

The most common responses to this question included social isolation (61%), loss of hobbies or activities (57%), loss of independence (46%), loss of job or inability to get job (40%), financial difficulties (37%), frustration (37%), depression and/or anxiety (32%).

Panel #1 Moderated Audience Discussion and Comments from Open-Ended Survey Questions:

The following is a sampling of insightful comments that were made by the broader attendees during the moderated audience discussion and in response to the open-ended questions posed in the post-meeting online survey.

Discussion Question 1: Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life?

"...there isn't an area of my life that is not affected by mitochondrial disease...even just basically personal hygiene or walking around the house. Before I'll walk before across the house I'll make a calculation or check a list to see what else can I do."

*"It's severe pain. The **fatigue, I can usually push through but the pain is more difficult.** And the pain and the stiffness never leave, but the pain levels can shift to the extremes."*

*"Tim recently told me that on a typical day three hours is about the most that's okay. And he wakes up **feeling horrible.** He takes a nap and he feels horrible. So, when he wakes up in the mornings, it's **as if he's been hit by a train and just excruciating pain,** and it takes at least an hour just to feel semi back into the world with being okay."*

Discussion Question 2: Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition? How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?

*"I have to plan every single part of my life days ahead, hours ahead. When I get really sick, I **can't manage my own medications or IVs by myself because my brain is just not functioning.** And it's gotten to the point where **if I have to walk long distances, I have to use a wheelchair.**"*

*"And even just planning ahead for how we're going to manage our energy takes energy. And then it's just **an endless spiral** of even that planning...So **even eating in order to get the nutrients we need to have energy takes energy, and that's just another spiral as well.**"*

*"The difference between good and bad days is **a good day for me, unfortunately, at this point is only happening once every few weeks.** Bad -- really, really bad days would be **asleep for 16 to 18 hours.** When I am up, I can **barely pull my head up.** A variation of a good day is where **I can get up, go to a concert, go do something fun** that requires a lot of energy, to a day that **you can't care for yourself,** is quite a range."*

*"On the **best days I battle through and get the household chores done** so it's not all left up to my husband. With 3 children there's always so much to do and the place looks like a bomb's gone off. However, the amount of housework that needs to be done usually leads me into a bad day. Bad days are bad, really bad. All I can do is **stay in bed.** I'm usually **overheating, nauseated and so lethargic with an enormous amount of***

all-over pain thrown in. I'm **hardly able to walk because of the nerve pain** in my feet and I can't make anything to eat."

"I have **extreme fatigue which makes it hard to do regular everyday chores**. I have **a lot of muscle weakness and have a hard time swallowing** and takes **a lot of effort to eat**."

"I **seldom leave my home because my symptoms sometimes worsen without warning** (periorbital paralysis, mild ataxia, changing vision, muscle weakness, etc.)."

"**On the best days, there is mild pain and fatigue**, but I can do most of the things I want or need to do that day. **On the worst days, I can barely get out of bed**; am extremely frustrated and tired and sore. **Normal daily activities are extremely difficult**."

Discussion Question 3: How has your condition and its symptoms changed over time? Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse? What worries you most about your condition?

"And even if he was to do no activity whatsoever, he could eat the exact same thing, sleep the exact same amount, or do everything exactly the same every day, and **you could have bad days and good days and there's no rhyme or reason or pattern at all** of why he has good or bad ones."

"My symptoms have been on a **continuous downward spiral with no end in sight** each day seems to be just worse and worse with **no hope for even achieving a baseline** hoping to be able to keep some basic living skills but **feeling hopeless**."

"**As I get older more symptoms seem to appear**. Some have been there since the beginning (pain, nausea) but for the most part I would say **nothing has gotten better, only worse**. Symptoms don't seem to go away, and they keep adding up. I have gotten **progressively weaker over the years** as well and doing day to day activities of **living has only gotten more challenging**."

"**Fatigue has become more disabling**, I can no longer "push" through - there just simply isn't enough energy to get through anymore. Muscle weakness has progressed. **Anxiety and depression are a daily battle now** as they were only intermittent before. **Dysautonomia is progressing** as my body weakness and becomes less conditioned."

"I do think that my **symptoms come and go**, which is part of what makes this disease so difficult for other people to understand and so difficult for doctors to diagnose. If I am well enough to get sufficient nutrition and hydration, then I can exercise, and I believe that **exercise always makes me better/stronger**. But any little thing can upset that equilibrium. **A virus, allergens, being too hot or too cold, lack of sleep can start a downward spiral that is very difficult to overcome**."

"I wanted to say that **the most consistent thing about mitochondrial disease is its inconsistency**. I had one of my bad days yesterday, and today I feel different. I call where I'm at right now my normal crappy self."

"And **the unknown is a major worry**, the unknown of the mitochondrial disease, what's going to happen."

PANEL #2 – CURRENT AND FUTURE APPROACHES TO TREATMENT (Adults with Mitochondrial Myopathy)

Panel #2 Patient Testimonies:

The full testimonies from each patient can be found in Appendix 2. Here are some of the most impactful comments made by each.

Luisa & Robert M -

*“As her respiratory muscles weakened, she required **BiPAP ventilatory support**. **Shortness of breath** worsened. **Fatigue was increasing**. Her **ability to walk declined**. She **relies entirely upon her gastric tube for nourishment**, her medications, and upon BiPAP to breathe whenever lying down or with increased exertion...**Difficulty handling her secretions** led to **repeated aspiration pneumonias**, several times **requiring admission to an ICU**.*

*In addition to the **two nucleosides**, Luisa takes **the typical mitochondrial cocktail consisting of creatine, CoEnzyme Q10, Carnitor, Vitamin C and Vitamin E**. The only adverse effect she has experienced with the nucleoside therapy is **diarrhea**, managed by taking **up to seven Immodium tablets a day**.*

*Luisa finds her **impaired speech most disabling**...She uses an iPhone App called “Big” in which is typed a sentence or two in large easy to read lettering and can be held up for everyone at the table to read at once. Our **family and friends have adapted to communication** with her.*

*I was asked which symptom I would wish to see addressed in new drug development. This is an impossible question. Would I rather breathe easy or eat? Would I rather hear or speak? I can do none of these things. What do I want? **I’d like to see a cure for Mitochondrial DNA Deficiency Syndromes**.”*

Deborah C -

*“After my extended illness in 2002, I was on **Oxycontin, Morphine, Fentanyl patches, Oxycodone, Methadone, and Avinza**. I was **hospitalized three times from pancreatitis** as a side effect from the **Avinza**, which is a long-acting narcotic. I was put on **Neurontin**, which caused **excessive swelling in my legs and hands**, but caused me to have the feeling that I was being zapped with a stun gun in my lower legs. I developed **pyelonephritis**, which is an abscess of the kidneys, along with **acute kidney failure**, after taking an **arthritis medication called Vioxx**. Because I didn’t have an infection, I was later told this was caused from the mitochondrial disease due to **autonomic dysfunction**. I take **Klonopin** for **Orthostatic hypotension and restless leg syndrome**, which causes **excessive sleepiness**. I went to rehabilitation for 5 days after my extended illness for **detoxification from the narcotics**.*

*I take 400 mg twice a day of **Magnesium**, which has helped with the **chest pain that I have had my entire life**; however, it has only helped a little bit with my **leg pain and spasms**. I have tried a **TENS unit for pain**, but it didn’t help.*

*It would be a blessing to have **medication available to have less pain**, as well as **increased energy and stamina** would allow me to **care for myself and improve my ability to be independent**. As I am still mobile, if my primary symptoms were controlled, it is possible that I would **be able to become employable**.”*

Michael M -

*"In regards to conventional medicine, the **Mitochondrial Vitamin Cocktail with L-Carnitine** was the start of my initial treatment. I **did not experience any benefit from the cocktail** even after the dosage was increased after three months. However, I **still continue to take them daily**. For **pain management** it **has been trial and error** with most medications.*

*The most significant symptom that I personally experience is **extreme fatigue**. Therefore, in my opinion the most beneficial part of my current treatment protocol is the stimulant I am prescribed, **Adderall**, which allows me to do **light graded exercise**. As my illness has progressed over the past few years, I have felt that regardless of what changes I have made in regards to my treatment it has **had less of a positive impact on my quality of life** and the result is a **consistent decrease in energy**.*

*Ideally, any medication or clinical treatment that would assist in the oxidation process at the cellular level to optimize mitochondrial function and assist with energy production would be a great goal. I can tell you **one of the hardest things to accept throughout this journey is not being able to do what I once could.**"*

Sharon S -

*"The past 18 years has been a journey of **trying anything I can find** to help myself. There are no real treatments for mitochondrial disease, let alone a cure. **All that I have tried over the years has not brought much lasting improvement to stay ahead of my progression**. If I make any changes to my regiment its due to having time to evaluate the effectiveness (is it bringing any relief? and not causing more side effect? Can I afford it?).*

*When I look back over 19 years, **the amount of money, time, energy I have spent trying to help my condition, I know that my effort has created a resiliency in me, but I am also very worn out** in a way regarding this uphill battle. I also know that if I stopped trying to help myself, I will reach despair. I no longer am satisfied with just my help. **I need your help now please.**"*

Nicole D -

*"Despite my attempts to address my treatment regimen as a lifestyle approach, **the disease is so unstable and unpredictable the treatment takes a lengthy trial and error approach**. At various points in my disease process, I have had to discontinue treatments that were previously effective.*

***The vitamin regimen (creatine, magnesium, and potassium) that treats my muscle pain and weakness often becomes very hard on my stomach causing extreme pain and irritation...**The process to find pharmaceutical grade vitamins that are reliable and effective has taken years and **endless amounts of research**. Because of the instability of the disease, and the research involved to acquire appropriate treatment, **my regimen is not efficient**.*

*I am extremely conservative with the use of **pain medications for my muscle and joint pain** because they **exacerbate the fatigue and muscle weakness**...I have found that **the most effective treatment for the fatigue is rest, clean diet, and high doses of Ubiquinol** (approximately 1000-1200 mg daily). However, I am in **a perpetual state of sleepiness and overall physical and mental fatigue**.*

*There isn't a treatment that I am using that is eliminating my symptoms. At best, they are giving relief but not absence. Therefore, I **have learned to work with the symptoms**. Ideally, any treatment that would be developed for mitochondrial disorders would **stabilize the muscles by minimizing or eliminating pain without the harmful side effects of current medications on the market**. Additionally, treatment for muscle myopathy would also **aid patients in physical strengthening and recovery of lost ability**."*

Panel #2 Polling Results:

Current and Future Approaches to Treatments Polling Questions (see appendix for full descriptions of possible answers):

What PRESCRIPTION MEDICATIONS do you take now to treat symptoms of your mitochondrial disease? Select ALL that apply.

The most common prescription medications taken are other medications not listed (54%), pain medications (49%), antidepressants or anti-anxiety medications (47%), heart medications (32%), and muscle relaxants (30%).

What VITAMINS or SUPPLEMENTS do you take now to treat symptoms of your mitochondrial disease? Select ALL that apply.

The most common vitamins or supplements taken are CoQ10 (78%), Carnitine (53%), Riboflavin (36%), Vitamin B3, Nicotinamide or Niacin (35%), and Vitamin E (34%).

What are you currently doing to help manage mitochondrial disease or mitochondrial disease symptoms? Select ALL that apply.

The most common answers to this polling question included choice of diet (60%), modifications / accommodations at work/in school/at home (52%), stretching (41%), exercise (40%), use of adaptive devices (36%), and physical therapy (32%). Rest/sleep/inactivity was not listed as one of the responses to this question but was frequently mentioned in the comments section.

Which surgical procedures have you undergone to treat or manage symptoms of mitochondrial disease? Select ALL that apply.

77% of respondents have not undergone surgical procedures to treat or manage their symptoms. 15% have had had a G Tube/GJ Tube placed for nutrition, and 9% have had a central line inserted.

In general, how much do the medications, therapies or lifestyle changes used improve your quality of life?

44% of respondents believe their medications, therapies or lifestyle changes have helped improve their quality of life somewhat. 18% of respondents are not sure of the impact, 17% believe they have had significant impact, and 16% believe they help a lot.

Which outcomes would be meaningful to you for a possible drug treatment? Select ALL that apply.

Gain in function (e.g., energy, strength, mobility, dexterity, cardiac function, speech) would be meaningful to 92% of respondents. 80% responded that slowing/stopping of disease progression is meaningful, and 50% responded that prolongation of life is meaningful.

Which ability or symptom would you rank as most important for a possible drug treatment today? Select up to 3.

In response to this survey question, a reduction in chronic fatigue (68%) and reduction in muscle weakness (57%) were most important. Other important targets for drug treatment included reduced pain (35%), reduced exercise intolerance (29%), and reduced gastrointestinal problems (28%).

Which of the following factors would influence your decision to take a new medication or participate in a clinical trial or research study? Select ALL that apply.

Significant risk of serious side effects is the most important factor that would influence a decision to take a new medication or participate in a clinical trial (with 82% of respondents). Cost is the second most important factor (60%), followed by burden of administration (41%) and common side effects such as nausea, loss of appetite, headache, etc. (39%).

Panel #2 Moderated Audience Discussion and Comments from Open-Ended Survey Questions:

The following is a sampling of insightful comments that were made by the broader attendees during the moderated audience discussion and in response to the open-ended questions posed in the post-meeting online survey.

Discussion Question 1: What are you currently doing to help treat your condition or its symptoms? What specific symptoms do your treatments address? How has your treatment regimen changed over time, and why?

*"I enjoy a lot of things and I've been able to significantly improve my quality of life. I do a **weekly IV nutrient cocktail**, which is some of the standard mito-cocktail but also customized to me based on extensive nutrient testing every nine months. I found increasingly **glutathione and branch chain amino acids have been able to reduce my fatigue and kind of delay fatigue**. I have done **hyperbaric oxygen therapy which has helped me tremendously**...My immune system kind of failed, so I've been doing **IVIG**....And I'm taking **POTS medicines like methanone**, which has really helped, as well as paying attention to my hormones, adrenals, hydrocortisone, thyroid medications, and bioidentical hormones. So, all of the above helped."*

*"I'm significantly more functional than a lot of folks in this room, but I made a list of everything that it takes for that to happen. So, I'm on **17 prescription medicines**...then I'm on **four other over-the-counter supplements for the mito-cocktail and one for sleep**...Every night I do **feeds through my feeding tube for gastroparesis** and use a **C-PAP for sleep apnea**. I go to **physical therapy once a week for balance issues**. And then I have **constant lifestyle modifications**"*

*"I just I guess want to give a shout-out for the mitochondrial cocktail. **It's not a prescription and it is costly**. When I was first probably two years diagnosed, but I was at the point where I was potential on disability and then **started the mitochondrial cocktail**, and actually **working full time**."*

*"So, it's sort of **a constant cycle of trial and error with different medications and different levels and different dosages**, and then starts over again."*

*"My doctor changes the mito-cocktail from time to time to try and help my symptoms. I feel my disease and symptoms **have only progressed over time and it's a constant battle to try and find meds and treatments that address my issues. Headaches, migraines and pain is a huge issue that I believe most mito patients deal with and finding treatments are very hard to find that help. I personally do not want to take opioids and in the past they have not helped much but there really are no good, reliable and safe options.**"*

Discussion Question 2: How well does your current treatment regimen treat the most significant symptoms of your disease? How well do these treatments improve your ability to do specific activities that are important to you in your daily life? How well have these treatments worked for you as your condition changed over time? What are the most significant downsides to your current treatments, and how do they affect your daily life?

*"Treatment addresses the **fatigue** and some of the **muscle pain**."*

*"All medications and supplements help with **fatigue, endurance, mood balance, cognition**."*

*"It **has helped but continually changes** and is modified as circumstances and my condition dictates."*

*"They have **kept pace with my decline** and given me **a better quality of life**."*

*"**Hard to tell** if they have made a **significant difference**."*

*"Treatments have worked well for the most part, but as my condition progresses I have really needed **further supplemental help** and am now fighting with my physicians to provide things needed like **IVIG for immune function, home physical therapy, home fluids, home oxygen would all be incredibly helpful**."*

*"Not very well. **No change** in function."*

Discussion Question 3: Short of a cure for your mitochondrial disease, what specific things would you look for in an ideal treatment for your condition?

*"Well, given what I've heard today from the various experiences we all have, I think there's got to be **a toolkit of solutions that can be personalized** for each of us, because I don't think it's going to be a magic pill that's going to cure all of us. And I think **it's going to have to take different forms**."*

*"So, to put on some **more muscle mass, that would be wonderful for me**, and I think that would help with overall fatigue also to feel less wiped out. So, **increase the energy capability of my muscles**, and to put on some muscle mass."*

*"I would **give anything for more energy**. I make excuses why **I can't attend a social function** because I'm **too embarrassed to say I'm too tired**."*

*"I just want to be **independent again**. I want to go for a walk in the countryside with my husband, I want to travel. I just **want what most people take for granted**. I want to **volunteer** and be **part of the community**. I want to know I **have a future and something to look forward to**. I want to **see properly** and be able to **read properly**. I want to be **pain free, physically, emotionally and mentally**."*

*"While it would be nice to gain function, **stopping or slowing seems more obtainable and would be a great place to start**."*

*"I do not care how long I live, especially as my body deteriorates...however **if I can maintain where I am at now, or at least not continue to lose functions I can remain mostly independent and not become a burden to my family and society.**"*

*"I feel that I **could cope with the other symptoms**, such as vision problems and migraines, if I were **not so affected by severe fatigue**"*

*"Something to **STOP fatigue** - it's **worse than living with pain.**"*

*"Less tiredness. **Be able to exercise and increase muscle tone.** Not feel that if I overdo it then I'll make myself ill."*

*"Something that provided more energy, not just being awake energy but so that **using one's muscles doesn't cause a crash and mean sleeping the next day.** Something that allowed me to **more actively participate in the community & also not fear germs so much.**"*

SESSION 2: THE VOICE OF THE MITOCHONDRIAL DISEASE PATIENT – PERSPECTIVES FROM PEDIATRIC PATIENTS AND CAREGIVERS ON NEUROLOGIC MANIFESTATIONS IN CHILDREN

In Session 2, the emphasis was on children with neurologic manifestations of mitochondrial disease. The session was divided into two panels. In Panel #3, the focus was on symptoms and daily impacts of disease. In Panel #4, current and future approaches to treatment were discussed. Each panel included personal testimonies from patients and caregivers. This was followed by audience and remote polling and then a moderated group discussion with the broader audience in attendance at the meeting. Following the meeting, a post-meeting online survey (which included several open-ended questions) was administered to ensure the broadest and most complete participation possible. The polling results shown here are from the more robust post-meeting survey, which included 119 responses representing children with neurologic manifestations of mitochondrial disease.

The results of the patient voice activities from Session 2, Panels #3 and #4 are summarized below.

PANEL #3 – SYMPTOMS AND DAILY IMPACTS (Neurologic Manifestations in Children)

Panel #3 Patient Testimonies:

The full testimonies from each patient can be found in Appendix 2. Here are some of the most impactful comments made by each.

Daniel M -

*“Carson (age 7) and Chase (age 6) have MEPAN Syndrome, an ultra-rare condition that results in impaired mitochondrial fatty acid synthesis and has rendered them **unable to walk, move independently or talk**. MEPAN is a **neurodegenerative condition**, so their symptoms may worsen, and **eventually they may suffer severe vision loss**. What I am sharing today is told through the eyes of our older Carson:*

I used to be able to turn myself over in bed, but not anymore. My body doesn't work like it should, and it's hard for my brother and me to move like other kids. I tell my brain what I want to move, but my body doesn't listen.

I used to be able to sit on my own, but I can't anymore. My hands don't work very well either and I can't hold a pencil, but I am learning to use a computer that works with my eyes to help me talk. It's really hard to use because my eyes get tired, they don't always look where they're supposed to, and the rest of my body moves around even when I don't want it to. I used to be able to walk a little in my walker, but I don't do that as much anymore.

*I have some signs that I use to tell people what I want, but most days my hands and fingers don't work like they're supposed to, and it's hard for people to understand my signs. I can't talk either, so it's **hard for me to tell people how I'm feeling or what I need**. Neither can my brother. It **makes me sad**.”*

Ann K -

*“When Mara was three months old she was hospitalized for **failure to thrive**. After many tests, it was determined she had, among other things, microcephaly, cortical blindness, epilepsy, cardio myopathy and a mitochondrial myopathy...We did not receive the **final PDCD diagnosis until shortly before her 21st birthday**.*

Despite how well Mara is doing, we struggle with **3 key symptoms**. These are: managing her **epilepsy**, her **reflux and ability to chew/swallow**, and her **physical limitations and blindness**...Mara is also **sensitive to extreme heat or cold**, either of which can bring on a **life-threatening seizure or a pulmonary issue**.

When she was approximately 9 years old her metabolic disorder manifested itself and caused her to be **unable to keep food down**. As a consequence, her weight dropped from 55 to 40 lbs. She was on the verge of being hospitalized for failure to thrive...**With the Peptamen Junior and careful preparation of Mara's food**, the possibilities of her failing to thrive (from low weight and poor nutrition) or having a life-threatening choking incident are significantly diminished. These have been two of our biggest fears over her lifetime."

Stacy T -

"Marshall and Sam were diagnosed with Mitochondrial Disease, specifically Combined Oxidative Phosphorylation Deficiency, Type 11. Mito affects the boys in similar, but different ways with Sam being more significantly impacted. They both have **a laundry list of diagnoses**, including **intellectual disability, global developmental delay, hearing loss, strabismus, cortical visual impairment, incontinence, epilepsy, gastroparesis, kidney disease, spasticity and more**. Concerns that might be pretty trivial in other kids can be catastrophic for them. **A common cold can land either of them in the ER** and a simple school field trip is fraught with logistical concerns.

Sam is diagnosed as being "non-verbal."...But the one thing that is consistent about Sam is how inconsistent he is...When Sam was 3 he experienced what we now think to have been **a metabolic stroke episode**. He had **significant regression to his skills**, including losing all the language he had developed up to that point. He has **never really gotten back to where he was** before that episode.

There are so many things I wish I could do for them, but if I had to pick only one, I would make **mobility easier** for Marshall and **communication easier** for Sam. Or, at the very least, **halt any deterioration that is occurring or could occur**. This would **improve the current quality of their lives** and **provide some reassurance about their futures**. I am biased, but they are both smart, silly, fun, thoughtful boys and **deserve a chance at the best life possible**."

Heather T -

"Arden's journey started at just 6 weeks old. Born 2 months premature and still in the NICU Arden began to have trouble breathing. It was evident she was struggling. Her heart had grown to take up 75% of her chest cavity and was crushing her lungs. She was on **life support within 36 hours and fighting for her life**. We didn't know then but know now that this was her first "**mito-crisis**" and **her body was crashing**. After weeks of failed interventions, Arden was listed for a **heart transplant**. She received her new heart at just 3 months old.

Arden is now six and she has shattered the ceiling on any limitations and obstacles set before her. Although Arden has come a long way, **life certainly isn't easy**.... To live in a world **unable to share her voice, her feelings, her wants, desires, and even dreams** has to be **isolating and extremely lonely**. If given the resources or **ability to speak even just a few words could be life-changing in many ways**. Having the ability to communicate whether it is verbal or physical would open endless opportunities.

Life is unpredictable, even more so when you are living with a disease that can appear or progress at any time with each time being very different than the last....We just **never know** which route she will take and the

uncertainty of it all makes is so unbelievably stressful. Illness wreaks havoc on her fragile body and even the slightest cold can be catastrophic.”

Annett C -

*“Jagger (age 8) suffers from **severe developmental delay, seizures, cardiomyopathy, scoliosis, gastroparesis, neurogenic bladder, respiratory failure and much more** all caused by his mitochondrial myopathy. Specifically, Leigh’s syndrome.*

*Developmentally Jagger is probably the age of a 3-month old. He has **muscle weakness** and is unable to hold his head, sit, stand or walk. He spends the majority of his time lying in bed, is **dependent on oxygen 24/7**, uses a **bipap** at night, has a **GJ feeding tube** and requires **daily IV infusions**. However, one of the most challenging and frustrating symptoms is the fact that Jagger **cannot communicate verbally** making it almost impossible to figure out what is wrong with him when he is **screaming and arching in agonizing pain**.*

*I am devastated just thinking about **what his future might look like**. No one wants to lose their child but also no one should have to suffer so much. As I was sitting down and writing this, Jagger has just suffered his third seizure of the day. We know the future isn’t bright for our sweet boy, however as long as Jagger has the energy to fight, we fight for him and with him”*

Panel #3 Polling Results:

Demographic Polling Questions:

Where do you currently reside?

Most of the participants are from the US South (30%), US Northeast/New England (14%), US Midwest (12%), US Pacific (9%), Europe (9%), US West and Mountain (6%), Asia (6%), and Australia (6%). 48% of participants live in a suburban area, 39% live in a city, and 12% live in a rural area.

How old is the patient now?

50% of the patients represented are 0-10 years old, 24% are 11-17 years old, and 9% are 18-20 years old.

At what age was the patient represented diagnosed with mitochondrial disease?

76% of the patients represented were diagnosed at 0-10 years of age and 15% were diagnosed between 11-17 years of age.

Symptoms and Daily Impacts Polling Questions (see appendix for full descriptions of possible answers):

What is the best description of the stage of disability for you or the person for whom you care?

This poll revealed that 37% have severe disability (dependency on others), 24% have symptoms that are overt and significant, 17% have mild symptoms, 10% require a walker or other aid, 8% require a wheelchair fulltime, and 5% have minimal disability.

Which mitochondrial disease symptoms most impact the patient’s daily quality of life (select up to 5)?

The most common responses to this questions included muscle weakness (70%), chronic fatigue (58%), gastrointestinal problems (56%), speech problems (47%), delayed milestones (41%), swallowing difficulties

(36%), learning disability (32%), movement disorders (29%), seizures (27%), exercise intolerance (26%), and pain (24%).

As mitochondrial disease progresses, development or progression of which of the following symptoms worries you the most (select up to 5)?

The most common responses to this question included muscle weakness (47%), seizures (45%), pain (42%), gastrointestinal problems (38%), fatigue (34%), and swallowing difficulties (31%).

What specific activities of daily life are most important to you that you (or the person for whom you care) are NOT able to do because of mitochondrial disease (select the top 3)?

This question revealed that the loss of gross motor activities (moving independently, walking, standing, sports, and recreational activities) is most important (72%). This was followed by communication (57%), fine motor activities (41%), going to school or work (33%), and personal hygiene (28%).

As a result of living with mitochondrial disease, which of the following social, emotional or economic consequences are most significant to the patient? Select up to 4.

The most common responses to this question included frustration (52%), social isolation (50%), communication issues (47%), loss of independence (45%), modified school/work hours (31%), and lack of hope for the future (27%).

Panel #3 Moderated Audience Discussion and Comments from Open-Ended Survey Questions:

The following is a sampling of insightful comments that were made by the broader attendees during the moderated audience discussion and in response to the open-ended questions posed in the post-meeting survey.

Discussion Question 1: Of all the symptoms that you (or your child) experience because of your condition, which 1-3 symptoms have the most significant impact on your life?

*“The **uncertainty of the disease**. What's the future hold?”*

*“I have a child who is 16. And so, **making plans for her life, experiencing that regression and being aware of the regression, and having that continually changing baseline is difficult** for her. That's probably been the most significant impact on her life, because she's trying to make plans and -- very respectable plans that just come at this stage of life, but **daily things get taken away from her**.”*

*“My daughter Katie has complex 1-3. I actually asked her the question what her top three symptoms are, and she said **tiredness, brain fog, and weird temperatures**.”*

*“But just the **heat and cold intolerance** and just any planning regarding that completely affects him...He just does not regulate temperature at all.”*

*“Our daughter **cannot eat and communicate** with us due to her **extreme muscle weakness and swallowing problems**. She also finds it very hard to communicate with her eyes due to **eye weakness**.”*

*"My 5-year old daughter is **very tired all the time**, she is **dependent on us 24/7** with suctioning and medication and feeds. She used a **g tube feeding tube** for all of her nutrition. Uses a **wheelchair** and needs support in body positioning all of the time."*

Discussion Question 2: Are there specific activities that are important to you (or your child) but that you cannot do at all or as fully as you would like because of your condition? How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?

*"But I think it comes down to, for us who are parents, **we wake up every day saying, can we just keep our child alive?**"*

*"I **struggle with muscle fatigue and weakness**, and it's hard sometimes going -- I live a very busy life, and I need to know what I need to stop and take a break and I struggle with that. To this day I **don't know my stopping point and I crash.**"*

*"And would I want my kids to play soccer or football, or would I want them to be able to bathe independently? And I think at this point **bathing independently would be a big plus**. My children who have mito are now at an age where puberty is rearing its ugly head, and even though they don't necessarily have the intellectual capacity or the ability to verbalize it they're kind of instinctively **wanting more privacy and more independence, and I can't give it to them.**"*

*"**Sitting unaided would open up so many opportunities** for her. She rolls everywhere independently but that is only at home as it is unacceptable and dangerous to do in public areas...Being trapped physically without the freedom she deserves as well as **unable to communicate her needs, wants, feelings, and dreams is devastating.**"*

*"Best days: **fatigue, not being part of the working "real" world, lack of social interaction with peers**. Worst days: **passing out, ambulance ride, ER visit, then extreme fatigue, sleeping at home**. Anger/sadness because "it happened again."*

*"**The best days still require being confined to a wheelchair** which hinders what activities are achievable or not. The best days still require around the clock care and tube feedings - never being able to taste food and eat by mouth. The best days require countless diaper changes...The worst days consist of hospitalization. The worst days may require oxygen support, suctioning to clear airways, and screaming due to nerve/muscle pain. The worst days could end in being put on life support and wondering if you will reach your baseline again or never regain skills you once had. **The worst days could easily be your last in a blink of an eye.**"*

Discussion Question 3: How has your (or your child's) condition and its symptoms changed over time? Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?

*"She used to walk. So, the **regressive nature of the disorder**. She used to walk with a walker, still assisted, but she used to love to dance and sing. She said dad and she said mom. She got sick when she was four with pneumonia and she lost all of that, and we tried to get it back and it never came back and that's the new baseline..."The scary part is **not knowing if something else will happen and we'll have to get used to a new baseline.**"*

*"She was diagnosed at age two. She was always delayed, and but we were reaching milestones. We were working on therapies and things like that. And then with that illness came the regression, that **she didn't get the skills back no matter how much we tried.**"*

*"From mildly affected to moderately affected after puberty onset. **Each year that passes brings more fatigue and less muscle endurance.** Despite physical therapy, muscles are starting to atrophy, and pain is increasing."*

*"Yes, some come and go. **Fatigue** seems to be the most constant. **Mental health symptoms** (severe anxiety, depression) **are always there**, but they're up and down; therapy helps some. The passing out episodes are infrequent, usually 3-6 months between episodes."*

*"**Weather highly impacts symptoms** negatively especially quick drops or raises of barometric pressure. Food highly impacts symptoms negatively if eat lots of carbohydrates and sugars. Voltaren gel, a topical gel Rx, helps significantly with pain with no balance or mental fog side effects. **Set routine - going to bed, waking, eating high protein diet, social interaction, all help lessen symptoms.**"*

*"I have called her a "finely tuned race car" forever. With the right dose of seizure medications, enough food (especially protein), enough sleep and just enough activity, you sometimes don't realize there is anything wrong with her. If any of the above are out of balance her abilities start to degrade. If she gets sick, **it takes weeks to get back to normal.**"*

Discussion Question 4: What worries you most about your condition?

*"Growing up as an adult and into adulthood knowing you have this and watching it and watching your body deteriorate with the knowledge that you are able to watch it happen is the most difficult thing...I think for me, the **anxiety and depression** that started around 13, 14, 15 and carries on today as an adult is probably the biggest struggle."*

*"I'm most worried about **increasing susceptibility to illness** as the disease progresses. She already gets many illnesses. Also worrisome is **increasing weakness** which could impact her ability to breathe on her own."*

*"Very few people share her unique set of challenges, so **isolation is a big issue**. Never being able to see a future of progressively learning, gaining new skills, "graduating" to be an independent adult is **very frustrating and disheartening to all of us**....Fearing that she will never have a real adult companionship/marriage relationship is her biggest frustration."*

*"Being **unable to communicate leads to frustration**. Unable to share what you are thinking or feeling at any given time along with being unable to respond to others causes **an increase in social isolation** which leads or can lead to **feelings of frustration depression and anger.**"*

*"**Frustration. communication issues, and loss of independence** affect our son every day and are things he deals with. **Financial difficulties** are something we as a family struggle with due to the costs of Casey's care. He is not aware and could not understand this."*

PANEL #4 – CURRENT AND FUTURE APPROACHES TO TREATMENT (Neurologic Manifestations in Children)

Panel #4 Patient Testimonies:

The full testimonies from each patient can be found in Appendix 2. Here are some of the most impactful comments made by each.

Carrie M -

*“Patrick’s doctors couldn’t find a reason for his developmental delays and as he got older, new issues began to emerge. When Patrick got sick, **even with what seemed to be a mild cold, he would become very lethargic.** Then, in February 2012, Patrick woke up one morning unable to walk...Patrick was admitted, and an EEG showed **continuous seizures.***

*When Patrick finally awoke from sedation, he was different. He had **lost all of his gross motor skills.** Since mitochondrial disease was suspected, Patrick was also started on a combination of vitamins and called the “mito cocktail”...He endured at least **3 hours daily of PT, OT and speech therapies** while inpatient over the next few months.*

*Patrick’s journey has been **a roller coaster of ups and downs.** He has periods of stability, but it doesn’t take much for things to go downhill...His disease has continued to progress with an increase in neurological symptoms like **tremors & myoclonus** and the development of an **adrenal insufficiency**, by itself a life-threatening condition.*

*Then, last January, Patrick again had a **long hospitalization due to an underlying infection.** This episode again put his body in metabolic crisis but this time, we utilized **an infusion of IVIG** to help boost his immune system and improve his brain health.*

*Our ultimate hope would be a cure, but **any interventions that would reduce the frequency of hospitalizations or minimize his neurological symptoms** would really improve his quality of life. We want him to experience all that life has to offer, in whatever time he has with us.”*

Lori M -

“Will’s symptoms and issues pertain to multiple bodily systems, organs and functions. Since every cell in our body contains mitochondria, there is no limit to the potential issues.

*Of the many issues, we have focused on the symptom we can actually “fix” – his immune system. Before starting and getting the correct dose of Hizentra he was **hospitalized 2 - 4 times per year usually for a week at a time. Time in the hospital creates a large setback for Will’s physical and emotional health.** His physical abilities drop significantly, his emotions are highly irregular, and **it taxes our entire family.** Now, it’s been three years since he was admitted for an illness...However, the downside of the subQ infusion of Hizentra is that it takes nearly three hours to complete.*

*An ideal treatment would give Will **a chance to lead a more normal, independent life** – instead of having an adult wipe his bottom or give him a bath or cut his food up - he could do it. Just like the immune system medicine has done for his life, a treatment for ataxia would give him a chance to **participate more fully in something as simple as personal hygiene** and maybe even play baseball instead of just watching.”*

Cheryl P -

*"In 2009, my middle son David was 22 years old and finishing up his second year of college when he began to experience **vision problems and dizziness**... Within 2 months of his first symptoms, David was diagnosed with Leigh's Syndrome, Surf 1 mutation and **given no hope for a future**. David had worsened tremendously during this time period and was confined to a wheelchair. He **could no longer walk, see or take care of his most basic needs**.*

*After 6 months of Leucovorin and the mito-cocktail, David began to regain his eyesight and some mobility. He **learned to walk again, although quite unsteadily, and could help care for his personal needs**. We were told that at any time a virus or stress to his system could cause the lesions to grow and cause another mito crash. Although we were very grateful for David's improvement, we **always felt like we were walking on eggshells, waiting for the next crash**.*

*David is not able to drive due to his neurological condition and, without significant changes, will never be able to. This is the number one factor that affects his life. In an ideal world, David **would love to be able to drive again**. We would love to see drugs approved that can **decrease or heal the lesions in his brain** thereby allowing him to process correctly and drive again."*

Gwen L -

*"As a result of his metabolic condition Joshua has Leigh's syndrome – central nervous system cell damage due to insufficient energy production. Joshua has bilateral damage to the basal ganglia region in his brain that directly affects his balance and motor coordination. He suffers from **low energy, global muscle weakness, and chronic ataxia or unsteady walking**. We **live in fear of disease progression**, as it is often central nervous system cell death in brain regions needed for respiration that can cause children with Leigh's disease to die.*

*Joshua takes **prescribed vitamins and supplements** that are monitored by his mitochondrial medicine doctors. We started Joshua on supplements immediately after learning of his genetic diagnosis and noticed that his **stamina and balance both improved**.*

*Some of the challenges that we face with Joshua's treatments are **financial burden, increased caregiver burden, and stress for Joshua**. The vitamin formulation has a noxious taste that cannot be masked by flavoring.*

*An ideal treatment for Joshua would of course cure Joshua's DLD deficiency. We have been following the field of **gene therapy** and hope that this can one day be a possible treatment for Joshua. Additional possible options are **enzyme replacement therapy** to introduce a functional DLD protein into Joshua's system, and **investigational compounds that boost mitochondrial functioning**."*

Anne T -

*"Bryan's daily challenges include **developmental delays, visual impairment, difficulty walking, muscle fatigue, low muscle tone, difficulty swallowing and chewing his food**. Remarkably, he remains positive and hopeful.*

*In our experience with Bryan, **treatment is focused on addressing specific symptoms**, e.g., seizure control, gastrointestinal, and neurologic, and so on. Since Bryan was diagnosed, he has taken some form of a **mitochondrial cocktail compounded at a special pharmacy**.*

As Bryan's primary caregivers we **constantly weigh the benefits of continuing with treatments that address only the symptoms but have little impact on tackling the condition.** Keeping up with medication schedules, side effects of multiple drugs, the costs of customized cocktails and supplements, therapies, and medical appointments is **a full-time job and impacts our entire family.**

So short of a cure, if I could envision what an ideal treatment would look like, I see two things. First, I would like to see **development of a treatment and/or a disease modifying drug to slow the progression of mitochondrial diseases...**Second, any potential new drug should also seek to **repair damaged mitochondria** so that organs, systems and other bodily functions could rejuvenate with the influx of healthier and more powerful mitochondria. If such a treatment option or new drug was developed, I feel the potential for our son to have **improved vision, care for his personal needs, walk without assistance, or live independently someday."**

Panel #4 Polling Results

Current and Future Approaches to Treatments Polling Questions (see appendix for full descriptions of possible answers):

What PRESCRIPTION MEDICATIONS does the patient take now to treat symptoms of your mitochondrial disease? Select ALL that apply.

The most common answers to this question included other medications not listed (66%), seizure medications (40%), antidepressants or anti-anxiety medications (26%), pain medications (22%), and muscle relaxants (19%).

What VITAMINS or SUPPLEMENTS does the patient take now to treat symptoms of your mitochondrial disease? Select ALL that apply.

The most common responses to this polling question included CoQ10 (77%), Riboflavin (50%), Carnitine (50%), Alpha lipoic acid (32%), Vitamin B3, Nicotinamide or Niacin (27%), Vitamin E (23%).

What is the patient currently doing to help manage mitochondrial disease or mitochondrial disease symptoms? Select ALL that apply.

The most common answers to this question included modifications/accommodations (67%), physical therapy (63%), occupational therapy (56%), speech therapy (53%), use of adaptive devices (47%), and nutritional modifications including G-tube, J-tube and TPN (44%).

Which surgical procedures has the patient undergone to treat or manage symptoms of mitochondrial disease? Select ALL that apply.

The most common response to this question is G Tube/GJ Tube placement for nutrition (49%). 42% of respondents have undergone no surgical procedures.

In general, how much do the medications, therapies or lifestyle changes used improve your child's quality of life?

For this polling question, 53% of respondents answered that these practices have helped somewhat. For 23% there was a significant benefit, and for 14% they helped a lot.

Which outcomes would be meaningful to you for a possible drug treatment? Select ALL that apply.

Respondents concluded that all of the possible choices would be meaningful with 84% looking for gain in function, 79% looking for slowing/stopping of disease progression (even if no gain in function), and 64% looking for prolonged life.

Which ability or symptom would you rank as most important for a possible drug treatment today? Select up to 3.

Respondents ranked the following as most important to be addressed by a new drug treatment: fatigue (43%), muscle weakness (38%), gastrointestinal problems (30%), speech (30%), seizures (21%), pain (19%), movement disorders (17%), and swallowing difficulties (17%).

Which of the following factors would influence your decision, on behalf of your child, to take a new medication or participate in a clinical trial or research study? Select ALL that apply.

In response to this polling question, 84% chose significant risks of serious side effects as the most important. This was followed by burden of administration (55%), common side effects (35%), length of treatment (31%), cost and/or travel (29%), and the way treatment is administered (24%).

Panel #4 Moderated Audience Discussion and Comments from Open-Ended Survey Questions:

The following is a sampling of insightful comments that were made by the broader attendees during the moderated audience discussion and in response to the open-ended questions posed in the post-meeting online survey.

Discussion Question 1: What are you currently doing to help treat your (or your child's) condition or its symptoms? What specific symptoms do your treatments address? How has your treatment regimen changed over time, and why?

*"As opposed to actively doing physical therapy or occupational therapy, we're **avoiding certain activities with our children**, including having them in a **reduced school day or home schooling** so they're not exposed to certain germs that kids are frequently exposed to in school, or **not participating in certain social activities** with peers or with family members, even avoiding like sports activities sometimes."*

*"One of the things we did at the very beginning was **massage therapy**. Unfortunately, all these things that we think are outside the box and cost us. We have to **pay for them out of pocket**. Nobody pays for this. "*

*"Our child reacted to neurontin, so uses carbamazepine and amitriptyline for neuralgic pain now. The **vitamin regime is just for general well-being** and maximizing health in the event that there might be anything lacking in the diet or as a consequence of the GIT effects of the illness. The arginine is to minimize strokes and also helps a little with the neuralgia."*

Discussion Question 2: How well does your current treatment regimen treat the most significant symptoms of your (or your child's) disease? How well do these treatments improve your ability to do specific activities that are important to you in your daily life? How well have these treatments worked for you as your condition changed over time?

*"**Limiting exposures to infections and limiting stress has helped**. GTube has been a big game changer, **vitamin supplements have not been super helpful**. We remain hopeful for new options."*

*"Huge amount of fatigue when first diagnosed **helped slightly by cocktail of vitamins** but significantly **improved when the dose of riboflavin went was increased** and no noticeable negative effects when the other vitamins were reduced and stopped."*

*"The **IVIG was one of the biggest things that helped** both my son and I (I have mito too), it changed our lives. It literally saved our lives. We used to get so many repeated **pneumonias, sinus infections, serratia infections, systemic infections and IVIG/now doing Sub-Q, changed our lives.**"*

*"She was **floppy with no energy before the supplements and is developing beautifully with them**, weight gain and growth and cognition improvement."*

*"**Ketogenic diet** stopped seizures and gave her more energy, **bipap at night** gives her better sleep and conserves energy for the day, **daily respiratory treatments** keep her out of the hospital when she gets sick, **reflux meds** keep her comfortable despite GI dysfunction, **no tube feedings** allow her to have consistent nutrition despite weakness and swallowing dysfunction."*

*"Because of the progressiveness of Leigh's Syndrome, it's **hard to tell if the prescription medications are working** and helping his high muscle tone. **We do feel the mito-cocktail is working**, because our son has hardly been sick all year. We do think **physical therapy, swim therapy, occupational therapy, and horse therapy help** our son."*

*"Continues to become more complicated as she ages and the disease progresses. There is never a stagnant moment between **hospitalizations, modifying treatments, adding medications**. it never gets easier - only more complicated."*

Discussion Question 3: What are the most significant downsides to your current treatments, and how do they affect your daily life?

*"There's that unknown. **Nothing is for sure with this disease as far as treatment...**So, I would say that's a downside, because there's always pros and cons to everything. Is it even working? I don't know. They say it could, so we do it."*

*"And then another downside to that also in how it affects us is that **cost financially is a huge burden on our family**. Our insurance personally doesn't cover the mito-cocktails, so **we pay everything out of pocket.**"*

*"It's really not day-to-day or week-by-week. It's like hour-by-hour. **Is what we're giving him going to be enough to last through the night?** Is he going to be comfortable to last the day without having some sort of episode?"*

Discussion Question 4: Short of a cure for your mitochondrial disease, what specific things would you look for in an ideal treatment for your (or your child's) condition?

*"Him **being calm**. Him either just not whining or crying or screaming. Just him **being kind of happy, engaged with us...**just being with us and knowing we're there, versus him just screaming."*

*"As far as treatment, I don't know...Maybe just **approval or streamline trials of drugs that already exist for use.**"*

*“So, **something that addresses the muscle and the fatigue** to sort of keep him comfortable. Because **whatever we have right now is not working....**My goal is just for him to have a **quality of life.**”*

*“The **quality of life**, like she said, is a big thing for us. I think we can handle being in a wheelchair, we can handle the ventilator, we can handle the trach, we can handle him not being able to eat. But him being able to have enough of the **brain power**, to have **good conversations**, to be able to **go out in public**, to be able to **be in a crowd and not have a seizure** would be such a big thing for us.”*

*“A medication that would **stop the sub-clinical seizures**. A medication that would **increase the function of her mitochondria** and **protect her from major degradation.**”*

*“Something with **low side effects**. Given the amount of medication we give him, particularly seizure medicine, it is always **difficult to understand what's a symptom, what's a side effect, and what is just natural/normal for his baseline.**”*

*“I worry about progression and how our son will cope with that as he doesn't understand. **Gains would be a miracle**, but I would be **very happy to not have him deteriorate further.**”*

*“**Gaining in function and prolong life** would be the most dream for us. However, anything a medication can do, will way better than what we have now, that is nothing.”*

*“To have **the ability to live life MORE** - more in terms of time spent **being alert and engaged**, and **without the agonizing symptoms of anxiety.**”*

*“To **increase muscle strength** would allow other areas of the body to improve as well as **improve the quality of life**. **Improved speech** for my daughter who has none would be absolutely amazing.”*

*“Because if he had **muscle strength** he would be able to **at least sit**. If his **seizures would stop** he would stop wasting energy his body needs. If he **could hear** he could **communicate** with us.”*

PRELIMINARY BENEFIT-RISK FRAMEWORK PROPOSAL FOR MITOCHONDRIAL DISEASE

Benefit-risk assessment is the foundation for FDA’s regulatory review of human drugs and biologics. These assessments capture the Agency’s evidence, uncertainties, and reasoning used to arrive at its final determination for specific regulatory decisions. Additionally, they serve as a tool for communicating this information to those who wish to better understand FDA’s thinking. Background and guidance on benefit-risk assessments can be found at the following link:

<https://www.fda.gov/industry/prescription-drug-user-fee-amendments/enhancing-benefit-risk-assessment-regulatory-decision-making>

The input provided by people with mitochondrial disease and their representatives at the Externally-Led PFDD Meeting was used to prepare the preliminary benefit-risk tables on the next two pages. One table summarizes the sample benefit-risk framework for adults with mitochondrial myopathy, and one table summarizes the sample benefit-risk framework for pediatric patients with neurologic manifestations of mitochondrial disease. These are sample frameworks that are intended to provide an understanding of the benefit-risk aspects for two of key decision factors, “Analysis of Condition” and “Current Treatment Options,” that factor into the benefit-risk assessment. These sample frameworks are likely to evolve over time and could be incorporated into a benefit-risk assessment framework for a drug under review.

Sample Benefit-Risk Framework for Adults with Mitochondrial Myopathy

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p>Patients continuously deal with very difficult issues in their daily lives:</p> <ul style="list-style-type: none"> • Muscle weakness • Chronic fatigue • Gastrointestinal problems • Pain • Exercise intolerance • Dysautonomia • Sleep difficulties • Balance problems • Eye muscle problems • Cognitive decline <p>Important activities of daily living that patients are unable to do:</p> <ul style="list-style-type: none"> • Moving around independently and safely • Understandable communications • Walking and standing independently • Understanding in noisy settings • Driving • Personal hygiene • Reading <p>The most concerning social, emotional or economic consequences:</p> <ul style="list-style-type: none"> • Social isolation • Loss of hobbies or activities • Loss of independence • Loss of job or inability to get job • Financial difficulties • Frustration • Depression and/or anxiety 	<p>Mitochondrial disease is a complicated, diverse and unpredictable family of diseases with high unmet need:</p> <ul style="list-style-type: none"> • Caused by hundreds of inherited genetic mutations, with new mutations still being discovered • Widely diverse and unpredictable symptoms and manifestations with many subpopulations • Illnesses (e.g., viral or bacterial) often causes significant disease progression and regression • Treatments managed by trial-and-error and constant re-evaluation; difficult to understand which drug and lifestyle interventions are providing benefit • Many drug treatments for one symptom may cause worsening of other symptoms and must be discontinued or modified • Interventions are expensive and often not covered by health insurance • Patients have days that are better and worse, and it is often difficult to understand why • Pediatric patients have difficulty transitioning into adult care within the healthcare system • Drug development is challenging due to disease variability (even within-patient) and lack of well-defined clinical trial end points
Current Treatment Options	<p>Symptoms managed by many drugs / lifestyle modifications, but no drugs are approved that target the specific causes of disease</p> <p>Current state of disease management:</p> <ul style="list-style-type: none"> • Rest, careful planning of activities, and inactivity • Diet management and trial-and error supplements • Trial-and-error treatment with prescription medicines (for pain, depression/anxiety, heart and muscle relaxation) • Modifications/accommodations at work/school/home • Stretching and exercise • Use of adaptive devices • C-PAP for sleep apnea • Immunotherapy, including IVIG 	<p>Only 17% of participants in EI-PFDD meeting believe their current medications, therapies and lifestyle changes have significantly improved their quality of life</p> <p>New treatments should focus on these unmet needs:</p> <ul style="list-style-type: none"> • Reduction in chronic fatigue and muscle weakness are most important • Reduction in pain, gastrointestinal problems and exercise intolerance • Gain in function (e.g., energy, strength, mobility, dexterity, cardiac function, speech) • Slowing / stopping disease progression • Prolongation of life is important, but not the primary focus <p>Very important that new treatments do not cause serious side effects</p>

**Sample Benefit-Risk Framework for
Pediatric Patients with Neurologic Manifestations of Mitochondrial Disease**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p>Patients are highly disabled, and disease is progressive. Families deal with very difficult issues in daily lives:</p> <ul style="list-style-type: none"> • Muscle weakness • Chronic fatigue • Gastrointestinal problems • Speech problems • Delayed milestones • Swallowing difficulties • Learning disability • Movement disorders • Seizures • Exercise intolerance • Pain <p>Important activities of daily living that patients are unable to do:</p> <ul style="list-style-type: none"> • Gross motor activities • Communication • Fine motor activities • Going to work/school • Personal hygiene <p>The most concerning social, emotional or economic consequences:</p> <ul style="list-style-type: none"> • Frustration • Social isolation • Communication issues • Loss of independence • Modified school/work hours • Lack of hope for the future 	<p>Mitochondrial disease is a complicated, diverse and unpredictable family of diseases with high unmet need:</p> <ul style="list-style-type: none"> • Caused by hundreds of inherited genetic mutations, with new mutations still being discovered • Widely diverse and unpredictable symptoms and manifestations with many subpopulations • Illnesses (e.g., viral or bacterial) often causes significant disease progression and regression • Treatments managed by trial-and-error and constant re-evaluation; difficult to understand which drug and lifestyle interventions are providing benefit • Many drug treatments for one symptom may cause worsening of other symptoms and must be discontinued or modified • Interventions are expensive and often not covered by health insurance • Patients have days that are better and worse, and it is often difficult to understand why • Pediatric patients have difficulty transitioning into adult care within the healthcare system • Drug development is challenging due to disease variability (even within-patient) and lack of well-defined clinical trial end points
Current Treatment Options	<p>Symptoms managed by many drugs / lifestyle modifications, but no drugs are approved that target the specific causes of disease</p> <p>Current state of disease management:</p> <ul style="list-style-type: none"> • Many types of prescription medications are used to manage a variety of symptoms (for seizures depression/anxiety, pain, and muscle relaxation) • Diet management and nutritional modifications (including the use of a G-tube, J-tube or TPN) • Trial-and error treatment with dietary supplements including personalized “mito-cocktails” • Modifications and accommodations • Physical therapy • Occupational therapy • Speech therapy • Use of adaptive devices • Infectious disease management and immunotherapy, including IVIG 	<p>Only 23% of participants in EI-PFDD meeting believe their current medications, therapies and lifestyle changes have significantly improved their quality of life</p> <p>New treatments should focus on these unmet needs:</p> <ul style="list-style-type: none"> • Reduction in chronic fatigue and muscle weakness are most important • Improvement in gastrointestinal problems, speech, pain, movement disorders and swallowing difficulties • Gain in function (e.g., energy, strength, mobility, dexterity, cardiac function, speech) or slowing/stopping disease progression (even without gain of function) both highly desired • Prolongation of life is very important <p>Very important that new treatments do not cause serious side effects</p>

CONCLUSIONS

On March 29, 2019 the UMDF hosted an Externally-Led Patient Focused Drug Development (EL-PFDD) Meeting. In attendance were patients, caregivers, government officials, healthcare providers, industry representatives, patient advocate and others. The EL-PFDD meeting was an opportunity for patients and families to inform the FDA, drug developers and other key stakeholders on the true burdens of living with mitochondrial disease and how patients view the benefits and risks of treatments for mitochondrial disease. This groundbreaking meeting included facilitated panel discussions designed to provide the FDA with perspectives from people with mitochondrial disease, advocates and caregivers.

"I will quote another participant from today's meeting, when they said my worst day is every day. You know, when they said that, I really thought that we need treatments. Regardless of the outcome of how they measure it, we want people to say that my next day would be better than their previous day. Or, if not better, at least stable or predictable, where you could potentially try to decrease the progression of the disease, prevent it from going downhill or stop it altogether...Today, I would like to use this opportunity to really encourage your advocacy community to continue educating product developers about what is meaningful -- meaningful to you -- in the reduction of the disease burden, so that the future trials of mitochondrial disorders can incorporate those clinical endpoints or measures that are tangible and important to you and meaningful to you and your loved ones."

- Larissa Lapteva, MD, MHS, MBA, Associate Director, Division of Clinical Evaluation, Pharmacology, and Toxicology, Office of Tissues and Advanced Therapies, CBER, FDA

The meeting was highly successful in bringing the voice of patients and caregivers to the FDA and other stakeholders who are important in bringing desperately-needed new medications to the market to treat the high unmet needs of patients with mitochondrial disease.

"For the patient community to come together and make your voices heard and make these perspectives inescapably clear is a powerful, powerful thing, and I hope you feel that power today...I can only imagine what you felt up here on this stage as you verbally uttered things that most of us are afraid to admit in our deepest, darkest corners of our heart, to utter those words about your life and the life of your kids...this day will forever live in my memory as one of the most special moments I've ever shared in this arena. But it's bigger than today. It has global impact that will go beyond today and this week, this month, this year."

- Brent Fields, UMDF Chairman

Many thanks to the hundreds of individuals that helped to make this meeting a success and who participated in-person, on the webcast, and through the post-meeting survey.

Your Voices were HEARD!

APPENDIX 1 – REFERENCES AND RESOURCE MATERIALS

The UMDF website page <https://www.umdf.org/pfddmeeting2019/> contains a full recording and transcript of the Mitochondrial Disease Externally-led Patient-Focused Drug Development Meeting. The same webpage also contains links to the meeting program and slide presentations, including the following:

Clinical Overview of Mitochondrial Myopathy in Adults

Michio Hirano, MD, Professor of Neurology, Columbia University

Clinical Overview: Neurologic Manifestations in Children with Mitochondrial Disease

Amy Goldstein, MD, Division of Human Genetics, Children's Hospital of Philadelphia

Finally, the full details of the post-meeting online survey (including many insightful open-ended comments) can also be found on the same webpage.

Panel # 1 – Symptoms and Daily Impacts (Adults with Mitochondrial Myopathy):

Laura P

“What part of dead do you not understand Mrs. G?” My 8-year-old son, Andrew quickly responded, “The part about dying. I refuse to talk to anybody unless they are going to talk to me about how I am going to live.” This was the first of many rare disease specialists we would consult as she reviewed his brain lesion MRI films. Her predictions were wrong, and Andrew is now 27 and still fighting.

I am Laura P; all of my children have hit the genetic lottery and have some symptoms of mitochondrial disease starting with immune system dysfunction. The absolute worst part about Mitochondrial disease is...whatever we are fighting that day. The unpredictability of symptoms, constant demand to adapt to a new level of care/need, and most importantly, as a family unit, manage the needs of the entire family while explaining to the world around us mitochondrial disease. I was five months pregnant with my youngest son when Andrew was diagnosed with complex I, IV, and III in Atlanta at the age of 8 after years of searching for answers.

His greatest quality of life altering symptom is fatigue. The inexplicable brown or blackouts where he has literally no energy and partial to total brain fog. Add to this life limiting is heat/cold intolerance. An otherwise intelligent, young man on the autism spectrum becomes dysfunctional- slurring words, staring into space, and flapping his hands- just to stay awake and cognizant of the world around him. Sadly, the world sees this and thinks he is mentally challenged rather than a college grad. The direct result of these two symptoms is under-employment and the ability to sustain independent living which carries a burden not only socially for the mito patient but also for the supporting family and ultimately for society. Add to this that he then cannot always walk distances, so he needs a wheelchair along with his other equipment and medicine needs.

Andrew's list of symptoms come and go and affect almost every bodily system: hand tremors, weakness particularly eccentric muscle weakness which is critical for going down stairs, overall tremors including his tongue and lips as fatigue sets in, eyes drooping, pulmonary dysfunction (he uses an assisted ventilator), swallowing problems, seizures, hypothyroid, hypogonadism (low testosterone function) and bipolar with schizophrenia. Andrew was very sick as a young mito patient but as each symptom was treated he began to stabilize, and we began to see a future. We never thought he would grow up much less finish college.

Andrew graduated from college in December of 2015 as an honor grad with a 3.8 GPA. He lived independently with an assistant for one semester and for the first time we saw a future of independence for Andrew. Andrew was preparing for his Graduate entrance exam and had secured an assistantship when he had a brief 2- 3-day mild virus. So mild that no one thought he needed to be admitted to a hospital, slight fever, mild vomiting, no dehydration. He began to refuse his meds, however, and food. Within days he began to spiral down into madness. I called his local docs and explained, and we tweaked his meds but to no avail as he kept purging himself as surely (in his mind) I was poisoning him.

Andrew's story takes a really sad twist as the emergency room did not know what to do so while I returned home to pick up his ventilator for the night, he somehow was mistaken for a typical patient and none of his life sustaining mito therapies were given. The hospital system completely failed Andrew and sent him to a small-town mental hospital. As he approached death he was returned to us catatonic and 30 lbs. lighter.

The absolute worst part about mitochondrial disease is that we never know when **everything** will change. It is a slow form of drowning. Just when you catch your breath, another big wave washes you under and each time it is harder to kick back up.

The activities that Andrew cannot do that are most missed are social independence- just being a young adult because of fatigue and predictability or staying out late (partying), being able to safely drive a vehicle, sports of various kinds, anything that requires planning ahead and knowing that you will be able to stay awake and attend a function is limited. Packing medicines, ventilators, wheelchairs and assistants is not sexy at 27.

Andrew: “My greatest worry is that I am sick of hiring doctors who cannot treat me and that I may never find someone who will actually be able to find a cure or at least something that can manage these critical life changing symptoms long-term. Most importantly, I have watched my friends with mitochondrial disease slip into madness and/or die. I am afraid the next time I am sick will be my last.”

Devin S

My name is Devin S, I am from Las Vegas, Nevada, I am 26 years old, and I have mitochondrial DNA depletion syndrome. I was diagnosed my junior year of high school, but I first developed symptoms when I was 13 and I got mono that just never seemed to go away. In middle school you could track the onset of my symptoms as you watched my mile time in PE slowly increase from 8 minutes, to 10 minutes, to finally when it became impossible for me to run at all. I can distinctively remember in 6th grade being in the neighborhood pool and not understanding why everyone else found swimming to be so much fun – to me swimming simply meant trying not to drown, and there’s nothing fun about that. At the time I didn’t recognize it, but that was my first experience with exercise intolerance.

When you’re a teen developing a medical condition, honestly it can all feel just so normal at times because everything else in your life is changing too – and yet -- you still somehow know that you’re completely alone in this particular experience. Friends can understand that sometimes you need to go to the doctor, but when I was missing 80 out of 180 days of school, that’s a little harder to relate to. Just going to a school dance for a couple of hours, or when I went off to college – just packing up my dorm room at the end of the year, would trigger a rhabdomyolysis episode. That is when I push my muscles so past their limits that they actively start to break down. This is a pretty serious complication from just going to a school dance, since it can lead to kidney failure. For a healthy 26-year-old it would take running a marathon to trigger this. If I had known what was going on with these episodes I would have probably gone to the ER at least once a month in high school – but luckily (for the sake of my memories) and sadly (for the sake of my health) I didn’t learn what these episodes actually were until a mito friend at a conference told me to tell my doctor because this was NOT normal. Now I mostly avoid the ER by tailoring my life, so I don’t put myself at risk.

Every year brings a new challenge, a new norm to adapt to. In college it was migraines that hurt so much I used to cry out in pain in the middle of lectures. In grad school it was dysautonomia that caused me to pass out while doing my clinical rotations. I spent hours of undergrad pacing my dorm room unable to sit still from the pain I was in, and I spent hours of my master’s degree education in hospitals having cardiology workups. These examples are just a few highlights of how mito young adults live knowing that we can never predict when our current norm will shift. Because it always shifts – and then you’re figuring out if the latest symptom is life-threatening or just annoying.

Mito has impacted every hour of my day, every day of my life. Choosing a college that would allow me to take a reduced course load, I considered mito. Choosing a career that I could someday do from home, I considered mito. Before doing dishes, vacuuming, walking somewhere, or planning a trip – I consider if the activity will trigger a migraine, if my health will be predictable enough that I can even follow through on the plan, and if I will have time to block off days after the activity to crash in bed or in an ER. On my best days I can ignore the pain, rest in between

every activity, and mostly ignore my mito – I’m lucky that way. On the worst days I will be crying in frustration because going to the kitchen seems equivalent to climbing a mountain and just trying to process what others are saying to me involves all of the energy and concentration that I have.

But you know what, with mito in the end what I am most worried about is not myself. The burden from this disease that keeps me up at night is my concern for my mito friends and for my brother. They are isolated to their homes, with very little contact with the rest of the world because mito’s fatigue and weakness has stolen their lives from them, sometimes literally. Almost every 6 months a mito friend, a teenager or young adult in their 20’s that I know, passes away from mito and unless serious progress is made towards treatments – we will continue to lose friends to this disease. There might not be an easy answer for mito, one medication to fix it all – but these children, these brothers, sisters, and friends, we deserve futures instead of funerals. Anything to ease the daily burden of mito and bring hope to families, is worth our time and I hope you’ll help -- because mito is my life, it is our lives, for better or for worse. Thank you

Rachel S

I’m Rachel S, and I’d like you to imagine: You’ve just celebrated your 25th birthday. You’re a vibrant young adult, living life to the fullest as you pursue your dreams. Even better, you’re getting to see your dreams become reality!

And then: **You swiftly become very old.**

Not *chronologically* old—you’re still in your twenties—but *functionally* your stamina and strength are now as fragile and limited as your own grandmother’s. What I’ve asked you to imagine sounds like a fantastical tale, doesn’t it? As impossible as Rip Van Winkle or Dorian Grey? I wish this *were* just fiction, but for those of us living with Mitochondrial Disease, this frightening state of at once experiencing both youth and advanced age is the reality we face each day.

2006 was the year I turned 25. Up until then, the only special need really affecting my life was my pervasive developmental delay and its sensory and attention disorders, but these didn’t keep me from living an active life as a young adult. Back then, during any given week I could easily commute to college 5 days in a row, keep up with 4 classes, make good grades in each, work a part-time job, stay on my feet for the entire 5-hr shift, and in my free time volunteer for community service, join a bowling league, go to concerts with friends, or go hiking in the mountains with my family.

That was me, the way I used to be. But those days have vanished.

My life today is painfully different. Listen to how my doctor recently described me for a research study: (Quote) “Rachel has... very low exercise tolerance which make it impossible for her to do even basic housework, cooking, or cleaning on most days...Her cognitive function has also declined...She would like to be more active and involved... without becoming exhausted and in pain from minimal activities. She is only 37 -years old but many days she functions like she is in her eighties...”

Now, rather than being able to volunteer my time and energy caring for children, senior citizens, and the homeless as I used to, **I’m** the one requiring others’ care for me. I’m the one needing people to make *my* food, drive *me* places, and be *my* company as I’m shut-in at home. Forget mountain hiking and bowling, I’m thrilled now when I can conquer a flight of steps or lift groceries. (Or even better, do both in the *same day*!)

If you get a good night’s sleep, do you wake up the next morning refreshed? I used to, before 2006. Now though, as the line from a favorite song says, “*I’m worn even before the day begins.*” No matter how much sleep I get, my brain

keeps right on feeling as sluggish and overwhelmed as the night before, and life with such relentless mental fatigue is like having a brain that tops out at 20 miles per hour in a 65 mile-per-hour world.

I can't tell you how much I would love for my brain to keep up with loads of college-level reading, writing, and socializing as it once did, but for now I'm just grateful for days when I have mental energy to compose a grocery list, check email, or read a chapter of a kids' adventure book to my son. These are simple abilities, but I don't have them every day. And honestly, most of the time even listening to music, making phone calls, or watching TV drain my mental energy so much that I actively avoid them.

While most of my peers are out and about living busy, busy lives surrounded every moment of the day with people and responsibilities and activities, I instead live with a tremendous amount of social isolation, spending most of my waking hours at home alone, very quietly, and with little activity or accomplishment. Some people think this sounds like a dream lifestyle—not going to work, having other people care for me, my kids, my home—and some have accused me of malingering just to avoid normal life. As cruel as such accusations are, I've sometimes wished they were true. *Because if my health problems were merely psychological, I could have a medical path for freedom out of the captivity of this relentless illness.*

I'd like you to imagine with me now what my life would look like without mitochondrial disease. I would finish my college degree, work in science, become a foster parent and have energy to give back to others. I'm looking forward to that day.

Debbie P

My name is Debbie P and I am 49 years old from Marietta, Georgia. In 2011 I had a muscle biopsy confirming Complex 1 and 3 mitochondrial disease and a spinal tap confirming a cerebral folate deficiency. Additional testing showed dysautonomia, myopathy, amplitude changes on fingers, connective tissue disease, abnormal CPET and a multitude of other diagnoses. I have significant difficulty with multiple levels of pain, fatigue, and muscle weakness.

Growing up there were random things that seem to be connected including pain, bleeding issues with cycles, surgery and childbirth. I remember finishing last in high school during the mandatory PE runs and not being able to keep up due to extreme pain in my legs and was exhausted. In college I tore my ACL multiple times and question the viability of my muscles and ligaments.

I earned my Bachelor's degree in Educational Psychology, a Master's in Rehabilitation Counseling with an emphasis in sign language as well as teacher Certification for Special education. I enjoyed my career working with people with special needs.

In 2001 while pregnant with my 2nd child, I had significant issues with pain and fatigue, which I thought was due to caring for a very energetic 2-year old with medical issues. Throughout the pregnancy, I became sicker with multiple infections. As soon as it was safe, my daughter was born via c section at 36 weeks. She was 7 pounds 11 ounces and healthy, but her journey with Mito began a couple months later.

In 2008 Issues were worsening and I began experiencing full body and needle like pain that I could not explain away. It was hurting to walk, grip things and on one of my hands, my fingers would get white and cold. I was falling for no reason. I went to the ER on several occasions for right sided numbness, chest pain, issues with my vision and difficulty being able to say words I was thinking. The neurologist indicated complex migraines can mimic stroke like episodes.

I began working part time but that still proved incredibly difficult. I worked 1 day and slept that afternoon and the next day. At work, I typed with a glove on to try and keep my fingers warm. After sitting for even 30 minutes I was in pain and when standing including chest pain, dizziness, losing balance and almost passing out.

I began having difficulty remembering basic things (password to get into email, route to work). I missed work because I was too exhausted to even use the restroom, had intense full body pain and visual blurring. In 2015, I had to stop working. This was beyond devastating because I loved my students and my “career” was a part of my being. I kept telling myself it will help slow up the progression, but it didn’t.

My balance/weakness continues to be unpredictable. When I walk out the front door and fall into the bushes because my legs aren’t working right, I know that I really need to concentrate on each step that I am taking to make sure I pick my feet up all the way. I always use some type of adaptive device, whether a cane, walker or wheelchair. I am struggling with losing my independence and tripping even with the walker.

My memory/brain fog is worsening, and it is frightening to me. My daughter was sick at school and I pulled up to her elementary school, parked, only to realize I was at the wrong school.....because she is in HIGH SCHOOL! She had not been in that school for 5 years!

I was prescribed medication for issues with my memory and did not realize until an appointment months later that I had forgotten about the prescription. I have been confusing my meds, and even have difficulty remembering my age. One of my worst “mom” moments was when my daughter went to take her pills and realized they looked different. Thankfully she told me because I realized I had confused her meds and put the wrong meds in her pill case. It is the worst feeling to know that things are slipping away, and I could have harmed my daughter. I am frightened because I feel like I am losing my identity and sense of being.

I am missing milestone events with my family. Whether it is a band performance, track meets for my son, or out of state medical appointments for my daughter, I have frustratingly had to miss some due to severe fatigue and pain. I think it is tough for folks to understand the depths of what is happening because I look fine on the outside but on the inside there is not enough energy to keep all of the systems running properly.

The pain/fatigue/weakness/depression/anxiety is always present, but the intensity is a moving target. What worries me most about Mitochondrial Disease is how unpredictable it is and the unknown. Will I be here in 5 years? Will we keep getting worse, will they find the gene causing what is happening? I am also worried that mitochondrial disease is misunderstood but am thankful for those who are dedicating their lives to help us.

Thank you for letting me be a part of this panel.

Alyssa D

I’ve come to learn that describing what Mitochondrial Disease feels like is a hefty task because words can’t fathom what we endure on a daily basis. The simplest explanation is that everyone is a phone battery. By the end of the day we are all plugged in and are expected to be on 100% in the morning. While the majority are, mitochondrial disease patients are stuck at 25% . We continually get plugged in, yet we never fully charge.

Good Morning. My name is Alyssa D. I am an 18-year-old high school student and was diagnosed with mitochondrial disease at the age of 14. I deal with debilitating symptoms on an everyday basis that range from mild to severe. The most crippling are fatigue, pain, and dysautonomia. The fatigue is almost impossible to describe because it seems other-worldly. It feels as though someone has taped cinder blocks to my eyelids some mornings and there is no way to keep them open. It can make it impossible to chew because I simply don’t have the energy to keep opening and

closing my mouth. Sometimes it can even make walking feel as though I am trapped in 4 feet of quicksand. Mito seems to reinvent the word fatigue. The symptoms vary day to day and when I go to sleep at night I never know what symptoms I'll have the next day. I might wake up and be able to walk without pain and have more energy than usual. Another day I might wake up unable to move; paralyzed by pain, fatigue, and weakness. It is like my body is playing Russian Roulette.

I never knew how many types of pain there were until I started experiencing them first hand. Joint and muscle pain can be overwhelming at times. It is an achy pain that can range from a dull feeling or can escalate into an intense stiffness. Nerve pain feels as though parts of your body are on fire and burning. It also gives a tingling feeling which can feel like you're being poked by a thousand needles. GI pain is like having a stomach virus every day and usually is accompanied by other things like nausea, vomiting, and diarrhea. These different kinds of pain affect me on an almost everyday basis, but the severity of the symptoms can alter from day to day. I've found that my pain goes up after exerting myself. I try to take breaks from some activities to prevent the crippling pain the next day. I almost never have pain free days.

Dysautonomia is like a drunk relative at a holiday party-----it doesn't leave! It is the mis regulation of the autonomic nervous system and for me causes high heart rate, low blood pressure when changing position, dizziness, fainting, and tremors to name a few. I experience these symptoms every day, all day. Dysautonomia can be quite a hindrance to my quality of life depending on the day.

Mito affects the activities I love, yet I have not let it stop me! Most teenagers hate having to go to school but I thrive in a learning environment. When I was 14, I could no longer go to school. I was in a wheelchair because of the debilitating symptoms of Mito. Most days I couldn't move because of the overwhelming fatigue and pain. I struggled to open my eyes, eat on my own, and to stay upright (because I couldn't hold my head up due to the fatigue). I had to be constantly monitored because I was too weak to do anything. I became enrolled in Virtual School/hospital homebound until I was rehabilitated enough to make the transition back to in person classes. This took almost 2 years. I am now able to split my time half and half. I have completely lost my ability to run, surf, and skateboard which were my favorite hobbies. I hope to one day return to those. Being sick affects social events with school friends too. There are days where I wake up with severe symptoms and have to cancel plans to meet up with them. I have even had to miss school dances that all my friends attended. The best thing is that I am lucky enough to have friends who understand and support me. If I am too sick to do anything they bring the fun to me!

Good days and bad days are on complete opposite sides of the spectrum. On good days I usually have little pain and less fatigue. I might be able to go out with friends, get extra school work done, or even go on a fun adventure. I can't exert myself though because the more I do, the sicker I'll be the next couple of days. Bad days can be pretty straining depending on the severity. I might have a hard time doing anything. I struggle to open my eyes and do basic tasks without help like brushing my hair, sitting up, or taking a shower. On bad days I can't get out of bed. I rest as much as I can. I used to have bad days pretty much every day, but since starting the "mito cocktail" the bad days have become less frequent.

I have come a long way since my diagnosis. While still bad, my symptoms are a drastic improvement from that point. My biggest concern is the fact that there are no treatments that target the root of the problem which are gene mutations and mitochondrial dysfunction. Right now, we are just chasing around symptoms but eventually these symptoms will worsen, and we need a plan of attack. These concerns are on the minds of every patient and caregiver who suffers from or experiences the horror we call mitochondrial disease. I hope that someday in the future this will change.

Panel # 2 – Current and Future Approaches to Treatment (Adults with Mitochondrial Myopathy):

Luisa & Robert M

My name is Robert M. and I am here to speak for my wife, Luisa. Luisa is a 59-year old physician, practicing medicine full-time in the State Hospital in Rhode Island. She is a wife and mother of two healthy adult children.

In 2016, a mutation on the TK2 gene was identified, allowing specific diagnosis of Thymidine Kinase 2 (or TK2) related Mitochondrial DNA Depletion Syndrome. The identification of this specific mitochondrial disorder was life changing for us as it allowed, for the first time, a treatment which addressed the underlying metabolic defect.

After decades with little to do to change the course of the disease, there was suddenly hope. Almost two years ago, Luisa began treatment with two nucleosides, deoxy-thymidine monophosphate and deoxy-cytidine monophosphate under a compassionate care waiver. These are the precursors of the enzyme TK2, which is needed for mitochondrial DNA synthesis.

The following is a description of Luisa's illness and treatments she has undertaken:

The first indication that something was wrong occurred in her mid-twenties when a routine blood test revealed an elevated CPK. Muscle biopsy followed demonstrating ragged-red fibers, and a non-specific diagnosis of mitochondrial myopathy.

It was not until her late 30's that disabilities began to accumulate. She left her position as an Emergency Room physician because of impaired speech. She developed difficulty swallowing. It was difficult to take nutrition or handle her own secretions. At 5'9", she weighed just over 100 lbs. Placement of a percutaneous gastric tube became necessary.

As her respiratory muscles weakened, she required BiPAP ventilatory support. Shortness of breath worsened. Fatigue was increasing. Her ability to walk declined. She relies entirely upon her gastric tube for nourishment, her medications, and upon BiPAP to breathe whenever lying down or with increased exertion.

Difficulty handling her secretions led to repeated aspiration pneumonias, several times requiring admission to an ICU. In time we became skilled at performing pulmonary toilet so that she has not experienced a significant pneumonia in over five years.

When she does still aspirate, we perform postural drainage and percussion, followed by vigorous suctioning. She must have a portable suction machine always at hand, whether in her office, in the car or at home. She uses an albuterol nebulizer and portable inhalers and employs incentive spirometry. Liquid albuterol and guaifenesin help to keep her airway relatively free of secretions.

In addition to the two nucleosides, Luisa takes the typical mitochondrial cocktail consisting of creatine, CoEnzyme Q10, Carnitor, Vitamin C and Vitamin E. The only adverse effect she has experienced with the nucleoside therapy is diarrhea, managed by taking up to seven Immodium tablets a day.

The following is a description of some of the adaptive measures she has employed:

Luisa finds her impaired speech most disabling. She carries a notepad and pen wherever she goes. Our children and I generally understand her speech, but for everyone else she must write whatever she wishes to say. She uses an

iPhone App called “Big” in which is typed a sentence or two in large easy to read lettering and can be held up for everyone at the table to read at once. Our family and friends have adapted to communication with her.

She takes a 2-3 hour nap each afternoon to rest her muscles and to eliminate the metabolic products that accumulate during the work day. When she does too much, weakness increases. Aching muscles may require Tylenol or Ibuprofen and bed-rest for several hours or a day.

Unsteady gait requires the use of a cane. Climbing stairs is very difficult. We installed a platform lift over the steps of our home. We rebuilt the steps on our deck to half-standard height. We have a chair lift for access to the second floor of our home.

Rising to stand from a chair is a struggle. The chair in her office is higher than standard. She carries a cushion in her car to use as a booster whenever chairs of only standard height are all that is available.

Just three months into the nucleoside treatment, there were subtle but objective signs of improvement. Although she still can't eat, she is able to drink an 8-ounce cup of coffee with less aspiration. Being able to drink coffee may not sound like much, but in terms of pleasure and quality of life, it's important. She still requires BiPAP at night, or when lying down, but she may now go days without becoming aware of air hunger. She believes she has more energy to approach daily life.

While improvements may be small, for the first time ever, Luisa is not experiencing noticeable progression of her disease!

I'll read the last paragraph of Luisa's words in the first person:

I was asked which symptom I would wish to see addressed in new drug development. This is an impossible question. Would I rather breathe easy or eat? Would I rather hear or speak? I can do none of these things. What do I want? I'd like to see a cure for Mitochondrial DNA Deficiency Syndromes. I write these words knowing how profoundly fortunate I am that this disease was not truly expressed until well into my 30s. I had an opportunity to become educated, fall in love, marry, establish a home and a career, and have children, whereas some, especially babies and children, may never get the chance at life that I have had. For this generation of children, I hope a cure, or an effective treatment will be found.

Deborah C

Hello, my name is Debbie C. I am 47 years old. I live in central Illinois with my 20-year-old son, Alex, and my fiancé, Derek. My journey began at the age of five years old when I ran with a “funny gait”, had severe muscle cramping after exercise, and would cry for hours from pain. At the age of 12, I underwent an emergency appendectomy, which I went into cardiac arrest. I was diagnosed with Malignant Hyperthermia. This is caused from a gene mutation

I am joining you through this recording today because I fell in December and have a tibial plateau fracture. Because people affected by mitochondrial disease heal more slowly, I am still not well enough to travel and be with you in person.

At the age of 31, I woke up in bed one morning and was unable to move from my waist down. I was in excruciating pain in my low back, had low potassium, and a plethora of other problems. I was treated for a possible staph infection and sent home after nearly 5 months. After some research, I believe that I had lumbar rhabdomyolysis caused from the Mitochondrial Disease.

After my extended illness in 2002, I was on Oxycontin, Morphine, Fentanyl patches, Oxycodone, Methadone, and Avinza. I was hospitalized three times from pancreatitis as a side effect from the Avinza, which is a long-acting narcotic. I was put on Neurontin, which caused excessive swelling in my legs and hands, but caused me to have the feeling that I was being zapped with a stun gun in my lower legs. I developed pyelonephritis, which is an abscess of the kidneys, along with acute kidney failure, after taking an arthritis medication called Vioxx. Because I didn't have an infection, I was later told this was caused from the Mitochondrial Disease due to autonomic dysfunction. I take Klonopin for Orthostatic hypotension and restless leg syndrome, which causes excessive sleepiness.

I went to rehabilitation for 5 days after my extended illness for detoxification from the narcotics. They gave me an injection called Buprenorphine, which worked well for my pain. I currently take Suboxone, which is Buprenorphine and Naloxone, taken in a sublingual film. However, it has side effects, such as my legs swelling and some mild memory loss. I have been on it for 12 years. Although, it doesn't work for my pain completely, it does enable me to get out of bed on most days and have some semblance of a normal life.

Even the easiest tasks, such as taking a shower or washing my hair are difficult. The fatigue overwhelms me at times. I am unable to clean my own home. I have a personal care attendant through the Department of Rehabilitation. I am given three hours a day for personal care, housekeeping, laundry, cooking, and shopping. I had friends for nearly thirty years, yet with chronic illness, I rarely see or talk to them anymore. I became unable to attend functions with them or visit. My life went from working twelve-hour shifts as a nurse to being home in bed nearly all the time.

I take 400 mg twice a day of Magnesium, which has helped with the chest pain that I have had my entire life; however, it has only helped a little bit with my leg pain and spasms. I can have muscle spasms in any muscle. I can have them in my legs, toes, feet, arms, chest, diaphragm, and stomach. I have been taken by ambulance to the hospital for muscle cramping that wouldn't stop. I have tried a TENS unit for pain, but it didn't help. I occasionally use Lidocaine patches, which they help temporarily.

I was put in physical therapy three times but released for failure to progress due to fatigue and other symptoms that would occur. I tried the "Mito Cocktail" and was taking Co-Enzyme Q-10, but it didn't help and although the prescribed Levocarnitine did help my leg pain, I was unable to take 29 pills a day due to gastroparesis, which is caused from the Mitochondrial disease. I have to eat several small meals a day. I feel full very fast. I have a lot of nausea and take 8mg Zofran.

I have severe allergies and used to take three shots a week. My allergy testing was off the charts. I woke up every day with headaches. I purchased an Ionic room filter and have noticed an improvement in my headaches. Although, I am on Topamax as a preventative. I became unable to take the Migraine medication, such as Imitrex due to a prolonged QT interval in my heart, which is caused from the Mitochondrial disease.

I live in a small, rural community. There are not any Mitochondrial specialists in the state of Illinois. Therefore, I have not seen one in eleven years. It would be a blessing to have medication available to have less pain, as well as increased energy and stamina would allow me to care for myself and improve my ability to be independent. As I am still mobile, if my primary symptoms were controlled, it is possible that I would be able to become employable. I would enjoy working at home performing medical transcription. The simple things that others take for granted such as walking the dog, vacationing with their child, swimming, would be a blessing if I could do them again by means of medication. However, as my life is right now there is no way that I am able to perform any skills, as I never know if I am able to get out of bed. The pain dictates my days and nights, it controls my life.

Michael M

My name is Michael M, I am 44 years old and live in Leominster, Massachusetts. I was diagnosed with a Mitochondrial Complex III Deficiency and a Fatty Acid Oxidation Disorder in 2012 after going undiagnosed for five years. An invasive cardio pulmonary exercise test along with two muscle biopsies confirmed my diagnosis.

The onset of my symptoms started when I was 34 years old. They include severe fatigue, muscle weakness, cramping, shortness of breath with light exertion, exercise intolerance, stomach dysmotility, abnormal body temperature regulation, muscle/nerve pain, sleep pattern disruptions and a constant mental fog/fatigue.

I have integrated several different treatment regimens throughout the course of my illness, whether it was due to my doctors suggesting lifestyle changes, prescribing additional or excluding medications and also personal research on any supplements. In regards to conventional medicine, the Mitochondrial Vitamin Cocktail with L-Carnitine was the start of my initial treatment. I did not experience any benefit from the cocktail even after the dosage was increased after three months. However, I still continue to take them daily. For pain management it has been trial and error with most medications. From Ibuprofen, to Lyrica, Neurontin, Tramadol, Morphine and Fentanyl. None of these helped, but ultimately oxycodone did provide some relief. I am also given Mestinon for Neuropathy/Mild Pre-Load Failure, a stimulant to help with energy, supplemental oxygen for shortness of breath and a bi-level breathing machine for nighttime. I have also tried Naturopathic Therapies, notably IV Ozone and IV Laser Treatment, Chiropractic, massage therapy and I also incorporate light graded resistance exercise along with a strict vegetarian diet.

The most significant symptom that I personally experience is extreme fatigue. Therefore, in my opinion the most beneficial part of my current treatment protocol is the stimulant I am prescribed, Adderall, which allows me to do light graded exercise. Being a former college athlete and an active person my entire life, exercise has always been extremely important to me and this medication allows me to have just enough energy to exercise when I can and have the ability to do simple daily living tasks, which essentially has a positive effect on my overall physical and emotional health.

As my illness has progressed over the past few years, I have felt that regardless of what changes I have made in regards to my treatment it has had less of a positive impact on my quality of life and the result is a consistent decrease in energy. Everything is physically challenging, and to me, living and not just merely surviving is the most important aspect. Receiving the endless amount of support from my family and significant other has been tremendous and I could not have made it this far without them.

Being from the Boston area I have been fortunate enough to have access to some excellent doctors and some of the best teaching hospitals in the entire country. However, due to this condition being so unpredictable and unstable I have learned to understand that it will take additional research and clinical studies in order to find possible effective treatments in the near future. Due to the disabling symptoms this has caused I am no longer able to work my position in law enforcement that I held for thirteen years. I will not stop trying to seek additional options in trying to feel better, but unfortunately, I do understand that the medical community is still attempting to learn more about this complex condition, and I have no choice but to be as patient as possible.

Ideally, any medication or clinical treatment that would assist in the oxidation process at the cellular level to optimize mitochondrial function and assist with energy production would be a great goal. I can tell you one of the hardest things to accept throughout this journey is not being able to do what I once could.

As invisible as this illness can be, many people may think that I can still do those things. And the answer is I simply cannot. I would be extremely content with having the chance to do the smallest things in life without having to exert

so much energy, that at times may take days to recover from. These are things that a healthy person may unintentionally take for granted.

Sharon S

I am Sharon S. I am 54 years old; I live in Tucson Arizona. I was diagnosed 19 years ago with Kearns Sayre Syndrome (KSS). Years later and through better diagnostics they were able to narrow it down to CPEO++ (which is in the Kearns Sayre Syndrome Spectrum) of mitochondria disease. It is my pleasure to be on this panel and help serve our community.

Living with mitochondrial disease means managing a long list of symptoms. Today I will only talk about my top symptoms which include:

- 1) Head to toe pain in all my muscles
- 2) Extreme weakness in my body
- 3) Severe fatigue and exhaustion which translate into terrible inconsistent energy levels. How I feel one hour can be drastically different in the next. Even if I sleep 12 hours this makes no difference in feeling rested.
- 4) My eyeballs are 75% paralyzed due to Chronic Progressive External Ophthalmoplegia (CPEO) which includes droopy eyelids, making it difficult to have a normal range of sight. I suffer with severe dry eye syndrome, due to my eyelids not opening or closing all the way.
- 5) Extreme neck weakness, making it hard to hold my head up due to neck muscle atrophy.

The past 18 years has been a journey of trying anything I can find to help myself. There are no real treatments for mitochondrial disease, let alone a cure. Today my self-help regiment consists of:

- Physical therapy program - designed to strengthen my body and stay ahead of my muscle wasting and atrophy. I go 3 times a week. I believe I'll need to bump this up to 5 times a week if I really want to stay ahead of my progression.
- I use a Tens unit which is (electrical stimulation) on my muscles. Helps to relax my muscles and block pain.
- I use 'Sore no More muscle cream' this brand helps reduce pain and soreness for a short time by about 50%.
- For my severe neck pain, I have had 2 cervical ablations on my C5 area, (a needle is inserted between the discs of my spine and it electrocutes the nerves so that the pain is gone. The upside -is that an Ablation can work for up to 2 years until the nerves regenerate. The downside is that it takes 2 weeks for the nerves to die 100% and during this time the pain is unbearable. It can be a dangerous procedure and it does not always work. I wear a Soft Cervical Neck collar to relieve my neck strain, and to help hold my head up as I am developing DHS (drop head syndrome)
- I have to use Celluvisc (extra thick eye drop) 1 drop, each eye, every 15 minutes otherwise I get blurred double vision and am not able to read or drive at night.
- I Had to have a Frontalis Sling Surgery (due to eyelids not closing or opening all the way.) Silicone slings were surgically implanted into my forehead muscle that attach to my eyelids. This surgery helps to keep my lids from drooping closed (ptosis); the slings are attached to my eye brow muscles so to raise my eyelid, I simply raise my eye brows. Unfortunately, this procedure only lasts 10 years. I need another one but cannot risk the surgery.
- I have to tape my eyes shut at night to prevent corneal ulcers. This acts like a fake lid to protect my eye environment. I have not had corneal ulcers since taping my eyes each night for the last 19 years.
- I carry a portable EKG device (Kardia brand), that works through my cell phone to monitor my heart arrhythmias and tachycardia. I can send the reports to my cardiologist as we assess if my heart abnormalities are changing and if medical intervention may be needed.

- I have been on high dose of Ubiquinol Co-Q for 18 years together with the standard “mito cocktail” Vit B, alpha lipoic acid. I used to take carnitor but had to stop as it caused stomach problems. I also had to stop creatine as it caused chronic diarrhea.
- I was diagnosed with CFD Cerebral Folate Deficiency through a spinal tap. I immediately went on RX of Folinic Acid which made a major difference helping my brain fog, brain sag and depression due to the deficiency.
- I have always taken nutritional “cocktails” but the last 5 years my main stay consists of Matcha, collagen, bone broth protein, fish oil, greens, cocurium (which helps with inflammation) and probiotics and aloe to help my gut. I have been on a special water called Vivo for 10 years to combat my migraines and to also properly hydrate my cells and help my body properly absorb all the nutrition that I take.
- I am currently in a clinical trial, going on 2 years specific to treat my mitochondrial myopathy. The first 5 months I noted inconsistent small improvement, a few days of feeling more energy than nothing. The last 7 months I have noted daily increase and consistency of my energy, stamina and endurance. So far, it’s done nothing for my muscle weakness or pain. The downside is I have to inject each day into my stomach, I have had welts, rash and skin scarring from the needles around the injection sites.
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All that I have tried over the years has not brought much lasting improvement to stay ahead of my progression. If I make any changes to my regiment its due to having time to evaluate the effectiveness (is it bringing any relief? and not causing more side effect? Can I afford it?).

When I look back over 19 years, the amount of money, time, energy I have spent trying to help my condition, I know that my effort has created a resiliency in me, but I am also very worn out in a way regarding this uphill battle. I also know that if I stopped trying to help myself, I will reach despair. I no longer am satisfied with just my help. I need your help now please. My life wish is to have more treatment options available to me soon. Like the clinical trial drug that I am currently on. A drug to stop my muscle weakness and wasting. A drug to help give me a better quality of life.

Nicole D

My name is Nicole D, I live in Lafayette, Louisiana and I was diagnosed with an unspecified Mitochondrial Disorder in 2010 at the age of 32. My symptoms include daily muscle and joint pain, muscle weakness, extreme fatigue, stomach pain and sluggishness, hypoglycemia, and disrupted sleep patterns.

I approach my treatment as a lifestyle and incorporate strategies throughout my day. As a foundation, I have labs drawn every six months to determine my vitamin and metabolic levels. The vitamin cocktail I take is determined by the results of these labs. I travel 5 hours round trip to see a Mitochondrial Disease specialist, one who can analyze the metabolic aspects of my condition. My diet consists of mostly fresh, raw, vegetarian meals prepared at home. I do yoga on a regular basis in order increase my activity tolerance and decrease my muscle weakness. I incorporate daily rest or nap periods in order to transition from my morning to my nighttime routine. Oral hydration is also vital to the health of my muscles in limiting the pain and weakness.

Despite my attempts to address my treatment regimen as a lifestyle approach, the disease is so unstable and unpredictable the treatment takes a lengthy trial and error approach. At various points in my disease process, I have had to discontinue treatments that were previously effective. I’ve tried prescriptions that treat various individual symptoms to include blood sugar instability and joint pain. However, these medications either had no effect or were more negative than therapeutic in their effects. Two of the prescriptions that I used the longest and eventually discontinued were Precose and Celebrex. Celebrex had absolutely no effect on the joint pain symptoms for which it was prescribed. I used Precose for a few years to address my hypoglycemic episodes. Eventually though, Precose amplified my existing muscle pain to the point that it hurt to sit, vision decline that required frequent, more intense

changes in eye glass prescriptions, and erratic glucose readings. I felt like my body was shutting down. Once I discontinued taking the medication, I no longer had the debilitating muscle pain, no longer needed eye glasses, and am now able to control most of my hypoglycemic episodes with diet and exercise.

The vitamin regimen (creatine, magnesium, and potassium) that treats my muscle pain and weakness often becomes very hard on my stomach causing extreme pain and irritation. I have had to take many breaks from the vitamins which then prompts the very symptoms I am trying to manage. The process to find pharmaceutical grade vitamins that are reliable and effective has taken years and endless amounts of research. Because of the instability of the disease, and the research involved to acquire appropriate treatment, my regimen is not efficient.

When my muscle pain becomes too challenging to treat with just the vitamin cocktail, I have experienced relief with IV saline infusions. I initiate this treatment when the pain interferes with both sleep and waking hours. This is generally short-lived because after too many infusion my veins begin wear out and can no longer be accessed.

I am extremely conservative with the use of pain medications for my muscle and joint pain because they exacerbate the fatigue and muscle weakness. In addition, I have an extensive family history of addiction, so I do not consider those medications an option. During the day, I use Ibuprofen which often dulls rather than eliminates the pain. I am currently using only one prescription medication, Neurontin, and despite it being the most effective, I can only use it at bedtime because it causes me to fall asleep.

Besides muscle and joint pain, my other, most significant symptom is pervasive fatigue. I am continuing to become more limited in my ability to function effectively for the entire day in my roles as mother, wife, and professional because of this. I have found that the most effective treatment for the fatigue is rest, clean diet, and high doses of Ubiquinol (approximately 1000-1200 mg daily). However, I am in a perpetual state of sleepiness and overall physical and mental fatigue.

There isn't a treatment that I am using that is eliminating my symptoms. At best, they are giving relief but not absence. Therefore, I have learned to work with the symptoms. I enjoy being outside in my garden and staying busy in our community at festivals and various events. My ability to engage in those activities is limited and I am budgeting time and energy according to the day's priorities. I do believe that my current regimen is allowing me to participate at a limited level and without any treatment my activity level would be even less.

Ideally, any treatment that would be developed for Mitochondrial disorders would stabilize the muscles by minimizing or eliminating pain without the harmful side effects of current medications on the market. Additionally, treatment for muscle myopathy would also aid patients in physical strengthening and recovery of lost ability. I am a veteran of the Louisiana Army National Guard. At one time, I was physically active and felt strong. Now, I often have feelings of physical weakness and my activity level is low. I can visibly see that I am losing muscle mass. Recently, I have had to quit a job that I love in order to keep up with my own physical health and my responsibilities as a wife and mother. If a drug was developed that would treat my primary mitochondrial disorder it would mean a return to balancing my work and personal life without having to forfeit one for the sake of the other.

Panel # 3 – Symptoms and Daily Impacts (Neurologic Manifestations in Children):

Daniel M

My name is Danny M. I live in Corte Madera, CA, with my wife Nikki and our two sons Carson and Chase, ages 7 and 6. Carson and Chase have MEPAN Syndrome, an ultra-rare condition that results in impaired mitochondrial fatty acid synthesis and has rendered them unable to walk, move independently or talk. MEPAN is a neurodegenerative condition, so their symptoms may worsen, and eventually they may suffer severe vision loss. Every day, my wife and I and their aides and caregivers at home and school do nearly everything for Carson and Chase from the time they wake up to the time they go to bed. What I am sharing today is told through the eyes of our older Carson:

I used to be able to turn myself over in bed, but not anymore. My body doesn't work like it should, and it's hard for my brother and me to move like other kids. I tell my brain what I want to move, but my body doesn't listen.

So sometimes I hurt because I can't roll over onto my back or side. I can yelp for my mom or dad at night and they will come and roll me over, but they don't always hear me, and I have to just lay there. My dad gets me and my brother dressed in the morning for school. We have to wake up extra early because my dad has to change our diapers, put our clothes on for us and get our AFOs on while mom makes us breakfast. Mom feeds me and dad gets us into our wheelchairs and down the ramp next to our house and straps our chairs into our van. We have lots of special equipment in our house, like standers, walkers, therapy benches and bath and potty chairs.

Chase and me get to our classrooms at school and our helpers get us out of the van and set up in class. We have a lot of helpers. I have a helper at school named Jason who is with me every day and helps me move around the classroom in my wheelchair. I can't sit with the other kids on the floor because I usually will fall over if I try to sit by myself. I used to be able to sit on my own, but I can't anymore. My hands don't work very well either and I can't hold a pencil, but I am learning to use a computer that works with my eyes to help me talk. It's really hard to use because my eyes get tired, they don't always look where they're supposed to, and the rest of my body moves around even when I don't want it to. I used to be able to walk a little in my walker, but I don't do that as much anymore. My brother doesn't use his walker much either. The other day some of the kids in my class were playing tag after school and my dad pushed me in my wheelchair to chase after some of them so I could play. That was fun, but I really just wish I could run on my own. I'd be ok with just walking on my own too, so I can go where I want to and not have to wait for a helper to push me in my wheelchair. I have to wait around for a lot of things.

My brother can move by rolling and crawling a little and he can hold things with his hands, but I can't. I have some signs that I use to tell people what I want, but most days my hands and fingers don't work like they're supposed to, and it's hard for people to understand my signs. I can't talk either, so it's hard for me to tell people how I'm feeling or what I need. Neither can my brother. It makes me sad.

Sometimes I see my mom and dad not smiling, and they look kind of worried. And I know they get worried on days when my body gets tight and they have to give me soft food because it's really hard for me to chew and they think I might choke on something. Mom looks worried when our teachers tell her how tired we look at school. My brother Chase puts his head down a lot when he needs to take a break and rest. My mom isn't as strong as my dad, and since we might be as tall as dad someday I think she's worried that she's going to hurt her back again as she's getting us into our chairs. At home she's always trying to do what the therapists do,

like trying to teach us to chew better, and sit up by ourselves, but I don't like that. I just want her to be my mom.

I wish my brother and me could just play with Legos, have sword fights and not have to keep going to a bunch of therapies and take pills and drink vitamin drinks every day to help us sit, stand, walk and talk like other kids do. I guess it's on account of the MEPAN that mom and dad say that makes our bodies not work so well. Dad says that there are a lot of other kids whose bodies don't work so well because of things like MEPAN, and that there are people trying to find out why and help them. It's ok that everybody is different, but nobody should have different experiences because of things like MEPAN -- that's not fun for anyone. That's why my dad is here today. To tell people about me and Chase and make sure that kids like us get help and a chance to run around like other kids someday.

Ann K

Hello, I'm Ann K from Mt Laurel, New Jersey. My husband Howard and I have been married for 33 years. We have 2 beautiful girls. Our older daughter, Dana, lives in Washington DC. I would like to Thank you for the opportunity to tell you about our younger daughter, Mara. Ironically, Mara's name in Hebrew means gift of peace. From the moment she was born she did not give us peace. When Mara was three months old she was hospitalized for failure to thrive. After many tests, it was determined she had, among other things, microcephaly, cortical blindness, epilepsy, cardio myopathy and a mitochondrial myopathy. Her neurologist at the time said, although the testing did not prove it, he instinctively felt she had a pyruvate dehydrogenase complex deficiency. We did not receive the final PDCD diagnosis until shortly before her 21st birthday. Howard and I were then told Mara would probably not live through her first birthday. We had to have the conversation that no parent should ever have - where to bury our baby girl.

We have still refused to buy burial plots, partly from denial and in part because Howard and I believe in a good fight. Our "gift" has fought hard; after heart surgery (PDA and collateral), 6 bouts of pneumonia, over 100 ear infections (I stopped counting, but Howard has not), swine flu in 2009 and many other illnesses, hospitalizations and trips to the ER, Mara is very much alive and now almost 23 years old. Her life is not without complications; she is severely developmentally delayed, non-verbal, confined to a wheelchair, has gastro-esophageal reflux, and a metabolic disorder which makes it difficult for her to digest milk proteins. Mara is small in size and we struggle to keep her weight appropriate for her 4 ft 7 frame, which is about 70 pounds. She is happy and deeply loved by all. Mara now attends an adult day program and enjoys listening to her special jazz music. Howard and I come from a family of music lovers. We played all kinds of music for her, but she has settled into Jazz, specifically Ella Fitzgerald, Louis Armstrong and Nelson Riddle.

Despite how well Mara is doing, we struggle with 3 key symptoms. These are: Managing her epilepsy, her reflux and ability to chew/swallow, and her physical limitations and blindness.

Now that Mara has matured we sometimes struggle with managing her seizures. They appear to be cyclic and occur most frequently just prior to menstruation. I never thought I would still be sleeping with a baby monitor, but we still sleep with one eye open and one ear to the monitor. Mara is also sensitive to extreme heat or cold, either of which can bring on a life-threatening seizure or a pulmonary issue.

Mara sees her neurologist regularly as a result of her seizures and mitochondrial disorder.

We are a social family, we enjoy eating and cooking good food, meals with friends, and happy hour. This is the environment Mara was born into. She loves to sit around a table at home or in a restaurant and listen to the chit chat. Although she is non-verbal she has always managed to add her two cents where appropriate with a raze, eye-

roll or cooing. We were determined she would enjoy a family life. However, her mitochondrial disease had other plans; when she was approximately 9 years old her metabolic disorder manifested itself and caused her to be unable to keep food down. As a consequence, her weight dropped from 55 to 40 lbs. She was on the verge of being hospitalized for failure to thrive and moments away from a feeding tube when her gastroenterologist suggested we try Peptamen Junior orally. She drank it voraciously and more importantly held it down. Mara now drinks four containers of this daily. It supplies approximately 75 % of her caloric intake per day. She is very happy and enjoys many different foods as long as we chop them up or puree them for her. We have learned to prepare Mara's food carefully, so she can still enjoy the flavors and not have a trip to the hospital for choking or aspirating. With the Peptamen Junior and careful preparation of Mara's food, the possibilities of her failing to thrive (from low weight and poor nutrition) or having a life-threatening choking incident are significantly diminished. These have been two of our biggest fears over her lifetime.

With regard to Mara's inability to walk, talk, and care for her own physical needs and her cortical blindness, our biggest problem over the years has been to make sure she is in safe surroundings. Of particular concern is having a safe sleeping environment and a safe play area because Mara cannot see or sense dangers and had occasionally fallen out of bed or hit her head on a wall. To accomplish this, we have "child proofed" the den, the room in which Mara now spends most of her time at home and purchased a child appropriate hospital bed.

Mara's conditions and limitations have changed our lives significantly. Family vacations or extensive trips have not been an option. Extreme care has to be taken in the environments she can go to, especially if a relative or friend we wish to visit is ill. The 2018 trip to the UMDF meeting in Nashville was the second time Howard and I have been away in almost 23 years. We do not expect another trip for an extended period of time to happen for many years to come.

Stacy T

Hello. My name is Stacy T. Thank you for the opportunity to tell you about my family. My husband and I live in Baltimore with our 4 boys – Lucas, Ben, Marshall and Sam. Marshall and Sam are my youngest at 11 and 10. In 2014, Marshall and Sam were diagnosed with Mitochondrial Disease, specifically Combined Oxidative Phosphorylation Deficiency, Type 11.

Mito affects the boys in similar, but different ways with Sam being more significantly impacted. They both have a laundry list of diagnoses, including intellectual disability, global developmental delay, hearing loss, strabismus, cortical visual impairment, incontinence, epilepsy, gastroparesis, kidney disease, spasticity and more. Concerns that might be pretty trivial in other kids can be catastrophic for them. A common cold can land either of them in the ER and a simple school field trip is fraught with logistical concerns.

When thinking about day to day living, the most impactful symptoms are communication and mobility issues. Sam is diagnosed as being "non-verbal." He is able to communicate some basic wants and needs to his father and me, but I liken it to how parents know what a baby wants before it can even talk. Two-way communication with others is almost nonexistent. Even communicating that he wants something to drink can be a challenge. I cannot even imagine the frustration of not being able to convey this most basic of needs, let alone more complex needs or feelings. He currently uses a combination of gestures, sign approximations and a few words. But the one thing that is consistent about Sam is how inconsistent he is. We may hear him say "milk" for a few weeks then not hear it again for months – or years. When Sam was 3 he experienced what we now think to have been a metabolic stroke episode. He had significant regression to his skills, including losing all the language he had developed up to that point. He has never really gotten back to where he was before that episode.

Sam uses a wheelchair for mobility and has to be lifted for most transfers. He currently weighs almost 90 pounds and is about 4 feet, 4 inches. This puts him at only about a foot shorter than me and while he will keep growing, I will not

necessarily get stronger. Getting him in and out of the car, bed or bath is literally more than I can do some days. When I wrote the first draft of this statement months ago, Sam's mobility issues were stable. Since then, the spasticity of his muscles has increased significantly. On Monday, he will be admitted to the hospital to have a Baclofen pump implanted. This is his first major surgery and to say that I am nervous would be an understatement. Even just saying that this is his 'first major surgery' puts him a different category than most kids his age. Mobility is certainly an issue for Sam, but with his wheelchair – and with the ADA - we can fairly easily get him where we need to go within the community. So, though Sam is more universally impacted, mobility is actually more of a day to day issue for Marshall.

Marshall can walk independently but not quickly or for long distances. He wants – and needs - a hand held most of the time. He is unwilling to walk on unstable surfaces like sand or dirt, to the point where he will sometimes get physically ill if he has to. This makes community outings, family vacations – everything - more challenging. Three years ago, the progressive spasticity of Marshall's muscles was causing his gait to deteriorate so significantly that he needed surgery to prevent or delay the ultimate need for a wheelchair. After 6 weeks in the hospital and months of at-home rehabilitation, we went from increased spasticity to generalized weakness and to see him trying to run around with his brothers or peers and never catch them can be heartbreaking. The gap between what he wants to do and what he is able to do is increasing, and as he gets older his awareness of that gap is increasing too. And the reality is that surgery may have only delayed his ultimate need for a wheelchair. In fact, we are currently planning for another surgery in June to correct flat feet and collapsing ankles. If allowed to go uncorrected, Marshall would not be able to bear weight within a few years.

But none of these challenges really tells you who they are. They both have an amazing sense of humor. Sam LOVES when things fall – he thinks it's hysterical. He loves an adventure – he will go anywhere, anytime. He loves to swim and loves music. The most recognizable words that he has are in his songs. Marshall thinks magic tricks and jokes are the best and will try to fool his daddy by telling him to "look over there," so he can win the race to the house or upstairs, wherever they are going. Marshall is more of a homebody and would prefer it if I stayed home along with him. He does also love to swim though. I imagine that weightless feeling of the water feels incredible to them both.

There are so many things I wish I could do for them, but if I had to pick only one, I would make mobility easier for Marshall and communication easier for Sam. Or, at the very least, halt any deterioration that is occurring or could occur. This would improve the current quality of their lives and provide some reassurance about their futures. I am biased, but they are both smart, silly, fun, thoughtful boys and deserve a chance at the best life possible. Thank you.

Heather T

Good afternoon, my name is Heather T and I'm from Orlando, Florida. I'm honored to have the opportunity to share my daughter, Arden's story to you all in hopes that it will help improve her life as well as those affected by mitochondrial disease.

Arden's journey started at just 6 weeks old. Born 2 months premature and still in the NICU Arden began to have trouble breathing. It was evident she was struggling. Her heart had grown to take up 75% of her chest cavity and was crushing her lungs. She was on life support within 36 hours and fighting for her life. We didn't know then but know now that this was her first "mito-crisis" and her body was crashing. After weeks of failed interventions, Arden was listed for a heart transplant. She received her new heart at just 3 months old.

Arden, like many others go undiagnosed for years till there is a catalyst of some kind, usually an illness onset. After 2 years of wondering what happened to Arden's heart, we received the devastating news that she had a mitochondrial disease known as Leigh Syndrome. Prognosis being poor, Arden wasn't expected to reach her 5th birthday and her physical skills were estimated to be nothing more than small head movements.

Arden is now six and she has shattered the ceiling on any limitations and obstacles set before her. Although Arden has come a long way, life certainly isn't easy. I want nothing more than to give her the world; to help her, and to meet all of her needs. In Arden's case that isn't always easy as she is non-verbal. She has great difficulty communicating her needs and desires. There was a time spanning 18 months of constant screaming. If her eyes were open she was crying and in obvious discomfort. Every 2-3 months this would happen and last anywhere from 10-30 days of no relief. As a parent and primary caregiver, I felt helpless. Knowing that I was frustrated and feeling defeated – I can only imagine how Arden was feeling. On top of the pain she was having, everyone around her wasn't providing any relief. Trapped in her body, she was doing all she could to show us something was wrong. It ended up being neuropathic pain and we were relieved to give her comfort but devastated her suffering lasted so long.

Being nonverbal not only hinders communication within our primary family unit but branches out to social interactions with other family, friends, and strangers. Arden is often left out or passed over as communicating with someone who is nonverbal can be awkward and a struggle to those that have not come into contact with someone who lacks the skills to speak. To live in a world unable to share her voice, her feelings, her wants, desires, and even dreams has to be isolating and extremely lonely. If given the resources or ability to speak even just a few words could be life-changing in many ways. Having the ability to communicate whether it is verbal or physical would open endless opportunities.

Arden requires around the clock care and lacks all independence and mobility. Having deficits physically has made a huge impact on her life. She is limited to what she can participate in and is always dependent on others to help her facilitate the activity at hand. Arden attends a medical daycare and a prime example of this is when they go on field trips. Although the facility provides Arden with everything she needs, giving her the experiences she deserves can be hard to accomplish at times. As parents, we are often asked to go with Arden and her class on field trips due to the care she requires in order to keep up with her peers as support staff is limited. Naturally as her mother, I jump at the opportunity to go and spend that quality time with her while being able to provide her with new experiences and inclusion. I work full time and it can be difficult to request off of work whether that be due to what is expected of me during that time or taking the day off and then therefore being impacted financially. If we weren't able to go with Arden, she would miss out on these memorable experiences. She may not realize what she misses out on but as parents we know, and she deserves those experiences. Her lack in physical mobility and independence should not interfere with her being able to experience what any normal child her age would and should be experiencing, but at times it does.

Life is unpredictable, even more so when you are living with a disease that can appear or progress at any time with each time being very different than the last. A lot of that unpredictability is due to Arden's lack of immune system and its inability to fight off illnesses like the rest of us. Her immune deficiencies from her disease on top of her also being immune suppressed from the anti-rejection medications she is required to take daily to keep her heart healthy have a huge impact on her body. About 4 years ago she came down with the rhinovirus, better known as the "common-cold." Arden ended up on life support for 2 months while her organs started to shut down. It was a very scary time and we didn't know if she was going to make it or not. If she did, no one knew if she would recover and be the same person she was before this illness. Then we have other times where she is able to fight off the cold with very little struggle. We just never know which route she will take and the uncertainty of it all makes it so unbelievably stressful. Illness wreaks havoc on her fragile body and even the slightest cold can be catastrophic.

Time is essential when it comes to fighting mitochondrial disease. Our biggest worry as parents would have to be losing Arden. We know it's inevitable with this disease but how can we accept that? Thank you for allowing me to share Arden's journey with you and for your efforts to help make her future brighter. It gives us hope to continue fighting and that better days are ahead.

Annett C

Hello. My name is Annett C. I live in Atlanta Georgia with my husband Sebastien and our 8-year old son Jagger and I am here today to share Jagger's story. Jagger suffers from severe developmental delay, seizures, cardiomyopathy, scoliosis, gastroparesis, neurogenic bladder, respiratory failure and much more all caused by his Mitochondrial myopathy. Specifically, Leigh's syndrome. His early diagnosis at age one meant that his symptoms are severe and life expectancy short. We were told he wouldn't live passed the age of 4. He is 8 years old now and still fighting.

Developmentally Jagger is probably the age of a 3-month old. He has muscle weakness and is unable to hold his head, sit, stand or walk. He spends the majority of his time lying in bed, is dependent on oxygen 24/7, uses a bipap at night, has a GJ feeding tube and requires daily IV infusions. However, one of the most challenging and frustrating symptoms is the fact that Jagger cannot communicate verbally making it almost impossible to figure out what is wrong with him when he is screaming and arching in agonizing pain.

I will never forget Jagger's first mito crash which occurred two months after his first birthday. We were at the hospital once again for feeding issues and he screamed for an entire day until he became too exhausted to breathe. He turned blue as he continued to cry but was unable to catch his breath. I vividly remember pushing the nurse out of the way reaching for the oxygen mask attached to the wall, so I could do manual ventilation. At this point, he stopped breathing completely. He was quickly intubated and remained on a ventilator for several days. We stayed in the hospital for one month until Jagger stabilized enough to go home on hospice care.

With each mito crash, pneumonia or even a simple cold (the last one leading to complete heart and respiratory failure and 15 days on life support) Jagger's baseline keeps regressing. We live in constant fear that each episode could be his last. His pain is getting worse and his seizures are increasing. Outings have become rare because sitting upright in his car seat or wheelchair is exhausting and painful for him.

Jagger is and always will be the center of our universe. He dictates when we eat, sleep, work, run errands. My husband, Sebastien, and I carefully coordinate our schedules so we can first and foremost meet Jagger's needs and without nursing or help of any kind, this is tricky most days. Any errand has to be carefully planned and communicated to ensure none of Jagger's competing priorities will interfere with such outing.

Jagger typically wakes up between 12 and 3 pm at which point, he claims our king size bed all to himself spreading his arms out left and right. If I'm lucky, he may leave me about 10 inches. He flops his arms continuously for hours due to his severe movement disorder making it nearly impossible to sneak in my 1000 kisses I had promised him when he opened his eyes. I use all available pillows to construct what could resemble the Great Wall of China, but Mr. Houdini manages to bypass my fortress and sinks his right fist into my left eye socket. I continue to snuggle and sneak in kisses knowing quite well I may walk away with facial bruising, but it's all worth it. Some may ask why I don't just get up. It's not that simple. Due to his underlying respiratory problems, Jagger has LOTS of secretions and 2-4 hours after he awakens are spend putting a tube down his throat to suction him. Often over 200 times day and night. His secretions not only cause him to cough a lot, but many times he gags himself and vomits, which commands the presence of either myself or my husband to be next to him at all times to ensure he doesn't choke or swallow which can cause aspiration pneumonia, something he suffers from frequently and which most times require hospitalization.

I sneak in as many kisses as possible and on a good day he blows me bubble kisses, makes noises like a motorboat or babbles "ahaha, and umpa, umpa's ". I procrastinate a bit on his 3-4 mandatory breathing treatments and enema which are all part of his daily routine. Once the treatments start, Jagger usually becomes severely agitated and the

rest of the evening is spend sitting with him, holding him, praying he won't start screaming and clutching his chin in an upward position to open his airway so he can breathe more easily.

We will never stop in seeking the best possible care for Jagger. He is currently enrolled in a drug trial specifically for Leigh's disease and we moved cross-country a couple of years ago to seek alternative treatments for his seizures and pain as pharmaceuticals are no longer doing their job. We really do not want to put him on sedative medicines as this will only prolong his life but won't actually help with his quality of life. His body would be with us, but his spirit would be gone. No more smiles, no more "ah-ha's" and "umpa, umpa's". I am devastated just thinking about what his future might look like. No one wants to lose their child but also no one should have to suffer so much. As I was sitting down and writing this, Jagger has just suffered his third seizure of the day. We know the future isn't bright for our sweet boy, however as long as Jagger has the energy to fight, we fight for him and with him, the reason why I am here today sharing his courageous journey.

Panel # 4 – Current and Future Approaches to Treatments (Neurologic Manifestations in Children):

Carrie M

My name is Carrie M. I am a resident of Pittsgrove, NJ and proud mother to two amazing boys, AJ (14) and Patrick (11). My youngest son Patrick has mitochondrial disease and I'm here today to share his story. Patrick was born in August 2007, a healthy, happy baby boy. He hit all his early milestones and was developing "normally" by all accounts. But at 9 months, we started noticing delays in his motor development – he couldn't sit unsupported and wasn't making efforts to crawl. He began early intervention services and while Patrick made great strides, he remained behind schedule for his developmental milestones, which now also included cognitive and verbal delays.

Patrick's doctors couldn't find a reason for his developmental delays and as he got older, new issues began to emerge. When Patrick got sick, even with what seemed to be a mild cold, he would become very lethargic. Then, in February 2012, Patrick woke up one morning unable to walk. When he crawled, he dragged his left arm and leg. We headed off to the ER and as we were approaching, Patrick started having seizures. Patrick was admitted and an EEG showed continuous seizures. Patrick was treated with progressive seizure meds (Keppra, Dilantin, Phenobarbital), which only slightly reduced his seizure activity. He then required an infusions of Midazolam, requiring intubation and a central line, so Patrick was moved to the PICU. The midazolam did not improve his seizure activity during the first 12 hours, so the team began to talk about the cause of the seizures. His previous MRI had shown increased lactate in his brain stem and his new MRI was now showing a metabolic stroke, in which the brain is starved of energy due to low metabolic activity. His symptoms resembled MELAS syndrome and so Patrick was given an IV infusion of L-arginine. Within 12 hours of the Arginine infusion, Patrick's EEG started to improve reducing his seizures from 10-15 per hour to 1-2 events daily and eventually none.

When Patrick finally awoke from sedation, he was different. He had lost all of his gross motor skills. Since mitochondrial disease was suspected, Patrick was also started on a combination of vitamins and called the "mito cocktail." which included L-Arginine, Levocarnitine, Leucovorin Calcium, Ubiquinol, B-Complex Vitamins, Vitamins C & E, Alpha Lipoic Acid and Biotin. He endured at least 3 hours daily of PT, OT and speech therapies while inpatient over the next few months. It was a joyous day when he was finally released home, but our lives were changed forever.

Not long after Patrick returned home from the hospital, we learned that Patrick conclusively had mitochondrial disease, specifically POLG-1 mutation. Mitochondrial disease is a severe and progressive, affects multiple systems and has no known cure.

Since that first episode in 2012, Patrick's journey has been a roller coaster of ups and downs. He has periods of stability, but it doesn't take much for things to go downhill. His hospital stays have ranged from 48 hours up to a few months, depending on the severity of the episode. His disease has continued to progress with an increase in neurological symptoms like tremors & myoclonus and the development of an adrenal insufficiency, by itself a life-threatening condition. He began daily steroid medications of hydrocortisone and fludrocortisone to help stabilize his adrenal function and in times of illness, Patrick receives stress dose steroids.

We've had two especially scary episodes in the past few years. In 2015, Patrick had another severe metabolic stroke, again with recurrent seizures. We again went through several seizure medications, ultimately placing him in a medical induced coma on Ketamine. His team also started him on Citrulline at that time and we again saw improvement in his scans and EEG as it helped heal his brain.

Then, last January, Patrick again had a long hospitalization due to an underlying infection. This episode again put his body in metabolic crisis but this time, we utilized an infusion of IVIG to help boost his immune system and improve

his brain health. With the IVIG infusions, we have seen remarkable improvement in Patrick's mental awareness and overall health.

Keeping up with Patrick's medical needs is a full-time job. Patrick now has a full-time nurse with him from 7 am until 10 pm Monday-Friday and for 6 hours a day on the weekends. He attends a school program for special needs students and has multiple sessions of PT, OT and Speech weekly. He sees specialists in Mitochondrial Medicine, Complex Care, Neurology, Endocrinology, GI, Pulmonology, Cardiology, Ophthalmology, Immunology, Audiology and PM&R, requiring multiple outpatient visits monthly.

Patrick is 11 now but has the functional abilities of a toddler. His mobility is limited, and he primarily uses a wheelchair to get around. His life is not easy, but he is a fighter and my personal hero. He is an inspiration and brings so much joy to my life and to so many others.

So, I'm here to ask for your continued help in giving Patrick the best, longest life possible. We are so thankful for the work that his doctors and researchers are doing to help provide support, but we need more options. Our ultimate hope would be a cure, but any interventions that would reduce the frequency of hospitalizations or minimize his neurological symptoms would really improve his quality of life. We want him to experience all that life has to offer, in whatever time he has with us. Thank you.

Lori M

Hello, my name is Lori M, our family lives in Houston Texas and we have an amazingly special nine-year old son and a vivacious four-year old daughter, both of these amazing kids fill our lives with joy and humor.

Our nine-year old son, Will, was diagnosed with Leigh syndrome at the age of two. Our lives were turned upside down and inside out. Even now, 7 years later, this diagnosis is crushing. He was diagnosed with the mtDNA mutation 9176 t>c. Leigh syndrome is a progressive and fatal form of mitochondrial disease. Our son has large, parallel lesions on his brain.

He has beaten the odds the doctors originally gave us. Now, at the age of nine, his ability for gross and fine motor skills range between a 12 to 24-month old child. His cognitive and verbal abilities appear to be unique for his disease as he is currently assessed to be at the level of a five-year old.

Will's symptoms and issues pertain to multiple bodily systems, organs and functions. Since every cell in our body contains mitochondria, there is no limit to the potential issues.

Currently, Will's biggest issues include:

- Due to the brain damage from the disease, Will struggles to maintain body balance. Will has weekly physical therapy and occupational therapy to help strengthen his muscles and learn safe ways to move his body. Will has worn leg braces since he was 18 months old. His ataxia and gross motor skills have continued to decline to the point of a very scary head wound which required 9 stitches.
- His immune system doesn't work the same way as others leaving him immunocompromised. He is on a weekly subQ infusion, Hizentra, to help keep him healthy. He has been on this drug for 5 years.
- Will's GI system doesn't work well resulting in constipation. He takes a cap of miralax every day and a probiotic.
- Will has been receiving EPI-743, a trial drug which is supposed to help increase ATP/energy production. He has been on this drug for 7 years. The major changes we noticed was an increase in his verbal skills,

his toes were previously pigeon toed, but his feet turned straight. We believe it has helped slow the disease, but we do not know for sure.

- Will's central nervous system is also affected. He lacks the proper fight/flight response and has extreme worry over a variety of seemingly normal issues. He is on 100 mg. of Zoloft.
 - He is unable to cool his body, living in Houston Texas that's a bit of a problem. He uses a cooling vest to help for short periods of time while outside in the heat.

In general, we work to make sure Will has a healthy diet / good nutrition, access to immediate care should he become sick, proactive measures such as quarterly lab and urine analysis as well as check-ins with: neurology, immunology, pulmonology, cardiology and palliative care.

Of the many issues, we have focused on the symptoms we can actually "fix" – his immune system. Often times he can avoid the common cold, but would have an extreme illness, usually a viral illness in his cerebellum resulting in brain inflammation and brain cell death. Before starting and getting the correct dose of Hizentra he was hospitalized 2 – 4 times per year usually for a week at a time. Time in the hospital creates a large setback for Will's physical and emotional health. His physical abilities drop significantly, his emotions are highly irregular and it taxes our entire family. Now, it's been three years since he was admitted for an illness.

This has been a HUGE game changer for Will and our family. He's able to attend a special school and be around other children his age. He attends birthday parties at those germ filled inflatable places, he is able to have friends over to play and most importantly, he's able to attend sports games to watch his favorite team the Texas Longhorns. Thankfully, the Hizentra continues to work and we modify the dosing as he gets older and as his IGG labs show the need.

However, the downside of the subQ infusion of Hizentra is that it takes nearly three hours to complete. So, for a large period of time every weekend, Will is confined to the couch for two – three hours while his infusion happens. He hates the needles; he hates sitting there and every week he wishes he didn't have to do it. Every weekend he asks if he can skip. And every weekend I have to say no.

An ideal treatment would give Will a chance to lead a more normal, independent life – instead of having an adult wipe his bottom or give him a bath or cut his food up - he could do it. Just like the immune system medicine has done for his life, a treatment for ataxia would give him a chance to participate more fully in something as simple as personal hygiene and maybe even play baseball instead of just watching. Will's body and brain do not have the time to wait for a cure; but he would benefit from drug development for ataxia.

Thank you for your time and for your compassion. Our son has battled more in his short life than most adults. He, along with his mito friends, deserve a chance at a better quality of life and a viable treatment for ataxia would be a good start.

Cheryl P

Good afternoon. My name is Cheryl P. My husband and I have 5 children and live in Atlanta, GA. In 2009, my middle son David was 22 years old and finishing up his second year of college when he began to experience vision problems and dizziness. After visits to many doctors, a neurologist requested an MRI which showed lesions on David's brainstem.

Within 2 months of his first symptoms, David was diagnosed with Leigh's Syndrome, Surf 1 mutation and given no hope for a future. David had worsened tremendously during this time period and was confined to a wheelchair. He could no longer walk, see or take care of his most basic needs. Our world, and his, had been turned upside down. At

that time the only treatment available was the Mito cocktail which is a combination of supplements and we began David on a regime of CoQ-10, L-Carnitine and B vitamins. After further testing, it was discovered that David had a cerebral folate deficiency, and the drug Leucovorin was added.

After 6 months of Leucovorin and the Mito cocktail, David began to regain his eyesight and some mobility. He learned to walk again, although quite unsteadily, and could help care for his personal needs. We were told that at any time a virus or stress to his system could cause the lesions to grow and cause another Mito crash. Although we were very grateful for David's improvement, we always felt like we were walking on eggshells, waiting for the next crash. We also had to grieve the person that we had lost. The lesions in David's brain had affected his personality to the point that he was and is no longer the same person. He has cognitive issues and struggles with fitting in with peers and still experiences extreme instability.

While we were told that nothing could be done, I began to hear about a new drug going through Phase 1 Clinical Trial developed by Edison Pharmaceuticals called EPI-743. David did not fit the protocol for the trial because he was too old. In 2013 it was agreed that David could receive the trial drug on a "Compassionate Use" basis. We were elated! At last, a tiny degree of hope.

In March of 2013 David received his first dose of EPI-743 at Stanford Medical Center in Palo Alto California. His dose was doubled 6 months later, and he continues on that same dose today. EPI-743 proposes to increase the glutathione uptake in the brain. After the first 13 weeks, our nuclear brain spect showed significantly increased uptake.

The reality of what I have seen in David is that he has improved during the past 5 years that he has taken EPI-743. We had to come off of CoQ-10 in order to take EPI-743. David saw a radical increase in muscle pain and terrible muscle weakness. Within 2-3 months of being on EPI-743, he was back to baseline as far as pain and weakness. In other words, EPI-743 worked as well as COQ-10 for David in these areas. However, we feel that he has surpassed where he was on CoQ-10 and experiences even less muscle pain and weakness and we have seen a slight increase in cognitive ability.

David still continues to take EPI-743, Leucovorin, L-Carnitine and B Vitamins. He is able to exercise which has increased his strength and stamina. He is able to endure longer periods of time walking and standing; things that he could hardly do at all before. Interestingly enough, all of this has done absolutely NOTHING for his gait and his balance. Two repeated MRIs have shown complete stability of the lesions with no growth at all.

David is not able to drive due to his neurological condition and, without significant changes, will never be able to. This is the number one factor that affects his life. In an ideal world, David would love to be able to drive again. We would love to see drugs approved that can decrease or heal the lesions in his brain thereby allowing him to process correctly and drive again. We are firm believers in the effectiveness of EPI-743. Recently we took a trip and did not bring enough of the drug with us. David did not take the correct dosage for 4 days. The resulting muscle pain and weakness was severe. And the lessening of it after returning to the correct dosage was remarkable.

Thank you for paying attention to how this disease affects our reality. We always try to remember that David is doing better than any medical professional ever promised and we can see that where there was no hope for a future, there just may be.

Gwen L

We welcomed our fourth son into the world on December 6, 2013. Joshua joined his three older brother Jacob, Gabriel, and Ben. When Joshua was not walking independently by fifteen months of age we knew that he was delayed. I enrolled Joshua in physical therapy when he was sixteen months old, and while he made progress he really struggled to walk. He did walk independently at 20 months but continued to fall down frequently. I took him to a pediatric neurologist just before his second birthday and the neurologist recommended an MRI. The MRI findings were devastating; Joshua has Leigh's disease that genetic testing confirms is caused by a pyruvate dehydrogenase deficiency.

Joshua has DLD deficiency, a single gene disorder with a G to an A base pair switch that results in his body producing a poorly functioning DLD protein. The DLD protein is needed for metabolism and Joshua's condition affects his body's ability to produce energy. As a result of his metabolic condition Joshua has Leigh's syndrome – central nervous system cell damage due to insufficient energy production. Joshua has bilateral damage to the basal ganglia region in his brain that directly affects his balance and motor coordination. He suffers from low energy, global muscle weakness, and chronic ataxia or unsteady walking. We live in fear of disease progression, as it is often central nervous system cell death in brain regions needed for respiration that can cause children with Leigh's disease to die.

Joshua is now four years old and has been relatively stable since his diagnosis at age two. We are currently addressing Joshua's global weakness and poor balance with regular physical therapy and occupational therapy to continue to build his strength. Joshua participates in weekly physical therapy sessions and we built a gym in our home where we practice the exercises that his physical therapist recommends. We have to adjust Joshua's physical therapy routine based on his state of health and his energy level when he is sick. Modifications often include easier exercises and shortened sessions. Joshua's occupational therapist will encourage him to lie down on a beanbag chair to rest if he is fatigued. Fortunately, we have had two to four-month intervals where Joshua remains healthy. When Joshua is sick or fatigued he does not have the strength needed to carry out his regular routine. It can take as long as one month for Joshua to recover his strength and stamina after a viral illness.

Joshua takes prescribed vitamins and supplements that are monitored by his mitochondrial medicine doctors. We started Joshua on supplements immediately after learning of his genetic diagnosis and noticed that his stamina and balance both improved. His gait was steadier with fewer falls. Joshua currently takes B vitamins, N-acetyl cysteine, Alpha Lipoic Acid, and vitamin E. We have also given him trials of arginine and carnitine. Many of the compounded vitamin preparations are noxious. When we added arginine to Joshua's supplements he started gagging and regularly vomited up his supplement. We have also observed a shift in his lab work with Joshua's initial serum lactic acid level significantly elevated at the time of diagnosis and six months into his supplement regimen Joshua's lactic acid level was closer to a normal range.

We are only two years into managing Joshua's condition. We remain fearful that his central nervous system cells are vulnerable to incremental cell death and damage that further impact Joshua's functioning. As Joshua grows bigger his ataxia is becoming more of a concern since he has further to fall and would also be at risk for further energy deficiencies on a cellular level if he is injured from falling. We do not currently have any treatment that addresses Joshua's poor balance or any treatment that we are confident protects his central nervous system from additional damage.

Some of the challenges that we face with Joshua's treatments are financial burden, increased caregiver burden, and stress for Joshua. The vitamin formulation has a noxious taste that cannot be masked by flavoring. Joshua shudders when he sees his vitamin supplements that he has to take both morning and night. We coax him to take the vitamins with juice and reward him with treats. He is now in a routine of taking the vitamin supplements yet requires daily coaching. It is hard to watch him grimace and shudder each time he sees the syringe filled with his supplement.

An ideal treatment for Joshua would of course cure Joshua's DLD deficiency. We have been following the field of gene therapy and hope that this can one day be a possible treatment for Joshua. Additional possible options are enzyme replacement therapy to introduce a functional DLD protein into Joshua's system, and investigational compounds that boost mitochondrial functioning.

We are hopeful that if we can preserve Joshua's current state of health while science advances that he can grow and develop into a healthy young man. Joshua is a joyful four-year-old boy who fills our home with happiness.. Our family has been blessed with a motivated clinical team at the Children's Hospital of Philadelphia. We are all working together to learn about Joshua's condition and seek out both potential treatments and cures.

Anne T

Good afternoon, my name is Anne T. I am from Alexandria, Virginia. Thank you for the opportunity to speak with you this afternoon. Before I move forward with my remarks, I'd like to first share with you some insight into the reason why I care so much. His name is Bryan.

Bryan is our 26-year old son who was diagnosed at age 4 with Leigh's Syndrome, a maternally inherited form of mitochondrial disease. Although diagnosed at age four, we knew that something wasn't quite right with our son from very early in his little life. Despite a very grim prognosis, Bryan continues to outlive his doctor's predictions. He is my hero, and his perseverance, kind spirit and positive attitude are in my opinion the most effective treatment option available to him. Bryan's daily challenges include developmental delays, visual impairment, difficulty walking, muscle fatigue, low muscle tone, difficulty swallowing and chewing his food. Remarkably, he remains positive and hopeful. My husband and I realize that as we grow older and our son's disease continues to progress it is imperative that treatments and drug therapies with great potential for slowing or eliminating mitochondrial diseases need to be found.

In our experience with Bryan, treatment is focused on addressing specific symptoms, e.g., seizure control, gastro-intestinal, and neurologic, and so on. Since Bryan was diagnosed he has taken some form of a mitochondrial cocktail compounded at a special pharmacy and comprised of Co Q 10, L-Carnitine and B vitamins. Bryan takes two OTC medications Prilosec and Zantac twice a day to help control the frequent and debilitating bouts of acid reflux. To treat neuropathy in his lower limbs and feet, Bryan has taken Neurontin for over 20 years which provides moderate relief from the tingling and numbness in his legs and feet. Currently, there are no known medical interventions to address his retinopathy that has left him legally blind.

During Bryan's adolescent years when his body was undergoing major hormonal and growth changes he developed a seizure disorder and was treated with Tripletal twice a day. Thankfully, Bryan experienced his last seizure over five years ago and tapered off seizure medication. Bryan continues to have low levels of essential amino acids, typical for patients with mitochondrial diseases. We mix a powdered form of L-Cutrulline into his morning beverage each day. As the disease continues its progression, Bryan's muscle tone in his mouth, throat and esophagus has decreased leaving him at risk for choking and aspirating thin liquids. Therefore, caution must be taken around meal times as beverages need to be thickened to the consistency of nectar and food must be cut into small pieces to prevent choking. Meal times and going out to eat can be challenging.

It is difficult to determine how well the current treatments are working to addressing Bryan's most significant symptoms. I feel that many of the treatments serve as a band aid, cobbled together to address immediate concerns, but without making any lasting progress towards slowing the progression of the disease or reversing the damage already caused. Can we attribute Bryan outliving the prognosis we received from his doctors in 1996 from this band aid approach or from the other more holistic approaches we've employed (physical activity, nutrition, social engagement, and his overall positive outlook/attitude?) The answer is we are not sure. With so few treatment

options, we have no choice but to stick with this band aid approach with the hope new treatment options become available.

When thinking about the approaches to treating mitochondrial disease, there are also downsides to the treatments and side effects from medications that mitochondrial disease patients experience. The individual medications used to address the symptoms that manifest from the disease each have their own set of side effects, some are manageable, and some may not be worth sacrificing one's quality of life.

As Bryan's primary caregivers we constantly weigh the benefits of continuing with treatments that address only the symptoms but have little impact on tackling the condition. Keeping up with medication schedules, side effects of multiple drugs, the costs of customized cocktails and supplements, therapies, and medical appointments is a full-time job and impacts our entire family.

So short of a cure, if I could envision what an ideal treatment would look like, I see two things. First, I would like to see development of a treatment and/or a disease modifying drug to slow the progression of mitochondrial diseases, similar to Tecfidera used for patients with Multiple Sclerosis. Second, any potential new drug should also seek to repair damaged mitochondria so that organs, systems and other bodily functions could rejuvenate with the influx of healthier and more powerful mitochondria. If such a treatment option or new drug was developed, I feel the potential for our son to have improved vision, care for his personal needs, walk without assistance, or live independently someday. Restoring dignity for patients like my son and so many other is so important. No one wants to be showered, assisted in the restroom and fed by their parents. It is humiliating experience for a 26-year old young man or anyone to endure. Implementing small steps to improve Bryan's quality of life could sustain him until a cure is found.

Thank you for the opportunity to provide my input into this very important process.

APPENDIX 3 – DETAILS OF POLLING QUESTIONNAIRES

Polling Questions – Perspectives from Adults with Mitochondrial Myopathy

Which of the following best describes you?

- I am an adult with a mitochondrial myopathy
- I am a caregiver of an adult with a mitochondrial myopathy (or have lost a loved one)
- I am a parent/caregiver of a child who has a neurologic manifestation with mitochondrial disease (or have lost a loved one)
- I am none of the above.

Demographics

1. Where do you currently reside?
 - a. US Pacific (AK, CA, HI, OR, WA)
 - b. US West and Mountain (AZ, CO, ID, MT, NM, NV, UT, WY)
 - c. US Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, WI)
 - d. US South (AL, AR, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)
 - e. US Northeast and New England (CT, NH, NJ, NY, MA, ME, PA, RI, VT)
 - f. Canada
 - g. Mexico
 - h. Asia
 - i. Africa
 - j. Australia
 - k. Europe
 - l. South America
2. Do you live in
 - a. a city
 - b. a rural area
 - c. a suburban area
3. How old is the patient now?
 - a. 18-20 years old
 - b. 21-30 years old
 - c. 31-40 years old
 - d. 41-50 years old
 - e. > 50 years old
4. At what age was the patient diagnosed with mitochondrial disease?
 - a. 0-10 years old
 - b. 11-17 years old
 - c. 18-20 years old
 - d. 21-30 years old
 - e. 31-40 years old
 - f. > 40 years old

Mitochondrial Disease Adult Patients with Myopathies – Symptoms and Daily Impact

1. Please select the answer that best describes the stage of disability for you or the person for whom you care.
 - a. Minimal disability. Able to run or jump.
 - b. Symptoms present but mild, able to walk and capable of leading independent life.
 - c. Symptoms are significant. Require regular or periodic holding on to wall or another person for stability and walking.
 - d. Walking requires a walker or other aid such as a service dog. May use a wheelchair or scooter for some activities or to conserve energy. Can perform several activities of daily living. Ability may vary from day to day.
 - e. Not able to walk, uses a wheelchair exclusively. Can perform some activities of daily living that do not require standing or walking.
 - f. Severe disability, dependency on others for assistance with all activities of daily living.
 - g. If any additional comments, please feel free to share
2. Please select the answer that best describes your ability to carry out daily activities
 - a. Normal – no limitations
 - b. Unlimited walking on flat, but symptomatic on inclines or stairs.
 - c. Able to walk < 12 city blocks on the flat, (or 1 mile) but restricted on

- inclines or stairs (rest needed after 12 steps on stairs)
 - d. Able to walk < 6 city blocks on the flat, (or 1/2 mile) Rest needed after 8 steps on stairs.
 - e. Able to walk < 1.5 city blocks on the flat (or 1/8 mile) Rest needed after 4 steps on stairs.
 - f. Able to walk < 100 feet on the flat. Unable to do stairs alone.
 - g. Not able to walk, uses a wheelchair exclusively. Can perform some activities of daily living that do not require standing or walking.
 - h. Additional Comments:
3. Select the mitochondrial disease symptoms that most impact your daily quality of life. Select up to 5.
- a. Chronic Fatigue (including tiredness, excessive sleeping, brain fog or mental fatigue)
 - b. Muscle Weakness
 - c. Gastrointestinal Problems (Gastroparesis, acid reflux, constipation, diarrhea, nausea, GI pain)
 - d. Exercise Intolerance
 - e. Sleep Difficulties (sleep apnea, insomnia, restless leg syndrome, narcolepsy)
 - f. Dysautonomia (Autonomic nervous systems problems, dizziness, difficulty with temperature modulation, low blood sugar, blood pressure issues)
 - g. Headache (including migraine headaches)
 - h. Pain (including Nerve Pain, Numbness, neuropathy, muscle pain, joint pain)
 - i. Peripheral Neuropathy
 - j. Eye Muscle Problems (including droopy eyelids, limited eye movement)
 - k. Mental Health Concerns (depression, anxiety, bipolar disorders, mood disorders)
 - l. Balance Problems
 - m. Impaired Vision
 - n. Dehydration
 - o. Delayed Milestones (including developmental delays)
 - p. Speech Problems
 - q. Swallowing Difficulties
 - r. Difficulty Maintaining Ideal Weight
4. As mitochondrial disease progresses, development or progression of which of the following symptoms worries you the most? Select up to 5.
- a. Chronic Fatigue (including tiredness, excessive sleeping, brain fog or mental fatigue)
 - b. Muscle Weakness
 - c. Gastrointestinal Problems (Gastroparesis, acid reflux, constipation, diarrhea, nausea, GI pain)
 - d. Exercise Intolerance
 - e. Sleep Difficulties (sleep apnea, insomnia, restless leg syndrome, narcolepsy)
 - f. Dysautonomia (Autonomic nervous systems problems, dizziness, difficulty with temperature modulation, low blood sugar, blood pressure issues)
 - g. Headache (including migraine headaches)
 - h. Pain (including Nerve Pain, Numbness, neuropathy, muscle pain, joint pain)
 - i. Peripheral Neuropathy
 - j. Eye Muscle Problems (including droopy eyelids, limited eye movement)
 - k. Mental Health Concerns (depression, anxiety, bipolar disorders, mood disorders)
 - l. Balance Problems
 - m. Impaired Vision
 - n. Dehydration
 - o. Delayed Milestones (including developmental delays)
 - p. Speech Problems
 - q. Swallowing Difficulties
 - r. Difficulty Maintaining Ideal Weight

- s. Heart Rhythm Problems
 - t. From the patient's perspective, please explain why these five symptoms are most worrisome. If your top symptoms are not listed, please share here.
5. What specific activities of daily life are most important to you that you (or the person for whom you care) are NOT able to do because of mitochondrial disease? Select TOP 3.
- a. Understanding conversation in noisy settings
 - b. Driving
 - c. Communication - speaking with others and being understood
 - d. Personal hygiene, taking a shower, bathing or dressing independently
 - e. Moving around independently and safely
 - f. Writing and typing
 - g. Feeding oneself, cutting food and handling utensils
 - h. Walking and standing independently
 - i. Manipulating small objects (e.g., a key, picking up items)
 - j. Reading books, seeing a computer screen or phone
 - k. Sitting unaided
 - l. Transferring independently (e.g. from wheelchair/scooter to bed, toilet, etc.)
 - m. Explain why these are important to the patient. Share any additional activities that are important to the patient and not listed.
6. As a result of living with mitochondrial disease, which of the following social, emotional or economic consequences are most significant to you? Select up to 4.
- a. Loss of hobbies or activities
 - b. Social isolation
 - c. Frustration
 - d. Depression and/or anxiety
 - e. Financial difficulties
 - f. Loss of job or inability to get a job
 - g. Trouble building or maintaining relationships
 - h. Lack of hope for the future
 - i. Loss of independence
 - j. Modified work/school hours
 - k. Communication issues
 - l. Explain why these are significant to the patient. Share any additional information that is not listed.
7. How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days? (if you are the caregiver, please provide information from patient's perspective)
8. How has your condition and its symptoms changed over time? (if you are the caregiver, please provide information from patient's perspective).
9. Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse? (if you are the caregiver, please provide information from patient's perspective).

Mitochondrial Disease Adult Patients with Myopathies – Current and Future Approaches to Treatment

1. What PRESCRIPTION MEDICATIONS do you take now to treat symptoms of your mitochondrial disease? Select ALL that apply.
 - a. Pain medications
 - b. Heart medications
 - c. Antidepressants or anti-anxiety medications
 - d. Muscle relaxants
 - e. Intravenous Immunoglobulin therapy (IVIg)
 - f. Diabetes medications
 - g. Experimental medications as a part of a clinical trial
 - h. Other prescription medications not listed
 - i. Nothing
 - j. Please list other prescription medications not listed
2. What VITAMINS or SUPPLEMENTS do you take now to treat symptoms of your mitochondrial disease? Select ALL that apply.
 - a. CoQ10
 - b. Carnitine
 - c. Riboflavin
 - d. Creatine
 - e. Vitamin E
 - f. Alpha lipoic acid

- g. Vitamin B3, Nicotinamide or Niacin
 - h. Idebenone
 - i. Nothing
 - j. Please list other supplements or vitamins not listed
3. Please further explain what specific symptoms your treatments address.
 4. What are you currently doing to help manage mitochondrial disease or mitochondrial disease symptoms? Select ALL that apply.
 - a. Choice of diet
 - b. Modifications/accommodations at work/in school/at home
 - c. Physical therapy, including aqua or hippo therapy
 - d. Stretching
 - e. Use of adaptive devices
 - f. Exercise (cardio or strength training)
 - g. Mental health services
 - h. Occupational therapy
 - i. Speech therapy
 - j. Nothing
 - k. Please list other ways you manage your condition.
 5. Which surgical procedures have you undergone to treat or manage symptoms of mitochondrial disease? Select ALL that apply
 - a. G Tube/GJ Tube placement for nutrition
 - b. Baclofen pump insertion
 - c. Cochlear implants
 - d. Central Line insertion
 - e. None
 - f. Other
 6. In general, how much do the medications, therapies or lifestyle changes used improve your quality of life?
 - a. No benefit
 - b. Helped somewhat
 - c. Helped a lot
 - d. Significant benefit
 - e. Not sure
 - f. Please describe how your medications and/or treatments have helped or not helped.
 7. How has your treatment regimen changed over time, and why?
 8. How well have these treatments worked for you as your condition changed over time?
 9. Which outcomes would be meaningful to you for a possible drug treatment? Select ALL that apply
 - a. Slowing/stopping of progression (even if no gain in function, symptoms won't get worse)
 - b. Gain in function (e.g., energy, strength, mobility, dexterity, cardiac function, speech)
 - c. Prolong life
 - d. Please explain why these are most meaningful and include additional outcomes not listed.
 10. Which ability or symptom would you rank as most important for a possible drug treatment today? Select up to 3.
 - a. Reduced Chronic Fatigue (including tiredness, excessive sleeping, brain fog or mental fatigue)
 - b. Reduced Muscle Weakness
 - c. Reduced Gastrointestinal Problems (Gastroparesis, acid reflux, constipation, diarrhea, nausea, GI pain)
 - d. Reduced Exercise Intolerance
 - e. Reduced Sleep Difficulties (sleep apnea, insomnia, restless leg syndrome, narcolepsy)
 - f. Reduced Dysautonomia (Autonomic nervous systems problems, dizziness, difficulty with temperature modulation, low blood sugar, blood pressure issues)
 - g. Reduced Headaches (including migraine headaches)
 - h. Reduced Pain (including Nerve Pain, Numbness, neuropathy, muscle pain, joint pain)
 - i. Reduced Peripheral Neuropathy
 - j. Reduced Eye Muscle Problems (including droopy eyelids, limited eye movement)
 - k. Reduced Mental Health Concerns (depression, anxiety, bipolar disorders, mood disorders)
 - l. Improved Balance Problems
 - m. Improved Vision
 - n. Improved Hydration

- o. Improved Meeting Milestones (including reduced developmental delays)
 - p. Reduced Speech Problems
 - q. Reduced Swallowing Difficulties
 - r. Maintaining Ideal Weight
 - s. Reduced Heart Rhythm Problems
 - t. Please explain why these are most important to you.
11. Which of the following factors would influence your decision to take a new medication or participate in a clinical trial or research study? Select ALL that apply.
- a. Significant risks of serious side effects such as cardiac or kidney issues
 - b. Cost
 - c. The burden of administration, such as the need for anesthesia, radiation exposure, surgical procedure, etc.
 - d. Common side effects of the treatment, such as nausea, loss of appetite, headache etc.
 - e. Travel
 - f. How long the treatment takes, whether it requires hospitalization, required doctor's visits, etc.
 - g. Changing my current treatment or management plan (stopping a medication or supplement, stopping exercise)
12. Short of a cure for your mitochondrial disease, what specific things would you look for in an ideal treatment for your condition?
- h. The way that treatment is administered (for example, orally, intravenously, subcutaneous)
 - i. None of these
 - j. Please explain why these influence your decision and any additional comments.
-

EL-PFDD Polling Questions – Perspectives from Pediatric Patients and Caregivers on Neurologic Manifestations in Children

Which of the following best describes you?

- I am an adult with a mitochondrial myopathy
- I am a caregiver of an adult with a mitochondrial myopathy (or have lost a loved one)
- I am a parent/caregiver of a child who has a neurologic manifestation with mitochondrial disease (or have lost a loved one)
- I am none of the above.

Demographics

1. Where do you currently reside?
 - a. US Pacific (including California)
 - b. US West and Mountain
 - c. US Midwest
 - d. US South (including Texas)
 - e. US Northeast and New England
 - f. Canada
 - g. Mexico
 - h. Outside of North America
 - i. Other
 2. Do you live in
 - a. a city
 - b. a rural area
 - c. a suburban area
 3. How old is the patient now?
 - a. 0-10 years old
 - b. 11-17 years old
 - c. 18-20 years old
 - d. 21-30 years old
 - e. > 30 years old
 4. At what age was the patient diagnosed with mitochondrial disease?
 - a. 0-10 years old
 - b. 11-17 years old
 - c. 18-20 years old
 - d. 21-30 years old
 - e. > 30 years old
- d. Walking requires a walker or other aid such as a service dog. Can perform several activities of daily living. May use a wheelchair for certain tasks.
 - e. Not able to walk, requires a wheelchair fulltime, can perform some activities of daily living that do not require standing or walking.
 - f. Severe disability, dependency on others for assistance with all activities of daily living.
 - g. If any additional comments, please feel free to share.
2. Select the mitochondrial disease symptoms that most impact the patient's daily quality of life. Select up to 5.
 - a. Muscle Weakness
 - b. Fatigue (tiredness, excessive sleeping, brain fog, mental fatigue, exhaustion)
 - c. Exercise Intolerance
 - d. Pain (neuropathy, numbness, muscle pain)
 - e. Gastrointestinal Problems (dysmotility , gastric reflux, constipation, diarrhea)
 - f. Impaired Vision (loss of central vision, low vision, blindness)
 - g. Movement Disorders (chorea, tremors, dystonia)
 - h. Seizures
 - i. Eye Muscle Problem (droopy eyelids (ptosis), double vision, decreased eye movement)
 - j. Delayed Milestones
 - k. Speech Problems
 - l. Swallowing difficulties

Pediatric Mitochondrial Disease Patients (Neuro) – Symptoms and Daily Impact

1. Please select the answer that best describes the patient's stage of disability.
 - a. Minimal disability. Able to run or jump.
 - b. Symptoms present but mild, able to walk and capable of leading independent life.
 - c. Symptoms are overt and significant. Require regular or periodic holding on to

- m. Mental Health Concerns (depression, anxiety, bipolar disorder, mood disorder)
 - n. Dysautonomia (Autonomic nervous systems problems, flushing, tachycardia, dizziness, balance, etc.)
 - o. Learning Disability
 - p. Maintain healthy weight
 - q. Hearing Loss
 - r. Headache including migraine headaches
 - s. Kidney/Liver/Heart Disease including Heart Rhythm problems
 - t. From the patient's perspective, please share how these five symptoms impact daily life. If your child's symptoms are not listed, please share here.
3. As mitochondrial disease progresses, development or progression of which of the following symptoms worries you the most? Select up to 5.
- a. Muscle Weakness
 - b. Fatigue (tiredness, excessive sleeping, brain fog, mental fatigue, exhaustion)
 - c. Exercise Intolerance
 - d. Pain (neuropathy, numbness, muscle pain)
 - e. Gastrointestinal Problems (dysmotility, gastric reflux, constipation, diarrhea)
 - f. Impaired Vision (loss of central vision, low vision, blindness)
 - g. Movement Disorders (chorea, tremors, dystonia)
 - h. Seizures
 - i. Eye Muscle Problem (droopy eyelids (ptosis), double vision, decreased eye movement)
 - j. Delayed Milestones
 - k. Speech Problems
 - l. Swallowing difficulties
 - m. Mental Health Concerns (depression, anxiety, bipolar disorder, mood disorder)
 - n. Dysautonomia (Autonomic nervous systems problems, flushing, tachycardia, dizziness, balance, etc.)
 - o. Learning Disability
 - p. Maintain healthy weight
 - q. Hearing Loss
 - r. Headache including migraine headaches
 - s. Kidney/Liver/Heart Disease including Heart Rhythm problems
 - t. From the patient's perspective, please explain why these five symptoms are most worrisome. If your child's top symptoms are not listed, please share here.
4. What specific activities of daily life are most important to the patient and is NOT able to do because of mitochondrial disease? Select TOP 3.
- a. Gross motor activities such as moving around independently and safely, walking and standing. Participating in sports, recreational activities. Transferring independently (e.g. from wheelchair/scooter to bed, toilet, etc.)
 - b. Communication – speaking with others and being understood. Social interaction, social engagement. Understanding conversation in noisy settings
 - c. Fine motor activities such as feeding oneself, cutting food, handling utensils, picking up small items, writing or typing
 - d. Sitting unaided
 - e. Driving
 - f. Personal Hygiene, taking a shower, bathing or dressing independently
 - g. Reading books, seeing a computer screen or phone
 - h. Going to school or work
 - i. Explain why these are important to the patient. Share any additional activities that are important to the patient and not listed.
5. As a result of living with mitochondrial disease, which of the following social, emotional or economic consequences are most significant to the patient? Select up to 4.
- a. Depression and/or Anxiety
 - b. Frustration
 - c. Social isolation
 - d. Communication issues
 - e. Loss of independence
 - f. Loss of hobbies or activities
 - g. Loss of job or inability to get a job
 - h. Modified work/school hours

- i. Trouble building or maintaining relationships
 - j. Lack of hope for the future
 - k. Financial difficulties
 - l. Explain why these are significant to the patient. Share any additional information that is not listed.
6. How do your child's symptoms and their negative impacts affect his/her daily life on the best days? On the worst days? (if you are the caregiver, please provide information from patient's perspective).
 7. How has your child's condition and its symptoms changed over time? (if you are the caregiver, please provide information from patient's perspective).
 8. Do your child's symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse? (if you are the caregiver, please provide information from patient's perspective).

Pediatric Mitochondrial Disease Patients (Neuro)

– Current and Future Approaches to Treatment

1. What prescription medications does the patient take now to treat symptoms for mitochondrial disease? Select ALL that apply.
 - a. Pain medications (e.g. Neurontin/gabapentin, Cymbalta, Lyrica, opioids etc.)
 - b. Heart medications (e.g. beta blocker, ACE-inhibitor, calcium channel blocker, diuretic, anti-arrhythmic, anti-coagulant)
 - c. Antidepressants or anti-anxiety medications
 - d. Muscle relaxants (e.g. Baclofen, Chlorzaxazone, Botox, medical marijuana etc.)
 - e. Intravenous Immunoglobulin therapy (IVIg)
 - f. Seizure medications
 - g. Diabetes medications
 - h. Experimental medications as a part of a clinical trial
 - i. Other prescription medications not listed
 - j. Nothing
 - k. Please list other prescription medications not listed
2. What vitamins or supplements does the patient take now to treat symptoms of your mitochondrial disease? Select ALL that apply.
 - a. CoQ10
 - b. Carnitine
 - c. Riboflavin
 - d. Creatine
 - e. Vitamin E
 - f. Alpha lipoic acid
 - g. Vitamin B3, Nicotinamide or Niacin
 - h. Idebenone
 - i. Nothing
 - j. Please list other supplements or vitamins not listed
3. Please further explain what specific symptoms your treatments address.
4. What is the patient currently doing to help manage mitochondrial disease or mitochondrial disease symptoms? Select ALL that apply.
 - a. Physical therapy, including aqua or hippo therapy and stretching
 - b. Modifications/accommodations at work/in school/at home
 - c. Occupational therapy
 - d. Use of adaptive devices
 - e. Speech therapy
 - f. Exercise (cardio or strength training)
 - g. Mental health services
 - h. Nutritional Modifications including G-tube, J-Tube and TPN.
 - i. Other
 - j. Nothing
 - k. Please list other ways you manage your condition.
5. Which surgical procedures has the patient undergone to treat or manage symptoms of mitochondrial disease? Select ALL that apply.
 - a. G Tube/GJ Tube placement for nutrition
 - b. Baclofen pump insertion
 - c. Cochlear implants
 - d. Central Line insertion
 - e. Other
 - f. None
6. In general, how much do the medications, supplements, therapies or lifestyle changes used improve your child's quality of life?
 - a. No benefit
 - b. Helped somewhat
 - c. Helped a lot

- d. Significant benefit
 - e. Not sure
 - f. Please describe how your medications and/or treatments have helped or not helped.
7. How has your child's treatment regimen changed over time, and why?
 8. How well have these treatments worked for your child as his/her condition changed over time?
 9. Which outcomes would be meaningful to the patient for a possible drug treatment? Select ALL that apply
 - a. Slowing/stopping of progression (even if no gain in function, symptoms won't get worse)
 - b. Gain in function (e.g. energy, strength, mobility, dexterity, cardiac function, speech)
 - c. Prolong life
 - d. Please explain why these are most meaningful and include additional outcomes not listed.
 10. Which ability or symptom would the patient rank as most important for a possible drug treatment today? Select up to THREE options.
 - a. Reduced Muscle Weakness
 - b. Reduced Fatigue (tiredness, excessive sleeping, brain fog, mental fatigue, exhaustion)
 - c. Reduced Exercise Intolerance
 - d. Reduced Pain (neuropathy, numbness, muscle pain)
 - e. Reduced Gastrointestinal Problems (dysmotility, gastric reflux, constipation, diarrhea)
 - f. Improved Vision (loss of central vision, low vision, blindness)
 - g. Reduced Movement Disorders (chorea, tremors, dystonia)
 - h. Reduced Seizures
 - i. Reduced Eye Muscle Problem (droopy eyelids (ptosis), double vision, decreased eye movement)
 - j. Improved Meeting Milestones
 - k. Improved Speech
 - l. Reduced Swallowing difficulties
 - m. Reduced Mental Health Concerns (depression, anxiety, bipolar disorder, mood disorder)
 - n. Reduced Dysautonomia (Autonomic nervous systems problems, flushing, tachycardia, dizziness, balance, etc.)
 - o. Reduced Learning Disability
 - p. Maintain healthy weight
 - q. Reduced Hearing Loss
 - r. Reduced Headache including migraine headaches
 - s. Reduced Kidney/Liver/Heart Disease including Heart Rhythm problems
 - t. Other
 - u. Please explain why these are most important to you.
 11. Which of the following factors would influence your decision, on behalf of your child, to take a new medication or participate in a clinical trial or research study? Select ALL that apply.
 - a. Significant risks of serious side effects (cardiac, kidney issues, etc.)
 - b. Common side effects of the treatment (nausea, headaches, etc.)
 - c. The way that treatment is administered (orally, intravenously, subcutaneous)
 - d. Length of treatment, requires hospitalization, frequent doctor visits, etc.
 - e. Burden of administration (need for anesthesia, radiation exposure, surgery, etc.)
 - f. Changing my current treatment or management plan (stopping a medication, supplement, or exercise)
 - g. Cost and/or travel
 - h. None of these
 - i. Other
 - j. Please explain why these influence your decision and any additional comments.
 12. Short of a cure for your child's mitochondrial disease, what specific things would you look for in an ideal treatment for his/her condition?