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Note: Please do not cast a response through the poll platform if you are not an adult who has been diagnosed with Mitochondrial Myopathy or the parent designee representing a child who has a Neurologic Manifestation with Mitochondrial Disease or a deceased individual. No more than one vote should be cast for each individual who has Mitochondrial Myopathy or Neurologic Manifestation of Mitochondrial Disease. Standard message and data rates apply.
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Brian Harman
President and CEO,
United Mitochondrial Disease Foundation
SPECIAL THANKS to those whose collaboration made this important meeting possible
SPECIAL THANKS to those whose generous support helped make this meeting possible

EDITH L. TREES CHARITABLE TRUST
SPECIAL THANKS to those whose generous support helped make this meeting possible.
Morning Session: Mitochondrial Myopathy - Adult Patient Perspective on the Burdens of the Disease and Current and Future Approaches to Treatments

Clinical Overview of Mitochondrial Myopathy in Adults
Michio Hirano, MD, Columbia University, New York, NY

Introduction, Overview of Meeting, and Audience and Remote Demographic Polling for Adults with Mitochondrial Myopathies
James Valentine, JD, MHS, Meeting Moderator

Morning Session: Mitochondrial Myopathy - Adult Patient Perspective on the Burdens of the Disease and Current and Future Approaches to Treatments

Panel #1 – Symptoms and Daily Impacts
• Presentations by 5 Affected Individuals and Caregivers
• Audience and Remote Polling Panel #1
• Moderated Audience Discussion Panel #1

Panel #2 – Current and Future Approaches to Treatments
• Presentations by 5 Affected Individuals and Caregivers
• Audience and Remote Polling Panel #2
• Moderated Audience Discussion Panel #2

Morning Session Closing Remarks
Lucas Kempf, MD, U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER), Rare Diseases Program
Clinical Overview of Mitochondrial Myopathy in Adults

Michio Hirano, MD
Columbia University Irving Medical Center
New York, NY
Mitochondria are the powerhouses of the cell.
Mitochondrial diseases are complicated because:

- Mitochondria are required by virtually all cells in the body.
- Mitochondria perform many functions.
- Mitochondria are the products of two genomes: nuclear DNA and mitochondrial DNA (mtDNA).
- There are many mitochondrial diseases.
Interaction between Genes Encoded by Nuclear DNA and Those Encoded by Mitochondrial DNA in Oxidative Phosphorylation
Mitochondrial disease patients reported an average of 16 symptoms.
Mitochondrial morbidity map - 2019

Mutations
Protein synthesis = 158
Polypeptides = 113
Total = 271

Courtesy of E.A. Schon
Mitochondrial DNA Rules

- Maternal inheritance
- Heteroplasmy
- Mitotic Segregation
- Threshold Effect
Kearns-Sayre syndrome (KSS)

- Progressive external ophthalmoplegia
- Pigmentary retinopathy
- Cardiac conduction block
- Myopathy
Myoclonus Epilepsy Ragged-Red Fibers (MERRF)

- Myoclonus epilepsy and ataxia
- Ragged-red fibers
- Other features: peripheral neuropathy, lipomas, short stature, hearing loss, and optic atrophy
Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS)

- Stroke-like episodes at a young age
- Encephalopathy manifesting as seizures, dementia, or both
- Lactic acidosis, ragged-red fibers, or both

T2-MRI
>250 nDNA mitochondrial disease genes and the number is expanding by about 1-2 per month.

Vafai and Mookha, Nature 2012
TK2 deficiency

Early onset: from birth to 30 months
Progressive weakness of skeletal and respiratory muscles
Elevated CK and lactic acid
Mean age of death: 2.6 years
## Disease Spectrum of 92 TK2-deficient Patients

<table>
<thead>
<tr>
<th>Onset</th>
<th>Infantile-onset myopathy</th>
<th>Childhood-onset myopathy</th>
<th>Late-onset myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤12 months</td>
<td>39 (42.4%)</td>
<td>37 (40.2%)</td>
<td>16 (17.4%)</td>
</tr>
<tr>
<td>&gt;1-&lt;12 years-old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥12 years-old</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Symptoms
- Diffuse muscle weakness, early respiratory failure
- Proximal muscle weakness, areflexia
- Muscle weakness

### EMG
- Myogenic +/- neuropathic pattern
- Myogenic +/- neuropathic pattern
- Myogenic pattern

### CK
- ↑↑↑
- ↑↑↑
- normal-↑↑

### mtDNA depletion
- +++
- +++
- +/-

### mtDNA deletions
- –
- –
- +++

### Other signs & symptoms
- seizures 7, encephalopathy 5, cognitive dysfunction 3, ptosis 4, facial diplegia 3, dysphagia 3, multiple bone fractures 2, nephropathy 1, rigid spine 1, coma episodes 1, cardiomyopathy 1, biventricular hypertrophy 1, arrhythmia 1 and esophageal atresia 1
- facial diplegia 11, ptosis 9, PEO 3, hearing loss 2, cognitive decline 1, encephalopathy 1, prolonged QT 1, arrhythmia 1, multiple bone fractures 1, renal tubulopathy 1, and gynecomastia 1
- ptosis 9, PEO 8, dysphagia 6, respiratory insufficiency 5, dysarthria 3, cardiomyopathy 2, gynecomastia 1, Neuropathy 1, Hearing loss 1
Phenotypic diversity of POLG mutations

- Autosomal dominant or recessive PEO (sometimes accompanied by hypogonadism, deafness, myoclonus, dementia, seizures, ataxia, parkinsonism and depression)
- SANDO (sensory ataxic neuropathy, dysarthria, ophthalmoplegia)
- MIRAS (mitochondrial recessive ataxia syndrome)
- Alpers-Huttenlocher syndrome
- Parkinsonism with peripheral neuropathy
- Leigh syndrome
- Axonal CMT
- MNGIE-like disease
- MELAS-like disease
- MERRF-like disease
Mitochondrial diseases are rare, but not so rare

- Among working age adults in the Northeast of England
  - 1 in 5,000 has a mtDNA disease
  - 1 in 34,000 has a mitochondrial nuclear DNA disease
  - Overall, 1 in 4,300 has a mitochondrial disease (Gorman et al. Ann Neurol 2015)

- ~75,000 people in the US have mitochondrial disease
NAMDC
the north american mitochondrial disease consortium

- Columbia University Medical Center
- Akron Children’s Hospital
- Baylor College of Medicine
- Case Western Reserve University School of Medicine
- Children’s Hospital of Colorado
- Children’s Hospital of Philadelphia
- Children’s National Medical Center
- Cleveland Clinic Foundation
- Hamilton Health Sciences
- Massachusetts General Hospital
- Mayo Clinic
- Seattle Children’s Hospital
- Stanford University
- University of California San Diego Medical Center
- University of Florida College of Medicine
- University of Pittsburgh
Myopathy is common among the NAMDC Registry Subjects

• 1066 of 1405 (76%) NAMDC Registry subjects have myopathy.
Primary mitochondrial myopathies (PMM)…genetically defined disorders leading to defects of oxidative phosphorylation affecting predominantly, but not exclusively, skeletal muscle.”
Philip Yeske, PhD
Science and Alliance Officer
United Mitochondrial Disease Foundation
Which of the following best describes you?

I am an affected adult with a mitochondrial myopathy

I am a caregiver for an affected adult with mitochondrial myopathy

I have lost a loved one who was an adult patient with mitochondrial myopathy
<table>
<thead>
<tr>
<th>Where do you currently reside?</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Pacific (including California)</td>
</tr>
<tr>
<td>US West and Mountain</td>
</tr>
<tr>
<td>US Midwest</td>
</tr>
<tr>
<td>US South (including Texas)</td>
</tr>
<tr>
<td>US Northeast and New England</td>
</tr>
<tr>
<td>Canada</td>
</tr>
<tr>
<td>Mexico</td>
</tr>
<tr>
<td>Outside of North America</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
Do you live in

- a city
- a rural area
- a suburban area
How old is the patient now?

- 18-20 years old
- 21-30 years old
- 31-40 years old
- 41-50 years old
- > 50 years old
At what age was the patient diagnosed with mitochondrial disease?

- 0-10 years old
- 11-17 years old
- 18-20 years old
- 21-30 years old
- 31-40 years old
- > 40 years old
Mitochondrial Disease Affected Patients with Myopathies
Symptoms and Daily Impacts
Alyssa D
Please select the answer that best describes the stage of disability for you or the person for whom you care.

Minimal disability, able to run or jump.

Symptoms present but mild, able to walk and capable of leading independent life.

Symptoms are significant. Require regular or periodic holding on to wall or another person for stability and walking.

Walking requires a walker or other aid such as a service dog. Abilities vary from day to day.

Not able to walk, confined to wheelchair. Can perform some activities of daily living that do not require standing or walking.

Severe disability, dependency on others for assistance with all activities of daily living.
Select the mitochondrial disease symptoms that most impact your daily quality of life. Select up to 5

- Chronic Fatigue
- Muscle Weakness
- Gastrointestinal Problems
- Exercise Intolerance
- Sleep Difficulties
- Dysautonomia
- Headaches or Migraines
- Peripheral Neuropathy
- Eye Muscle Problem and/or Vision Impairment
- Mood Disorder
- Other
As mitochondrial disease progresses, development or progression of which of the following symptoms worries you the most? Select up to 5

- Chronic Fatigue
- Muscle Weakness
- Gastrointestinal Problems
- Exercise Intolerance
- Sleep Difficulties
- Dysautonomia
- Headaches or Migraines
- Peripheral Neuropathy
- Eye Muscle Problem and/or Vision Impairment
- Mood Disorder
- Other
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

- Speaking with others, being understood (especially in noisy settings)
- Driving
- Personal hygiene, taking a shower, dressing independently, etc.
- Walking, moving around independently and safely
- Writing and typing
- Feeding oneself, cutting food and handling utensils
- Manipulating small objects (e.g., a key, picking up items)
- Reading books, seeing a computer screen or phone
- Other
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

- Loss of hobbies or activities
- Social isolation
- Frustration
- Depression and/or anxiety
- Financial difficulties
- Loss of job or inability to get a job
- Trouble building or maintaining relationships
- Lack of hope for the future
- Loss of independence
- Modified work/school hours
- Communication Issues
- Other
1. Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life? (Examples include: muscle weakness, fatigue, exercise intolerance, speech problems, eye muscle problems, pain, etc.)
2. Are there specific activities that are important to you but you cannot do at all or as fully as you would like because of your condition? *(Examples of activities include: social activities, working, caring for family, driving, hobbies, etc.)*

a. How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
3. How has your condition and its symptoms changed over time?

   a. Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?
4. What worries you most about your condition?
Externally-led Patient-Focused Drug Development Meeting for Mitochondrial Disease

Break

We will resume at approximately 10:35 am EDT
Externally-led Patient-Focused Drug Development Meeting for Mitochondrial Disease

Welcome Back
Mitochondrial Disease Affected Patients with Myopathies

Current and Future Approaches to Treatments
Michael M
What PRESCRIPTION MEDICATIONS do you take now to treat symptoms of your mitochondrial disease? Select ALL that apply

<table>
<thead>
<tr>
<th>Pain medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart medications</td>
</tr>
<tr>
<td>Antidepressants or anti-anxiety medications</td>
</tr>
<tr>
<td>Muscle relaxants</td>
</tr>
<tr>
<td>Intravenous Immunoglobulin therapy (IVlg)</td>
</tr>
<tr>
<td>Diabetes medications</td>
</tr>
<tr>
<td>Experimental medications as a part of a clinical trial</td>
</tr>
<tr>
<td>Other prescription medications not listed</td>
</tr>
<tr>
<td>Nothing</td>
</tr>
</tbody>
</table>
What VITAMINS or SUPPLEMENTS do you take now to treat symptoms of your mitochondrial disease? Select ALL that apply

- CoQ10
- Carnitine
- Riboflavin
- Creatine
- Vitamin E
- Alpha lipoic acid
- Vitamin B3, Nicotinamide or Niacin
- Idebenone
- Other supplements or vitamins not listed
- Nothing
<table>
<thead>
<tr>
<th>Choice of diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modifications/accommodations at work/in school/at home</td>
</tr>
<tr>
<td>Physical therapy, including aqua or hippo therapy</td>
</tr>
<tr>
<td>Stretching</td>
</tr>
<tr>
<td>Use of adaptive devices</td>
</tr>
<tr>
<td>Exercise (cardio or strength training)</td>
</tr>
<tr>
<td>Mental health services</td>
</tr>
<tr>
<td>Occupational therapy</td>
</tr>
<tr>
<td>Speech therapy</td>
</tr>
<tr>
<td>Nothing</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Benefit Level</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>No benefit</td>
</tr>
<tr>
<td>Help somewhat</td>
</tr>
<tr>
<td>Help a lot</td>
</tr>
<tr>
<td>Significant benefit</td>
</tr>
<tr>
<td>Not sure</td>
</tr>
</tbody>
</table>
Which outcome is MOST important for a possible drug treatment?

- Slowing/stopping of progression (even if no gain in function, symptoms won't get worse)
- Gain in function (e.g., energy, strength, mobility, dexterity, cardiac function, speech)
- Prolong life
- Other
<table>
<thead>
<tr>
<th>Reduced Chronic Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Muscle Weakness</td>
</tr>
<tr>
<td>Reduced Gastrointestinal Problems</td>
</tr>
<tr>
<td>Reduced Exercise Intolerance</td>
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<td>Reduced Dysautonomia</td>
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<td>Reduced Headaches or Migraines</td>
</tr>
<tr>
<td>Reduced Peripheral Neuropathy</td>
</tr>
<tr>
<td>Reduced Mood Disorder</td>
</tr>
<tr>
<td>Reduced Eye Muscle Problems and/or Improved Vision</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
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 risks of serious side effects (cardiac, kidney issues, etc.)
- Cost and/or travel
- The burden of administration (need for anesthesia, radiation exposure, surgical procedure, etc.)
- Common side effects of the treatment (nausea, loss of appetite, headache, etc.)
- Length of treatment, requires hospitalization, requires numerous doctors visits, etc.
- Changing my current treatment or management plan (stopping a medication, supplements or exercise)
- The way that treatment is administered (orally, intravenously, subcutaneous)
- None of these
- Other
1. What are you currently doing to help treat your condition or its symptoms? (Examples include: prescription medicines, over-the-counter products, and other therapies including nondrug therapies like physical therapy, diet/nutrition, exercise, adaptive devices, etc.)

   a. What specific symptoms do your treatments address?

   b. How has your treatment regimen changed over time, and why?
2. How well does your current treatment regimen treat the most significant symptoms of your disease?

a. How well do these treatments improve your ability to do specific activities that are important to you in your daily life?

b. How well have these treatments worked for you as your condition has changed over time?
3. What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples of downsides include: bothersome side effects, going to the hospital for treatment, restrictions on driving, etc., etc.)
4. Short of a cure for your mitochondrial disease, what specific things would you look for in an ideal treatment for your condition?
Lucas Kempf, MD
Associate Director
Rare Diseases Program
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)
Externally-led Patient-Focused Drug Development Meeting for Mitochondrial Disease

Lunch Break

We will resume at approximately 1:00 pm EDT
Each session in today’s meeting will include a series of polling questions on mitochondrial disease and its impact on your family’s life. In-person and remote attendees are encouraged to use their mobile devices or computer to participate in these polling questions.

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Externally-led Patient-Focused Drug Development Meeting for Mitochondrial Disease

Welcome Back
Kira Mann
CEO
MitoAction
Clinical Overview: Neurologic Manifestations in Children with Mitochondrial Disease
Amy Goldstein, MD, Children’s Hospital of Philadelphia, PA

Audience and Remote Polling – Attendee Demographics for Children with Neurologic Issues
James Valentine, JD, MHS, Facilitator

Panel #3 – Symptoms and Daily Impacts
• Presentations by 5 Parents and Caregivers
• Audience and Remote Polling Panel #3
• Moderated Audience Discussion Panel #3

Break
Brittany Hernandez
Director of Advocacy
Muscular Dystrophy Association (MDA)
Panel #4 – Current and Future Approaches to Treatment
• Presentations by 5 Parents and Caregivers
• Audience and Remote Polling Panel #4
• Moderated Audience Discussion Panel #4

Afternoon Session Closing Remarks
Larissa Lapteva, MD, MHS, MBA, U.S. Food and Drug Administration (FDA)

Next Steps and Closing Remarks
Philip Yeske, PhD, UMDF Science and Alliance Officer, and Brent Fields, UMDF Trustee Chair
Clinical Overview: Neurologic Manifestations in Children with Mitochondrial Disease

Amy Goldstein, MD

- Clinical Director, Mitochondrial Medicine Frontier Program, Children’s Hospital of Philadelphia
- UMDF Scientific and Medical Advisory Board
- MitoAction, Medical Advisory Board
- Mitochondrial Medicine Society, Immediate Past-President
Outline

Burden of Disease
• general symptoms with focus on the nervous system
• genetic: affect on families

General Approaches to Management
• no current FDA approved medication or therapy
• Very few Clinical Trials currently available; many previous failures
• Empiric trials of supplements: not universally accepted
• Standards of Care are evolving through Clinical Networks and Consortia worldwide
Primary Mitochondrial Disease: Clinical Features

*Gorman G et al, Nat Rev Dis Primers, 2016*
# Neurologic Symptoms

<table>
<thead>
<tr>
<th>Neurologic symptom or sign</th>
<th>Red flag signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STROKE</strong></td>
<td>Non-vascular distribution; MRI/ADC map shows a mixture of hyper- and hypo-intensity</td>
</tr>
<tr>
<td><strong>BASAL GANGLIA LESIONS</strong></td>
<td>Bilateral (symmetric) (characteristic of Leigh syndrome); also with brainstem lesions; elevated lactate in blood or CSF</td>
</tr>
<tr>
<td><strong>ENCEPHALOPATHY-HEPATOPATHY</strong></td>
<td>Precipitated by valproic acid (Depakote) exposure; associated fulminant hepatic failure</td>
</tr>
<tr>
<td><strong>EPILEPSY</strong></td>
<td>Epilepsia Partialis Continua (EPC), myoclonus, status epilepticus</td>
</tr>
<tr>
<td><strong>COGNITIVE DECLINE</strong></td>
<td>Regression with illness requiring extensive rehab</td>
</tr>
<tr>
<td><strong>ATAxia</strong></td>
<td>In association with epilepsy or other systemic symptoms; neuroimaging may show cerebellar atrophy, white matter lesions, basal ganglia lesions</td>
</tr>
<tr>
<td><strong>OCULAR SIGNS</strong></td>
<td>Optic nerve atrophy, ophthalmoplegia, ptosis; retinopathy</td>
</tr>
<tr>
<td><strong>SENSORINEURAL HEARING LOSS</strong></td>
<td>At early age, accompanied by other systemic symptoms</td>
</tr>
</tbody>
</table>

Parikh, 2010, Dev Dis Res Rev
Individually these are rare disorders

• Highly heterogeneous genetic causes & clinical features

Exercise has therapeutic value in mitochondrial disease

• Both aerobic and resistance exercises, as tolerated
• Assure cardiopulmonary status cleared prior to exercise
• Mechanism: increased mitochondrial biogenesis, heteroplasmy shift
• How can we assure patients are exercising effectively yet safely?

Lack of clarity on optimal diet & nutrition in mitochondrial disease

*Parikh S et al, Curr Treat Options in Neurol, 2009
Clinical treatment trials have been limited in primary mitochondrial disease

- No universal clinical trial design, outcome measure, or biomarker: difficult due to clinical and genetic heterogeneity
- Current trials now emerging involve common clinical outcomes in genetically-confirmed mitochondrial disease cohorts

**ANTI-OXIDANTS:**
- Coenzyme Q10 – trial never filled/completed
- Idebenone – approved in Europe in 2015 for LHON
- EPI-743 (Edison) – failed primary outcome in Leigh disease
- RP-103 (Cysteamine bitartrate, Raptor)-phase II, Leigh disease, discontinued

**OTHER MECHANISMS:**
- Elamipretide (Stealth BioTherapeutics) – phase II→III for PMM
- RT-408 (nrf-2 agonist, Reata) – phase II/III, myopathy/EI
Are there specific treatments for Primary Mitochondrial Disease?

- Ubiquinol (or Coenzyme Q10)
- Alpha-Lipoic acid
- L-creatine
- L-carnitine if deficient
- Vitamin B2 (Riboflavin)
- Vitamin B50
- Vitamin E
- Leukovorin (folinic acid)
- N-acetylcysteine

Are you the parent or caregiver of a child with Neurologic Manifestations of Mitochondrial Disease?

Your polling questions will be starting soon
Which of the following best describes you?

I am a parent/caregiver of a child who has a neurologic manifestation of mitochondrial disease.

I have lost a child who had a neurologic manifestation of mitochondrial disease.
<table>
<thead>
<tr>
<th>Where do you currently reside?</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Pacific (including California)</td>
</tr>
<tr>
<td>US West and Mountain</td>
</tr>
<tr>
<td>US Midwest</td>
</tr>
<tr>
<td>US South (including Texas)</td>
</tr>
<tr>
<td>US Northeast and New England</td>
</tr>
<tr>
<td>Canada</td>
</tr>
<tr>
<td>Mexico</td>
</tr>
<tr>
<td>Outside of North America</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>a city</td>
</tr>
<tr>
<td>a rural area</td>
</tr>
<tr>
<td>a suburban area</td>
</tr>
</tbody>
</table>
How old is the patient now?

- 0-10 years old
- 11-17 years old
- 18-20 years old
- 21-30 years old
- > 30 years old
<table>
<thead>
<tr>
<th>Age Range</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10 years</td>
<td>old</td>
</tr>
<tr>
<td>11-17 years</td>
<td>old</td>
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<td>18-20 years</td>
<td>old</td>
</tr>
<tr>
<td>21-30 years</td>
<td>old</td>
</tr>
<tr>
<td>&gt; 30 years</td>
<td>old</td>
</tr>
</tbody>
</table>
Pediatric Mitochondrial Disease Patients with Neurologic Manifestations

Symptoms and Daily Impacts
Daniel M
Stacy T
Please select the answer that best describes the patient's stage of disability.

- Minimal disability, able to run or jump.
- Symptoms present but mild, able to walk and capable of leading independent life.
- Symptoms are overt and significant. Require regular or periodic holding on to wall or another person for stability and walking.
- Walking requires a walker or other aid such as a service dog. Can perform several activities of daily living.
- Not able to walk, confined to wheelchair. Can perform some activities of daily living that do not require standing or walking.
- Severe disability, dependency on others for assistance with all activities of daily living.
Select the mitochondrial disease symptoms that most impact the patient's daily quality of life. Select up to 5

<table>
<thead>
<tr>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Weakness</td>
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<tr>
<td>Speech Problems</td>
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<tr>
<td>Chronic Fatigue</td>
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<tr>
<td>Gastrointestinal Problems</td>
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<td>Balance Problems</td>
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<tr>
<td>Sleep Difficulties</td>
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<tr>
<td>Learning Disability</td>
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<tr>
<td>Movement Disorders (chorea, tremors, dystonia)</td>
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<tr>
<td>Delayed Milestones</td>
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<tr>
<td>Decreased Vision</td>
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<tr>
<td>Exercise Intolerance</td>
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<td>Seizures</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Other</td>
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**Start the presentation to see live content. Still no live content? Install the app or get help at PoLiEv.com/app**
As mitochondrial disease progresses, development or progression of which of the following symptoms worries you the most? Select up to 5

- Muscle Weakness
- Speech Problems
- Chronic Fatigue
- Gastrointestinal Problems
- Balance Problems
- Sleep Difficulties
- Learning Disability
- Movement Disorders (chorea, tremors, dystonia)
- Delayed Milestones
- Impaired Vision
- Exercise Intolerance
- Seizures
- Headache
- Other
What specific activities of daily life are most important to your child they and are NOT able to do because of mitochondrial disease? Select TOP 3

- Moving around independently and safely, walking and standing
- Speaking with others, being understood (especially in noisy settings)
- Personal hygiene, taking a shower, dressing independently, etc.
- Feeding oneself, cutting food and handling utensils
- Going to school or work
- Writing and typing
- Reading books, seeing a computer screen or phone
- Manipulating small objects (e.g., a key, picking up items)
- Other
As a result of living with mitochondrial disease, which of the following social, emotional or economic consequences are most significant to your child?  

Select up to 4

<table>
<thead>
<tr>
<th>Consequence</th>
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<tbody>
<tr>
<td>Frustration</td>
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<tr>
<td>Social isolation</td>
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<tr>
<td>Loss of independence</td>
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<td>Communication issues</td>
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<tr>
<td>Lack of hope for the future</td>
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<tr>
<td>Depression and/or anxiety</td>
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<tr>
<td>Trouble building or maintaining relationships</td>
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<tr>
<td>Modified school hours</td>
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<tr>
<td>Loss of hobbies or activities</td>
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<tr>
<td>Other</td>
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</tbody>
</table>
1. Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life? (Examples include: muscle weakness, fatigue, exercise intolerance, speech problems, eye muscle problems, pain, etc.)
2. Are there specific activities that are important to you but you cannot do at all or as fully as you would like because of your condition? (Examples of activities include: participating in sports and recreational activities, speaking with others and being understood, social interaction, going to school, eating without help, etc.)

a. How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
3. How has your condition and its symptoms changed over time?

   a. Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?
4. What worries you most about your condition?
Externally-led Patient-Focused Drug Development Meeting for Mitochondrial Disease

Break

We will resume at approximately 2:50 pm EDT
Externally-led Patient-Focused Drug Development Meeting for Mitochondrial Disease

Welcome Back
Pediatric Mitochondrial Disease Patients with Neurologic Manifestations

Current and Future Approaches to Treatment
<table>
<thead>
<tr>
<th>What PRESCRIPTION MEDICATIONS does the patient take now to treat symptoms for mitochondrial disease? Select ALL that apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain medications</td>
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<tr>
<td>Heart medications</td>
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<tr>
<td>Antidepressants or anti-anxiety medications</td>
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<tr>
<td>Muscle relaxants</td>
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<tr>
<td>Intravenous Immunoglobulin therapy (IVIg)</td>
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<tr>
<td>Diabetes medications</td>
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<tr>
<td>Experimental medications as a part of a clinical trial</td>
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<tr>
<td>Other prescription medications not listed</td>
</tr>
<tr>
<td>Nothing</td>
</tr>
</tbody>
</table>
What VITAMINS or SUPPLEMENTS does the patient take now to treat symptoms for mitochondrial disease? Select ALL that apply

- CoQ10
- Carnitine
- Riboflavin
- Creatine
- Vitamin E
- Alpha lipoic acid
- Vitamin B3, Nicotinamide or Niacin
- Idebenone
- Other supplements or vitamins not listed
- Nothing
What are you currently doing to help manage mitochondrial disease or mitochondrial disease symptoms? Select ALL that apply

- Physical therapy, including aqua or hippo therapy
- Modifications/accommodations at school/home
- Occupational therapy
- Use of adaptive devices
- Speech therapy
- Choice of diet
- Stretching
- Exercise (cardio or strength training)
- Mental health services
- Nothing
- Other
### In general, how much do the medications, therapies or lifestyle changes used improve the patient's quality of life?

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<table>
<thead>
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<tbody>
<tr>
<td><strong>No benefit</strong></td>
<td></td>
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<tr>
<td><strong>Help somewhat</strong></td>
<td></td>
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<tr>
<td><strong>Help a lot</strong></td>
<td></td>
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<tr>
<td><strong>Significant benefit</strong></td>
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<tr>
<td><strong>Not sure</strong></td>
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<tr>
<td>Which outcome is MOST important for a possible drug treatment?</td>
<td></td>
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<tr>
<td>-------------------------------------------------------------</td>
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<tr>
<td>Slowing/stopping of progression (even if no gain in function, symptoms won't get worse)</td>
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<tr>
<td>Gain in function (e.g. energy, strength, mobility, dexterity, cardiac function, speech)</td>
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<tr>
<td>Prolong life</td>
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<tr>
<td>Other</td>
<td></td>
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</tbody>
</table>
Which ability or symptom would you rank as most important for a possible drug treatment today? Select up to 3

- Reduced Muscle Weakness
- Improved Speech
- Reduced Chronic Fatigue
- Reduced Gastrointestinal Problems
- Improved Balance
- Reduced Sleep Difficulties
- Reduced Learning Disability
- Improved Movement Disorders (chorea, tremors, dystonia)
- Improved Meeting Milestones
- Improved Vision
- Reduced Exercise Intolerance
- Reduced Seizures
- Reduced Headache
- Other
Which of the following factors would influence your decision to have your child take a new medication or participate in a clinical trial or research study? Select ALL that apply.

- Significant risks of serious side effects (cardiac, kidney issues, etc.)
- Common side effects of the treatment (nausea, headaches, etc.)
- The way that treatment is administered (orally, intravenously, subcutaneous)
- Length of treatment, requires hospitalization, frequent doctors visits, etc.
- Burden of administration (need for anesthesia, radiation exposure, surgery, etc.)
- Changing my current treatment or management plan (stopping a medication, supplement, or exercise)
- Cost and/or travel
- None of these
- Other
1. What are you currently doing to help treat your condition or its symptoms? *(Examples include: prescription medicines, over-the-counter products, and other therapies including nondrug therapies such as physical therapy, diet/nutrition, exercise, adaptive devices, etc.)*

   a. What specific symptoms do your treatments address?

   b. How has your treatment regimen changed over time, and why?
2. How well does your current treatment regimen treat the most significant symptoms of your disease?

   a. How well do these treatments improve your ability to do specific activities that are important to you in your daily life?

   b. How well have these treatments worked for you as your condition has changed over time?
3. What are the most significant downsides to your current treatments, and how do they affect your daily life? *(Examples of downsides include: bothersome side effects, going to the hospital for treatment, etc., etc.)*
4. Short of a cure for your mitochondrial disease, what specific things would you look for in an ideal treatment for your condition?
Larissa Lapteva, MD, MHS, MBA
Associate Director
Division of Clinical Evaluation, Pharmacology, and Toxicology
Offices of Tissue and Advanced Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration (FDA)
Philip Yeske, PhD

Science and Alliance Officer
United Mitochondrial Disease Foundation
SPECIAL THANKS to those whose collaboration made this important meeting possible
SPECIAL THANKS to those whose generous support helped make this meeting possible
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- MDA (Muscular Dystrophy Association)
- mito ACTION
- SUMMIT HEALTH PHARMACY
- MODIS THERAPEUTICS
- Reneo
- PhRMA
- NEUROVIVE
- B-MOGEN
- EVERYLIFE FOUNDATION
Next Steps

Post-Meeting Survey:

www.umdf.org/PFDDSurvey
Next Steps

The Voice of the Patient

A REPORT FROM THE
MITOCHONDRIAL DISEASE EXTERNALLY-LED
PATIENT-FOCUSED DRUG DEVELOPMENT MEETING

PUBLIC MEETING: MARCH 29, 2019
Brent Fields
Chair
UMDF Board of Trustees
Externally-led Patient-Focused Drug Development Meeting for Mitochondrial Disease

THANK YOU for your participation!