Focus on Information, Resources, Support, and Treatments
The United Mitochondrial Disease Foundation is redefining hope for families affected by mitochondrial diseases - hereditary disorders, which are now considered as common as childhood cancers and affect the cell’s ability to produce life sustaining energy. The UMDF offers support to all sufferers of mitochondrial disorders regardless of their diagnosis being suspected or confirmed.

We invite you to contact the UMDF at 1-888-317-UMDF (8633) or visit our website at www.umdf.org to learn more about mitochondrial diseases or to find out how to become a member.

When you call, you will find that the UMDF will enable you to:

- Talk to caring, professional staff who can answer non-medical questions
- Locate mitochondrial specialists closest to your vicinity
- Connect with a local chapter or support group
- Request a professional packet of literature to be sent to your local physician(s)

UMDF Membership Benefits:

- Receive an electronic quarterly newsletter
- Learn ways to increase awareness of mitochondrial diseases in your community
- Attend a national symposium for researchers, physicians, and affected families (some scholarships are available to members)
- Online access to video-taped symposium seminars
- Ask a “mito doc” question online
- Receive a resource guide

For membership information, call 1-888-317-UMDF (8633) or visit www.umdf.org.
Dear Friend,

The fact that you are reading this MitoFIRST Handbook means that you have likely been impacted by a mitochondrial disease in some way. Whether you, your child, a family member, or a friend has been diagnosed with a mitochondrial disease, our goal is to provide you with the knowledge and understanding, the resources, and the support you will need as you grapple with a diagnosis that is often under-recognized and misunderstood.

Living with mitochondrial disease presents many twists and turns and a maze of questions. It is our hope that this introductory guide will give you some answers. To gain the most from this guide, we suggest that you read each section in context and, if possible, consult any suggested online links for the complete articles.

While it was once thought that mitochondrial disorders were limited to children, it is now understood that onset of symptoms can begin in adulthood. Therefore, most of the information in this guide is applicable both to children and adults.

Please understand that this introductory guide is merely to be used as a tool. It is not meant to be a substitute for professional advice and services rendered by qualified doctors, allied medical personnel, and other professional and legal services. The responsibility for any use of this information, or for proper medical treatment, rests with you and your physician.

Yours toward a cure,

Charles A. Mohan, Jr.
CEO/Executive Director

UMDF MISSION:
To promote research and education for the diagnosis, treatment, and cure of mitochondrial disorders and to provide support to affected individuals and families.
Mitochondrial diseases are not a single disorder, but represent a widely variable group of metabolic diseases. These diseases commonly result from failure of the mitochondria, which are specialized organelles present in almost every cell of the body. Mitochondria are responsible for providing more than 90% of the energy that is needed by the body to sustain life and support growth. Food is converted within mitochondria into stored energy (ATP) by means of large enzyme complexes that make up the respiratory chain (or electron transport chain). The process by which this is accomplished requires oxygen and is called oxidative phosphorylation. Genetic defects in either the mitochondrial DNA or the DNA located in the cell nucleus can impair this process and cause mitochondrial failure.

When mitochondria fail, less and less energy is generated within the cell. Eventually, cell injury and even cell death follow. If this process is repeated on a large scale throughout the body, whole systems begin to fail. The life of the affected person is compromised, changed, or even ended.

Hallmarks of Mitochondrial Disease

1. A “common disease” has atypical features that set it apart from the pack.
2. More than one organ system is involved
3. Recurrent setbacks or flare-ups in a chronic disease occur with infection or stress

How many individuals are affected?

Every 30 minutes, a child is born who will develop a mitochondrial disease by the age of 10. We now know that this group of diseases is approaching the prevalence of childhood cancers. The exact numbers of children and adults with a mitochondrial disease are hard to determine because many people who suffer from a mitochondrial disease remain undiagnosed or are misdiagnosed. Some common but non-specific disease manifestations that often lead to misdiagnoses include such conditions as: atypical cerebral palsy, various seizure disorders, chronic fatigue, or fibromyalgia. Still others aren’t diagnosed until after death.
Mitochondrial diseases can be due to inherited gene mutations or acquired mutations in the mitochondrial genome. There are primary (something inherently wrong with mitochondrial function) and secondary (the mitochondria are injured as a bystander to another process) disorders.

Mitochondrial disorders can be inherited in different ways. In fact, nearly every known inheritance pattern has been demonstrated to occur in mitochondrial disease. However, most mitochondrial disorders known to date are inherited in either an autosomal recessive (both parents are unaffected carriers) or maternal manner (so called mitochondrial DNA inheritance pattern).

In many cases, the patient is the only family member affected with a mitochondrial disease. These cases are called “sporadic” and make answering the questions regarding inheritance more challenging. Such individuals may still have a disease-causing genetic mutation that occurred newly (“de novo”) in them rather than being inherited from a parent, or may have an autosomal recessive genetic disease in which they inherited two mutations in a given gene from their asymptomatic carrier parents.

The first question is to address whether the problem is due to genetics, environment, or some combination of the two. Not all mitochondrial disorders are primarily genetic. For example, certain medications can damage mitochondria and cause symptoms due to resultant energy failure. Removal of these drugs may reverse the process, and the symptoms may resolve. There are other environmental causes of mitochondrial disease and likely many that we do not know about.

It is the opinion of some experts that most mitochondrial diseases are probably both genetic and environmental in origin. Even in the case of drugs such as HIV medications, thousands of individuals on these drugs have no problem while a small handful might. Likely, there are genetic reasons for the high susceptibility to some drugs in an unlucky few - a genetic predisposition to an “environmental” disease.
Patients’ symptoms can range from extremely mild to severe, involve one or more body systems, and can emerge at any age. Most patients’ symptoms fluctuate over the course of their illness -- at some times experiencing no or few symptoms while at other times experiencing many and/or severe symptoms. Even family members with the same disorder can experience vastly different symptoms. Symptoms may present unexpectedly at any age, or they may be evident from birth or infancy. Diseases of the mitochondria appear to cause the most damage to cells of organs and systems that require a great deal of energy: the brain, the heart, the skeletal muscles, the GI system, the kidneys, the liver, and the endocrine and respiratory systems. As a result, children and adults who have these diseases can experience a vast array of symptoms. Although a few may have only mild symptoms such as learning disabilities and susceptibility to fatigue, many others face numerous, severe problems and the potential for premature death. Mitochondrial diseases are extremely complex, which makes it difficult to predict the severity of disease and the range of symptoms in a given individual.

**Adult Symptoms**

Symptoms in adults tend to develop and progress over a period of years, which makes it is distinctly uncommon for these diseases to be diagnosed when symptoms first begin. The early phase might be mild and may not resemble any mitochondrial disease. In addition, chronic symptoms such as fatigue, muscle pain, shortness of breath and abdominal pain can easily be mistaken for collagen vascular disease, chronic fatigue syndrome, fibromyalgia, or psychosomatic illness.

1. Reprinted from “Myths and Facts about Mitochondrial Disease”, Sumit Parikh, MD and Bruce Cohen, MD. Cleveland Clinic Journal Of Medicine
2. Reprinted from “Mitochondrial Cytopathy in Adults”, Bruce Cohen, MD and Deborah Gold, MD. Cleveland Clinic Journal of Medicine
POSSIBLE SYMPTOMS

**Brain**
- Developmental delay
- Mental retardation
- Dementia
- Seizures
- Neuro-psychiatric disturbances
- Migraines
- Atypical Cerebral Palsy
- Movement Disorders
- Strokes
- Autistic features

**Kidneys**
- Renal tubular acidosis or wasting
- Renal glomerular disease

**Heart**
- Cardiac conduction defects (heart block or arrhythmia)
- Cardiomyopathy

**Liver**
- Hypoglycemia (low blood sugar)
- Liver failure

**Nerves**
- Weakness (may be intermittent)
- Absent reflexes
- Fainting
- Neuropathic pain (pins and needles, burning)
- Dysautonomia - temperature instability and other dysautonomic problems

**Eyes & Ears**
- Visual loss/blindness
- Ptosis (droopy eyelids)
- Ophthalmoplegia
- Optic atrophy
- Hearing loss/deafness
- Acquired strabismus
- Retinitis pigmentosa

**Endocrine**
- Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
- Parathyroid failure (low calcium)
- Hypothyroidism
- Short stature

**Muscles**
- Weakness
- Muscle pain
- Low muscle tone
- Exercise intolerance

**Gastrointestinal problems**
- Pseudo-obstruction
- Irritable Bowel Syndrome
- Cramping
- Diarrhea or Constipation
- Dysmotility
- Gastroesophageal reflux

**Systemic**
- Failure to gain weight
- Fatigue
- Unexplained vomiting
- Respiratory problems
Mitochondrial diseases are difficult to diagnose, and unfortunately, there are few physicians who specialize in these diseases. Referral to an appropriate medical center is critical. If experienced physicians are involved, diagnoses can be made through a combination of medical history, clinical observations, laboratory screening studies, genetic diagnostic testing, brain imaging, and muscle biopsies. Despite these advances, many cases do not receive a specific diagnosis. A single normal blood or urine lab test does not exclude the possibility of mitochondrial disease. This is true for urine organic acid analysis, as well as blood lactic acid, carnitine and amino acid analyses. Even muscle biopsies are far from perfect, as the studies performed may be normal at certain times in the disease course or in certain types of mitochondrial disease. Ultimately, there is no substitute for good clinical judgment.

**Laboratory Evaluation for Disorders of Energy Metabolism**

Laboratory screening evaluations in blood and urine are the usual means by which physicians begin to evaluate patients for disorders of energy metabolism (which include mitochondrial disorders, disorders of oxidative phosphorylation, and fatty acid oxidation disorders). Most hospitals do not have a metabolic laboratory and therefore can run only the most basic tests. However, these hospitals can send specimens to any laboratory in the country. Not all laboratory tests are required for all patients, and your physician may decide that some tests are not necessary.

If the results of this evaluation are suggestive of a specific disorder, a direct enzyme and/or genetic test for the disease in question may be able to be performed. If the results of the initial evaluation are normal and there is a strong suspicion of a mitochondrial disease, more invasive secondary evaluations may be recommended, such as brain imaging and/or spinal tap under sedation. Since some of the tests may require urine specimens to be collected over time, a bladder catheter may be required in young children. Many of these tests require the specimens to be sent to a special laboratory. As with the initial testing, normal results on more invasive testing make the possibility of a mitochondrial disease less likely but do not eliminate it completely.
Tertiary tests are invasive and/or expensive, and may carry with them some risks, such as metabolic decompensation during a fast. However, if the physician strongly suspects a metabolic disease, such tests may be diagnostic. The muscle biopsy is a tertiary test, is the most complicated and invasive of all tests, and in children requires general anesthesia. Some centers can do all of the muscle testing using a modified needle biopsy with a short (< 10 min) conscious sedation protocol. Although a muscle biopsy can be performed at any medical center, very few centers have the ability to do all of the testing necessary to make a diagnosis. Therefore, the physician must be very conscientious in planning where to send the biopsy before the test is performed.

<table>
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<tr>
<th>Metabolic Screening (in all patients)</th>
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<tr>
<td>- Basic Chemistries</td>
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<td>- Liver enzymes &amp; Ammonia</td>
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<tr>
<td>- Complete Blood Count</td>
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<tr>
<td>- Creatine Kinase</td>
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<tr>
<td>- Blood Lactate &amp; Pyruvate</td>
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<tr>
<td>- Quantitative Plasma Amino Acids</td>
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<tr>
<td>- Quantitative Urine Organic Acids</td>
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<td>- Plasma Total, Free and Acylcarnitine Profile</td>
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<tr>
<th>Metabolic Screening In Spinal Fluid (for patients with neurological symptoms)</th>
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<tr>
<td>- Lactate &amp; Pyruvate</td>
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<tr>
<td>- Quantitative Amino Acids</td>
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<tr>
<td>- Neurotransmitter studies and CSF Folate</td>
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<tr>
<td>- Routine Studies, including Glucose, Protein, and Cell Count</td>
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<th>Clinical Neurogenetic Evaluation (for those with developmental delays)</th>
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<tr>
<td>- Chromosomal Analysis By Karyotype or Genome-Wide Microarray</td>
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<tr>
<td>- Fragile X Testing</td>
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<tr>
<td>- Neurology Consult</td>
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<td>- Genetics Consult</td>
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<th>Characterize Systemic Involvement</th>
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<tbody>
<tr>
<td>- Echocardiogram</td>
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<td>- Electrocardiogram (EKG)</td>
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<td>- Ophthalmologic Exam</td>
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<tr>
<td>- Audiology Exam</td>
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<td>- Brain MRI/MRS</td>
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Negative results on preliminary screening do not exclude mitochondrial disease; if mitochondrial disease is suspected, refer the patient to a mitochondrial disease center.

The lab tests above are from the Mitochondrial Medicine Society Website. A list of tests and centers performing these tests can be found at: www.mitosoc.org/blogs/diagnosis.
Even though mitochondrial disorders are long term and currently incurable, treatments are available. Early treatment of symptoms can reduce their impact and limit further disability. Avoiding various medications and stressful situations that worsen symptoms is also helpful. Certain medications and supplements may improve mitochondrial disease-related symptoms - just as they do for other incurable diseases such as diabetes and emphysema.

**Purposes of Treatment**
- alleviate symptoms
- slow down progression of the disease

**Effectiveness of Treatment**
- varies from patient to patient, depending on the exact disorder and the severity of the disorder.
- as a general rule, patients with mild disorders tend to respond to treatment better than those with severe disorders.
- in some circumstances, the treatment can be tailored specifically to the patient, and that treatment is effective; whereas in other circumstances, the treatment is “empiric,” meaning that the treatment makes sense, but that the benefit of treatment is not obvious or proven to be effective.

It is not possible to predict the response to vitamins, supplements or diet changes before they are tried.

**Benefits of Treatment/Effectiveness of Therapies Vary**
- treatment may be beneficial and noted immediately in some disorders
- benefit of treatment may take a few months to notice
- benefit of treatment may never be noticed, but the treatment may be effective in delaying or stopping the progression of the disease
- some patients may not benefit from therapy

**Key Points for Treatment**
- dietary
- vitamins and supplements
- avoidance of stressful factors
- exercise
- additional therapies
Although a “cure” for mitochondrial disorders may theoretically include a mitochondria “transplant” or genetic therapy to correct the underlying defect, these therapies are a long way off. In the meantime, it is important to minimize further mitochondrial damage and to improve function at the tissue and whole body level. Although none of the non-genetic therapeutic strategies mentioned are “curative”, it is important that mitochondrial and tissue structure and function are maintained until genetic therapies become a reality.¹

Another factor to consider in therapies for mitochondrial diseases is that single therapies targeting only one of the final common pathways of mitochondrial dysfunction are not likely to be beneficial. It is probable that the best therapy for mitochondrial disorders would be to target a number of negative consequences of mitochondrial dysfunction simultaneously. In general, this approach has been taken by many clinicians in that most patients are treated with a mitochondrial “cocktail” of supplements.

The decision to initiate therapy for mitochondrial disorders and the choice of the agents must be made on a case-by-case basis and with consultation from a physician with experience in the theory and practical issues related to mitochondrial therapies.¹

*Treatment recommendations must be tailored by the patient’s physician to meet that patient’s needs. No treatment should be implemented or terminated without the direct supervision of a physician. In some cases, the treatment could be dangerous. It is not possible to predict the response to vitamins, supplements, diet, or exercise changes before they are tried.*

¹ Reprinted from “Myths and Facts about Mitochondrial Disease”, Sumit Parikh, MD and Bruce Cohen, MD, Cleveland Clinic Journal Of Medicine
Vitamins and co-factors are compounds that are required in order for chemical reactions, which make energy, to run efficiently. For most people, a regular diet contains all of the vitamins one could possibly need, and their bodies can make as much of any specific co-factor that they need. For those with mitochondrial disorders, added vitamins and co-factors can be useful. Most of these vitamins can be purchased from many sources, including the drugstore.

For disorders of OXPHOS, coenzyme Q10 is considered as a generally accepted effective therapy, although it may not ultimately be effective for an individual patient. Other treatments are proven therapies in specific disorders, but in other disorders those same therapies cannot be considered as “proven and effective” although they still may be helpful.


## VITAMINS AND SUPPLEMENTS THAT MAY BE HELPFUL

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Purpose</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Coenzyme Q10</td>
<td>Provide energy beyond enzyme defect site, antioxidant</td>
<td></td>
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<tr>
<td>Creatine monohydrate</td>
<td>Energy booster/alternative energy source, antioxidant</td>
<td></td>
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<tr>
<td>Riboflavin (B2)</td>
<td>Precursor of two co-factors involved in electron transport chain</td>
<td></td>
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<tr>
<td>Alpha-lipoic acid</td>
<td>Antioxidant</td>
<td></td>
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<tr>
<td>Vitamin E</td>
<td>Antioxidant</td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Antioxidant</td>
<td></td>
</tr>
<tr>
<td>Levo-carnitine (Carnitor®)</td>
<td>Transports long-chain fatty acids, binds unused metabolic products</td>
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<tr>
<td>Thiamine (B1)</td>
<td>Co-factor and activator of pyruvate dehydrogenase, reduce lactate levels</td>
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**Disclaimer:** This list is not meant to be a substitute for professional advice and services rendered by qualified doctors, allied medical personnel, and other professional and legal services. The responsibility for any use of this information, or for proper medical treatment, rests with you and your physician.
Some medications should be taken with caution when you have a mitochondrial disorder. This is not an exhaustive list and does not pertain to every patient with a mitochondrial disorder. Review your individual disorder and medications with your personal physician.

Medications that should generally be avoided include: valproic acid, statins, erythromycin, and propofol. Propofol may be safe when given for short periods of time. There are no absolute contraindications and these medications can be given if an alternative drug is not available or appropriate. Certain older antiretroviral drugs (anti-HIV drugs) are toxic to mitochondria and should be avoided if possible. Check with your mito specialist to see if you need to take an antiretroviral drug.

Doxorubicin, a chemotherapy medication, causes cardiomyopathy as a side effect, most likely through mitochondrial damage, and should be avoided.

Aminoglycoside antibiotics, such as gentamicin, amikacin streptomycin, and tobramycin, can induce hearing loss by damaging mitochondria. These antibiotics should be avoided if the cause of the mitochondrial disorder is unknown. There are specific point mutations in the mtDNA that make one more susceptible to hearing damage.

Certain antipsychotic medications can increase the risk of diabetes and should be used with caution and frequent monitoring.

If IV fluids are necessary, Lactated Ringers solution should be avoided as it contains lactic acid which may falsely elevate the lactate reading in blood.

Some individuals with mitochondrial diseases are more sensitive to volatile anesthetics and need a much lower dose to achieve a bispectral index of <60. Sevoflurane is tolerated better than isoflurane and halothane.

*Medications can be essential to your health and well-being. Please review any concerns you have with your physician.*
Many patients have already “self-adjusted” their diet because they know what foods their bodies seem to tolerate. The following points below are not meant to be suggested therapies for all patients with OXPHOS disorders.

A dietitian experienced in metabolic disorders may be helpful with providing general dietary advice. Please do not make any of these dietary changes without consulting a physician.

**Guidelines That Can Be Considered**

1. Avoiding fasting is perhaps the most important part of dietary treatment. This means avoiding prolonged periods without a meal (even an overnight “fast” from 8 pm to 8 am may be dangerous in some patients). This also means that some patients should not intentionally try to lose weight. Some patients with an acute illness causing vomiting or loss of appetite (like the flu) should be hospitalized to ensure continuous nutrition (intravenous glucose for example).

2. Small, frequent meals may be better than a typical three-meals-a-day routine for some patients.

3. A protein/complex carbohydrate snack before bedtime may be helpful to prevent low blood sugar overnight in some patients. This snack should not be mainly “sugar”, like a candy bar, flavored gelatin or sweetened cereal.

4. Ingesting excess iron is theoretically harmful to mitochondrial patients. There is no need to give supplemental iron in vitamins, or to purposely eat foods rich in iron unless there is significant iron deficiency. This does not mean that the person should not eat red meat. There is no reason to take vitamins with added iron. In addition, vitamin C should not be given around a meal rich in iron. This is important to remember because some experts feel that vitamin C is a good antioxidant and also may be helpful in some disorders of OXPHOS.
Essentially, there are two main forms of exercise: endurance exercise and resistance/strength. Endurance exercise in healthy individuals increases the number of mitochondria and oxygen consumption and reduces lactate production in any given exercise intensity. Resistance/strength exercise uses predominately anaerobic pathways and results in an increase in muscle size and strength.

**Exercise Precautions**

Many “mito” specialists strongly believe that exercise is necessary and can improve muscle strength, endurance, and general well-being in patients with mitochondrial disease. The best advice is moderation: don’t over do it or under do it. The patient should exercise up to his/her individual tolerance (which will vary from time to time) and stop once symptoms become significant. Exercise should be fairly frequent (perhaps at least twice a week), and the patient should push to the point of fatigue. Excessive exercise, however, especially in the presence of concomitant illness (ie. a flu or cold) or in hot or cold (shivering) weather, can precipitate a dangerous metabolic decompensation and should be avoided. The problem lies in determining “the point of fatigue”. Distinguishing true metabolic fatigue from simple laziness is not always easy. When the patient experiences significant pain or weakness, that is the time to stop. The amount of allowable activity varies substantially among patients, and from time to time, even in the same patient.

In some patients, rhabdomyolysis (muscle breakdown) can occur with exercise. Other potential triggers for rhabdomyolysis include illness, fever, fasting, alcohol and stress. Rhabdomyolysis should be suspected when the urine becomes “cola colored”. If present, medical attention should be immediately sought and hydration (by mouth or IV) given to avoid possible kidney damage.

**Endurance Exercise**

The rationale behind using endurance exercise in mitochondrial disease is to increase mitochondrial capacity, oxygen consumption and to decrease secondary deconditioning. If exercise is started at a low level and very gradually increased, this appears to be well tolerated.
Resistance Exercise

Depending on the type of mitochondrial disorder, some patients have actual weakness instead of just decreased endurance. Consequently, strength exercise may be very important. Given that strength/resistance exercise does not require aerobic metabolism, many patients can perform several of these contractions. It is important for patients with mitochondrial disease to have a prolonged rest period between each exercise set to allow for ATP recovery.

Theoretically, resistance exercise may cause damage to the muscle and proliferate a satellite cell (a form of stem cell in muscle), which could lead to a reduction in the percentage of abnormal mitochondrial DNA (DNA shifting). This has been shown with direct damage to the muscle with various toxins and more recently with resistance exercise.

In patients with mitochondrial disorders, resistance exercise can improve strength; however, the concept of DNA shifting remains to be fully explored.

Again, it is very important to start at a low level and tailor the program to the base line strength of the individual and most importantly to allow for a very long recovery. (Normally the two minutes between each set should be extended to five to ten minutes between sets. A circuit set type program works best - 10 arm curls, followed by 10 sit ups, followed by 10 calf raises, followed by 10 knee extensions, and then back to the arm curls with at least a minute or two between each bout of activity.)

Additional Therapies

Other therapeutic interventions may be necessary for some mitochondrial disease patients. While they will not change the primary condition, they may be necessary to preserve and possibly improve current function, strength, and mobility.

Some additional therapies may include: speech therapy, physical therapy, occupational therapy, and respiratory therapy. Other therapies specific to the patient’s needs may be beneficial as well.
**Physiological “Stress”**
Stress, good or bad, can cause energy depletion, which may result in temporary, or sometimes permanent, worsening of the condition. It is impossible to avoid all physiologically stressful conditions. However, recognizing what may be stressful for a patient allows one to adjust the lifestyle.

**Cold Stress** avoidance is extremely important. Thermal regulation (temperature control) is not always normal in people with mitochondrial diseases and exposure to cold can result in severe heat loss and trigger an energy crisis. When going out into the cold, all exposed body parts should be covered, and exposure to extreme cold should be avoided for anything more than a short period. Overbundling can be a problem, too (see below).

**Heat Stress** can be a problem in some people. This is especially true of those with an inability to sweat normally. Heat exhaustion and heat stroke may occur on hot days. An example of a typical scenario for this situation would be a child who seems to “wilt” in situations like hot classrooms, whereas other students function normally. Light clothing is important. Patients should avoid direct sunlight on hot days and stay indoors if it is too warm outside. An air conditioned environment may be needed.

**Starvation or fasting - see nutrition/diet information**  
**Lack of Sleep - may be harmful**  
**Illness - especially with fever should be treated as soon as possible**  
**Stressors specific to the individual patient.**

**Toxins**
**Alcohol** has been known to hasten the progression of some conditions.

**Cigarette smoke** is known to hasten the progression of some conditions probably due to the carbon monoxide, which possibly inhibits complex IV of the OXPHOS chain. If there is already a dysfunction of OXPHOS, cigarette smoke will make it worse.

**MSG (monosodium glutamate)** has for years been known to cause migraine headaches in otherwise healthy individuals and may trigger these events in susceptible people with mitochondrial disease. **Read the label and avoid MSG.**
It is not possible to chart the future of a person with a mitochondrial disorder. Those with a higher number of defective mitochondria do worse, on average, than those with a lesser number, but this is only valid for populations of patients and cannot be used to predict what will occur in any one patient.

Some of the information used in this introductory guide was taken from the following articles, which are also on our website at: www.umdf.org.

**Mitochondrial Cytopathies - A Primer**
Bruce H. Cohen, MD

**Myths and Facts about Mitochondrial Disease**
Sumit Parikh, MD and Bruce Cohen, MD

**Nutritional, Pharmacological, and Exercise Treatment Strategies for Mitochondrial Disorders**
Mark A. Tarnopolsky, MD, PhD, FRCP (C)

**Supplements and Nutrition**
Mark Tarnopolsky, MD, PhD, FRCP (C)

**Mitochondrial and Metabolic Disorders**
- A Primary Care Physicians Guide

**The Mitochondrial Medicine Society**- www.mitosoc.org

Special thanks to the physicians that contributed to the revision of this introductory guide:

Marni Falk, MD, The Children’s Hospital of Philadelphia, Philadelphia, PA
Sumit Parikh, MD, Cleveland Clinic, Cleveland, OH
Mark Tarnopolsky, MD, PhD, FRCP (C), McMaster University Medical Center, Hamilton, Ontario, Canada
(Insert patient’s name) has a disorder of ***. Some individuals with metabolic and mitochondrial diseases are more sensitive to physiologic stressors such as minor illness, dehydration, fever, temperature extremes, surgery, anesthesia, and prolonged fasting/starvation. During such stress, rapid systemic decompensation may occur. Preventative measures are aimed at avoiding, or at very least not exacerbating such decompensation.

Mainstays of treatment during or prior to acute metabolic decompensation in mitochondrial and metabolic disease includes keeping patients well-hydrated, providing sufficient anabolic substrate, correcting secondary metabolic derangements, avoiding pharmacological mitochondrial toxins, and providing cofactor and/or salvage therapies.

**IV fluids and substrate therapy**
- Dextrose/electrolyte therapy should be considered if a patient is unable to maintain oral fluid intake in the face of a catabolic stressor, including fever, illness or vomiting.
- A hospital admission should be considered, not exclusively for dehydration, but to prevent catabolism by providing an anabolic food in the form of dextrose.
- Routine chemistries, CBC, liver function (synthetic and cellular), ammonia, glucose, ketosis and lactic acidosis should be monitored and any derangements corrected.
- Assessment of the patient’s cardiac and renal status must be performed prior to aggressive fluid therapy.
Hydration and substrate therapy involves providing 5 or 10% dextrose containing IV fluids given at 1.25-1.5X times the maintenance rate. A high dextrose delivery with D10 or D20 might be needed, especially if acidosis or metabolic derangements are not correcting with 5% dextrose containing fluids. When a higher dextrose delivery is given, insulin may also be needed. Insulin not only controls hyperglycemia but also serves as a potent anabolic hormone, promoting protein and lipid synthesis. Insulin is typically given in the intensive-care-unit setting with the initial dose in the 0.05-0.1 U/kg/hour range, and titrated accordingly.

- IV fluids should never contain Lactated Ringers solution.
- Fluids should be weaned based on laboratory parameters, oral intake and resolution of the underlying metabolic stressor.
- Once the initial crisis passes, enteral feeding should be considered. Protein can be added if hyperammonemia has resolved and there is no concomitant disorder of protein catabolism. If there is no primary or secondary fatty acid oxidation dysfunction, lipids may also be added.
- Once the patient’s laboratories begin to normalize, restarting the patient on their home-based diet is advised.

**Laboratory Parameters**

- If acutely acidotic with a pH < 7.22 or bicarbonate level < 14 mM, metabolic acidosis can be controlled by administering sodium bicarbonate as a bolus (1 mEq/kg) followed by a continuous infusion.
- Hyperammonemia can occur due to secondary inhibition of the urea cycle. As treatment for the metabolic decompensation proceeds, the ammonia level should diminish. A level > 200 uM may require salvage therapy or dialysis.
- Any underlying infection and fever should be aggressively treated.

**Antioxidant therapy**

- Levo-carnitine therapy during an acute illness may be beneficial. It should be given intravenously at a dose of at least 100 mg/kg/day. Doses of up to 300 mg/kg/day have been used. If the patient is on a higher oral dose, that dose should be used intravenously for treatment.
- Any other home-based supplements and antioxidants being given should be continued by mouth if possible.
Medication contraindications

• Medications that should generally be avoided during times of illness in individuals with mitochondrial disease include valproic acid, statins, aminoglycoside antibiotics, and erythromycin. These medications should be used with extreme caution if given long-term.

• There are no absolute contraindications and these medications can be given if an alternative medication is not available or appropriate as long as a prior adverse reaction to the medication has not occurred.

• Should a medication such as valproate be used for the first time during an acute illness, liver enzymes, ammonia and synthetic liver function should be closely monitored.

• In addition to the medications noted above, long-term use of anti-HIV therapy, traditional neuroleptics, and select chemotherapeutic agents may worsen mitochondrial function.

Anesthesia

• Questions on anesthetic sensitivity in mitochondrial patients remain.

• Some individuals with mitochondrial metabolic diseases are more sensitive to volatile anesthetics and need a much lower dose to achieve a bispectral (BIS) index of <60. This effect has been seen more in patients with reduced complex 1 capacity. Sevoflurane might be better tolerated than isoflurane and halothane.

• Debate remains as to the potential risk of propofol administration in mitochondrial disease patients. However, propofol has been routinely used in many mitochondrial patients for brief periods of sedation (less than 30-60 minutes) without apparent clinical problems. Limiting propofol use to short procedures and brief periods of sedation is advisable for now.

Fasting with surgery

• During pre- and post-operative fasting, catabolism can be prevented by using dextrose-containing IV fluids. IV fluids are continued until the time of discharge, since they are intended to deter catabolism and not simply treat dehydration.

• IV fluids should never contain Lactated Ringers solution.

• Routine chemistries, a complete blood count, liver function (synthetic and cellular), ammonia, glucose, ketosis and lactic acidosis should be monitored and any derangements corrected.

Please contact my office if you have any questions regarding this letter.

Sincerely,

(Your doctor’s signature)
For additional information on the topics covered in this booklet, as well as other topics, please explore the United Mitochondrial Disease Foundation website at: **www.umdf.org**.

A few links that may be of particular interest include:

- **www.umdf.org/askthemitodoc**: Questions and answers provided by a team of mitochondrial disease experts.

- **www.umdf.org/diseasetype**: For more in depth information on specific disorders and articles to share with your health care professionals.

- **www.umdf.org/partofthecure**: Want a free membership? See what the UMDF offers in your state. You will find information on UMDF groups, activities, events, and local resources.

- **www.umdf.org/mito101**: A primer for physicians and patients. Mito 101 is a compilation of information intended to familiarize general practitioners and families alike with the most common problems raised by mitochondrial diseases.

- **www.umdf.org/symposium**: Looking for an opportunity to learn more about mitochondrial disorders and to network with others facing similar challenges? The annual Mitochondrial Medicine Symposium is designed for you! On this link you will find all of the up-to-date details.

- **www.umdf.org/researchgrants**: Learn how the UMDF spends its research dollars. This peer-review process selects best-of-the-best applications for funding.

- **www.umdf.org/AACT**: UMDF’s Adult Advisory Committee Team. ACTT represents and serves the unique needs of the affected adult community ensures that those needs are adequately represented to UMDF resulting in enhanced services to the affected adult population.