Summary – How Do I Know if I Have Mito?
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The Basics
Mitochondria are located within the cell and they produce the energy that the body needs to function. This energy, in the form of ATP, is the key that turns on all bodily functions, like the heart, lungs, brain, etc. This is a very efficient energy pathway that affects the function of about 1500 different proteins. However, because of the number of proteins this pathway affects, if there is a problem along the way, the resulting symptoms can be extremely varied.
People with mitochondrial disease, therefore, can present with symptoms ranging from seizures or developmental delays in children to GI problems or weakness and fatigue in adults. Because of this widespread array of symptoms, there is often a delay in getting a diagnosis or, for some, never getting a diagnosis.

At one time it was believed that the incidence of Mito was only 1 in 50,000 to 100,000 people but now we know that it occurs in about 1 out of 2000 people.

When do we decide someone has mitochondrial disease? When patients present with multiple, widespread symptoms that appear to be unrelated or don't fit together, then we might look to see if Mito is the cause. There is a list of such symptoms that can be found on the Virtual Medical Practice website as well as the MitoAction website.

There are several ways that Mito can be diagnosed:

1. A certain constellation of symptoms may be particularly indicative of Mito, such as seizures with stroke-like features and increased lactic acid. In such cases, MELAS is probably the diagnosis and can be confirmed with DNA testing (invasive testing is no longer necessary). This situation covers only a very small percent of those affected.

2. There are clinical symptoms which can be highly suggestive of Mito that include specific ophthalmic changes, ptosis, & MRI changes (for Leigh's Disease in children). These too can then be confirmed with a blood test for certain gene markers.

3. Most cases of Mito, however, do not present themselves so easily and are not so easily diagnosed. What usually causes a physician to look for Mito would be symptoms that don't fit together, are multiple, and widespread. This should raise a red flag for further investigation.

TraditionalTesting versus New Techniques In the past, the gold standard for diagnosing Mito was the *muscle biopsy* followed then by enzyme testing and histology. A muscle biopsy requires getting a sample of muscle cells and looking at them under a microscope, looking for what are known as "ragged red fibers". These are accumulations of mitochondria on the outside of the tissue and can be detected using a special staining process. If these fibers are detected, then Mito can be confirmed.Often, however, this test can be negative but this does not rule out Mito. A recent article reportedresearch which demonstrated that ragged red fibers were actually found in only a small percentage of patients with mitochondrial disease. *En*zyme studiescan also be done on the muscle biopsy to detect enzyme levels, and this can help diagnose mitochondrial changes in the electron chain, complex 1 or 2, which could result in disease. Until the 1990's, fresh muscle biopsies were much preferred over frozen samples but now both fresh and frozen are deemed appropriate for studies. There are some studies that can only be done on fresh samples, but it is questionable as to how helpful these studies actually are. One problem with the traditional muscle biopsy test is first of all that it is invasive. Mito patients have a very difficult time with anesthesia and muscle biopsy requires removing a small piece of muscle tissue. Also, this test can be quite costly. Depending on the laboratory, the whole diagnostic procedure can cost as much as $10,000 or more. Most importantly, muscle biopsy diagnosis is not 100%. Someone could have a complex 1 defect but still

not have mitochondrial disease (for example, Parkinson's disease and Alzheimer's also show complex 1 defects). Pediatric diseases can also be misdiagnosed especially with abnormal enzyme results.

There are some laboratory tests which can be indicators of Mito, like increased lactic acid, increase in pyruvate levels or increased CSF lactate, but these should be considered metabolic markers or indicators rather than definitive in the diagnosis process.

Genetic Studies Up until the end of 2010, genetic identification of Mito was still very low because only about 10% of all the genes had been identified (about 100 or so). Additional genes have been identified over the recent year, and we now can screen much more accurately for Mito. *DNA testing* has become the diagnostic method of choice because it requires only a blood test, and is more accurate. Even those who have had a muscle biopsy in the past can have the diagnosis confirmed with the DNA blood test, because there are false positive muscle biopsy and enzyme tests.
The genes which effect Mito can be from the nuclear DNA or the mtDNA (mitochondrial DNA). From 75% to 90% of pediatric Mito cases are caused by nuclear DNA. Because we still don't have all of these genes identified, this can still be an area where diagnosis is difficult. But research is progressing. Only a small portion of Pedi Mito is transmitted through the mtDNA. There are 37 genes which are transmitted exclusively from the maternal side (mtDNA), and these have all been identified. Because of this, we are now able to diagnose more accurately, but diagnosis still remains a difficult process.

Interpreting the results One of the most important aspects of diagnosing and treating Mito is the physician/clinician's familiarity with the diagnosis of mitochondrial disease. Because of the manner in which symptoms present (that is, very different for each patient), diagnosis may still be difficult.
A person may have a widespread set of symptoms, yet test negative for mitochondrial disease. If a physician is unfamiliar with other forms of Mito testing, he or she may discount this diagnosis. Clinicians who see lots of Mito patients will be more likely to recognize the fact that Mito patients do not fit into a certain set of specific symptoms. Mito diagnosis is complicated, and it takes someone who has seen many patients with the disease to recognize the possible/probable diagnosis. The MitoAction site has a list of all clinicians who see Mito patients grouped geographically - and those with asterisks are those who are the experts in the field, ie, those who specialize in Mito.

Insurance Coverage In the diagnosis process, an important question becomes: will insurance cover the diagnostic procedures? It is difficult to get coverage if there is no diagnosis, but what can help is to have a step by step diagnostic procedure outlined by the clinician. This can then be accompanied by letters which outline what procedures are being done and why. The question also comes up about testing an entire family if there seems to be multiple symptoms in several members. This, however, can be expensive, especially if some family members are asymptomatic. The best thing to do for now is to test those who are showing symptoms.

Summary Though we have come a long way in being able to diagnose mitochondrial disease, it remains a difficult process, and patients are often left with a diagnosis that is not definitive. Because of the research and advances that have been made over the past 5-10 years, patients with mitochondrial disease have a much better chance at getting correct diagnosis and treatment today