SYMPTOMS I — listed on www.virtualmdpractice.com

- **BRAIN**
  - Developmental Delays
  - Migraines
  - Seizures
  - Dementia
  - Autistic Features
  - Atypical Cerebral Palsy
  - Neuro-psychiatric Disturbances
  - Mental Retardation
  - Strokes
Symptoms II — listed on www.virtualmdpractice.com

- **Nerves**
  - Absent reflexes
  - Fainting
  - Neuropathic pain
  - Weakness (may be intermittent)
  - Dysautonomia - temperature instability & other dysautonomic problems

- **Pancreas & Other Glands**
  - Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
  - Parathyroid failure (low calcium)
SYMPTOMS III — listed on www.virtualmdpractice.com

- MUSCLES
  - Weakness
  - Cramping
  - Hypotonia
  - Muscle pain

- GASTROINTESTINAL PROBLEMS
  - Pseudo-obstruction
  - Dyssmotility
  - Irritable bowel syndrome
  - Gastroesophageal reflux
  - Diarrhea or constipation
SYMPTOMS IV — listed on www.virtualmdpractice.com

- **KIDNEYS**
  - Renal tubular acidosis or wasting

- **HEART**
  - Cardiomyopathy
  - Cardiac conduction defects (heart blocks)

- **LIVER**
  - Liver failure
  - Hypoglycemia (low blood sugar)
**EARS & EYES**
- Visual loss & blindness
- Ptosis
- Ophthalmoplegia
- Optic atrophy
- Hearing loss and deafness
- Acquired strabismus
- Retinitis pigmentosa

**SYSTEMIC**
- Failure to gain weight
- Chronic Fatigue
- Unexplained vomiting
- Short stature
- Respiratory problems
COMMON PROBLEMS IN MITOCHONDRIAL ENERGY DISORDERS

- Central Nervous system (Brain) problems such as developmental delays including AUTISM AND AUTISTIC FEATURES, loss of function, seizures, hypotonia & weakness
- Failure to thrive
- Chronic fatigue
- Gastrointestinal issues such as chronic constipation
- Autonomic dysfunction such as irregular heart rate and blood pressure and temperature instability with heat intolerance.
CLINICAL FEATURES SUGGESTIVE OF MITOCHONDRIAL ENERGY DISORDERS

- Typical brain changes suggestive of Leigh disease or abnormalities in white matter
- Persistent, significant elevations in lactate (especially if in the brain) and other specific biochemical features
- Problems in many body systems suggestive of mitochondrial disease
- Strong family history of mitochondrial disease
How is Mitochondrial Disease Diagnosed? Traditional Evaluation

- Clinical features, physical findings and minimal laboratory/radiographic studies, example specific brain lesions as seen in Leigh disease.

- Clinical phenotype consistent with one of the well described subtypes of mitochondrial disease, such as MELAS and confirmed by gene test.

- Clinical features and findings suggestive of mitochondrial disease – tissue studies completed.
Leigh Disease MRI Lesions
Diagnosis of Mitochondrial Energy Disorders

- Abnormalities in mitochondrial structure/size/shape/number on tissue biopsy
- Enzymatic abnormalities on testing of the energy producing system (respiratory chain or electron transport chain)
- Specific DNA changes that cause mitochondrial disease
Ragged Red Fibers
Examples of Nuclear Gene Mito Disease

- Complex I nuclear gene mutations - example NDUFS1 patients with leukodystrophy and myoclonic epilepsy
- Complex IV assembly gene mutations - example SURF1 mutations associated with Leigh disease
Examples of mtDNA Disease

- MELAS (Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke Like Episodes) due to tRNA 3243 mtDNA mutation
- MERRF (Myoclonic Epilepsy and Ragged Red Fibers) due to tRNA 8344 mutation
**Prognosis of Mitochondrial Energy Disorders**

- Quite variable but typically progressive over time
- Patients can face severe disabilities and early death
- Many patients stabilize or show improvements with institution of care
- Problems typically worsen with stressors such as illness and surgery
Current Treatment of Mitochondrial Energy Disorders

- Symptomatic – treat existing problems
- Preventative – early detection of associated problems
- Therapeutics very limited and include use of Coenzyme Q10
INHERITANCE OF MITOCHONDRIAL ENERGY DISORDERS

Autosomal Recessive Inheritance
INHERITANCE OF MITOCHONDRIAL ENERGY DISORDERS

mtDNA Inheritance (Maternal Line)

(Common female ancestor)

- Females
- Males

Black circles & boxes show how mtDNA is passed from females to all their offspring.

Maternal Inheritance
INHERITANCE OF MITOCHONDRIAL ENERGY DISORDERS

- Autosomal Dominant forms
- Sporadic
- X-linked
Advancements And the Future

- Edison Pharma EPI 743 trial for Leigh Disease and MELAS patients
- Hemopoietic stem cell transplant for MNGIE
- Elimination of mtDNA mutation with nuclear transplant into healthy egg cells
- New less invasive testing including buccal swab enzyme testing and expanded gene panels to identify hundreds of the known mito genes