Table 1: Screening Guidelines

	At diagnosis, if not previously obtained	At 1-2 year intervals and as needed	As needed depending on symptoms or disease type	Comments
Audiology	*	*		
Cardiology				Holter recording depending on the underlying diagnosis and risk of heart block; up to every 3-6 months for disorders associated with high-risk of arrhythmias, such as mtDNA deletion disorders Echocardiograms may be performed less frequently in low-risk patients after several years of monitoring
Blood Pressure	*	*		
Echocardiogram	*	*		
Electrocardiogram	*	*		
Holter			*	
Cardiac MRI			*	
Endocrinology				Endocrine screening strongly recommended in those with mtDNA deletion disorders
Basic chemistries	*	*		
Calcium (Ca), Magnesium (Mg) & Phosphate	*	*		
Cortisol-ACTH-Aldosterone-Renin			*	
Ca & phosphate, urine	*	*		
Gonadotrophins			*	
Hemoglobin A1c	*	*		
Parathyroid hormone	*		*	
Thyroid stimulating hormone & free thyroxine	*	*		
Vitamin D	*	*		
Dual X-ray Absorptiometry (DXA)			*	DXA especially if unexpected fractures
Gastroenterology				
Amylase-lipase			*	
Transaminases	*	*		
Stool elastase			*	
Swallow evaluation			*	
Growth and anthropometric parameters	*	*		Recommended at each visit
Hematology				Obtained more routinely in those with high risk of or

CBC with differential Iron studies including ferritin	* 	 	* *	symptomatic bone marrow dysfunction
Immunology			*	With recurrent infections
Neurology Developmental & Cognitive Assessments Electroencephalogram	*	*	 *	Clinical appraisal or formal neuropsychological tests; formal testing recommended with regression
Ophthalmology Exam Electroretinogram Optical Coherence Tomography	*	*	 * *	
Psychiatry Mood and Anxiety Disorder Screening	*	*		
Pulmonology Pulmonary function Polysomnogram			* *	Especially with myopathy & if non-ambulatory or with brainstem dysfunction
Renal CMP with Mg and Phos Albumin/creatine, urine	 * *	 * *		

Table 2: Other specialist consultations to consider at time of diagnosis and at 1-2 year intervals as needed based on symptoms

Audiology
Cardiology
Endocrinology
Ear, Nose and Throat
Gastroenterology
Genetics
Hematology
Immunology
Nephrology
Neurology
Ophthalmology
Orthopedics
Palliative Care
Physical Medicine & Rehab/Physiatry

Psychiatry (for patient or family)
Psychology (including Family Counseling)
Pulmonology
Social Work
Sleep Medicine
Therapy services including PT, OT and ST

Table 3: Illness, Anesthesia and Stroke Management

Illness Management[3]

1. Specific decisions about patient management including hospitalization require clinical judgment and should be case-specific. Decisions should reflect the individual patient's presentation as well as an understanding of the etiology for the acute decompensation and the pathophysiology of the underlying mitochondrial disorder.
2. Patients with a mitochondrial disease should carry an emergency care plan that details their underlying disorder and provides management recommendations.
3. Patients with a mitochondrial disease should consider wearing a Medic Alert bracelet when appropriate depending on their clinical symptomology.
4. Mitochondrial patients should take precautions to prevent entering catabolism, especially when exposed to medical stressors, including avoiding prolonged fasting and receiving dextrose-containing intravenous (IV) fluids before, during, and after procedures and surgeries. (Dextrose should not be provided or provided in limited quantity as indicated by clinical status in suspected or confirmed disorders of pyruvate metabolism, if the patient is on a ketogenic diet, or the patient has had a previous adverse response to high glucose delivery.)
5. Evaluation of a mitochondrial patient in the acute setting should include evaluation of routine chemistries, glucose, transaminases, and lactate; all other testing is as clinically indicated, although one must keep in mind the potential for cardiac and neurologic decompensations in these patients.
6. Treatment during acute decompensation should include dextrose-containing IV fluids, stopping exposure to potentially toxic medications, and correction of any metabolic derangements. (Note: dextrose should be provided only in limited in quantity or not at all, as indicated by clinical status in suspected or confirmed disorders of pyruvate metabolism, if the patient is on a ketogenic diet, or the patient has had an adverse response to high glucose delivery.) IV fluid rate should be based on the clinical situation. Outpatient mitochondrial therapies should be continued when possible.
7. Lipids can be used when needed in mitochondrial patients, even in the presence of secondary fatty-acid oxidation dysfunction.
8. The following medications should be avoided in patients with mitochondrial disease when possible and, if given, they should be used with caution: valproic acid; statins; metformin; high-dose acetaminophen; and selected antibiotics, including aminoglycosides, linezolid, tetracycline, azithromycin, and erythromycin.

9. Repeat neuroimaging should be considered in any mitochondrial patient with an acute change in neurologic status.

Anesthesia and Surgical Management[3]

1. Patients with mitochondrial diseases are at an increased risk of anesthesia-related complications.
2. Preoperative preparation of patients with mitochondrial disease is crucial to their perioperative outcome. Patients should minimize preoperative fasting and have glucose added to their perioperative IV fluids, unless they are on a ketogenic diet or have been demonstrated to have adverse reaction to higher glucose intake.
3. Caution must be used with volatile anesthetics because mitochondrial patients may potentially be hypersensitive.
4. Caution must be used with muscle relaxants in those mitochondrial patients with a preexisting myopathy or decreased respiratory drive.
5. Mitochondrial patients may be at a higher risk for propofol infusion syndrome and propofol use should be avoided or limited to short procedures.
6. One should consider slow titration and adjustment of volatile and parenteral anesthetics to minimize hemodynamic changes in mitochondrial patients.
7. Local anesthetics are generally well-tolerated in patients with mitochondrial defect.
8. There is no clear established link between malignant hyperthermia and mitochondrial disease.

Stroke Management[3, 72]

1. Stroke-like episodes in primary mitochondrial disease typically have correlating visible magnetic resonance imaging abnormalities.
2. IV arginine hydrochloride should be administered urgently in the acute setting of a stroke-like episode associated with the MELAS m.3243 A>G mutation in the *MTTL1* gene and considered in a stroke-like episode associated with other primary mitochondrial cytopathies as other etiologies are being excluded. Patients should be reassessed after 3 days of continuous IV therapy.
3. The use of daily oral arginine supplementation to prevent strokes should be considered in MELAS syndrome.
4. The role of monitoring plasma arginine and citrulline levels and oral citrulline supplementation in the treatment of MELAS requires further research.

Table 4: Medication Cautions

Medication	Common Uses	Concern in Mitochondrial Disease
Acetaminophen	Analgesic, fever prevention, headaches	Chronic or frequent use may deplete glutathione and cause hepatopathy
Aminoglycosides	Antibiotic	Hearing loss

Antiretrovirals	HIV therapy	Impaired mtDNA replication and worsening peripheral neuropathy, liver dysfunction or myopathy
Botulinum toxin	Dystonia, Spasticity	Worsening of weakness
Butterbur	Headache	May contain pyrrolizidine alkaloids (oxidants) and cause hepatopathy
Metformin	Diabetes	Lactic acidosis
Topiramate	Epilepsy, Headache, Intracranial Hypertension	Lactic acidosis
Statins	Hypercholesterolemia	Worsening myopathy and elevated creatine kinase (CK)
Valproic Acid	Epilepsy, Headache, Mood disorders, Movement disorders, Tone abnormalities	Irreversible liver failure and onset of hepato-encephalopathy, especially in *POLG*-related disorders; worsening of seizures
Vigabatrin	Epilepsy	Inhibition of the mitochondrial nucleoside salvage pathway and worsening of mtDNA depletion disorders

*With the exception of valproic acid in POLG-related disorders, these medications are **not contraindicated** and **may be used** with caution*