The MMS consensus guidelines review and updates

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Disclosures

- President, Mitochondrial Medicine Society
- Board member, Mitochondrial care network

Acknowledgement

- Some slide are courtesy of Dr. Sumit Parikh

Optimizing Mitochondrial Disease Care

- Practice Patterns, Challenges and Consensus

Mitochondrion 2013
Genetics in Medicine 2015
Genetics in Medicine 2017

Optimizing Mitochondrial Disease Care

- How is mitochondrial medicine practiced in North America?
- Is there an optimal way of practicing mitochondrial medicine?
- Is care standardized?
- Who is in charge of care?

Practice patterns of mitochondrial disease physicians in North America. Part 1: Diagnostic and clinical challenges ☆

Sumit Parikh [a,*], Amy Goldstein [b], Mary Kay Koenig [c], Fernando Scaglia [d], Gregory M Enns [e], Russell Saneto [f], for the Mitochondrial Medicine Society Clinical Directors Working Group, Other members of the MMS Clinical Director's Work Group
Irina Anselm [1], Abigail Collins [2], Bruce H. Cohen [3], Suzanne D. DeBrosse [4,5], David Dimmock [6], Marni J. Falk [7,8], Jaya Ganesh [9], Carol Greene [10], Andrea L. Gropman [11,12], Richard Haas [13], Stephen G. Kahler [14], John Kamholz [15], Fran Kendall [16], Mark S. Korson [17], Andre Mattman [18], Margherita Milone [19], Dmitriy Niyazov [20], Phillip L. Pearl [11], Tyler Reimschisel [21], Ramona Salvarinova-Zivkovic [22], Katherine Sims [23], Mark Tarnopolsky [24], Chang-Yong Tsao [25], Johan van Hove [26], Laurence Walsh [27], Lynne A. Wolfe [28]

Practice patterns of mitochondrial disease physicians in North America. Part 2: treatment, care and management

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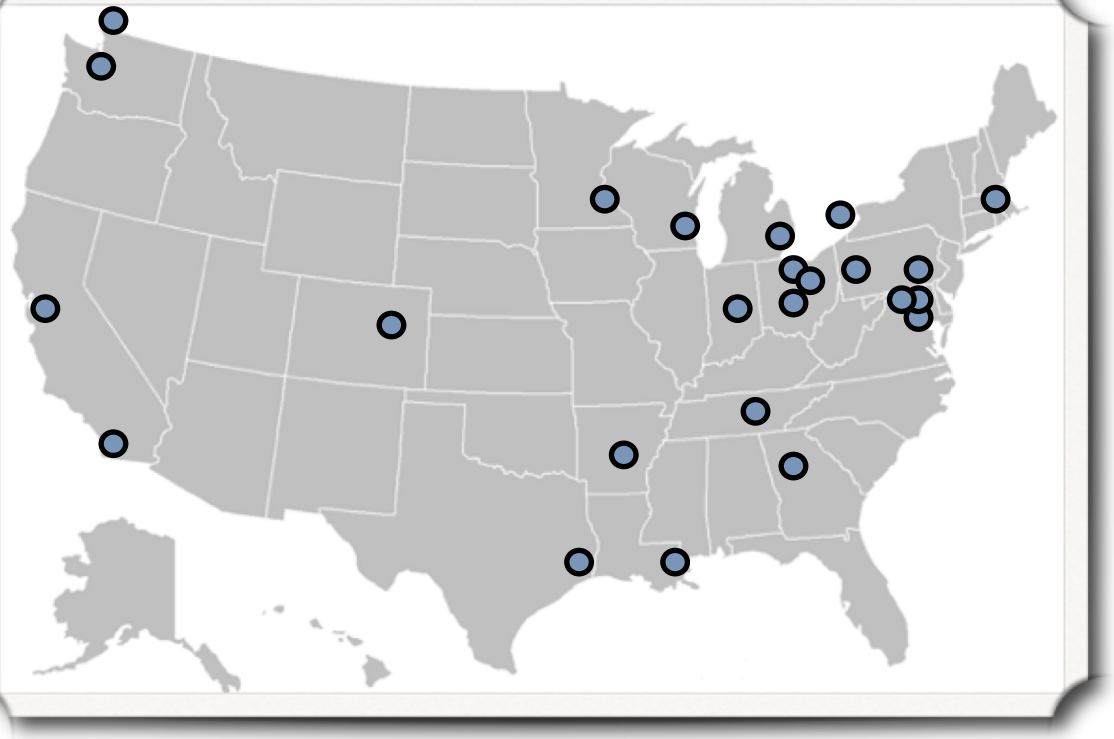
Practice Locations

Little Rock, Arkansas
San Diego, California
Stanford, California
Vancouver, BC, Canada
Hamilton, Ontario, Canada
Aurora, Colorado
Washington, DC
Atlanta, Georgia
Indianapolis, Indiana
New Orleans, Louisiana
Baltimore, Maryland
Bethesda, Maryland
Boston, Massachusetts
Detroit, Michigan
Rochester, Minnesota
Akron, Ohio
Cleveland, Ohio
Columbus, Ohio
Nashville, Tennessee
Houston, Texas
Philadelphia, Pennsylvania
Pittsburgh, Pennsylvania
Seattle, Washington
Milwaukee, Wisconsin



Variability in diagnostic care

Biochemical testing protocol
Genetic testing protocol
Muscle biopsy testing
Interpretation of muscle biopsy
Use of diagnostic criteria

Variability in treatment

Use of supplements
Cocktail vs no cocktail
Monitoring of organ system involvement
Monitoring lab work

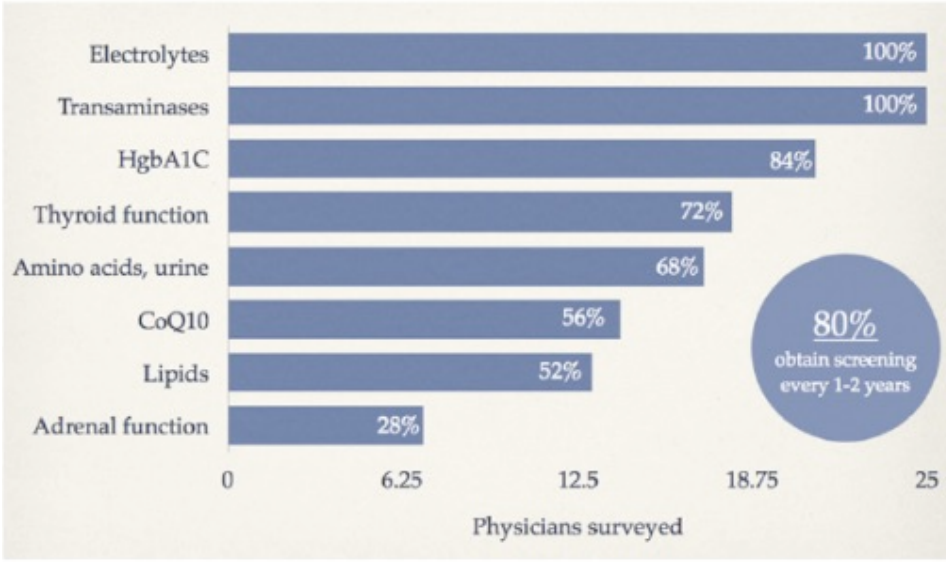


Fig. 1. Preventative lab work obtained.

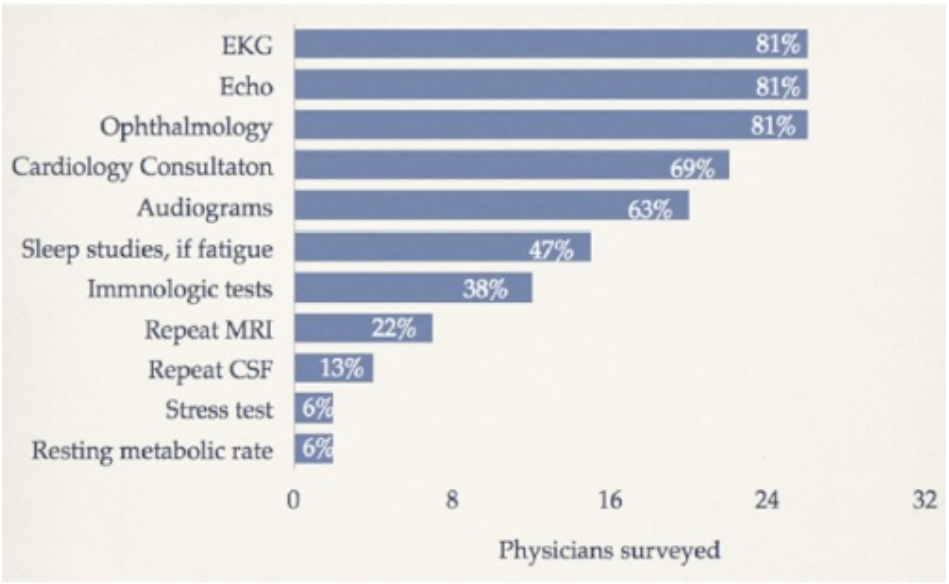


Fig. 2. Preventative testing obtained.

Management during periods of catabolic stress.

	N out of 32 unless stated	%
Illness precautions		
Hospital admission for IV dextrose	30	94%
Only when oral intake has decreased or vomiting	19/30	63%
With any illness (for select patients depending on clinical history)	11/30	37%
Fluid type used		
Use of D5 IV fluids	9/30	30%
Use of D10 IV fluids	11/30	37%
Depends on patient lab work	10/30	33%
Use of supplemental carnitine in fluids	29	59%
Carnitine dose increased from home dose	10/29	34%
Use of additional supplements when ill	6	18%
Use of an emergency protocol letter	28	88%
Medication and fluid avoidance		
Select antibiotics (list varied between providers)	21	66%
Valproic acid (regardless of mitochondrial disease type)	25	70%
Sequencing of POLG1 prior to beginning valproate in patients with epilepsy and no clear diagnosis	20	63%
Lactated Ringer's	28	88%
Anesthesia precautions		
Recommended	32	100%
Use of an anesthesia protocol letter	23	72%
Propofol avoidance		
Unrestricted use	0	0%
Restricted to short procedures (less than 2 h)	20	63%
Avoid if possible	15	47%
Sevoflurane	3	9%
Succinylcholine avoidance due to concerns of malignant hyperthermia	5	16%
Surgical precautions		
Admission for IV fluids preoperatively	19	59%
Admission only if prior history of adverse response	13	41%
Vaccinations/immunizations recommended	32	100%
Restricting vaccinations to times of good health	21	66%
Pre-medication with anti-inflammatories or anti-oxidants	9	28%
Alter schedule to provide fewer immunizations at one time	11	34%

Results

Similarities in practice but a general lack of consensus

Agreement in care

- Clinic structures and organization
- Physician perceptions of various diagnostic laboratories
- Care requires significantly more time
- Shortage of adult trained experts

Establishing Consensus?

Methods to develop consensus

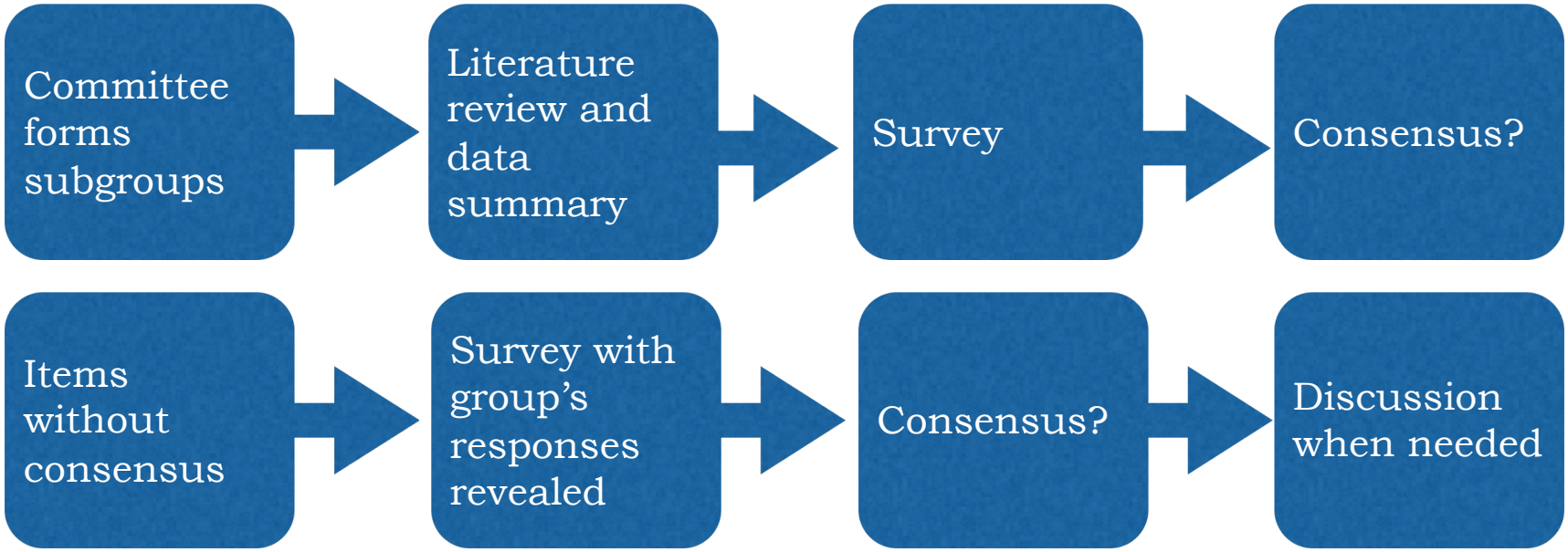
- Evidence-based
- Eminence based (grey heads in the room)
- Committee based (may the strongest personality win)
- NIH style consensus (non-experts decide)
- Individual (I'll decide)

borrowed from Georgianne Arnold

Delphi Method

"Pooled intelligence enhances individual judgement and captures the collective opinion of a group of experts".

Developing consensus in the absence of sufficient evidence utilizing a committee of content experts



SYSTEMATIC REVIEW | Genetics inMedicine

Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

Sumit Parikh, MD[1], Amy Goldstein, MD[2], Mary Kay Koenig, MD[3], Fernando Scaglia, MD[4], Gregory M. Enns, MD[5], Russell Saneto, MD, PhD[6,7], Irina Anselm, MD[8], Bruce H. Cohen, MD[9], Marni J. Falk, MD[10], Carol Greene, MD[11], Andrea L. Gropman, MD[12], Richard Haas, MB BChir, MRCP[13], Michio Hirano, MD[14], Phil Morgan, MD[15], Katherine Sims, MD[16], Mark Tarnopolsky, MD, PhD[17], Johan L.K. Van Hove, MD[18], Lynne Wolfe, MS, CRNP[19] and Salvatore DiMauro, MD[20]

19 specialists

Irina Anselm
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Gregory Enns
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Amy Goldstein
Carol Greene
Andrea Gropman
Richard Haas
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Phil Morgan
Sumit Parikh
Russell Saneto
Fernando Scaglia
Katherine Sims
Mark Tarnopolsky
Johan Van Hove
Lynne Wolfe

Salvatore DiMauro

US & Canada

Diagnostic Consensus Criteria

Biochemical Testing in Blood, Urine and Spinal fluid

Genetic Testing

Pathology and Biochemical Testing of Tissue

Neuroimaging

Treatment of Acute Stroke

Exercise

Anesthesia

Treatment During Illness

Treatment with vitamins and supplements

Prevention and Care Guidelines

Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

Sumit Parikh, MD[1], Amy Goldstein, MD[2], Amel Karaa, MD[3], Mary Kay Koenig, MD[4], Irina Anselm, MD[5], Catherine Brunel-Guitton, MD, FRCPC[6], John Christodoulou, MBBS, PhD[7], Bruce H. Cohen, MD[8], David Dimmock, MD[9], Gregory M. Enns, MB, ChB[10], Marni J. Falk, MD[11], Annette Feigenbaum, MD[12,13], Richard E. Frye, MD, PhD[14], Jaya Ganesh, MD[15], David Griesemer, MD[16], Richard Haas, MB BChir, MRCP[17,18], Rita Horvath, MD, PhD[19], Mark Korson, MD[20], Michael C. Kruer, MD[21], Michelangelo Mancuso, MD, PhD[22], Shana McCormack, MD[23], Marie Josee Raboisson, MD[24], Tyler Reimschisel, MD, MHPE[25], Ramona Salvarinova, MD, FRCPC[26], Russell P. Saneto, DO, PhD[27], Fernando Scaglia, MD[28], John Shoffner, MD[29], Peter W. Stacpoole, PhD, MD[30], Carolyn M. Sue, MBBS, PhD[31], Mark Tarnopolsky, MD, PhD[32], Clara Van Karnebeek, MD, PhD[33,34], Lynne A. Wolfe, MS, CRNP[35], Zarazuela Zolkipli Cunningham, MBChB, MRCP[36], Shamima Rahman, FRCP, PhD[37] and Patrick F. Chinnery, FRCP, FMedSci[38]

35 specialists

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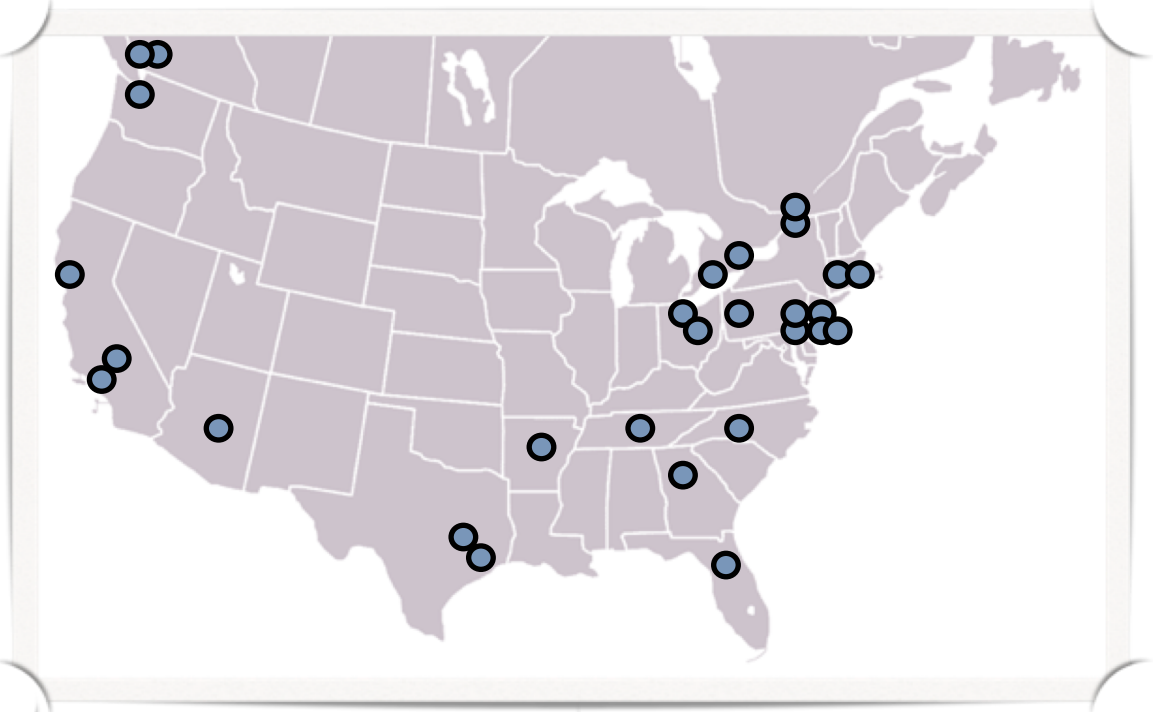
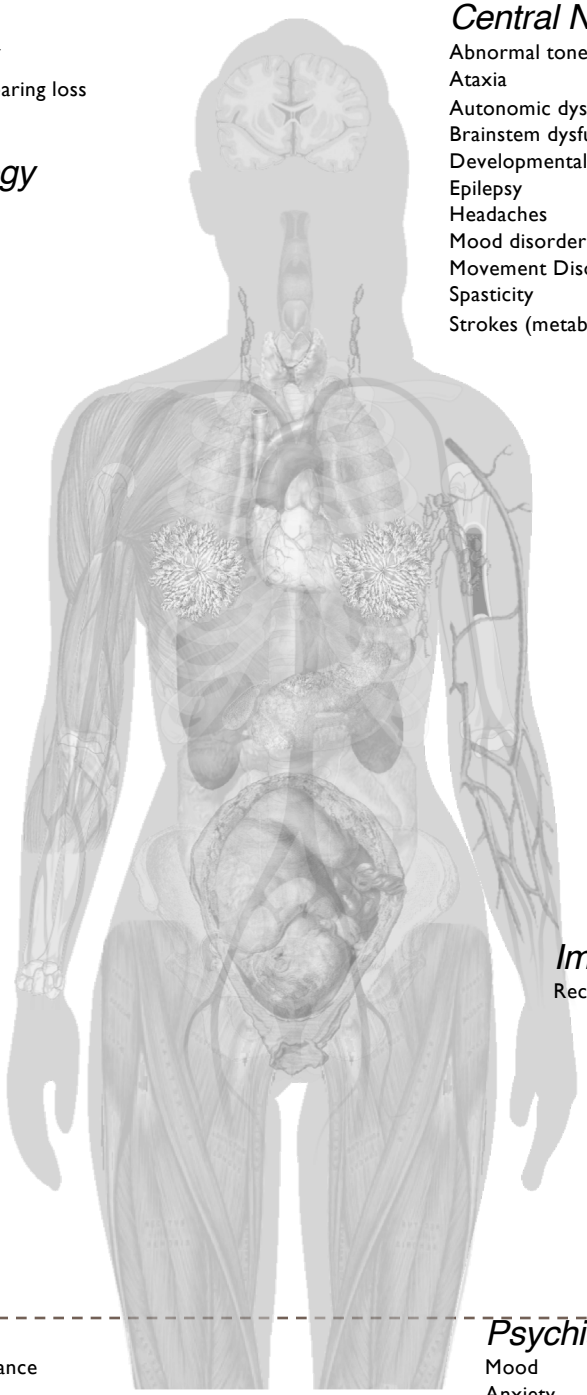




Audiology
Sensorineural hearing loss

Ophthalmology
Cataracts
Ophthalmoplegia
Optic nerve atrophy
Ptosis
Retinopathy

Endocrinology
Adrenal insufficiency
Diabetes mellitus
Growth hormone deficiency
Hypoparathyroidism
Hypothyroidism
Osteopenia
Short stature

Gastroenterology
Constipation
Dysphagia
Dysmotility
Failure to thrive
Liver dysfunction
Pancreatic insufficiency
Pseudo-obstruction

Hematology
Iron deficiency
Pancytopenia
Sideroblastic anemia

Pregnancy
Gestational diabetes
Preeclampsia
Preterm labor

Central Nervous System
Abnormal tone
Ataxia
Autonomic dysfunction
Brainstem dysfunction
Developmental disability
Epilepsy
Headaches
Mood disorder
Movement Disorders
Spasticity
Strokes (metabolic)

Cardiology
Arrhythmia
Cardiomyopathy
Conduction defects
Heart block

Pulmonology
Apnea
Aspiration
Hypoventilation
Pulmonary hypertension
Sleep Disorders

Nephrology
Fanconi syndrome
Glomerular dysfunction
Tubulopathy

Immunology
Recurrent infections

Neuromuscular
Myopathy
Neuropathy

Orthopedic
Contractures
Fractures
Scoliosis

Systemic
Exercise intolerance
Fatigue

Psychiatry
Mood
Anxiety

Table 1 Screening guidelines

	At diagnosis, if not previously obtained	At 1- to 2-year intervals and as needed	As needed depending on symptoms or disease type	Comments
Audiology	•	•		
Cardiology				
Blood pressure	•	•		
Echocardiogram	•	•		Echocardiograms may be performed less frequently in low-risk patients after several years of monitoring
Electrocardiogram	•	•		
Holter			•	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
Cardiac MRI			•	
Endocrinology				Endocrine screening strongly recommended in those with mtDNA deletion disorders
Basic chemistries	•	•		
Calcium (Ca), magnesium (Mg), and phosphate	•	•		
Cortisol–ACTH–aldosterone–renin			•	
Ca and phosphate, urine	•	•		
Gonadotropins			•	
Hemoglobin A1c	•	•		
Parathyroid hormone	•		•	
Thyroid-stimulating hormone and 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 symptomatic bone marrow dysfunction
Complete blood count with differential	•		•	
Iron studies including ferritin			•	
Immunology			•	With recurrent infections
Neurology				
Developmental and cognitive assessments	•	•		Clinical appraisal or formal neuropsychological tests; formal testing recommended with regression
Electroencephalogram			•	
Ophthalmology				
Exam	•	•		
Electroretinogram			•	
Optical coherence tomography			•	
Psychiatry	•	•		
Mood and anxiety disorder screening				
Pulmonology				
Pulmonary function			•	Especially with myopathy, if nonambulatory or with brain stem dysfunction
Polysomnogram			•	
Renal				
CMP with Mg and phosphate	•	•		
Albumin/creatine, urine	•	•		

ACTH, adrenocorticotropic hormone; CMP, comprehensive metabolic panel; DXA, dual-energy X-ray; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA.

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 and rehab/physiatry
Psychiatry (for patient or family)
Psychology (including family counseling)
Pulmonology
Social work
Sleep medicine
Therapy services including physical therapy, occupational therapy, and speech therapy

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 medical 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 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. Strokelike 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 strokelike episode associated with the MELAS m.3243A > 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
Valproic acid	Epilepsy, headache, mood disorders, movement disorders, tone abnormalities	Irreversible liver failure and onset of hepatoencephalopathy, especially in *POLG*-related disorders; worsening of seizures
Vigabatrin	Epilepsy	Inhibition of the mitochondrial nucleoside salvage pathway and worsening of mtDNA depletion disorders

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

What's new?

- Who manages mitochondrial patients?
- Where is their medical home?
- Who will deliver these guidelines?

Mitochondrial care network

- Standardization and excellence of care
- Improve quality and consistency of health services delivered
- Improved care coordination
- Clinical research and trial infrastructure
- Facilitate Outcome and Natural History research fluidly

Mitochondrial care network

Preparation

- Review of criteria used by most established centers of excellence for other diseases
- Review of pitfalls and challenges
- Establishing new network based on best practices for other organizations
- Step-wise/staged execution

Mitochondrial care network

Planning

- Focus groups of patients and families

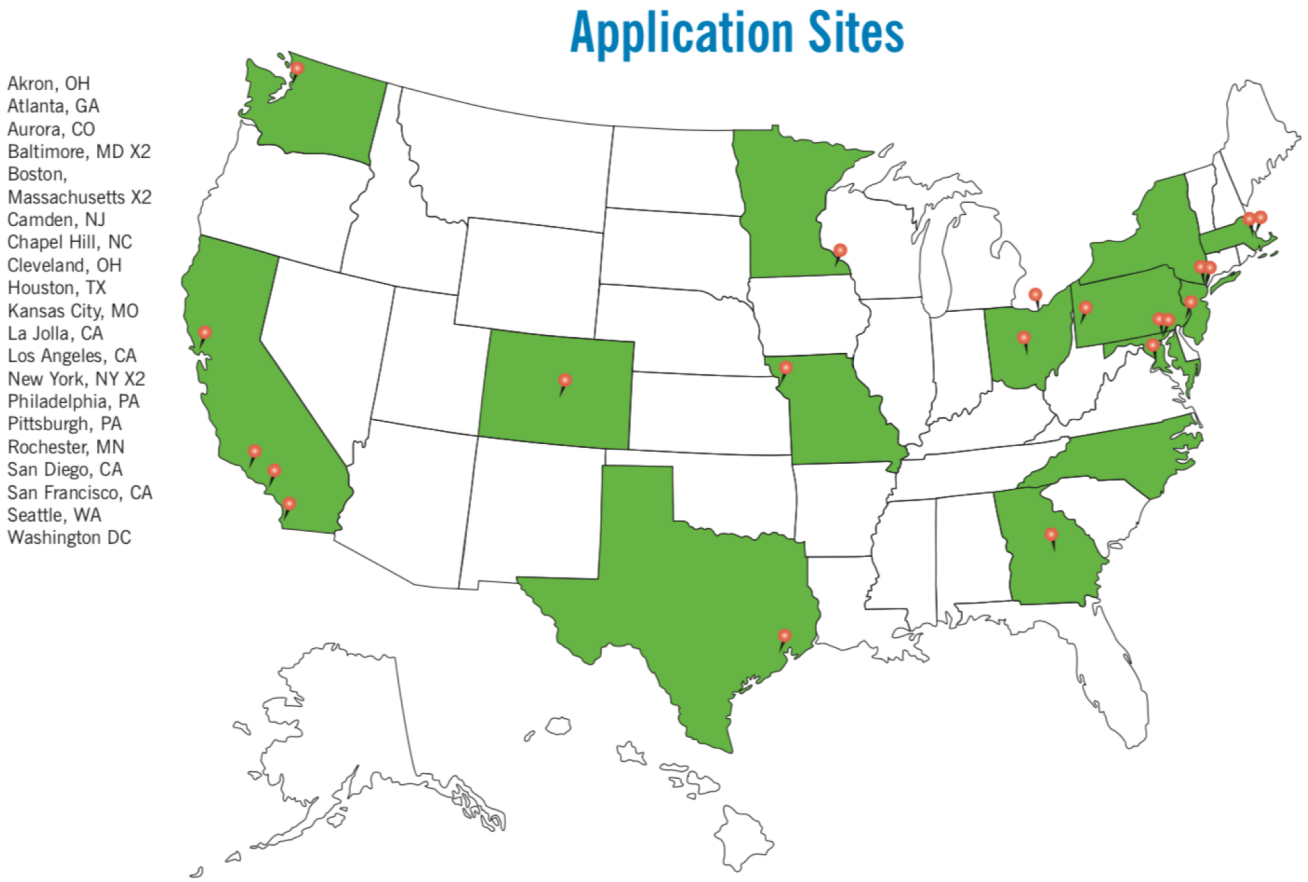
  Families want multi-disciplinary care, better social support and care coordination
- Survey from clinicians (93% support idea)
- Input from Advocacy Groups (MitoAction, UMDF, FMM)

Mitochondrial care network

Selection Criteria

- Clinic site based on number of patients, level of clinician experience, academic engagement and availability of comprehensive care resources
- Physician-clinician driven with Patient Advocacy Group partnership
- Governance Committee

Mitochondrial care network



NEXT STEPS?

- Creation of a Mitochondrial Care Network (MCN)
- Announcement of Mitochondrial Medicine Centers

NEXT STEPS?

An observational database of phenotype, genotype, and natural history.

Supported by NIH, governed by physicians and scientists experts in mitochondrial disease

1343 patients (adults and children/males an females)

The changing paradigm in healthcare: From evidence-based medicine to value-based medicine

- Effect of healthcare reform
  - Interventions and therapies are judged by payers and society by metrics of Value-Based Medicine
    - The effect of therapy on patient-centered outcomes = the incidence of disease complications, QOL, and survival vs. adverse events
  - Evidence-based medicine = The effect of intervention and therapies on surrogate markers, i.e.,

    cholesterol in CAD

    strict glucose level in diabetes

On behalf of the MMS,

Thank you!