Published in final edited form as:

Curr Genet Med Rep. 2018 June ; 6(2): 62–72. doi:10.1007/s40142-018-0138-9.

Mitochondrial Disease: Advances in clinical diagnosis, management, therapeutic development, and preventative strategies

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Abstract

Purpose of review—Primary mitochondrial disease encompasses an impressive range of inherited energy deficiency disorders having highly variable molecular etiologies as well as clinical onset, severity, progression, and response to therapies of multi-system manifestations. Significant progress has been made in primary mitochondrial disease diagnostic approaches, clinical management, therapeutic options, and preventative strategies that are tailored to major mitochondrial disease phenotypes and subclasses.

Recent findings—The extensive phenotypic pleiotropy of individual mitochondrial diseases from an organ-based perspective is reviewed. Improved consensus on standards for mitochondrial disease patient care are being complemented by emerging therapies that target specific molecular subtypes of mitochondrial disease. Reproductive counseling options now include preimplantation genetic diagnosis at the time of in vitro fertilization for familial mutations in nuclear genes and some mtDNA disorders. Mitochondrial replacement technologies have promise for some mtDNA disorders, although practical and societal challenges remain to allow their further research analyses and clinical utilization.

Summary—A dramatic increase has occurred in recent years in the recognition, understanding, treatment options, and preventative strategies for primary mitochondrial disease.

Keywords

mitochondrial disease; diagnosis; treatment; prevention

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Conflict of Interest

Marni J. Falk reports other from REATA Pharmaceuticals, grants, personal fees and other from Stealth Pharmaceuticals, other from United Mitochondrial Disease Foundation, other from GENESIS, grants and other from Raptor Pharmaceuticals, outside the submitted work. The other authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

INTRODUCTION

Primary mitochondrial diseases encompass a wide range of heritable conditions having greatly variable age of onset across the lifespan, clinical and biochemical manifestations, and molecular etiologies (1). Collectively, they affect at least 1 in 4,300 individuals across all ages (2). As understanding of mitochondrial pathophysiology had expanded over the past three decades so, too, has clinical care standards (3) and the development of precision therapies that are aimed at targeting the precise pathophysiology of the underlying gene defect (4). This review highlights the historical context and impact of recent rapid advancements made in diagnosing and treating mitochondrial disease.

MITOCHONDRIAL DISEASE OVERVIEW

Mitochondrial disease manifestations are notoriously heterogeneous, with involvement of potentially any organ system at any age. Clinical manifestations may range from isolated organ involvement with onset late in life to onset of severe multisystem problems in the newborn period leading to early death. Single organ symptoms may be the cardinal or only symptom, but more commonly progressive problems develop over time in additional systems. Disease courses may be characterized by rapid decline or prolonged periods of stability with intercurrent decompensation with stressors such as infections, fevers, or anesthesia. Symptom severity may range from mild to severe, and fluctuate over time. Multi-system manifestations, particularly when progressive over time, should prompt consideration of primary mitochondrial disease, especially when involving functional rather than structural manifestations. Dysmorphic features are recognized in some primary mitochondrial diseases, but remain relatively uncommon, as are rheumatologic, dermatologic, oncologic, and primary orthopedic problems.

While isolated organ involvement can be seen in primary mitochondrial disease, it is increasingly recognized that this may represent the mild end of the pleiotropic disease spectrum with more “plus” multi-system phenotypes often recognized when careful clinical evaluation is performed. This is exemplified by *OPA1* disorders, primarily recognized for causing isolated optic neuropathy in an autosomal dominant fashion (5) but now recognized to variably cause a range of additional features including hearing loss, ataxia, and peripheral neuropathy (6). Similarly, while Lebers Hereditary Optic Neuropathy (LHON) that results from pathogenic mtDNA mutations in complex I subunit genes is still largely considered to be an isolated optic neuropathy onset in early adulthood, individuals can manifest in mid-childhood and additional features including neurologic problems, cardiomyopathy, and arrhythmia can occur (7,8). In addition, adult-onset progressive external ophthalmoplegia (PEO) that is characterized primarily as an eye movement disorder with ptosis is often identified as PEO-plus, with additional multi-system involvement such as exercise intolerance and myopathy (9-11). The increased recognition of a broader spectrum of manifestations beyond classically defined clinical syndromes is reflected in updated expert-consensus based clinical care management guidelines (3).

Childhood-onset primary mitochondrial disease is more commonly caused by nuclear DNA pathogenic variants (typically recessive but also X-linked can be seen), although

improvements in mtDNA genome sequencing sensitivity has enabled recognition of a growing number of early-onset mtDNA disorders. Conversely, while adult-onset mitochondrial disease is more commonly caused by pathogenic mtDNA variants, improved genomic sequencing technologies has led to a growing number of adult-onset nuclear gene etiologies. In general, mtDNA heteroplasmy levels that are causal of childhood-onset severe phenotypes are typically higher than levels seen in adult-onset clinical diseases, including within members of a given family.

Neurologic manifestations

While none are pathognomonic, several neurologic “red flag” manifestations raise high concern for primary mitochondrial disease including Leigh syndrome (bilateral symmetric necrotic lesions in the basal ganglia, brainstem, and midbrain that may fluctuate over time and present as hyperintense lesions on brain magnetic resonance imaging) that is now recognized to result from mutations in more than 75 distinct genes across both genomes (12,13). Other common neurologic manifestations include epilepsy partialis continua (EPC) (14,15), occipital stroke-like episodes and strokes that do not follow a vascular distribution, and axonal sensorimotor neuropathy. Other common neurologic features include myoclonus, ataxia, a range of other seizure types, movement disorders, and developmental regression. While neurodevelopmental features such as autism, developmental regression, and intellectual disability can certainly be seen in those with primary mitochondrial disease, it is rare that these would be the only manifestation of a primary mitochondrial disease (16).

Ophthalmologic manifestations

Ophthalmic features of mitochondrial disease commonly include PEO, ptosis, pigmentary retinal dystrophy, and optic atrophy that can reduce visual acuity and be progressive over time (17). In fact, over time 81% of mitochondrial disease pediatric and young adult patients may develop significant eye problems (18).

Audiologic manifestations

Hearing loss in primary mitochondrial disease is typically bilateral, high frequency, sensorineural hearing loss that can range from mild to profound with variable age of onset.

Specific pathogenic mtDNA mutations, particularly in *MT-RNR1* and *MT-TS1*, have been found to cause isolated hearing loss. The m.1555A>G mutation in *mt-RNR1* has been associated with hearing loss that may acutely occur following exposure to an aminoglycoside antibiotic (19-21), and hearing loss may develop in individuals who carry this mutation at any time during their life even in the absence of aminoglycoside exposure, accounting for approximately 5% of isolated sensorineural hearing loss (22). Isolated sensorineural hearing loss has also been associated with several mtDNA variants in *mt-TS1*, with presentation typically in childhood (23).

Cochlear implants have been shown to be an effective therapy for both syndromic and non-syndromic types of hearing loss in mitochondrial disease, with improvements seen both immediately following surgery and long-term (24).

Cardiac manifestations

Hypertrophic cardiomyopathy is the most common cardiac feature of primary mitochondrial disease, occurring in approximately 40% of affected individuals (25-28). Dilated cardiomyopathy is less common but does occur.

Arrhythmias are also seen in primary mitochondrial disease, and recently has been associated with sudden cardiac death in MELAS (29). Common arrhythmias include Wolff-Parkinson-White and ventricular pre-excitation.

Cardiac conduction defects are also seen, most notably in mtDNA deletion disorders such as Kearns-Sayre syndrome. As this can rapidly progress to high grade AV block and sudden cardiac death, cardiac pacemaker and defibrillator is strongly recommended if symptoms or early conduction changes on electrocardiogram appear (3,30).

Given the frequent incidence of cardiac defects in primary mitochondrial disease and the potential for life-saving interventions when cardiac problems are identified early, cardiac evaluation performed at least annually to include echocardiogram and electrocardiogram is recommended when an individual is suspected to have mitochondrial disease or is first diagnosed.

Cardiopulmonary exercise testing (CPET) is an increasingly useful tool to non-invasively evaluate mitochondrial disease severity, exercise capacity, and to monitor disease progression over time. Characteristic CPET findings in mitochondrial disease include reduced peak work rate and peak exercise oxygen delivery ('VO₂ max'), elevated respiratory exchange ratio, and early lactic acidosis threshold (31-33).

Gastrointestinal manifestations

Gastrointestinal manifestations of mitochondrial disease are common, disabling, and often untreated due to being poorly recognized by treating clinicians. Gastrointestinal symptoms are commonly characterized by dysmotility, including dysphagia, gastroesophageal reflux disease, delayed gastric emptying, constipation, pseudoobstruction, and vomiting. Failure to thrive, malabsorption, and exocrine pancreatic insufficiency may occur. Irritable bowel syndrome or isolated diarrhea is less frequent. Liver involvement can also occur, including hepatic steatosis and mtDNA depletion, and in some cases may only be exacerbated by stressors such as dehydration or antiepileptic drugs (such as valproate) in POLG-related mitochondrial disease.

Endocrine manifestations

Diabetes mellitus is the most commonly seen endocrine manifestation of mitochondrial disease. It can be type I or type II, although combined insulin deficiency and resistance appears more common in patients with primary mitochondrial disease (34-37). Adrenal dysfunction, hypoparathyroidism, thyroid dysfunction, hypoparathyroidism, growth failure, underweight or overweight are also common endocrine manifestations (34,38).

Hypogonadism may occur in primary mitochondrial disease, including hypergonadotrophic or hypogonadotrophic hypogonadism. Infertility and premature ovarian failure may be a

feature of some mitochondrial diseases such as *POLG* disease. Poor bone health has also been shown to occur in those with primary mitochondrial disease (39).

Renal manifestations

Kidney involvement has been seen in up to 25% primary mitochondrial disease patients (40). Renal manifestations may be characterized by impairment of either tubular (renal tubular acidosis, hypercalciuria with hyperuricosuria, hypouricemia, nephrocalcinosis, renal calculi) and/or glomerular (proteinuria, aminoaciduria, decreased GFR) function.

CLINICAL DIAGNOSTIC APPROACH

The evolving diagnostic approach to suspected primary mitochondrial disease has been expertly reviewed and summarized in several key manuscripts by the Mitochondrial Medicine Society (41-43). With the exception of molecular genetic diagnostic testing, diagnostic testing in blood, urine, and tissues largely evaluate for biochemical evidence of mitochondrial dysfunction. Detailing specific metabolite alterations and their association with mitochondrial dysfunction falls outside the scope of this current review, but has been reviewed previously (41). Here, we outline a general diagnostic approach for suspected mitochondrial disease, an overview of which is provided in Figure 1.

Molecular testing

The importance of identifying the underlying molecular etiology causing primary mitochondrial disease cannot be overstated. Not only is this needed to confirm that an individual has a primary mitochondrial disease, a molecular diagnosis is now also increasingly required for patients to participate in clinical treatment trials. Additionally, proper molecular diagnosis can lead to tailored treatments (4). Further, some conditions having considerable phenotypic overlap with mitochondrial disease including biotin and thiamine responsive basal ganglia disease (*SLC19A3* disease) and riboflavin transport deficiencies (*SLC52A2* or *SLC52A3* disease), are important to detect given the therapies that have been shown to improve clinical outcome.

While panel-based testing that includes sequencing of select nuclear genes and mtDNA can be helpful in those with multiple features highly concerning for classical mitochondrial disease syndromes, clinically-based whole exome sequencing that includes mtDNA sequencing in both proband and parental samples is increasingly used as a first-line genetic test in both classical as well as more poorly-defined presentations. Mitochondrial disease specific panel-based genetic testing would miss the treatable conditions having phenotypic overlap with primary mitochondrial disease, as well as secondary genetic disorders that may contribute to a complex phenotype and are now recognized to occur in 3 to 5 percent of individuals (44). Limited gene panel-based diagnostic testing often does not include parental or family member samples, which are essential for segregation analysis and to identify de novo dominant mutations in the affected individual. Parental sequencing at the time of proband analysis provides crucial information to facilitate more rapid and accurate variant pathogenicity interpretation. Further, if this testing is not obtained at the time of the initial diagnostic test it becomes exceedingly challenging to obtain insurance coverage for

subsequent segregation analysis in healthy parents even if it is needed to understand potential health risks to themselves and accurate disease diagnosis in their child.

Non-invasive biochemical screening studies

Metabolic screening studies in blood and urine are useful to perform to determine whether an individual with suspected primary mitochondrial disease has evidence for mitochondrial dysfunction. Caution must be used when interpreting these findings, as any alterations identified will not be specific to mitochondrial disease and are typically not diagnostic in isolation. Common tests used to screen for evidence of primary mitochondrial disease, other recognizable inborn errors of metabolism, or common secondary problems seen in mitochondrial disease include comprehensive chemistry panel, complete blood count with differential, blood lactate and pyruvate, ammonia, creatine kinase, hemoglobin A1C, plasma amino acid analysis, carnitine and acylcarnitine profile, lipoprotein profile, hormone screening studies, and urine studies such as urinalysis, urine organic acid analysis, and urine amino acid analysis. Elevations of lactic acid and pyruvate are neither sensitive nor specific for all mitochondrial diseases, and may only be present intermittently in some individuals, but are important to recognize when present. To definitely confirm or exclude primary mitochondrial disease, additional diagnostic testing must be pursued beyond blood and urine based biochemical screens.

Minimally-invasive tissue testing

Establishing a fibroblast cell line from a skin biopsy can enable mitochondrial enzyme and function testing. Diagnostic testing may include polarographic analysis to measure integrated mitochondrial oxidative phosphorylation (OXPHOS) capacity, spectrophotometric analyses of electron transport chain (ETC) complex enzyme activities, or fatty acid oxidation analysis. Cells can also be useful to validate dysfunction in novel disease genes. The absence of abnormalities in fibroblasts, however, may warrant pursuit of more invasive analyses in symptomatic tissues in which mtDNA mutations or mitochondrial dysfunction may be present.

Buccal sample electron transport chain testing has become available in some centers, but has overall poor sensitivity and specificity for mitochondrial disease and not been proven to be reflective of ETC enzyme dysfunction in high energy demand tissues (45). Thus, additional research is needed before biochemical testing of ETC activity in buccal samples can be reliably used to aid in the diagnosis of primary mitochondrial disease.

Invasive tissue testing

For many years, skeletal muscle biopsy was considered the gold standard approach to diagnose primary mitochondrial disease. With the increased availability, turn-around-time, and diagnostic success of next-generation sequencing diagnostic methodologies, however, invasive tissue testing is less frequently pursued. However, it may be useful following completion of genetic testing to better understand the degree of mitochondrial dysfunction or to confirm the presence of mitochondrial dysfunction in the event no clear molecular etiology is identified in genetic testing of blood. Further, invasive testing may be crucial to obtain tissue in which to perform mtDNA content and mtDNA sequencing testing, since

depletion or mutations may only be detectable in symptomatic high energy demand tissue, such as muscle or liver. ETC complexes I-IV enzyme activity analyses can be performed on a clinical diagnostic basis in muscle or liver samples, although complex V (ATP synthase) activity analyses are not currently performed in the United States.

MITOCHONDRIAL DISEASE THERAPIES AND A LOOK TOWARD THE FUTURE

Current Therapies

No cure or FDA-approved therapies currently exist for mitochondrial disease. However, increased understanding of the natural history of the various molecular subtypes of mitochondrial disease has allowed for more standardized screening evaluations and symptom-based management. Standard therapies are used to manage each underlying clinical manifestation identified, such as diabetes mellitus, adrenal insufficiency, thyroid hormone insufficiency, hearing loss, cardiac arrhythmias, and other disease related symptoms. It is imperative that patients are routinely screened for the multitude of symptoms known for each condition, with appropriate multi-specialist management provided. Detailed expert consensus guidelines were recently reported by the international members of the Mitochondrial Medicine Society (MMS) to standardize clinical care recommendations for various organ and disease symptoms (3).

Routine and Acute Clinical Management

Management of routine medical care needs to optimize health of mitochondrial disease patients is critical in mitochondrial disease, which includes obtaining recommended immunizations, avoiding fasting, minimizing febrile periods, achieving good sleep hygiene, and assuring proper nutrition. Treatment during acute illness, decompensation episodes, and other intercurrent stressors includes proper hydration and nutrition support, following recommendation anesthetic guidelines, and closely following for new-onset neurologic disorders such as metabolic strokes or seizures. Extensive research has examined the use of intravenous arginine and citrulline nitric oxide (NO) precursors in patients with classical MELAS (46,47). The recent expert consensus guidelines from the Mitochondrial Medicine Society recommend consideration for using intravenous arginine in patients with the common mtDNA mutation in MELAS m.3243A>G in *MT-TL1* (3). Recent retrospective analysis of intravenous arginine in other mitochondrial diseases with acute metabolic strokes further suggests consideration for using intravenous arginine at the time of acute metabolic strokes in non-MELAS patients in attempt to improved clinical outcomes and reduce residual deficits; more than 50 percent of pediatric mitochondrial disease patients who received intravenous arginine at the time of acute metabolic stroke-like episode showed clinical response, particularly for hemiplegic symptoms, with no adverse events of the therapy observed (48). Chronic administration of enteral arginine or citrulline therapy is an additional therapeutic strategy that may help prevent further the occurrence of future metabolic strokes in at-risk mitochondrial disease patients (3).

Anesthesia is generally tolerated well in patients with mitochondrial disease. However, some patients, particularly those having complex I dysfunction, have been found to have volatile

anesthetic sensitivity and subsequent adverse events such as respiratory depression, regression, and white matter changes (49). Current clinical guidelines support a cautious approach to using anesthesia in patients with mitochondrial disease. Recommendations suggest avoiding or limiting propofol for short procedures (under 1 hour in duration); limiting fasting and having glucose added to perioperative IV fluids to prevent catabolism, unless contraindicated; and slow titration of anesthetics to reduce hemodynamic changes (3).

Exercise and Dietary Supplements

Exercise has been studied extensively and when tolerated, is a proven therapy to improve the well-being of mitochondrial disease patients (50). Aerobic and isotonic exercise has been shown to increase mitochondrial copy number, ETC enzyme activities, maximize mitochondrial oxygen uptake, and improve muscle strength. Consensus guidelines support the use of slowly accelerating exercise after patients are cleared by cardiac screening (3,43). Patients should ideally maintain an exercise program to reduce their deconditioning under the supervision of a professional therapist or exercise physiologist. Maintaining a regular exercise regimen can provide improved quality of life for patients and increased independence for activities of daily living.

Dietary supplements have long been used in variable combinations and doses for mitochondrial disease. Understanding the pathophysiology of the underlying biochemical disorders has supported rationale for the empiric use of vitamin and co-factor supplements (51). The most commonly used supplements include antioxidants (ubiquinol, α -lipoic acid, vitamins C and E), metabolites that increase free Coenzyme Q10 pools (carnitine), enzyme co-factors (B vitamins), and various metabolite therapies (arginine, folinic acid, creatine). While most appear to be well-tolerated overall, limited preclinical data and no robust clinical trial has determined the efficacy, potential toxicity, or optimal dose of any of these supplements in mitochondrial disease patients (52,53). These supplements are also typically given together in compounded formulations to ease patient adherence, which makes it difficult to determine which supplement is most advantageous alone, whether synergistic effects result from specific treatment combinations. A survey of mitochondrial disease providers revealed extensive variability as to precisely which supplements were standardly recommend for mitochondrial disease patients (43). Supplements are not subject to the regulatory framework required for medication quality and safety, may be high cost, and are not typically covered by insurance (54). The current expert panel consensus guidelines from the Mitochondrial Medicine Society recommend the following supplements be offered to patient with mitochondrial disease: ubiquinol, α -lipoic acid, riboflavin, folinic acid in patients with neurological manifestations, and L-carnitine in patients with documented deficiency (43).

Novel Therapies

Mitochondrial disease therapeutic development has been at the forefront of precision medicine. It is commonly recognized that successful improvement of health in individuals with primary mitochondrial disease might lead to effective therapies for more common and complex disorders whose pathogenesis involves secondary mitochondrial dysfunction, such

as diabetes mellitus and neurodegenerative disease of aging like Alzheimer's Disease and Parkinson's Disease.

A novel therapeutic approach being developed for some molecular subclasses of mitochondrial disease models is enzyme replacement therapy (ERT). Specifically, ERT has shown promising evidence in Mitochondrial Neuro Gastro Intestinal Encephalopathy (MNGIE) syndrome, where treatment in one patient involved erythrocyte-encapsulated thymidine phosphorylase, with additional study needed (55). For mtDNA depletion disorders, a trial in thymidine kinase 2 (TK2) deficiency with combined nucleoside therapy, deoxynucleotide thymidine (dTMP) and cytidine monophosphates (dCMP) showed improvement in the neuromuscular manifestations in several patients (56). Additional therapies are being investigated in research models to assess their ability to improve mitochondrial disease outcomes by modulating mitophagy, cellular translation, or hypoxia, as well as gene correction therapies using AAV vectors and mito-TALENS (57-61). Further research is ongoing to translate these therapies from bench concepts to bedside interventions aimed to improve the health of mitochondrial disease patients (62).

Clinical Trials

Over the past five years, there has been initiation of multiple clinical trials in primary mitochondrial disease. Substantial hurdles remain, however, due to extensive variability in mitochondrial disease genetic etiologies, pathophysiology, symptoms, and clinical outcomes measures.

To address the underlying variability, small cohort and individualized ('n-of-1') trial designs may be appropriate, allowing for each patient to be compared to their own unique symptom constellation baseline rather than to that of all subjects enrolled with highly pleiotropic disorders. This model has been successful in ultrarare genetic disease and pediatric oncology trials (63). The community has recognized the need for robust clinical trial design, including development and validation of mitochondrial disease-specific scales that can be standardized outcome measures across trials (52). A recent example is the launch of a multi-center, randomized, placebo-controlled, crossover, double blinded, phase III treatment trial to evaluate dichloroacetate in children with pyruvate dehydrogenase complex deficiency from multiple molecular causes, where the primary outcome measure is an observer-reported daily electronic survey completed by parents to assess disease related symptoms in patients (64). While many trials are being planned as detailed in Table 1, there has not been an FDA-approved pharmaceutical drug for mitochondrial disease.

Mitochondrial disease recurrence preventative strategies

Reproductive options have long been available for families who have a confirmed a nuclear gene cause for the mitochondrial disease in their family. Specific options vary from testing prior to pregnancy by pre-implantation genetic diagnosis (PGD) in the setting of in vitro fertilization (IVF), in which one or two cells from a day 3 or day 5 embryo are tested for the specific gene mutation that is known to cause disease in their family. Diagnostic options available during a pregnancy include mutation testing by chorionic villus sampling (CVS) at 10-12 weeks' gestation, or amniocentesis at 16-20 weeks' gestation (65).

For individuals with mtDNA disease that are complicated by heteroplasmy, reproductive options have been limited. Women who are asymptomatic and harbor a low level of mutation in their own blood may produce oocytes with high mutant loads that increase the risk their child will inherit high mutation levels and manifest severe disease. Testing for heteroplasmic mtDNA disorders during a pregnancy can be both technically and clinically challenging, given the variability of mutation load in different tissues and inherent difficulty in accurately predicting clinical outcomes based on mtDNA mutation loads measured in amniotic fluid cells (that are fetal in origin) or chorionic villus cells (that derive from placenta). Recent research has improved understanding of bottleneck impact on mtDNA mutation inheritance (66-69), to establish clearer understanding of which mtDNA mutations may benefit from PGD diagnostic approach (70). In the United States, PGD is allowable but may not be suitable or successful for individual patients, and requires demonstrated diagnostic laboratory expertise in accurate single cell mtDNA mutation heteroplasmy analysis (71). Modeling studies have suggested that embryo mutation loads below 5 (and possibly as high as 18) percent are unlikely to become sufficiently enriched in the resulting organs of the child to manifest with clinical disease (72); however, it may not be possible to identify a viable embryo that has sufficiently low mtDNA mutation heteroplasmy to reduce the likelihood they themselves will ultimately be affected with the severe mtDNA disease.

MRT involves not just quantifying but first actively replacing the mother's mitochondria that contains mutant mitochondrial DNA in oocytes or zygotes with healthy mitochondria (73). There are currently two methods MRT can be technically performed: metaphase spindle transfer and pronuclear transfer. Metaphase spindle transfer is performed in an oocyte prior to fertilization, replacing the maternal karyoplast with that of a donor oocyte (nuclear genome with spindle chromosome complex) (74). Pronuclear transfer is similar but performed post-fertilization at the pronuclei stage at the early zygote stage (73,75). In either scenario, the intention is to generate an embryo to be selected for uterine implantation that has the intended parents' nuclear genetic material together with healthy mitochondria that harbor the lowest possible heteroplasmy level for the familial pathogenic mtDNA mutation. The mutant heteroplasmy carry-over with MRT is typically not zero but based on research testing appears to be below 2 percent. Regardless, the inherently unpredictable nature of mtDNA replication warrants careful long-term follow-up in an experienced mitochondrial disease clinical center for any child born following PGD or MRT procedures in which detectable mtDNA heteroplasmy is confirmed.

The United Kingdom approved the pronuclear transfer technique for mitochondrial replacement therapy (MRT) under certain conditions in February 2015, which as of early 2018 is now proceeding with initial family selection to undergo this procedure (76). Despite National Academy of Medicine (now renamed Institute of Medicine) ethics panel review that suggested it is ethical under certain conditions to pursue MRT research for mitochondrial disease (77), it remains illegal to implant an embryo generated by MRT due to a congressional ban on the Food and Drug Administration considering applications to perform these trials. Careful attention will be focused on early MRT trial outcomes in the United Kingdom (78). Transparent reporting of all long-term outcomes reported from women who undergo PGD or MRT will provide valuable information to assess the safety of offering these options to all women who harbor a mtDNA mutation.

CONCLUSION

Understanding the clinical spectrum, diagnosis, management, and prevention of primary mitochondrial disease has markedly improved over the past three decades. Distinguishing the underlying genetic cause for complex clinical phenotypes affecting individual patients is increasingly feasible and necessary to enable development of precision therapies and disease prevention. These advances are leading to improved clinical management options and emerging therapeutic trials for the highly heterogeneous group of complex, multi-system, energy deficiency mitochondrial diseases.

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Figure 1.
Diagnostic algorithm for suspected mitochondrial disease

Table 1

Mitochondrial disease clinical trials currently active in clinicaltrials.gov.

Pediatric Clinical Trials						
Study	Phase	Design	Medicine	Primary Outcome	Sites	
Safety, Tolerability, Efficacy, PK and PD of RP103 in Children With Inherited Mitochondrial Disease (RP103-MITO-001)	II/III	Open Label	RP103 *	Changes in Newcastle Pediatric Mitochondrial Disease Scale (NPMDS)	USA	
Open-Label, Dose-Escalating Study Assessing Safety, Tolerability, Efficacy, of RP103 in Mitochondrial Disease (MITO-001)	III	Open Label	RP103 *	Changes in NPMDS	USA	
EPI-743 for Mitochondrial Respiratory Chain Diseases	II	Open Label	EPI-743	Improvement in NPMDS; improvenet in neuromuscular exam; AEs	USA	
Safety and Efficacy Study of EPI-743 in Children With Leigh Syndrome	II	Open Label	EPI-743	Improvement in Newcastle Pediatric Efficacy Syndrom Scale	USA	
EPI-743 for Metabolism or Mitochondrial Disorders	II	Double-blind cross over, placebo, randomized	EPI-743	Improvement in Newcastle Pediatric Efficacy Syndrom Scale	USA	
Phase 2 Study of EPI-743 in Children With Pearson Syndrome	II	Open Label	EPI-743	Occurrence of episodes of sepsis, metabolic crisis or hepatic failure	USA	
Phase III Trial of Coenzyme Q10 in Mitochondrial Disease	III	Double-blind, placebo, randomized	Conezyme Q10	Non-parametric Hotelling T-square Bivariate Analysis of McMaster Gross Motor Function (GMGF 88) and Peds QOL Scale	USA Canada	
Study to Assess the Efficacy and Safety of Raxone in LHON Patients (LEROS)	IV	Open Label	Raxone (Idebenone)	Clinically relevant recovery of visual acuity from baseline	USA Europe	
Trial of Dichloroacetate in Pyruvate Dehydrogenase Complex Deficiency: (DCA/PDCD)	III	Double-blind, placebo, randomized	DCA	Efficacy measured in the Observer Reported Outcome (ObsRO); AEs	USA	
Adult Clinical Trials						
A Study Investigating the Safety, Tolerability, and Efficacy of MTP-131 for the Treatment of Mitochondrial Myopathy	I/II	Double-blind, placebo, randomized	MTP-131 **	Adverse events; Change in vital signs; Changes in clinical laboratory evaluations	USA	
RTA 408 Capsules in Patients With Mitochondrial Myopathy - MOTOR	II	Double-blind, placebo, randomized	RTA-408	Improvement in peak workload	USA Denmark	
Safety Evaluation of Gene Therapy in Leber Hereditary Optic Neuropathy (LHON) Patients	I/II	Open label	GS010 (AAV-ND4)	Adverse events	France	
Safety and Efficacy Study of rAAV2-ND4 Treatment of Leber Hereditary Optic Neuropathy (LHON)	I/II	Open label	RAAV2-ND4	Visual acuity	China	
Trial of Cyclosporine in the Acute Phase of Leber Hereditary Optic Neuropathy (CICLO-NOHL)	II	Open label	Cyclosporine	Visual acuity	France	

Pediatric Clinical Trials		Phase	Design	Medicine	Primary Outcome	Sites
Study						
Safety Study of an Adeno-associated Virus Vector for Gene Therapy of Leber's Hereditary Optic Neuropathy (LHON) Caused by the G11778A Mutation (LHON GTT)		I	Open label	scAAV2-P1ND4v2	Adverse events	USA
MNGIE Allogeneic Hematopoietic Stem Cell Transplant Safety Study (MASS)		I	Open label	Hematopoietic allogeneic stem cells	Neutrophil count	USA
A Study to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Injections of Elamipretide (MTP-131) in Subjects With Genetically Confirmed Mitochondrial Disease Previously Treated in the Stealth BioTherapeutics SPIMM-201 Study (MMPOWER-2)		II	Double-blind, placebo, randomized	Elamipretide **	Distance walked on 6MWT	USA
Open-Label Extension Trial to Characterize the Long-term Safety and Tolerability of Elamipretide in Subjects With Genetically Confirmed Primary Mitochondrial Disease (PMD)		II	Open label	Elamipretide **	Adverse Event	USA
A Study of Bezafibrate in Mitochondrial Myopathy		II	Open label	Bezafibrate	Change in Respiratory Chain Enzyme Activity	UK
Nicotinamide Riboside and Mitochondrial Biogenesis		II	Open label	Nicotinamide Riboside	Safety and changes from baseline in mitochondrial biogenesis	UK
Study to Assess the Efficacy and Safety of Raxone in LHON Patients (LEROS)		IV	Open Label	Raxone (Idebenone)	Clinically relevant recovery of visual acuity from baseline	USA and Europe

Date sourced from NCT (www.clinicaltrials.gov) for historical and active interventional clinical trials in individuals with mitochondrial disease listed as of February 2018

Study drugs with multiple names

* Cysteamine, Bitartrate, and RP103

** MTP131, Bendavia, Elamipretide