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Title: Prevention and Therapeutic Development in Mitochondrial Disease: A Review of Recent Real-World Clinical Evidence

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Clinical Question Box

How is clinical research in primary mitochondrial disease progressing?

Recent years have seen more rigorous studies in primary mitochondrial disease. Genotype-directed therapies have improved outcomes in selected disorders, and gene therapy for Leber hereditary optic neuropathy has demonstrated sustained visual benefits. Preventive strategies have also advanced, including preimplantation genetic testing for monogenic diseases and the first regulated clinical application of mitochondrial donation in carefully selected patients.

Abstract

Although individually rare, primary mitochondrial diseases (PMD) collectively represent a substantial cause of inherited metabolic and multisystem diseases. Advances in genomic testing have broadened the recognized spectrum of mitochondrial diseases and improved molecular diagnosis, while progress in disease modeling has accelerated therapeutic development. Concurrently, an expanding body of clinical research has evaluated supportive, pharmacological, preventive, and emerging advanced interventions across genetically and clinically heterogeneous mitochondrial disease subtypes. However, the available evidence remains fragmented, with considerable variability in study design, patient selection, outcome measures, and follow-up duration. In this review, we summarize recent therapeutic and preventive interventions for PMD, including supplement and dietary strategies, mechanism-based drug therapies, reproductive prevention approaches for mitochondrial DNA disease, and emerging advanced therapies such as gene, cell, and enzyme-based treatments. We also examine the strengths and limitations of the current evidence base and discuss implications for clinical practice, trial design, and future translational research.

Keywords: mitochondrial diseases; clinical trials; reproductive prevention; mitochondrial donation

1. Introduction

Mitochondria are semi-autonomous organelles present in multiple copies in most human cells. They are essential for cellular energy metabolism through the mitochondrial respiratory chain and oxidative phosphorylation (OXPHOS), which generate adenosine triphosphate (ATP). Mitochondrial function relies on proteins encoded by both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA). Pathogenic variants in either genome can lead to primary mitochondrial diseases (PMDs)—a genetically heterogeneous group of inherited metabolic disorders.[1] These disorders affect approximately 1 in 4,300 adults and 1 in 5,000 live births, often presenting with progressive, multisystem involvement.[2,3]

The pathophysiology of PMDs extends beyond ATP deficiency to encompass oxidative stress, impaired mitochondrial quality control, and signaling abnormalities. PMDs primarily affect high-energy-demand organs such as the brain, skeletal muscle, heart, liver, and kidneys. In mtDNA-related disorders, heteroplasmy and tissue-specific biochemical thresholds further shape the clinical expression of PMDs, leading to wide variation in age at onset, severity, and organ involvement.[4] The clinical spectrum includes Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and Leber hereditary optic neuropathy (LHON), as well as cardiomyopathies and skeletal myopathies. This heterogeneity complicates diagnosis, outcome assessment, and therapeutic development.

Most PMDs lack curative therapy, with limited disease-modifying treatment options. Current management remains largely supportive, focusing on symptom control, rehabilitation, nutritional optimization, and prevention of metabolic decompensation. Supplements such as coenzyme Q10 (CoQ10) and riboflavin, as well as dietary strategies such as the ketogenic diet in selected settings, are widely used, though the strength of evidence varies across interventions and

disease subtypes. Advances in next-generation sequencing have improved molecular diagnosis and patient stratification, facilitating more targeted clinical studies and therapeutic development.[5] At the same time, the therapeutic landscape is expanding beyond empirical supportive care to include mechanism-based pharmacological agents, reproductive prevention strategies for mtDNA disease, and advanced approaches such as gene, cell, and enzyme-based therapies.[6] However, the available evidence remains fragmented, with substantial heterogeneity in study design, patient selection, outcome measures, and duration of follow-up.

This review provides a clinically oriented synthesis of real-world clinical evidence in primary mitochondrial disease, spanning supportive, pharmacological, preventive, and emerging advanced therapeutic strategies. The studies discussed were selected for their clinical relevance, recency, and contribution to illustrating the current direction of therapeutic development in genetically and phenotypically heterogeneous mitochondrial disorders. We summarize therapeutic and preventive interventions in PMDs with particular attention to translational progress, implications for future trial design and patient care, and the extent to which current clinical applicability is relatively established or remains preliminary.

2. Supplement and Dietary Interventions

Supplement-based and dietary approaches remain central to PMD supportive care, encompassing empirical vitamin and cofactor supplementation, metabolically targeted compounds, individualized nutritional support, and dietary therapies such as the ketogenic diet.

2.1 Empiric supplements and mitochondrial cocktails

Empirical supplement regimens for PMDs often include CoQ10, riboflavin, L-carnitine, thiamine, biotin, alpha-lipoic acid, niacin, and other vitamins or cofactors, although supporting evidence varies considerably among individual agents and prescribing practices differ across centers.[7,8] Among these agents, CoQ10 has been the most extensively studied. As an electron carrier in the respiratory chain and an antioxidant, CoQ10 remains a core component of mitochondrial cocktail regimens, though evidence for its benefit in unselected mitochondrial disease is limited. In an early study of 16 clinically heterogeneous patients treated with CoQ10 in combination with multiple vitamins, plasma CoQ10 levels increased substantially, while objective metabolic indices and overall clinical outcomes showed no improvement.[9] A randomized, double-blind, crossover trial of 30 patients receiving 1,200 mg/day for 60 days reported attenuation of post-exercise lactate rise and a modest increase in early exercise oxygen uptake, but no clear improvement in muscle strength, resting lactate, or quality of life.[10] In contrast, in genetically confirmed primary CoQ10 deficiency, CoQ10 serves as a replacement therapy and may improve symptoms in some patients.[11] Recent reviews also note that, despite its widespread use, high-quality clinical evidence supporting CoQ10 supplementation remains limited, particularly in children and adolescents.[12]

Riboflavin is another commonly used component of empirical supplement therapy, with a more clearly defined role in selected disorders. In children with complex II deficiency, riboflavin

treatment was reported to stabilize neurological status in a small case series of three patients.[13] Riboflavin has also been used in ACAD9-related complex I deficiency, where clinical and biochemical improvement has been reported in a substantial proportion of patients. More broadly, riboflavin is often employed in conditions involving flavin-dependent respiratory chain dysfunction, although the strength of evidence varies according to the underlying genotype and phenotype.[14]

2.2 Metabolic and redox-targeted supplementation

Several nutritional and metabolic interventions have been developed to improve cellular redox balance and lactate metabolism. Pyruvate therapy aims to reduce the elevated nicotinamide adenine dinucleotide to reduced nicotinamide adenine dinucleotide (NAD+:NADH) ratio associated with OXPHOS dysfunction and thereby facilitate glycolytic flux and oxidative metabolism. In experimental work, pyruvate exerted marked and sustained effects on energy metabolism in cybrid cells carrying the m.3243A>G mutation.[15] Clinically, among four bedridden pediatric patients with OXPHOS disorders treated with sodium pyruvate at 0.5–1.0 g/kg/day for more than 12 months, three showed improvement in Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) and Gross Motor Function Measure-88 scores.[16] In a 48-week prospective exploratory study of 11 Japanese adults with genetically, biochemically, and clinically confirmed mitochondrial disease, pyruvate therapy was associated with significant reductions in plasma lactate, lactate/pyruvate ratio, serum growth differentiation factor 15 (GDF-15), and lateral ventricular lactate, alongside a decreasing trend in total Newcastle Mitochondrial Disease Adult Scale (NMDAS) score.[17]

L-arginine has been studied most extensively in MELAS, particularly in relation to stroke-like episodes or ictuses. MELAS is a progressive and potentially life-threatening mitochondrial

encephalomyopathy characterized by recurrent ictuses.[18] In a clinical trial of oral L-arginine in patients with the m.3243A>G mtDNA mutation who had experienced ictuses within the past two years, treatment at 0.3–0.5 g/kg/day for two years significantly prolonged the interictal period and reduced the incidence and severity of ictuses.[19] Intravenous L-arginine has also been evaluated in acute settings, administered at 0.5 g/kg per dose in patients presenting within six hours of ictus onset, with a further 0.5 g/kg added if symptoms persisted. This regimen was associated with reductions in headache, nausea/vomiting, impaired consciousness, and visual disturbance.[19] L-citrulline has also attracted interest as a nitric oxide precursor in MELAS, with metabolic studies suggesting that it may enhance nitric oxide production more effectively than arginine.[20]

Hydroxytyrosol, a phenolic compound with antioxidant properties, has also been investigated. Preclinical studies have suggested neuroprotective effects against oxidative stress and neurodegeneration.[21] In a small open-label pilot study involving nine pediatric patients with mitochondrial disease, hydroxytyrosol supplementation was associated with improved health-related quality of life as measured by the Pediatric Quality of Life Inventory, with possible benefit in a subgroup of patients with MELAS.[22]

2.3 Nutritional support and dietary intervention

Beyond individual supplements, nutritional status is increasingly recognized as an important modifier of disease burden in mitochondrial disease. Malnutrition is common in pediatric population and may exacerbate symptoms by further compromising mitochondrial function.[23,24] In patients with m.3243A>G-related mitochondrial disease, a randomized controlled trial of an individually tailored dietary intervention showed that the intervention group more frequently achieved prespecified nutritional goals and demonstrated improvements in body composition, handgrip strength, gastrointestinal function, and quality of life compared with controls.[25]

Consistent with the high prevalence of gastrointestinal dysmotility in mitochondrial disease, a phase II study of a low-fiber diet (<10 g/day) reported good tolerability, along with improved stool consistency and reduced gastrointestinal symptoms, including bloating and abdominal pain, in patients with chronic constipation.[26]

2.4 Ketogenic diet

Ketogenic diet has received increasing attention as a dietary therapy for selected mitochondrial disorders. By redirecting energy utilization from carbohydrates toward fatty acids and ketone bodies, this diet mimics fasting and may support mitochondrial metabolism through several mechanisms, including enhancement of respiratory chain energy production, limitation of glycolytic flux, increased fatty acid oxidation, reduction of oxidative stress, and modulation of neuronal excitability.[27,28]

Additional proposed mechanisms include metabolic gene reprogramming, enhanced mitochondrial biogenesis, and regulation of seizure pathways via peroxisome proliferator-activated receptor-γ and astrocyte metabolism.[28] Clinical studies suggest that ketogenic diet may be particularly useful in patients with epilepsy and selected metabolic subtypes. In 2022, Huang et al. reported that 1- and 3-month ketogenic diet interventions achieved >50% seizure reduction in 31.8–72.3% of patients with mitochondrial disease.[29] In another series, clinical improvement was observed in 9 of 11 patients aged 1 month to 18 years treated with ketogenic diet, with outcomes appearing more favorable than in patients who did not receive the diet.[30] Ketogenic diet has also been reported to be highly effective in defects of the mitochondrial malate–aspartate shuttle and the mitochondrial pyruvate carrier, with benefit observed in 11 of 13 patients, particularly with marked seizure reduction.[31] However, more recent studies indicate that tolerability and safety may vary across mitochondrial disease subgroups, and modified ketogenic approaches may be

unsuitable for patients with mtDNA deletion-related myopathy.[32] Accordingly, ketogenic diet should be viewed as a selective rather than universal dietary strategy in mitochondrial disease.

Overall, supplement and dietary interventions continue to play an important role in supportive care for PMD, but their clinical relevance is not uniform across disorders. The strongest practical indications are generally confined to selected settings, such as replacement therapy in primary CoQ10 deficiency, riboflavin-responsive defects, L-arginine-based management in MELAS, and ketogenic diet in selected epilepsy-predominant or metabolic phenotypes. For many empiric supplements used across broad PMD populations, however, the available evidence remains limited, heterogeneous, and insufficient to support generalized disease-modifying benefit.

3. Drug Therapy

Pharmacological treatment of PMD is shifting from empirical metabolic support toward mechanism-based intervention. A growing number of agents targeting key pathogenic pathways—including pyruvate metabolism, redox regulation, cardiolipin remodeling, mtDNA maintenance, NAD(H) homeostasis, and respiratory chain dysfunction—have entered clinical development. At the same time, therapeutic translation remains difficult owing to marked genetic and phenotypic heterogeneity, small and fragmented study populations, and the challenge of translating biochemical effects into consistent clinical benefits.

3.1 Agents targeting pyruvate metabolism and lactic acidosis

Sodium phenylbutyrate has attracted renewed interest as a treatment for mitochondrial lactic acidosis based on preclinical evidence indicating improved mitochondrial function and oxidative capacity.[33] In a recent six-month phase I/II open-label pilot study in patients with PMD and lactic acidosis, treatment at 10 g/m²/day reduced lactate exposure, though adverse events were common in adults. A lower dose of 5 g/m²/day was better tolerated but failed to meet the primary endpoint.[34] Although these data indicate biological activity, dose-limiting toxicity and uncertain clinical efficacy remain key limitations.

Dichloroacetate (DCA), a pyruvate dehydrogenase kinase inhibitor that promotes pyruvate oxidation, has long been investigated as a lactate-lowering agent in mitochondrial disorders associated with lactic acidosis.[35] Early open-label studies reported reductions in blood and cerebrospinal fluid lactate, alongside possible stabilization of neurological symptoms.[36] Subsequent controlled studies—particularly in MELAS—highlighted peripheral neurotoxicity as a major safety concern and failed to demonstrate consistent clinical benefits despite measurable effects on lactate metabolism.[37] The therapeutic role of DCA in PMDs therefore remains limited.

3.2 Redox-modulating therapies

Redox imbalance is a recurrent feature of mitochondrial disease that is increasingly recognized as an important therapeutic target. Vatiquinone (EPI-743), a para-benzoquinone derivative developed as a redox-active analogue of coenzyme Q10, was designed to overcome the pharmacological limitations of coenzyme Q10 and idebenone. Early open-label studies reported signals of benefit across several mitochondrial phenotypes. In a subject-controlled emergency treatment study involving patients with severe mitochondrial disease at high risk of near-term clinical deterioration, most survivors showed improvement in clinical and quality-of-life measures, with imaging findings correlating with clinical response.[38] In children with genetically confirmed Leigh syndrome, a phase 2A open-label trial reported improvement in motor and disease severity measures, alongside altered glutathione homeostasis.[39,40] A small exploratory study in acute LHON also reported possible benefits in visual outcomes.[41] These studies suggest potential clinical and biochemical activity of vatiquinone in selected mitochondrial phenotypes, although interpretation remains limited by small sample size, open-label design, and the lack of controlled confirmation.

Sonlicromanol (KH176) is another redox-modulating compound under clinical development. Its proposed mechanism includes restoration of redox balance and anti-inflammatory effects mediated by inhibition of microsomal prostaglandin E synthase-1.[42,43] A phase 2b development program on adults with m.3243A>G-associated PMD reported benefits across several domains, with additional changes observed during the open-label extension phase.[44] By contrast, an earlier crossover phase IIA study did not demonstrate significant improvement in gait or most secondary outcomes, apart from possible effects on alertness and mood.[45] Findings to date vary across studies.

3.3 Cardiolipin-targeted therapy

Elamipretide is a mitochondria-targeted tetrapeptide that binds cardiolipin in the inner mitochondrial membrane and has been shown to improve membrane stability, respiratory efficiency, and ATP production.[46] A randomized, double-blind, placebo-controlled crossover trial on primary mitochondrial myopathy demonstrated that short-course daily subcutaneous elamipretide alleviated patient-reported fatigue and muscle symptoms, with a clinically meaningful improvement in the six-minute walk test.[47] The most substantial clinical outcome was seen in a 28-week randomized placebo-controlled trial and a 168-week open-label extension on Barth syndrome, which showed sustained tolerability alongside improvement in functional assessments and cardiac function.[48] Additional case-series data suggest that weight-based dosing is well tolerated in pediatric patients.[49] Based on these trial and extension data, elamipretide received accelerated approval in the United States in 2025 as the first therapy for Barth syndrome. Outside Barth syndrome, however, broader applicability across heterogeneous PMD populations remains less certain.

3.4 Nucleoside therapy for mtDNA maintenance disorders

Nucleoside supplementation has emerged as one of the clearest examples of genotype-directed therapy in mitochondrial medicine. In thymidine kinase 2 (TK2) deficiency, treatment with deoxycytidine and deoxythymidine is intended to restore intramitochondrial nucleotide pools and improve mtDNA replication. Clinical studies have demonstrated improvements in motor and respiratory outcomes, and this strategy has now translated into regulatory approval. The success of nucleoside therapy in TK2 deficiency provides proof-of-principle that targeted correction of nucleotide imbalance can modify the course of mtDNA maintenance disorders.[50,51]

This approach is now being evaluated in other disorders of mtDNA maintenance. In an open-label phase 2 study, patients with POLG-related disease exhibited improvement in Newcastle

Mitochondrial Disease Scale (NMDS) scores, with stable or reduced GDF-15 levels during treatment.[52] Similar observations were reported in a phase 2 study of patients with pathogenic variants in FBXL4, SUCLG1, SUCLA2, or RRM2B.[53] Although these studies were limited and uncontrolled, they suggest that manipulation of nucleotide homeostasis may have broader applicability beyond TK2 deficiency.

3.5 NADH modulation and metabolic reprogramming

KL1333 is an orally administered small molecule designed to restore the intracellular NAD+:NADH ratio, thereby supporting oxidative phosphorylation and ATP generation.[54] In a phase 1a/1b study conducted on adults with mitochondrial disease, KL1333 was generally well tolerated, with gastrointestinal adverse events indicating dose dependence. Exploratory analyses suggested possible reduction in fatigue and improvement in measures of functional strength and endurance.[55] Although these findings are preliminary, KL1333 is of interest because it targets a central metabolic disturbance that may be relevant across multiple mitochondrial disease phenotypes.

Bezafibrate, a pan-peroxisome proliferator-activated receptor (PPAR) agonist that promotes mitochondrial biogenesis and oxidative metabolism, has also been investigated as a metabolic therapy. In an open-label study of adults with m.3243A>G-related mitochondrial myopathy, bezafibrate reduced the proportion of complex IV-deficient muscle fibers and improved cardiac parameters. However, these changes were accompanied by increases in circulating biomarkers such as fibroblast growth factor 21 (FGF-21) and GDF-15, as well as broader metabolic disturbances, raising concerns regarding long-term tolerability.[56] Isolated case reports suggest potential benefit of bezafibrate combined with nicotinamide riboside in infantile complex I

deficiency.[57] Further studies are needed to define the clinical role of bezafibrate in mitochondrial disease.

3.6 Respiratory chain support and heme pathway augmentation

5-Aminolevulinic acid combined with sodium ferrous citrate has been shown to enhance heme production and upregulate mitochondrial respiratory chain activity in vitro and in vivo.[58] In a Japanese clinical study comprising a double-blind, placebo-controlled phase, an open-label phase, and subsequent long-term administration in pediatric patients with Leigh syndrome and central nervous system disorders, sustained treatment was associated with a gradual reduction in average serum lactate levels and stabilization or improvement in NPMDS scores.[59]

3.7 Genotype-specific therapy in LHON

Idebenone remains the most established pharmacological therapy for LHON. As a short-chain benzoquinone, idebenone can facilitate electron transfer downstream of complex I dysfunction and may help preserve or reactivate viable retinal ganglion cells. Evidence from a randomized, placebo-controlled trial, together with subsequent follow-up and observational studies, supports beneficial effects on visual outcomes, including reduced risk of further visual decline and promotion of visual recovery across different stages of the disease.[60-62] These findings support idebenone as an established treatment option for LHON.

3.8 Emerging repurposing strategies

Drug repurposing has recently attracted increasing interest in mitochondrial medicine. A recent translational study suggested that phosphodiesterase type 5 inhibitors may improve mitochondrial coupling efficiency and reduce hypermetabolism. In that report, tadalafil treatment was associated with acute and sustained symptomatic improvement in three individuals with PMD,

295 supported by complementary fibroblast data.[63] These observations are preliminary and warrant
296 further evaluation.

297 Taken together, the current pharmacological landscape in PMD is best interpreted in terms
298 of evidentiary maturity and disease specificity. The clearest clinically actionable signals are
299 currently seen in selected genotype- or disease-specific contexts, such as idebenone in LHON and
300 deoxynucleoside therapy in TK2 deficiency. By contrast, many other agents targeting redox
301 balance, cardiolipin, lactate metabolism, or NAD(H) homeostasis remain promising but
302 investigational, with interpretation limited by small sample size, mixed cohorts, short follow-up,
303 and non-comparative study designs.

4. Emerging Advanced Therapies

Although advanced therapeutic development in mitochondrial disease remains limited, several strategies have progressed beyond symptomatic treatment and aim to correct primary molecular defect or modify downstream tissue injury. To date, the strongest clinical outcome has been observed in LHON, where gene replacement has emerged as the leading translational strategy. Most studies have focused on allotopic expression of the wild-type ND4 gene delivered via intravitreal rAAV2. Across the major ND4 programs, including early-phase and later confirmatory studies, unilateral treatment has demonstrated an acceptable safety profile, alongside clinically meaningful improvements in best-corrected visual acuity that may persist for years after a single injection. A striking and consistently reported finding is improvement in the contralateral untreated eye, suggesting a bilateral biological effect despite unilateral administration, potentially related to vector or transgene transfer along the visual pathway.[64,65] More recently, gene therapy has been extended to the rarer ND1 form of LHON. In a 2025 pilot study, unilateral intravitreal rAAV2-ND1 was well tolerated, and some patients showed improvement not only in the injected eye but also in binocular visual function, supporting the broader applicability of mutation-specific ocular gene replacement in mtDNA disease.[66] Beyond LHON, however, gene therapy remains largely preclinical. In Barth syndrome, an X-linked disorder caused by TAZ mutations, systemic AAV9-mediated TAZ gene replacement restored mitochondrial structure, improved respiration, and ameliorated both cardiac and skeletal muscle dysfunction in animal models. These findings provide a strong proof-of-concept for nuclear gene replacement in mitochondrial disorders caused by defects in nuclear-encoded mitochondrial proteins, though clinical translation has not yet been achieved.[67]

Cell-based and enzyme-based strategies have also been explored, though clinical evidence remains extremely limited. In LHON, the Stem Cell Ophthalmology Treatment Study investigated autologous bone marrow–derived stem cells delivered via combinations of retrobulbar, intravitreal, subtenon, intra-optic nerve, subretinal, and intravenous routes. The proposed mechanism included paracrine neuroprotection and possible transfer of functional mitochondria from donor cells to injured retinal ganglion cells. Reported visual gains in some patients were encouraging. However, since the study was uncontrolled and heterogeneous in both delivery route and disease severity, its findings should be interpreted cautiously.[68] In contrast, a more mechanism-based metabolic replacement approach has shown promise in mitochondrial neurogastrointestinal encephalomyopathy. Erythrocyte-encapsulated thymidine phosphorylase (EE-TP), designed to reduce the toxic accumulation of thymidine and deoxyuridine in patients with thymidine phosphorylase deficiency, was associated with biochemical improvement in two of three treated patients, while weight gain and broader clinical improvement were observed in a subset of patients; overall safety was considered acceptable in this very small cohort.[69]

Other interventional approaches are better regarded as exploratory adjuncts than as established advanced therapies. Transcranial direct current stimulation has shown potential in refractory focal epilepsy associated with mitochondrial disease. In a POLG-related case of epilepsia partialis continua, seizures ceased after three days of treatment, and a subsequent controlled trial protocol was developed to test this strategy more rigorously.[70,71] By contrast, frequent transcutaneous electrical stimulation in LHON did not significantly improve visual acuity or other efficacy endpoints in a 2025 prospective study, despite good tolerability.[72] Overall, these data indicate that advanced therapies for mitochondrial disease are beginning to progress from

conceptual promise to disease-specific application. At present, however, their benefits remain confined to a few disorders, with LHON providing the clearest clinical proof-of-principle to date.

Future therapeutic development is likely to diverge according to genetic architecture. Gene replacement and potentially gene editing may offer a more direct path for disorders caused by nuclear-encoded mitochondrial genes, whereas mtDNA-targeted therapies still face major barriers, including mitochondrial genome delivery and heteroplasmy. Recent studies using optimized mitochondrial base editors and mitochondria-targeted nucleases further highlight the rapid progress of mutation-specific mtDNA manipulation, although these approaches remain largely preclinical at present.[73,74] Mitochondrial transplantation and related cell-based approaches are also being explored; encouraging results have been reported in preclinical mitochondrial disease models, but evidence remains limited and broader therapeutic applicability is still uncertain.[75,76]

5. Prevention

Prevention of mitochondrial DNA disease is increasingly approached as a continuum of reproductive risk reduction rather than a single intervention. For women carrying pathogenic mtDNA variants, the main established options are prenatal diagnosis (PND) and preimplantation genetic testing (PGT), both of which rely on estimating fetal or embryonic mutant load against variant-specific thresholds.[77] These approaches are most useful in selected heteroplasmic mtDNA disorders, where embryos with sufficiently low heteroplasmy may be identified for transfer. However, their predictive value is limited by the variable relationship between heteroplasmy and clinical phenotype, which may be influenced by tissue distribution, age, and nuclear or environmental modifiers.[77,78] PGT and PND have limited utility for women with very high heteroplasmy levels and are generally ineffective for homoplasmic pathogenic mtDNA variants, since all or nearly all embryos are expected to remain at substantial risk.

Mitochondrial donation represents the most significant recent advance in prevention for this group of patients. An important development is that this approach has been introduced within a regulated clinical pathway that includes counseling, patient selection, assisted reproduction, pregnancy monitoring, and follow-up. This model was first implemented in the United Kingdom, where women carrying pathogenic mtDNA variants were evaluated in dedicated mitochondrial reproductive clinics and offered individualized reproductive options based on variant type, heteroplasmy level, recurrence risk, reproductive capacity, and patient preference.[79,80] Within this approach, women with heteroplasmic variants were offered PGT, whereas those with homoplasmic variants or high heteroplasmy were considered for pronuclear transfer as a form of mitochondrial donation.[79,80]

In the reproductive care study, 22 women had commenced or completed pronuclear transfer, resulting in eight live births; all eight children were healthy at birth and recorded absent or low blood heteroplasmy. At the time of reporting, developmental progress was normal in all children, although two experienced medical events that required clinical attention and continued surveillance.[80] In parallel, an accompanying study of pronuclear transfer and PGT showed that pronuclear transfer supported embryo development and substantially reduced transmission of maternal pathogenic mtDNA, with neonatal blood showing a 95–100% reduction in six newborns and a 77–88% reduction in two others.[79] Together, these findings support mitochondrial donation as a clinically relevant option for women who are unlikely to benefit from embryo selection alone.

Nevertheless, mitochondrial donation should be regarded as risk reduction rather than absolute prevention. Since it is difficult to entirely avoid maternal mtDNA carryover during nuclear transfer, there remains a possibility of later expansion of residual maternal mtDNA.[77,79] This concern is supported by earlier observations in embryonic stem-cell lines and by maternal spindle transfer experience in infertility treatment, where one child showed an increase in maternal mtDNA to 30–60% at birth despite low carryover at the blastocyst stage.[81] Long-term follow-up therefore remains essential. These uncertainties, together with the technical challenge of minimizing maternal mtDNA carryover, mean that mitochondrial donation should currently be regarded as a regulated risk-reduction strategy rather than definitive elimination of transmission risk. At present, the available evidence supports a tiered approach in which PGT and PND remain first-line options when applicable, while pronuclear transfer serves as an additional option for carefully selected women in whom these approaches are unsuitable.

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Table 1. Selected supplement and dietary interventions in primary mitochondrial disease (PMD)

Intervention	Rationale / proposed mechanism	Target disease / subgroup	Key clinical evidence
Coenzyme Q10 (CoQ10) / Ubiquinol	Respiratory-chain electron carrier and antioxidant	Broad PMD use; primary CoQ10 deficiency	Widely used in mitochondrial cocktail therapy. In unselected PMD, controlled studies showed modest effects on exercise lactate or oxygen uptake but no clear improvement in strength or activities of daily living (ADL) / quality of life (QOL). In genetically confirmed primary CoQ10 deficiency, CoQ10 serves as replacement therapy and may improve symptoms.
Riboflavin	Cofactor for flavin-dependent enzymes and respiratory chain function	Complex II deficiency; ACAD9-related complex I deficiency; selected flavin-dependent defects	Neurological stabilization has been reported in children with complex II deficiency. Clinical and biochemical improvement has been documented in a proportion of patients with ACAD9-related disease.
Pyruvate	Lowers NAD+:NADH ratio and supports glycolysis and oxidative metabolism	OXPHOS disorders; m.3243A>G-related disease	Preclinical studies documented improvement in cellular energy metabolism. Small clinical studies reported improvement in motor scales and reductions in lactate, lactate/pyruvate ratio, GDF-15, and ventricular lactate.
L-arginine / L-citrulline	Nitric oxide precursor strategy	MELAS, especially ictuses	Oral and intravenous L-arginine have been associated with reduced frequency/severity of ictuses and improvement in acute symptoms. Metabolic studies suggest that citrulline may increase nitric oxide production more effectively than arginine.
Hydroxytyrosol	Antioxidant and neuroprotective effects	Small pediatric PMD cohort; possible relevance to MELAS subgroup	In a small open-label pilot study, supplementation was associated with improved health-related quality of life, with possible benefit in a MELAS subgroup.
Individualized dietary intervention	Optimization of nutritional status and body composition	m.3243A>G-related mitochondrial disease	A randomized controlled trial reported better achievement of nutritional goals and improvement in body composition, handgrip strength, gastrointestinal function, and quality of life.
Low-fiber diet	Symptom-directed dietary management for gastrointestinal dysmotility	PMD with chronic constipation	A phase II study reported good tolerability, improved stool consistency, and reduced bloating and abdominal pain.
Ketogenic diet	Shifts metabolism toward fatty acids and ketone bodies; may support respiratory chain function, reduce oxidative stress, and modulate neuronal excitability	Selected PMD, especially epilepsy and specific metabolic defects	Clinical studies reported seizure reduction and clinical improvement in selected patients. Marked benefit was observed in defects of the mitochondrial malate–aspartate shuttle and mitochondrial pyruvate carrier, although tolerability may vary across subgroups.

NAD+:NADH: nicotinamide adenine dinucleotide to reduced nicotinamide adenine dinucleotide ratio, OXPHOS: oxidative phosphorylation, MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, GDF-15: growth differentiation factor 15.

Table 2. Selected pharmacological therapies in primary mitochondrial disease (PMD)

Agent	Principal mechanism	Target disease / subgroup	Key clinical evidence
Sodium phenylbutyrate	Improves oxidative metabolism; may reduce lactate accumulation	PMD with lactic acidosis	A six-month phase I/II open-label pilot reported lactate-lowering activity at 10 g/m²/day, but adverse events were common in adults; 5 g/m²/day was better tolerated, although the primary endpoint was not met.
Dichloroacetate (DCA)	Activates pyruvate oxidation via pyruvate dehydrogenase kinase inhibition	PMD with lactic acidosis	Open-label studies reported reductions in blood/CSF lactate and possible neurological stabilization. A randomized trial in MELAS was terminated early due to peripheral neuropathy without convincing clinical benefit.
Vatiquinone (EPI-743)	Redox modulation; glutathione-related effects	Mixed PMD cohorts, Leigh syndrome, exploratory use in LHON	Small open-label studies reported improvements in clinical and quality-of-life measures in severe mitochondrial disease and gains on pediatric neurological scales in Leigh syndrome.
Sonlicromanol (KH176)	Redox modulation; anti-inflammatory effects	m.3243A>G-associated PMD	An early phase IIA crossover study showed limited benefit apart from possible effects on alertness and mood; a later phase 2b program reported benefit in clinically affected individuals, with further improvements noted during open-label extension.
Elamipretide	Binds cardiolipin and supports inner mitochondrial membrane function	Primary mitochondrial myopathy; Barth syndrome	Randomized crossover data in primary mitochondrial myopathy reported improvements in fatigue and symptom burden. In Barth syndrome, trial and extension data supported functional and cardiac benefit, leading to FDA accelerated approval in 2025.
Deoxynucleoside therapy	Restores intramitochondrial deoxynucleotide pools and supports mtDNA replication/maintenance	TK2 deficiency; POLG-related disorders; FBXL4, SUCLG1, SUCLA2, and RRM2B-related disease	Clinical studies reported improvement in motor and respiratory outcomes in TK2 deficiency, leading to FDA approval of deoxycytidine/deoxythymidine in 2025. Open-label phase 2 studies also reported improvement in NMDS scores in POLG-related disease and in most participants with other nuclear-encoded mtDNA maintenance disorders.
KL1333	Restores NAD+:NADH balance	Genetically heterogeneous mitochondrial disease	Phase 1a/1b data supported safety and tolerability, with exploratory signals for reduced fatigue and improved endurance/strength-related outcomes.
Bezafibrate	Pan-PPAR agonism; promotes mitochondrial biogenesis and oxidative metabolism	m.3243A>G-related mitochondrial myopathy; isolated use in complex I deficiency	An open-label study reported reduction in complex IV-deficient fibers and improved cardiac indices, but with increases in FGF-21, GDF-15, and broader metabolic perturbation. A single infant case combined bezafibrate with nicotinamide riboside.
5-Aminolevulinic acid + sodium ferrous citrate	Enhances heme synthesis and may support respiratory chain function	Leigh syndrome and related CNS mitochondrial disease	In a pediatric randomized/placebo-controlled study with extension, no significant between-group difference in the primary clinical scale was shown in the blinded phase, although lactate trajectories and longer-term observations suggested possible benefit.
Idebenone	Facilitates electron transfer distal to complex I dysfunction	LHON	Randomized and long-term observational studies support benefit on visual recovery or reduced further deterioration, particularly in the subacute/dynamic phase.
PDE5 inhibitors	Proposed modulation of mitochondrial coupling efficiency and hypermetabolism	Exploratory use in selected PMD	A recent translational report described acute and sustained symptomatic improvement in three individuals, supported by fibroblast experiments.

LHON: Leber hereditary optic neuropathy, CSF: cerebrospinal fluid, TK2: thymidine kinase 2, FGF-21: fibroblast growth factor 21, GDF-15; growth differentiation factor 15.

Therapeutic and Preventive Landscape of Primary Mitochondrial Disease