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C-Path Primary Mitochondrial Diseases Task Force: A Vision to Solve Data Unmet Needs in Primary Mitochondrial Diseases (PMD)

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Abstract

Background

Primary mitochondrial diseases (PMD) have a minimum point prevalence of approximately 1 in 5000 births worldwide[1], although prevalence estimates may differ by region and population studied. Despite this significant prevalence and the identification of over 470 causative genes, most PMD still lack FDA-approved treatments, leaving patients dependent on supportive and off-label care. While recent approvals for Barth Syndrome and Thymidine Kinase 2 Deficiency (TK2d) represent important progress, nearly all other PMD remain without targeted therapies. In response to these challenges, the Critical Path Institute's Primary Mitochondrial Diseases Task Force (PMD-TF), launched in January 2024, was established as an unprecedented collaborative effort to accelerate therapeutic development through data integration, standardization, and evidence-based endpoint development. This white paper outlines a strategic approach to overcoming key barriers in PMD drug development, including the recent failure of traditional outcome measures and the urgent need for disease-specific assessment tools. Recent regulatory successes further demonstrate that PMD drug development is feasible and have been enabled by improvements in trial design, a deeper understanding of genotype–phenotype relationships, and the integration of patient and caregiver perspectives. Building on this progress, patient and clinician-led registries have emerged as critical tools, supporting rapid enrollment and the collection of detailed, patient-centered real-world data. The PMD-TF's preliminary work represents the first coordinated cross-registry harmonization effort in the PMD community, facilitating broader collaboration and data integration.

Results

Analysis of the current PMD landscape highlights ongoing challenges, including disease heterogeneity, limited patient enrollment, and the lack of sensitive, disease-specific endpoints, all of which have contributed to repeated clinical trial failures. Evaluation of existing registries shows areas of overlap and substantial misalignment in collected data elements, limiting cross-study comparability and large-scale analyses. In this context, PMD-TF efforts demonstrate the feasibility of cross-registry harmonization through alignment of data dictionaries and identification of shared and distinct domains.

Conclusion

Coordinated data harmonization and cross-sector collaboration are essential to advancing PMD drug development. Establishing common data standards and leveraging aggregated datasets will improve study design, inform regulatory decision-making, and accelerate the development of effective, patient-centered therapies that enhance outcomes and quality of life for individuals with PMDs.

Background

2.1 Primary Mitochondrial Diseases Background

Diseases caused by dysfunctional mitochondria as consequence of either nuclear DNA (nDNA) or mitochondrial DNA (mtDNA), or both are categorized as "primary mitochondrial diseases" (see Table 1 for an overview of historical PMD descriptions and Table 2 for a list of key resources on PMD)[1,2]. In contrast, secondary mitochondrial dysfunction (SMD) is described as mitochondrial dysfunction arising from non-mitochondrial genetic defects or acquired factors (such as neurodegenerative diseases, metabolic syndromes, or environmental exposures), which indirectly impair mitochondrial function[3]. PMD are a diverse group of genetic disorders primarily affecting mitochondrial oxidative phosphorylation, significantly impacting high-energy demand organs such as the brain, skeletal muscle, heart, and endocrine systems. As such, these disorders lead to a wide variability of phenotypic expressions (Table 1)[4–9]. PMD have an estimated minimum prevalence ranging from approximately 1 in 4,000 to 1 in 5,000 individuals[10,11] and a median survival of 0.3 to 26.5 years depending on the specific PMD[12]. However, determining the global incidence of mitochondrial diseases remains challenging due to their rarity, substantial clinical and genetic heterogeneity, and under-recognition of affected individuals, many of whom remain undiagnosed[13]. Inherited or de novo pathogenic variants in over 470 genes in both nDNA and mtDNA have been identified to cause PMD[14], which significantly contributes to diagnostic challenges[15]. The genetically complex Leigh syndrome exemplifies the complexity of PMD, with over 110 identified variants, underscoring the challenges in developing targeted treatments[16,17].

Table 1
Overview of historically described canonical PMD syndromes

Disease	Cause	Key Signs & Symptoms	Refs
Alpers Syndrome	Multiple *POLG* gene mutations	Seizures, liver degeneration, and progressive developmental regression ("classical triad").	18,19
Autosomal Dominant Optic Atrophy **(ADOA)**	Primarily caused by mutations in the *OPA1* gene (3q29), affecting mitochondrial dynamics. Other mutations found in *SPG7* gene affecting mitochondrial proteostasis and *MFN2* gene, also affecting mitochondrial dynamics	Progressive vision loss, dyschromatosia, optic disc pallor, mild nystagmus, central or ceccocentral scotomas, myopathy, ataxia, peripheral neuropathy.	20–22
Barth Syndrome	Mutations in *TAZ* gene (TAFAZZIN, formerly G4.5) on Xq28, disruption of cardiolipin remodeling in mitochondria	Cardiomyopathy, neutropenia, skeletal myopathy, prepubertal growth delay, and distinctive facial gestalt (most evident in infancy).	23–25
Chronic Progressive External Ophthalmoplegia **(CPEO)**	Large scale deletions of mtDNA. Point mutations of mtDNA. Mutations of nDNA (*POLG*, others)	Bilateral ptosis, ophthalmoplegia, proximal myopathy, (possible dysphagia, ataxia).	26–31
Kearns-Sayre Syndrome **(KSS)**	Large scale deletion of mtDNA ranging from 2.0 to 7.0kb, common is 4.9kb spanning 8469–13147. Duplications and rearrangements of mtDNA as hallmark	Chronic progressive external ophthalmoplegia (CPEO) associated with pigmentary retinopathy, cardiac conduction defects, endocrine abnormalities, muscle weakness, cerebellar ataxia, hearing loss.	32–34
Leber Hereditary Optic Neuropathy **(LHON)**	Point mutations in mtDNA: m.3460G > A, m.11778G > A, m.14484T > C. Mutations of nDNA (*DNAJC30*, others)	Bilateral painless, subacute visual loss. Ataxia, peripheral neuropathy,, movement disorders, brain white matter changes ("LHON plus").	35–39
Leigh Syndrome **(LS)**	> 110 mutations in mtDNA and nDNA	Developmental delay, developmental regression, weak muscle tone (hypotonia), difficulty coordinating movements (ataxia), breathing problems, feeding difficulties, seizures, vision and eye movement problems, elevated lactate levels (lactic acidosis), fatigue, weakness, heart problems (cardiomyopathy).	40–44
Maternally Inherited Diabetes and Deafness **(MIDD)**	Mutation in mtDNA, m.3243A > G	Diabetes, accompanied by hearing loss. Other possible features includeexternal ophthalmoparesis, ptosis bilateral macular pattern dystrophy.	45–48
Mitochondrial encephalomyopathy, Lactic Acidosis and Stroke-like Episodes **(MELAS)**	Most common: m.3243A > G mutation in gene encoding mitochondrial tRNA for Leucine. Less common: m.3271T > C mutation in same gene. Other rare mutations: m.3252A > G, m.3344G > A, m14709T > C	Stroke-like episodes, encephalopathy, seizures, dementia, recurrent headaches, failure to thrive, exercise intolerance. Lactic acidosis and possible presence of ragged red fibers on muscle biopsy. Other multisystemic manifestations can be seen.	49–55
Mitochondrial Neurogastrointestinal Encephalomyopathy **(MNGIE)**	Mutation in the gene for thymidine phosphorylase (*TP*)	Gastrointestinal dysmotility, cachexia, peripheral neuropathy, diffuse leukoencephalopathy.	56–61
Mitochondrial Recessive Ataxia Syndrome **(MIRAS)**	Mutation 1399G–>A (A467T) in the catalytic alpha subunit of DNA polymerase gamma (*POLG*)	Ataxia, epilepsy, sensory ataxia, ophthalmoplegia, dysarthria, cognitive impairment, neuropathy.	62–65
Myoclonus Epilepsy and Ragged Red Fibers **(MERRF**)	Most common: m.8344A > G in gene encoding for mitochondrial tRNA for Lysine. Other mutations: m.8356T > C in same gene.	Epilepsy, myoclonus, myopathy, lipomatosis, dementia, hearing loss, cardiac dysfunction. Some cases may overlap with MELAS, KSS and Leigh Syndromes.	66–68
Neuropathy, Ataxia and Retinitis Pigmentosa **(NARP)**	Most frequent mutation m.8993T > G (ATPase 6 subunit gene *MT-ATP6*), 70–90% mutation load leads to NARP phenotype, a higher load may lead to LS. Less frequent mutations observed in *MT-ND6* and *MT-TV* genes.	Ataxia, retinitis pigmentosa, sensory neuropathy with proximal neurogenic muscle weakness are major symptoms. Others are optic atrophy, seizures, cardiac conduction block.	69–71
Pearson Syndrome **(PS)**	Large scale deletion of mtDNA between 2.3 and 9kb, with 4,977bp the most common variant	Sidero-blastic anemia (infants), metabolic acidosis, exocrine pancreatic failure, poor growth, muscle hypotonia, renal tubulopathy, cardiac dysfunction, neutropenia and/or thrombocytopenia. Phenotypical change to KSS possible.	72–78
Sensory Ataxic Neuropathy with Dysarthria and Ophthalmoparesis **(SANDO)**	Mutations in *POLG* gene,	Sensory ataxia, dysarthria, progressive external ophthalmoparesis (PEO).	64,79–81

Table 2
General databases for primary mitochondrial diseases.

Name[85]	Website/URL	Brief description
ClinVar	https://www.ncbi.nlm.nih.gov/clinvar/	Public Archive of reports of clinical significance of genetic variants: provides genetic variants, variant classification, phenotypic/disease and molecular data. Includes mtDNA and nDNA mitochondrial gene variants.
GeneCards	https://www.genecards.org	Integrative database of human genes: provides genomic, transcriptomic, proteomic, genetic, clinical and functional data. Searchable for mitochondrial disease genes.
HmtVar ("Human Mitochondrial Variants")	https://www.hmtvar.uniba.it	Variant-centered database designed for analyzing human mtDNA variability and pathogenicity: provides variant information, pathogenicity assessment, variability information, contextual data and annotations from external sources.
Human Protein Atlas	https://www.proteinatlas.org	Human protein database: provides spatial distribution, expression levels, and localization data for over 15,000 genes, categorized into tissue, cell, pathology, blood, and single-cell datasets. Includes data on subcellular localization and expression of mitochondrial proteins.
International classification of inherited metabolic disorders (ICIMD)	http://www.icimd.org/user/pages/01.home/_home-banner/ICIMD_manuscript.pdf	Hierarchical, group-based disease classification system of all currently known inborn errors of metabolism, designed to improve understanding of metabolic disorder interconnections. Includes genetic, molecular, biochemical and clinical/phenotypic data.
MitoCarta3.0	https://www.broadinstitute.org/mitocarta/mitocarta30-inventory-mammalian-mitochondrial-proteins-and-pathways	Inventory of human and mouse genes encoding proteins with strong support of mitochondrial localization, with sub-mitochondrial compartment and pathway annotations, and assign genes to a custom ontology of 149 mitochondrial pathways.
MITOMAP	https://www.mitomap.org	Human mitochondrial genome database. Includes mtDNA variations, pathogenic mutations, population polymorphisms, and gene-gene interactions data.
MSeqDR ("Mitochondrial Disease Sequence Data Resource")	https://mseqdr.org	Aggregated resource of mitochondrial disease sequence information, including genomic, pathogenic variants and phenotypic data accessible for research and clinical use.
NAMDC ("North American Mitochondrial Disease Consortium")	https://namdc.rarediseasesnetwork.org/	Mitochondrial diseases clinician registry and biorepository. Includes genetic (mtDNA and nDNA mitochondrial gene variants), biochemical, histologic, sociodemographic, clinical data and therapeutic data.

We refer here to the most complete resources providing overview of the PMD subtypes and their key clinical and genetic features. For a more complete list of available databases see ref[82–84].

2.2 Status of Drug Development for PMD

Despite recent progress, the overwhelming majority of PMD remain without any FDA-approved therapies, with only two conditions (Barth Syndrome and TK2d) having a treatment approved to date, leaving people with hundreds of PMD still facing substantial unmet medical need. Despite promising early-phase results, there have been repeated failures of high-profile drug development programs (Table 3). These unsuccessful programs represent significant setbacks for the pharmaceutical industry and impose a considerable emotional and physical burden on patients awaiting effective treatments. However, the discontinuation of several high-profile programs has provided critical insights for future PMD drug development.

Bocidelpar (plate number 1 / MA-0211, Astellas Pharma) received FDA Fast Track designation in 2020 but is now discontinued. Its Phase 2/3 MOUNTAINSIDE trial faced significant challenges. The trial was terminated early in November 2022following a prespecified futility analysis and was hampered by insufficient patient enrollment. Development program for mavodelpar (REN001, Reneo Pharmaceuticals) was terminated in December 2023 after the pivotal STRIDE Phase 2b trial failed to meet its primary and secondary endpoints; specifically, there was no significant change in the 12-minute walk test at week 24, nor improvement in the PROMIS Fatigue 13a score. Despite orphan drug designations and promising Phase 1b data showing an average improvement of 94 meters, the drug did not succeed in larger, controlled studies. Vatiquinone (PTC Therapeutics) was unsuccessful in the MOVE-FA trial for Friedreich's ataxia, and although there was a potential benefit observed in post hoc analyses utilizing a more sensitive endpoint, further studies are warranted. Similarly, vatiquinone was unsuccessful in the MIT-E trial for mitochondrial disease-associated seizures; however, a directional improvement in seizures was observed in the Leigh-syndrome subgroup. The development of vatiquinone for seizures was discontinued, but the study results support targeting mitochondrial epilepsy phenotypes and seizure-specific outcome measures in future studies. More recently, the trial of dichloroacetate to treat PDCD failed to meet its primary endpoint (SL1009, Saol Therapeutics), but the company is continuing the trial via an open-label extension (Table 3). Despite these setbacks, the PMD drug development space remains dynamic with multiple active pipelines (Table 4) and two new treatments (for Barth Syndrome and TK2d) having been approved in 2025.

Elamipretide (Stealth BioTherapeutics) initially failed in the MMPOWER-3 trial, showing no significant improvement versus placebo in patients with primary mitochondrial myopathy (PMM); however, subsequent studies revealed genotype-specific benefits, and post-hoc analysis indicated meaningful responses in nuclear DNA "replisome" subgroups. Building on these insights, elamipretide was investigated as a treatment for Barth Syndrome. The treatment failed to meet its primary endpoints in the phase 2 TAZPOWER trial, but received FDA accelerated approval (FORZINITY), based on a secondary endpoint improvement deemed as an intermediate endpoint likely to predict clinical benefit. The knee-extensor muscle strength improved from study baseline during the OLE phase; a muscle used to straighten the leg at the knee and expected to translate into improvement in the ability to stand more easily or walk farther. As a condition of accelerated approval, Stealth is required to conduct a post-approval randomized, double-blind, placebo-controlled trial to confirm that the changes seen on knee muscle strength translate into patient benefit. Finally, the combination of Doxecitine + doxribtimine (Kygevvi, UCB S.A.) was approved for the treatment of TK2d patients who start to show symptoms when they are 12 years old or younger. Efficacy was established based on data from one phase 2 clinical study, two retrospective chart review studies, and an expanded access program. Survival in patients treated with Kygevvi was compared with survival in an untreated external control group composed of untreated patients from published literature and one of the retrospective studies in this drug development program. Mean survival time at 10 years was 9.6 years for the group receiving Kygevvi compared with 5.7 years in the external control group.

2.3 Status of Biomarkers for PMD

The identification of reliable biomarkers for PMD remains a critical need for diagnosis, disease monitoring, and drug efficacy evaluation. Most biomarkers investigated in mitochondrial disease remain diagnostic or mechanistic, with no validated pharmacodynamic biomarkers demonstrating consistent responsiveness to therapeutic intervention. Multiple diagnostic biochemical biomarkers, measurable in the blood or CSF, have been investigated for PMDs[86]. Lactate reflect altered mitochondrial energy metabolism but have shown inconsistent diagnostic utility, while the lactate to pyruvate ratio may improve diagnostic specificity compared to the individual metabolites[87–89]. More recently, cytokine-based stress biomarkers, including growth differentiation factor 15 (GDF-15) and fibroblast growth factor 21 (FGF-21), have emerged as supportive biomarkers of cellular and mitochondrial stress in mitochondrial disease, with greatest utility in mitochondrial myopathy and selected mtDNA maintenance, deletion, and translation disorders. However, their sensitivity and specificity vary across cohorts, genotypes, phenotypes, and comparator populations, and neither biomarker is specific to primary mitochondrial disease. Accordingly, they should be interpreted as supportive stress-response markers rather than validated diagnostic or pharmacodynamic biomarkers[90,91]. For more information on additional metabolic biomarkers and emerging biomarkers under investigation see reference[86]. Overall, while multiple biochemical biomarkers have been identified, none demonstrates sufficient accuracy as a standalone diagnostic tool, and their utility is influenced by disease heterogeneity and overlap with non-mitochondrial conditions; therefore, molecular testing remains the diagnostic standard, with biomarkers serving complementary roles in supporting diagnosis and monitoring disease status.

There are no clearly established biochemical biomarkers for drug efficacy, dose-response, and treatment monitoring. In addition, very few clinical trials in PMD have used biochemical biomarkers as primary or robust pharmacodynamic endpoints. KL1333, a NAD+ modulator, was evaluated in patients with PMD (Phase Ia/b, NCT03888716), with exploratory biomarkers including lactate, pyruvate, NAD+/NADH, FGF21, and GDF15; the lactate-to-pyruvate ratio showed an exposure-related signal in one healthy-volunteer cohort[92]. The elamipretide trial (see Table 3) in Barth syndrome/PMM assessed exploratory biomarkers comprising lactate, glutathione, FGF-21, 8-isoprostane, and urinary 8-hydroxy-2-deoxyguanosine; results were not reported[93]. Sonlicromanol was studied in m.3243A > G (MELAS), with exploratory biomarkers including glutathione (GSH), glutathione disulfide (GSSG), FGF21, GDF15, and PRDX1; no differences in biomarkers levels were observed between active and placebo arms[94]. Because of high biological variability, poor specificity, and weak correlation with clinical outcomes, most trials rely on clinical or functional outcomes, with biochemical biomarkers used as exploratory or secondary endpoints.

Table 3
Historic look at Primary Mitochondrial Disease trials (2006–2025): Outcomes & Insights for future clinical trial programs

Drug / Trial (Sponsor)	Mechanism / Target Pathway	Study Population	Phase (Study Start) / Primary Endpoint	Outcome	Successes and/or Lessons Learned	Refs
*Dichloroacetate – MELAS cross-over trial (NIHCD)	PDH kinase inhibitor lowers plasma lactate by activating pyruvate dehydrogenase complex (PDC)	30 patients with MELAS (m.3243A > G)	Ph. II (2000); NIH-CD global neurologic score; brain lactate (MRS)	17/19 on DCA withdrew for peripheral neuropathy; study halted	Characterized DCA neuro-toxicity risk, ending off-label use in MELAS and steering metabolism-modulation research toward safer PDH activation routes.	95
*Cysteamine bitartrate (RP103) – RP103-MITO-001 & 0002 (OLE) (Raptor Pharmaceutical Corp.)	Glutathione precursor / cystine-depleter; intended to restore redox balance via elevated intracellular GSH	36 children with diverse Mitochondrial Disease	Ph. II (2014) & OLE (2015); change in International or Newcastle Paediatric Mitochondrial Disease Scale (IPMDS/NPMDS)	No significant benefit in primary endpoint analysis; 30% serious AEs; program terminated	Yielded glutathione pharmacodynamic data; illustrated that antioxidant strategies need biomarker-driven enrichment and rigorous safety thresholds.	96,97
**Omaveloxolone (RTA 408) – MMPOWER-A (Reata Pharmaceuticals)	NRF2 activator / NF-κB inhibitor; reduces NF-κB-driven inflammation and oxidative stress; improves mitochondrial biogenesis	53 adults with PMM	Ph. II (2015); 6-minute walk test (6MWT)	Sponsor terminated for strategic reasons after a limited signal, pivoted to Friedreich's ataxia	Safety and target engagement data accelerated the success of NRF2-based therapy in Friedreich's ataxia, approved in 2023. The pivot to FA illustrates cross-disease knowledge transfer.	98
*Elamipretide – MMPOWER-3 (Stealth BioTherapeutics)	Cardiolipin-targeting tetrapeptide; stabilises inner mitochondrial membrane and improves ETC coupling	218 adults with PMM	Ph. III (2017); 6MWT total fatigue on PMMSA (co-primary endpoints)	−3.2 m vs placebo; no fatigue benefit; high placebo effect; single-domain endpoint inadequate	Post-hoc showed gain in nDNA "replisome" subgroup, prompting genotype-stratified NuPOWER study and highlighting need for composite outcome tools instead of 6MWT alone.	99,100
***Elamipretide (FORZINITY) – TAZPOWER (Stealth BioTherapeutics)	Cardiolipin-targeting tetrapeptide; stabilises inner mitochondrial membrane and improves ETC coupling	12 patients with Barth syndrome. (12 years and older)	Ph. II (2017) with OLE; 6MWT and Total Fatigue Score on BTHS-SA (key secondary)	Primary endpoints missed	Approval based on one of the secondary endpoints considered to be an intermediate endpoint expected to reasonably predict clinical benefit.	101,102
*Resveratrol – PMM cross-over RCT (NIH)	SIRT1/AMPK Activator; intended to improve mitochondrial biogenesis via PGC-1α	11 adults with mitochondrial myopathy	Ph. II (2018); Heart rate during submaximal cycling and VO_2max	No functional improvement detected	Confirmed tolerability and PK but showed SIRT1 activation alone is insufficient; data now inform combination-therapy designs.	103
***Doxecitine + doxribtimine (KYGEVVI), (UCB S.A.)	Nucleoside substrate enhancement therapy; Restores mitochondrial DNA copy number	82 unique patients treated with Kygevvi or pyrimidine nucleosides (78 matched pairs for survival analysis); symptom onset ≤ 12 years	Ph. II (2019) (safety endpoints) + retrospective studies + EAP; Survival (vs. matched external controls)	Survival: 9.6 years (Kygevvi) vs 5.7 years (untreated external controls); 86% reduction in risk of death	Regulatory acceptance following demonstration of increased in comparison to match-paired external controls. Establishes nucleoside substrate enhancement as viable therapeutic class.	104
*Vatiquinone – MIT-E (PTC Therapeutics)	15-Lipoxygenase inhibitor ; modulates redox stress and reduces oxidative damage	68 children with mitochondrial disease–associated seizures	Ph. II/III (2020); reduction in observable motor seizures (ObsRO)	No overall efficacy; primary endpoint missed	Directional improvement in seizures in Leigh-syndrome subgroup; supports targeting mitochondrial epilepsy phenotypes and seizure-specific outcome Measures.	105
*Mavodelpar (REN001) – STRIDE (Reneo Pharmaceuticals)	PPAR-δ agonist; boosts fatty acid oxidation and mitochondrial oxidative substrate use	203 adults with mtDNA-PMM	Ph. IIb (2021); 12-minute walk test (12MWT)	No difference in 12MWT or PROMIS-Fatigue; heterogeneity of exercise endpoints	Built largest 12MWT natural-history dataset; excellent safety profile over 24w; informed move toward multi-domain fatigue/strength composites.	106

Drug / Trial (Sponsor)	Mechanism / Target Pathway	Study Population	Phase (Study Start) / Primary Endpoint	Outcome	Successes and/or Lessons Learned	Refs
*Bocidelpar (ASP0367) – MOUNTAINSIDE (Astellas Pharma/Mitobridge)	PPAR-δ modulator; enhances mitochondrial biogenesis and oxidative phosphorylation capacity	34 patients with PMM	Ph. II/III (2021); 6MWT	Trial stopped for futility & slow recruitment; primary endpoint unlikely to be met	Demonstrated dose-related safety; reinforced challenges with global PMM enrollment and need for adaptive designs & remote assessments.	107
*Sodium Dichloroacetate (SL1009) – (Saol Therapeutics)	PDC activator/stabilizer; restores pyruvate dehydrogenase complex (PDC) activity; lowers lactate	34 children with PDCD	Ph. III (2020); novel Observer Reported Outcome (ObsRO)	Primary ObsRO endpoint missed	Decreased plasma lactate concentration. Despite ObsRO endpoint failure, lactate lowering provides mechanistic proof-of-concept.	108

Trials listed chronologically by year of study start. Outcome classifications per published results and trial registries: Row color key: Red = primary endpoint not met / trial halted; orange = program discontinued for non-efficacy reasons; Green = regulatory approval granted. Phase/year refer to primary trial; subsequent open-label extension (OLE) data noted where applicable.

Table 4
Active industry pipeline

Company	Target Disease	Asset	Development Stage	Website
Minovia Therapeutics	Pearson, KSS	MNV-201	Phase I	https://minoviatx.com/
Pretzel Therapeutics	POLG disorders	PTZ-001	Phase I	https://www.pretzeltx.com/
PYC Therapeutics	ADOA	VP-001	Phase I/II	https://pyctx.com/
Stoke Therapeutics	ADOA	STK-002	Phase I/II	https://www.stoketherapeutics.com/
BPG Bio	Primary CoQ10 Deficiency	BPM31510IV	Phase II	https://bpgbio.com/
Omeicos Therapeutics	PMD (MERRF, MIDD)	OMT-28	Phase II	https://omeicos.com/
Tisento Therapeutics	MELAS	Zagociguat (CY6463)	Phase II	https://www.tisentotx.com/
Pharming (Abliva)	mtDNA PMD	KL1333	Phase II/III	https://abliva.com/
Neurophth Biological	ADOA, LHON	NR082*	Phase II/III	https://www.neurophth.com/
GenSight Biologics	LHON	Lumevoq (GS010)	Phase III	https://www.gensight-biologics.com/
Khondrion	m.3243A > G PMD	Sonlicromanol (KH176)	Phase III	https://www.khondrion.com/
Saol Therapeutics	PDCD	SL1-009	Phase III	https://saolrx.com/
Stealth Biotherapeutics	Barth Syndrome, nPMM	ELAMIPRETIDE	Phase III	https://stealthbt.com/
UCB S.A.	TK2 Deficiency	MT1621	Phase III	https://www.ucb.com/
*Gene therapy				

2.4 PMD Registries Landscape Overview and Challenges

A registry is an organized system that uses observational study methods to collect uniform data (clinical and other) and serves one or more predetermined scientific, clinical, or policy purposes. Registries can be used to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure. PMD registries include both clinician-led registries and patient-led registries. Clinical/researcher led registries usually collect clinician-entered data or medical records and sometimes patient reported data. They have the potential to provide higher quality longitudinal outcome data, including clinical assessments and biomarkers. High-quality data are fit-for-use, demonstrated by their relevance and reliability. Relevance refers to the inclusion of key study variables (exposures, outcomes, covariates) and a sufficient number of patients to address the research question. Reliability encompasses accuracy (correctness of measurements and coding), completeness (capture of required data with minimal missingness), and traceability (clear provenance showing how data were generated, transformed, linked, and versioned). However, such registries are expensive, burdensome on patients (e.g., may require travel for data collection), may only be able to enroll a limited number of patients, and may not share their data externally[109].

Patient-led registries primarily collect patient reported data, though some of these registries connect to Electronic Health Records (EHR) or clinician reported data. While patient organization-developed registries cannot replace clinical center-led natural history studies or clinical trials, they offer unique advantages. They can enroll an unlimited number of patients globally with ease and speed, support community building, raise awareness, and enrich clinical research and trials, including informing future research and natural history studies. They provide patient-centered data with greater accessibility to the community than other data collection effort. However, they present limitations, including higher likelihood of data missingness, and sometimes less reliable data. Patient-led registries are often limited by low funding levels, bandwidth in small team settings, and the lack of data management expertise through the data lifecycle. There are many registries in the mitochondrial disease space, and governance, structure, and goals are distinct (Table 5).

Table 5
PMD registries overview

Registry Name	Disease	Data Collection*	Number of enrolled participants	Status	Link	Pub resu
Barth Syndrome Patient-Inputted Registry & Repository	Barth Syndrome	Patient-reported	~ 160	Active	https://www.barthsyndrome.org/research/registryrepository.html	Yes
Champ Foundation Registry (CFR)[2]	Single large-scale mitochondrial DNA deletion syndromes disorders (SLSMDS)	Patient-reported + clinical + EHRs	~ 150	Active	https://www.thechampfoundation.org	Yes 112
CoRDS Mito Data[3]	PMD	Standardized patient data	~ 300	Active	https://sanfordresearch.org	No
CureARS MAPS Registry	ARS disorders	Patient-reported	enrollment started in Nov 25	Active	https://curears-maps-registry.iamrare.org/	No
GENOMIT Global Registry[1]	PMD	Clinician-entered	> 4500	Recruiting	https://www.genomit.eu	Yes
Hope for PDCD[2]	PDCD	Patient-reported	95	Active	https://www.hopeforpdcd.org	No
Leigh Syndrome Global Registry[2]	Leigh Syndrome	Patient-reported	> 400	Active	https://www.curemito.org	Yes 117
Leber Hereditary Optic Neuropathy - Data Collection Program[3]	Leber Hereditary Optic Neuropathy	Patient-reported	~ 250	Active	https://rare-x.org/lhon/	No
mitoNET mitoRegistry (Germany)[1]	PMD	Clinician-entered + biobank	~ 650	Active	https://www.mitonet.org	Yes
mitoSHARE (UMDF)[2]	PMD	Patient-reported and Clinician-entered	> 3000	Active	https://umdf.org/mitoshare	No
MyMito Tracker[2]	PMD	Daily symptom tracking app, Patient-reported	> 800	Active	https://www.mitoaction.org	No
MitoCohort (MRC Centre Mitochondrial Disease Patient Cohort: A Natural History Study and Patient Registry)[1]	PMD	Comprehensive clinical + genetic	> 1,000	Active	https://www.ncl.ac.uk/medical-sciences/research/research-themes/mitochondrial-neuromuscular/	Yes
NAMDC Registry[1]	PMD	Clinician-entered + Biobank	> 2200	Active	https://rarediseasenetwork.org/ncmds	Yes

**Most data collections include EHR upload capacities*

[1]Clinician-led [2]Patient-led [3]Hybrid

Active registries for PMD face several important challenges related to the marked genetic and phenotypic heterogeneity of these disorders. Designing registry infrastructures capable of simultaneously supporting broad natural history characterization while also addressing the specific needs of individual ultra-rare PMD remains inherently complex. Large umbrella mitochondrial disease registries provide substantial value by facilitating longitudinal data collection, patient engagement, multicenter collaboration, and recruitment across geographically dispersed populations. However, because they encompass a wide spectrum of disorders and disease severities, they may not always fully capture the unique clinical trajectories, outcome measures, or therapeutic priorities of specific PMD subtypes.

In particular, rare or ultra-rare genotypes may remain underrepresented, limiting the ability to generate sufficiently powered disease-specific analyses or trial-enabling datasets. Furthermore, umbrella registries often include heterogeneous populations spanning pediatric and adult-onset disease, with considerable variability in severity, progression rates, and diagnostic pathways. For example, patients with milder adult phenotypes may experience prolonged diagnostic journeys, whereas severe pediatric presentations such as Leigh syndrome are often recognized more rapidly. In some registries, a proportion of participants may also lack molecular confirmation, reflecting both historical diagnostic limitations and the evolving nature of PMD classification.

While these broader registries remain essential for advancing the field, complementary disease-specific or genotype-focused registries may be necessary to support deep phenotyping, endpoint development, therapeutic readiness, and hypothesis generation for individual PMD. Geographic dispersion and variable referral patterns may additionally create logistical and recruitment challenges for both umbrella and disease-specific registry efforts.

In general, there appears to be a lack of available information on existing registries and their willingness to collaborate, leading to the creation of new registries in an uncoordinated and potentially duplicative fashion. Additionally, motivated patient populations may be unwilling to wait for researchers to include their specific conditions in broader studies or to share study results. This leads them to take proactive steps and start their own registries. All these factors create multiple levels of complexity in the PMD registry ecosystem.

There is little to no collaborative creation of data dictionaries across current PMD registries, which leads to a wide variability in data elements collected in different studies. This lack of standardization poses a major challenge, as uniform data interpretation is essential for aggregating or querying data across multiple registries. Misalignment can occur for many reasons, including the asking of entirely different questions, asking similar questions but phrasing questions differently, referencing different timeframes, or providing different response options to the same questions. Referring to the individual with the disease in inconsistent ways (such as "patient," "participant," or using second-person pronouns like "you") can influence responses and introduce variability. Other sources of misalignment include lack of clarity about whether a patient or caregiver is completing the survey or collecting data using different units without proper conversion or documentation (e.g. age, medication, laboratory data). Even seemingly minor differences - such as recording sex as "Male/Female" in one registry, "M/F" in another, and "Man/Woman" in a third - must be standardized to enable proper aggregation. Genetic mutation data presents a special challenge: some registries curate genetic information through genetic counselors, others standardize patient-reported entries internally, while others leave the data fully patient-entered. Source data (such as genetic reports) may or may not be available.

Together, these challenges highlight the need for a collective effort to create a centralized database for PMDs that is accessible to the community, the development of recommendations to better align data collections and standards across registries, and greater communication, education and data sharing.

Methods

3.1 Primary Mitochondrial Diseases Task Force

The Primary Mitochondrial Disease Task Force (PMD-TF) is facilitated by the Rare Disease Cures Accelerator Data and Analytics Platform (RDCA-DAP®) at the Critical Path Institute (C-Path). C-Path is a nonprofit organization established in 2005 in collaboration with the FDA, aimed at accelerating drug development and improving treatments worldwide[121]. Sponsored by the FDA, RDCA-DAP offers a centralized infrastructure for rare disease characterization, promoting the standardization of data collection and the sharing of existing patient-level data. It enhances understanding of disease progression and facilitates innovative clinical trial designs. As of September 2025, RDCA-DAP hosts over 100 datasets covering 43 rare diseases and continues to expand. The platform is GDPR-compliant and adheres to FAIR data principles[122]. Additionally, RDCA-DAP has initiated task forces to address specific needs in rare diseases through public-private partnerships. These efforts aim to drive advancements in treatment and data integration across various therapeutic areas.

From 2021 to 2023, C-Path and the Cure Mito Foundation collaborated to engage stakeholders and raise awareness in the PMD community about the critical importance of data sharing.[123] This collaboration included conference presentations, social media campaigns, newsletters, targeted presentations, and stakeholder meetings. These efforts were instrumental in ensuring that key voices within the PMD community were not only informed but also actively involved in shaping this important initiative. As these awareness activities gained momentum, a clear need emerged for a coordinated effort to address the challenges in PMD drug development. In January 2024, C-Path officially launched the PMD-TF with seed funding from Astellas Pharma and the Cure Mito Foundation. The Task Force currently has 19 members, including 15 patient organizations and 4 SME participants (Table 6)[123]. This is the largest, most inclusive and most patient-centric collaboration in the mitochondrial disease field to date, featuring a true diversity of patient groups and broad community representation, with a cross-section of expertise within the PMD field. The effort benefits from C-Path's neutral convener expertise, facilitating open and unbiased collaboration among all PMD community members. TF goals were developed and aligned by its members to prioritize high impact unmet needs best suited to be addressed by C-Path core competencies. The PMD-TF aims to 1- Aggregate, standardize and integrate mitochondrial and inherited metabolic diseases data into the RDCA-DAP; 2- Optimize clinical trial design and endpoints; and 3- Enhance communication and collaboration among the patient, medical and research communities at large, all aimed at improving the lives of those affected by these diseases.

Table 6
Task Force Members

Member Name	Entity type	Representative(s)	Disease(s) of interest	Main activities	Website
Barth Syndrome Foundation	Foundation	Melissa Huang, Lindsay Marjoram	Barth Syndrome	Saving lives through education, advances in treatment and finding a cure for Barth syndrome	https://www.barthsyndrome.org/
The Champ Foundation	Foundation	Elizabeth Reynolds	SLSMDS: Pearson syndrome, Kearns-Sayre syndrome, and CPEO	Research toward better treatment and a cure for SLSMDS, like Pearson Syndrome	https://www.thechampfoundation.org/
CortexBio	SME	Dima Martini-Drew	Inherited Metabolic Diseases	Metabolic Medicine Cross-Therapeutic Innovation	https://www.cortexbio.co.uk/
CureARS	Foundation	Desiree Magee	ARS	Spreading awareness, connecting and providing support to affected families and funding research for ultra-rare Mitochondrial ARS genes	https://www.curears.org/
Cure LBSL Foundation	Foundation	Michael McGinn, Morgan Voigt	LBSL	Raising awareness of LBSL, funding research and supported affected individuals and their families	https://www.curelbsl.org/
Cure Mito Foundation	Foundation	Danielle Boyce, Sophia Zilber	Leigh Syndrome	Fund research for Leigh syndrome and mitochondrial disease and provide comprehensive resources to the community	https://www.curemito.org/
Global Genes: RARE-X Platform	Non-Profit, data platform	Charlene Son Rigby, Zohreh Talebizadeh	LHON, Multiple	Provides a collaborative platform for global data sharing and analysis to accelerate treatments for rare disease	https://rare-x.org/
Hope for PDCD	Foundation	Frances Pimentel, Carly Domos	PDCD	Accelerating research to cure PDCD	https://www.hopeforpdcd.org/
LHON Collective	Foundation	Malinda Marsh, Amie Koch	LHON	Research, raising awareness and data collection for LHON	https://www.lhon.org/
MEPAN Foundation	Foundation	Danny Miller	MEPAN Syndrome	Drive collaborative scientific research	https://www.mepan.org/
Midwestern University *	SME	Volkmar Weissig	Multiple	N/A	N/A
MitoAction	Foundation	Kira Mann	Multiple, Leigh Syndrome	Support, education, outreach, advocacy and clinical research initiatives	https://www.mitoaction.org/
MitoCanada	Foundation	Kate Murray	Multiple	Education, support, awareness and transformational research efforts	https://mitocanada.org/
Mitochondria World *	Foundation	Gordan Freeman, Alex Sercel, Stephanie Tomlinson	Multiple	Support researchers by providing a collaborative web presence for the mitochondrial communities	https://mitoworld.org/
National Institutes of Health	SME	Srikanth Ranganathan	Multiple	N/A	N/A
Sanford Research	Non-profit, data platform	Alyssa Mendel	Leigh Syndrome, PDCD, other	Coordinate the advancement of research into more than 10,000 rare diseases	https://research.sanfordhealth.org/rare-disease-registry
United Mitochondrial Diseases Foundation	Non-profit	Amel Karaa	Multiple	Promote research and education for the diagnosis, treatment and cure of mitochondrial disorders and to provide support to	https://umdf.org

Member Name	Entity type	Representative(s)	Disease(s) of interest	Main activities	Website
				affected individuals and families	
Center for Rare Childhood Disorders at TGen	Non-profit	Vinodh Narayanan, Newell Belnap	Multiple	Genomics research Institute	https://tgen.org/
Washington University in St. Louis	SME	Jonathan Brestoff	Leigh Syndrome, metabolism, other	N/A	N/A

3.2 Task force data sharing model for PMD

Drug development for PMD is accelerating, but most registries and natural history studies that exist do not share their data through an accessible database and may only share their data to individual investigators for one-off analysis or share aggregated results through publications. Making rare disease data accessible to the scientific community, including industry, is critical to accelerate drug development. The PMD-TF aims to build a comprehensive database for PMD and make it accessible internationally to scientists and clinicians. Datasets from clinical trials, natural history studies and real-world data (RWD), including registry data are curated to maximize the value of each dataset, and integrated with other rare disease data on the RDCA-DAP platform. The utility of the shared data is maximized by making it discoverable on the RDCA-DAP interface, according to FAIR standards, and requestable by scientists who can analyze it in free analytical workspaces (upon acceptance of their scientific plans, and according to the governance decided by the data contributors). The available PMD data can therefore be leveraged to improve understanding of disease progression and patient variability, inform clinical endpoints development and selection, facilitate identification of biomarkers, aid trial design (including patient stratification, patients clustering, propensity match analyses), and the development of regulatory-grade tools to accelerate drug development including clinical trial simulation tools.

3.3 Task Force Deliverables

The PMD-TF is leveraging C-Path's key strengths to advance solutions aimed at solving disease unmet needs and lifting roadblocks in drug development. This section summarizes the data landscape, methods, and results based on the experience thus far on data integration of PMD registries with RDCA-DAP platform.

3.3.1 Data landscape

The Task Force performed a landscape analysis of available data for PMDs from registries, natural history studies, and clinical trials. Key datasets for integration into the RDCA-DAP were prioritized based on enrollment, availability of longitudinal data, and availability of disease relevant endpoints (see Table 7). The RDCA-DAP team is working with the PMD-TF to negotiate sharing of the data dictionaries and de-identified patient level data for integration into RDCA-DAP. Status of integration is indicated in Table 7.

Table 7
Prioritized datasets and current integration status in RDCA-DAP

Dataset name/origin	Data Type	Disease(s)	Enrollment	Data Dictionary shared with PMD-TF	RDCA-DAP Integration
Abliva AB (NCT03888716)	Trial; Ph. II	PMD	72	No	No
Astellas (NCT04641962)	Trial; Ph. II	PMM	34	No	No
Barth Syndrome Foundation	Registry	Barth Syndrome	~ 160	Yes	Planned
Cure Mito Foundation: Leigh Syndrome Global Patient Registry	Registry	Leigh Syndrome	> 400	Yes	Yes
CureARS MAPS Registry	Registry	Mitochondrial (mt) Aminoacyl tRNA Synthetase (ARS) genes mutations	ongoing	Yes	Planned
Global Genes/RARE-X - LHON Data Collection Program	Registry	Leber Hereditary Optic Neuropathy	273	Yes	No
Genomit	Registry	PMD	> 4500	No	No
Hope for PDCD	Registry	Pyruvate dehydrogenase complex deficiency	?	Yes	Planned
Khondrion (NCT04165239)	Trial; Ph. II	Genetically Confirmed Mitochondrial DNA tRNALeu (UUR)Mutation	27	No	No
MitoAction: MyMITO	Registry	PMD	794 users	N/A	Yes
MitoCohort (MRC)	Natural History/Registry	PMD	> 1000	No	No
mitoNET – German Network for Mitochondrial Diseases	Registry	PMD	~ 650	No	No
mitoSHARE	Registry	PMD	> 3000	Planned	Planned
PTC Therapeutics (NCT01721733)	Trial; Ph. II	Leigh Syndrome	35	No	No
PTC Therapeutics (NCT02352896)	Trial; Ph. II	Leigh Syndrome	30	No	No
PTC Therapeutics (NCT04378075)	Trial; Ph. II/III	Mitochondrial Epilepsy	68	No	No
Raptor Pharmaceutical Corp (NCT02023866)	Trial; Ph. II	PMD	36	No	No
Raptor Pharmaceutical Corp (NCT02473445)	Trial; Ph. II OLE	PMD	22	No	No
Reneo Pharmaceuticals (NCT04535609)	Trial; Ph. IIb	PMM	213	No	No
Reata Pharmaceuticals	Trial; Ph. II	PMM	53	No	No
Saol Therapeutics (NCT02616484)	Trial; Ph. III	PDCD	34	No	No
Stealth Bio Therapeutics (NCT05162768)	Trial; Ph. III	PMM	102	No	No
Stealth Bio Therapeutics (NCT03323749)	Trial; Ph. III	PMM	218	No	No
The Champ Foundation Registry (CFR)	Registry	SLSMDS	~ 150	Yes	Yes
The Champ Foundation: SLSMDS Natural History Study (NCT05029843)	Natural History	SLSMDS	30	No	Planned
UCB S.A. (NCT03845712)	Trial; Ph. II	TK2d	47	No	No

3.3.2 Data elements alignment

The heterogeneity of data elements (i.e., variables) used across PMD registries, observational studies and clinical trials is a serious barrier to data reuse. The PMD-TF is gathering available data dictionaries from PMD registries to evaluate what information is being collected across mitochondrial diseases. This includes a manual alignment of the data elements extracted from the data dictionaries to understand how much overlap is present and what gaps exist. In addition, the variability in data elements nomenclature and survey questions phrasing is being evaluated to delineate what elements should be systematically collected by PMD registries and harmonize how this information should be collected in the future. The goal is to develop a first set of recommendations

defining what data elements need to be collected across all PMDs, followed by a set of disease-specific recommendations. Initial data elements alignment results and recommendations are presented below under **3.4 PMD Data Elements Alignment**.

3.3.3 Data standards harmonization and recommendations

RDCA-DAP has integrated 3 PMD datasets to date (Cure Mito, CFR and MitoAction) and collected 5 data dictionaries (Cure ARS, Cure Mito, CFR, Hope for PDCD and LHON/Rare-X). Each dataset was cleaned, standardized and curated to the platform data format to maximize the utility and fitness for use of the contributed data. The curation effort will be used to perform a gap analysis of the data collection performed for each contributed dataset. This will help delineate recommendations specific to each of these datasets (disease and contributor specific) including data elements, data standards, and address any other issue we may uncover. As RDCA-DAP continues to aggregate more PMD data, it will leverage these analyses to develop broader data recommendations for PMD. General recommendations for registry data collection are also available from RDCA-DAP[124], and from its partner the National Organization for Rare Disorders (NORD)[125].

3.3.4 Longer-term deliverables

The PMD-TF aims to address PMD unmet needs and remove roadblocks in drug development. The aggregated database will provide a unique resource that will be leveraged to inform the building of solutions that will facilitate drug development activities. Making the database accessible to industry will further accelerate the development of such solutions. The aggregated database will be used to increase understanding of PMD natural history and determine patient variability in terms of disease progression and clinical presentation. The data will be used by C-Path's Quantitative Medicine team to develop model informed drug development (MIDD)[126] activities, including disease progression modeling that may lead to drug development tools (stratification apps, trial simulation tools) and inform the identification of new clinical endpoints or biomarkers. RDCA-DAP will leverage the core competencies from C-Path's Patient Report Outcome (PRO) and Clinical Outcome Assessment (COA) consortia to provide resources to help PMD communities select available COAs that could be implemented for their data collections. The integration of the PMD database into the RDCA-DAP knowledge graph will further help us inform understanding of phenotypes and genotype-phenotype associations within and across diseases to perform patients/diseases clustering that can inform COA recommendations and basket trials design. Finally, developing reliable and responsive biochemical biomarkers for PMD drug development is critical, as the lack of validated biomarkers limits both diagnostic precision and therapeutic development[127]. The TF will seek to identify sources of reliable biomarker data to integrate into the database. When appropriate, the PMD-TF will seek regulatory endorsement of our solutions.

3.4 PMD Data Elements Alignment

We conducted a manual alignment and comparison of four data dictionaries shared with the PMD-TF. The primary objective was to systematically evaluate and compare the content and structure of the questionnaires covered by these dictionaries to elucidate common elements and overarching themes shared and to make initial suggestions for harmonizing PMD data.

3.4.1 Manual alignment methods

Questions from four questionnaires, Cure Mito, CureARS (Aminoacyl t-RNA Synthetase), CFR, and Hope for PDCD (Pyruvate Dehydrogenase Complex Deficiency), were aligned using their data dictionaries. Structural aspects were examined, including assessment of questionnaire length (as measured by the number of questions), organizational layout, and the logical flow of question sequencing. We determined core themes that were consistently represented across all questionnaires and quantified the proportion of questions within each instrument that were devoted to specific domains. Additionally, unique themes that were exclusive to a single questionnaire or present in only a subset of instruments were identified to highlight gaps or specialized areas of focus.

The alignment process involved transforming the data dictionaries for each registry into Excel spreadsheets and manually comparing both the questions and their corresponding response options. When questions related to age were compared, the units of measurement were reviewed for consistency. For symptom-related questions, attention was paid to whether the questions referred to current symptoms or symptoms that occurred at any point in the past, to ensure that the intent and meaning of each question were truly comparable across registries. We also examined whether different surveys captured equivalent information, even when questions were phrased differently, by identifying semantically similar items across instruments. Questions were compared according to their response formats (e.g., multiple choice, free text, numerical entry) to analyze patterns in how key topics were queried to inform recommendations for improving consistency in future data collection efforts.

We used subject matter expertise from the Cure Mito Foundation within the PMD-TF to divide the questions into overarching domains. To ensure analytical coherence, questions addressing the same underlying concept in a questionnaire were consolidated into a single harmonized question within the analysis. For each question, key metadata was extracted, including the exact question text, mode of response capture (such as radio group, checkbox, free-text or numeric inputs), and the set of possible answer options when available. We defined three distinct matching types. First, questions classified as "same" were those that were not only present in multiple questionnaires but were identical in both wording and conceptual intent wherever they appeared (e.g.: Cure Mito, Hope for PDCD, CureARS: "If the participant was diagnosed, how long did it take the participant to be diagnosed after the first onset of symptoms?). Second, the "similar" category captured questions that, while not verbatim matches, addressed the same clinical concept with variations in phrasing, structure, or response options (e.g.: CFR: What was the affected individual's very FIRST medical concern?; Cure Mito and Hope for PDCD: Please check the concerns or symptoms that were first noticed/checkbox options; CureARS: What were the initial symptoms that caused concern?/free text entry). Third, "unique" questions were those encountered exclusively in a single questionnaire, with no equivalent or comparable item in the remaining datasets.

Results

Question domains:

Questions were assigned to one of 22 domains to facilitate standardized comparison. These domains are listed in Table 9. The domains are based on the content of the surveys with input from SMEs and have not been mapped to any existing standards or data models.

Number and distribution of questionnaire items:

The number of questions included in each questionnaire provides an indication of its potential scope and the level of detail sought. For this analysis, the total question count represents the number of consolidated questions per questionnaire. The CFR contains the highest number of questions, with 370 consolidated questions, followed by 230 questions in CureARS and 127 and 126 respectively in Cure Mito and Hope for PDCD questionnaires. The distribution of questions is uneven across surveys, with the CFR having the most questions on symptoms, procedures, and quality of life, CureARS having the most on symptoms and medical history (Fig. 1). Question domains are more evenly distributed and very similar in Cure Mito and Hope for PDCD (expected, due to their collaboration)[128] with the most questions in domains that describe participants (diagnosis, symptoms, loss of milestone information).

Match type distribution by questionnaire and domains:

The analysis revealed both commonalities and divergence within the registry landscape. For instance, as illustrated in Fig. 2, the CFR is characterized by a large proportion of unique questions. Cure Mito and Hope for PDCD exhibit a high proportion of “same” or “similar” matches, because Cure Mito and Hope for PDCD collaborated on their registries.[128] The distribution of match type by domains (Fig. 3) enables quick qualitative and quantitative comparisons by identifying clusters where questionnaires converge with high “same”/ “similar” counts and diverge with high “unique” counts. Domains like "Quality of Life" and "Symptoms" show a substantial number of both "unique" and "same" questions, indicating both instrument-specific content and overlapping, harmonized questions.

Key differences and similarities among data dictionaries:

Figure 2: **Distribution of match type i.e. same, similar or unique questions per questionnaire**

Figure 3: **Distribution of question match type for each domain**

Table 8
Key differences and similarities among data dictionaries, by domain

Domain Group	Domain or data type collected	Questions Included	Registries Covering the Domain	Comment
Participant and contact information	Parent/Legal authorized representative information	Name and contact information of parent or legal authorized representative	Cure Mito, Hope for PDCD, CFR	Questions are aligned in Cure Mito and Hope for PDCD
	Accommodations	Special communication needs	Cure Mito, Hope for PDCD	The questions are aligned in the two surveys
	Demographics	Sex, age, race, education, income	Collected in all registries	Some response options differ between registries. Questions are aligned between Cure Mito and Hope for PDCD
Data governance and linkage	Data sharing permissions	Sharing permissions that participants can set indicating with whom the data is allowed to be shared	Cure Mito, Hope for PDCD	The questions relating to data sharing permissions are described in the data dictionary in Cure Mito and Hope for PDCD.
	De-ID entry (CRID)	Option for participants to enter their CRID (unique Clinical Research ID which can be used to link patient registry data to the same person's biosamples or other data)	Cure Mito, CureARS	
	Personally identifiable information	Personally identifiable information collected at registration (e.g. participant's name, date of birth, address) inclusion in the data dictionary	Collected in all registries	Not consistently described in the data dictionaries
Diagnosis	Diagnosis	Age at diagnosis, time to diagnosis, test done to confirm diagnosis and genetic mutation information, genetic reports collection	Collected in all registries	Only Cure Mito standardizes the genetic report information before reporting; Cure Mito and Hope for PDCD ask patients to specify their genetic mutation; CureARS asks to select one of the ARS genes. The CFR does not ask participants to upload genetic records.
Family history	Family history	Presence (or absence) of family members with the same disease	Collected in all registries	CureARS has a more extensive section
Disease Course and outcomes	Death information	Question on whether participant is currently alive or has passed away, along with either the date of death or age at death	Collected in all registries	
	Developmental issues	Concerns regarding developmental milestones	CureARS	
	Infections and Complications	History of infections	Cure Mito and Hope for PDCD	Questions partially align between Cure Mito and Hope for PDCD
	Loss of milestones	Loss of milestones (what milestone was lost, what age): collected	Collected in all registries but CureARS. CureARS has developmental milestones instead.	Complete questions alignment between Cure Mito and Hope for PDCD
	Symptoms	Symptoms related questions	Inconsistent across registries	Alignment can only be partial as symptoms can vary substantially between different mitochondrial diseases
	Medical history	History of seizures and other	CureARS	
Treatment and Management	Disease management	Questions related to use of feeding tubes, mobility devices and other disease management strategies	Collected in all registries	Complete questions alignment between Cure Mito, CureARS, and partial overlap with CFR
	Medications	Use of medications	Collected in all registries but Cure Mito	Misaligned questions across the other registries
	Procedures	Questions about surgical and other procedures (e.g. MRIs, CT scans, EEG, colonoscopies and other)	CFR	
Healthcare utilization and access	Healthcare utilization	Hospital admissions and emergency visits	Collected in all registries	Questions partially align between Cure Mito, Hope for PDCD, and CFR
	Insurance coverage	Health insurance	Collected/upload available in all registries	Misaligned questions across registries

Domain Group	Domain or data type collected	Questions Included	Registries Covering the Domain	Comment
Clinical trial and research participation	Clinical trial and research participation	Individual interest and prior history of participating in research and clinical trials	Collected in all registries	Complete questions alignment between Cure Mito, CureARS, and partial overlap with CFR
Quality of Life and Caregiver Experience	Caregiver burden	Collected with either the Zarit Burden Interview or Neuro-QoL Caregiver v2.0—TBI-CareQOL Caregiver Strain—Short Form 6a (validated survey initially created for individuals with traumatic brain injury[99,108])	Collected in all registries: Zarit Burden Interview: CFR, CureARS; Neuro-QoL: Cure Mito, Hope for PDCD	
	Quality of life	Questions about registry participant's quality of life	Collected in all registries but CureARS	Complete questions alignment between Cure Mito and Hope for PDCD

Table 9
Key differences and similarities among data dictionaries within domains, for Demographics and Diagnosi

Domain	Specific Questions	Registries Covering the Domain	Comment
Demographics	Biological sex	Collected in all registries but not CureARS which collects gender identity instead.	
	Participant's age	Only CFR collects age of participants	All other registries collect date of birth listed in "personally identifiable information" domain
	Participant's most recent weight	Only CFR collects weight of participants	
	Parents' highest level of education	Collected in all registries	Some response options differ
	Participant's level of education	CFR; and CureARS	
	Participant's school type	CFR	
	Participant's employment status	CureARS	
	Participant's marital status	CureARS	
	Members in participant's household	CFR	
	Participant's household income	CFR and CureARS	
	Race/Ethnicity	Separate race and ethnicity questions included in Cure Mito and Hope for PDCD	
	Demographic influence on diagnosis and/or treatment	Hope for PDCD	
	State disability benefits	CFR	
Diagnosis	Rare disease/condition diagnosis	Collected in all registries	
	Age at first symptom	CFR, Cure Mito, Hope for PDCD	CureARS asks the date of first symptoms
	Age at diagnosis	Collected in all registries	Cure Mito and Hope for PDCD align
	Date of diagnosis	CureARS	
	Location where diagnosis was made	Cure Mito and Hope for PDCD	
	Genetic mutation information	All registries provide an option to upload a genetic report	Cure Mito standardizes the genetic report information before reporting; Cure Mito and Hope

		for PDCD ask patients to specify their genetic mutation; CureARS asks to select one of the ARS **genes. CFR asks participants to upload genetic report.**
Participant's first concerns	Collected in all registries	CureARS collects free text input with no prespecified options to select from; other registries give a list of symptoms to select from. CFR collects free text input for additional concerns
Time from symptom onset to diagnosis	Collected in Cure Mito, Hope for PDCD, and Cure ARS registries (with exact same questions and response options). The CFR calculates this by asking age of symptom onset and age of diagnosis.	
Diagnosing physician information	CFR	
What testing was done to confirm the diagnosis	Collected in all registries	Partial alignment between all registries, full alignment between Cure Mito and Hope for PDCD
Concerns at the time of diagnosis	CFR	
Other diagnosis/misdiagnosis	Collected in all registries	Questions in Cure Mito and Hope for PDCD align
Undiagnosed symptoms	Cure Mito, Hope for PDCD	

Discussion

5.1 Key Challenges and Opportunities in PMD Clinical Research and Data Sharing

Lessons learned from discontinued drug development programs for PMD highlight multiple challenges. Broadly, lack of appropriate endpoints and outcome measures and improper trial design (including target population subgroup, genotype-phenotype selection, and study duration) and slow patient enrollment are common challenges that need to be addressed to increase the chances of success of future trials. Most existing clinical trials also target adult patients while many PMD affect pediatric populations, a caveat that should be addressed both in future trial designs and by performing further epidemiological studies to improve our understanding of mitochondrial disease prevalence. Despite unsuccessful clinical trials, the PMD drug development space remains dynamic with multiple active pipelines, and the patient community is motivated and engaged. For current and future trials to succeed, understanding disease progression through robust natural history data is vital, as it can guide efficient trial design. Embracing trial designs that account for disease heterogeneity (eg., adaptive trials designs) and implementing genotype-specific patient stratification are essential steps toward discovering meaningful treatments[130].

As with most rare diseases, PMD data are siloed and scattered across different geographical locations. Additionally, current data sharing in PMD is insufficient and inefficient, and data sharing policies vary across registries. Aggregating data after collection - when data was gathered without alignment - is costly, time-consuming, and often ineffective. To improve our understanding of disease mechanisms and progression across PMD, currently dispersed data needs to be aggregated so it can be leveraged effectively by scientists and clinicians.

One possible solution would be to have all registries use the same data sharing platform. Among the registries reviewed here, the CFR uses the Ordinal data platform; Cure Mito and Hope for PDCD use the CoRDS platform; and CureARS uses NORD's IAMRARE platform. While using the same platform can greatly facilitate alignment, it is not always feasible, as platform selection involves many factors, and migrating data between platforms can be complex and, in some cases, not possible. Platform selection can also impact how much or what data can be collected, or what kind of access the patient organization has to the data. Therefore, it is unlikely that all registries will move to a shared platform at this stage in their development. Instead, we recommend the registries in the PMD community come together to converge on a set of common data elements and consistent data collection practices. Creating uniform data collection standards will support future research and aggregation and allow for more efficient mapping of existing registry data, so that they can be combined for larger-scale analyses.

Cure Mito and Hope for PDCD both use the CRID (Clinical Research ID) system for data linkage, and most registries include data elements that allow creation of a GUID (Global Unique Identifier). Although both serve as mechanisms for linking data across sources, they produce different types of identifiers. The CRID is patient-initiated and patient-derived - participants generate their own ID via thecrid.org and choose which registries or research studies to share it with. In contrast, the GUID must be generated independently by each registry or research study based on identifying data they collect, meaning resulting IDs may not match across systems if data entry or formatting differ. Again, it is important for all stakeholders in the primary mitochondrial disease community to establish a common and consistent method of data linkage to ensure interoperability, enable cross-registry analyses, and reduce fragmentation of valuable patient data.

Finally, it is recommended that each registry makes its data-sharing policies - what can be shared, how access is requested, and who approves requests - transparent and publicly available.

5.2 Alignment among registries and areas for improvement

Our evaluation highlights some areas of alignment across registries. All questionnaires collect data in the domains of caregiver burden, clinical trial and research participation, death information, demographics, diagnosis, disease management, family history, healthcare utilization, loss of milestones (or developmental milestones), personally identifiable information, and procedures. Information on insurance coverage, medications, and quality of life is collected in all but one registry. Information on symptoms is collected in all registries, but is inconsistent, possibly due to the variability of signs and symptoms among PMD. There are three domains (infections and complications, accommodations, and data sharing permissions) collected only in Cure Mito and Hope for PDCD. High similarity in domain coverage (Table 8) combined with limited matching of questions (Table 9, Fig. 2, Fig. 3) across registries indicates shared interests in related topics and lack of coordination early in registry formation. The presence of the "similar" category scattered across domains highlights domains where comparable content is present but phrased differently by separate questionnaires, presenting an opportunity for future alignment. Cure Mito and Hope for PDCD have the greatest overlap in collected data (Fig. 2), as they have intentionally collaborated on registry questions and both use the CoRDS platform (approximately 25–35% of PDCD patients are diagnosed with Leigh syndrome, and they present with a significant clinical overlap). These registries are designed to allow individuals with both conditions to register and complete one of the surveys only once.[112] This kind of collaboration reduces participant burden and improves data quality, and we encourage registries to identify opportunities to expand this kind of collaboration in the future.

Our evaluation also reveals areas of misalignment. Misalignment can occur for many reasons, including: registries asking entirely different questions (462 instances); asking similar questions but referencing different timeframes (e.g., one registry asking about the history of a symptom at any point, while another asks about experience at time of answer) (30 instances); asking similar questions but providing different response options (71 instances); asking similar questions phrased differently (93 instances); referring to the individual with the disease in inconsistent ways (such as "patient," "participant," or using second-person pronouns like "you") (42 instances), all of which can influence responses. Other sources of misalignment include collecting age, medication, or laboratory data using different units without proper conversion or documentation (20 instances). Even seemingly minor differences - such as recording sex as "Male/Female" in one registry, "M/F" in another, and "Man/Woman" in a third - must be standardized to enable proper aggregation. Registries also varied widely in the number of questions they asked. While a larger number of questions could indicate a broader potential scope for data collection, actual data quality and utility depend on the relevance and completeness of responses, as well as alignment with the registry's goals. The number of questions should be considered in the context of participant burden, as an excessive number of questions can lead to increased missing or incomplete data making responses harder to interpret, and ultimately compromising the overall quality of the data collected.

5.3 Alignment Recommendations

Based on our analysis of PMD registry information collected to date, we make the following general recommendations, with the intent of raising awareness as soon as possible about potential missing elements in ongoing data collection and the need for alignment in future data collection.

General recommendations:

- Use a permanent, globally unique patient identifier (e.g. CRID). Ideally, the same identifier systems should be used across all PMD registries to support interoperability and de-duplication.
- Include a data dictionary and ensure that all collected data elements are adequately described in the data dictionary, including personally identifiable information (PII) that is not included in the de-identified dataset.
- Refer to registry individuals consistently as "participants" (rather than "you," "your child," "patient," "subject," etc.): "participant" is currently the most commonly used term in clinical trial protocols and reporting. It also conveys respect for the individual's active involvement and contribution.
- Make surveys as concise as possible: industry use of natural history data relies on clinical information collected through studies with strict regulatory standards including pre-specified protocols and visit schedules[131]. Patient-reported data often does not meet these requirements. Therefore, collecting large amounts of patient-reported data may not result in information that is usable for regulatory purposes, and instead may increase respondent burden while diminishing data quality. Longer surveys are also more likely to result in missing data and can increase participants burden patients.
- Use appropriate age units. Some registry questions only ask for age in years, yet mitochondrial disease symptoms and interventions can begin within days of life. Using appropriate age units, such as days, improves data accuracy and facilitates alignment across different registries. Age units can differ among questions but should be consistent across surveys.
- Use the appropriate time frame. Questions that ask only about a participant's current experience may miss important historical information, and questions that ask only about past experience do not allow inference of current disease state.
- Seek permission to share data before collecting it. Include data sharing permissions in the shared dataset if they exist, either at the dataset level or the participant level as appropriate.
- Registries should publish survey results and anyone analyzing the data should publish their results. This demonstrates transparency and shows that the data are not merely collected but actively analyzed and shared. Sharing results is a keyway to give back to participants by showing how their contributions are driving insights and advancing understanding of PMD.

Domains:

- Given the level of consistency in domains covered by questionnaires, we recommend the PMD community agree upon a core set of domains that should be required or considered optional for all registries and map them to an existing standard. Based on initial results, they all should cover participant and contact information (including demographics, accommodations, parent/legal authorized individual information), diagnosis, family history, disease course and outcomes (including developmental milestones, loss of milestones, medical history, symptoms, infections and complications, and death information), treatment and management (including disease management, medications and procedures), health care utilization and access to care

(including insurance coverage), clinical trial or research participation, caregiver burden, and quality of life. Within these domains, both questions and response options should be aligned between registries to enable meaningful aggregation of data and facilitate robust, comparable analyses across studies.

- Individual groups may cover other domains in their surveys, if there is a need for additional information specific to the disease or registry goals. Where possible, these domains should align with existing standards.

Questions:

- Diagnosis information is where harmonization may be most valuable. Genetic diagnosis is required for clinical trial participation, and usually researchers and industry find it most valuable to use patient-driven registries to understand what genetic mutations are represented. It is recommended that genetic information - whether self-entered by the participant or obtained from an uploaded genetic report - be reviewed regularly to ensure its validity and to confirm whether it indicates a genetically confirmed mitochondrial disease. Because mitochondrial diseases can be caused by hundreds of genetic mutations, standardizing such information promptly and understanding whether each participant's disease has been genetically confirmed is critical.
- Time to diagnosis is also critical as it can inform the need for genetic testing programs for the community. While it has been shown that for mitochondrial disease overall time to diagnosis can be long and involve seeing many specialists[103], it can be significantly shorter for pediatric neurodegenerative diseases such as Leigh syndrome[104].
- 'Current' responses are only meaningful if longitudinal data is collected, which can be challenging in patient-driven registries where participants may only respond to questions once or infrequently.
- Comorbidities: information on comorbidities is necessary to build high risk population testing (e.g. % of PMD in Diabetes population, or hypothyroidism).

5.4 Next Steps

The PMD-TF is making substantial progress in supporting the data needs of PMD drug development through our data landscape and data element harmonization efforts. As more data are ingested into RDCA-DAP and cross-dataset integration begins, we aim to work on drug development tools (such as disease progression models, stratification apps, and trial simulation tools) and inform trial design and development of new endpoints or identification of biomarkers.

The next most important step is to work with registries to improve harmonization of data collection. The preliminary recommendations conveyed in this publication will be consolidated and expanded by incorporating additional data dictionaries from other PMD registries. To enhance the efficiency and accuracy of the manual data dictionaries comparisons, we plan to develop a Natural Language Processing (NLP) and Large Language Model (LLM)-based tool capable of identifying semantic similarities and mapping relationships between variables across questionnaires. Additionally, we intend to align the identified domains with standardized frameworks such as the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM)[132] and the Study Data Tabulation Model (SDTM)[133] to improve interoperability, facilitate data harmonization and support consistent cross-study analyses. The Cure Mito Foundation has already implemented both OMOP and SDTM alignments in its patient registry, providing an important foundation and practical model for this work[115,134]. Finally, as more patient-level data are incorporated into RDCA-DAP, we will extract lessons-learned from the curation work to improve develop disease-specific recommendations, including data elements and standards. These consolidated recommendations will be provided in a follow-up to this white paper.

Conclusions

PMD remain a highly diverse group of disorders with substantial unmet medical needs. Historically, clinical trial failures and participant attrition rates have limited drug development progress. Yet, the recent FDA approvals of therapies for Barth Syndrome and TK2d provide proof-of-concept that drug development for PMDs is feasible—and mark a turning point for the field. This progress is built on innovations in trial design, a deeper understanding of genotype-phenotype correlations, and meaningful patient and caregiver input informing both drug development and regulatory review. However, the fact that a large majority of PMD still lack targeted therapies, underscores the continued urgency for innovative new solutions and the importance of collecting high quality, RWD. Patient- and clinician-led registries are now central to this effort, facilitating broad, rapid enrollment and enabling the collection of detailed, patient-centered outcomes. When harmonized to common data models and standards, these registries can provide the standardized, high-quality data needed to power clinical research, optimize study designs, and inform regulatory decision-making. The C-Path PMD-TF was founded as a public-private partnership to meet these challenges and accelerate therapy development for all affected individuals. The preliminary work presented in this white paper represents the first coordinated, cross-registry evaluation and harmonization effort within the primary mitochondrial disease community. Through coordinated data harmonization, cross-registry collaboration, and the development of disease-specific standards, the PMD-TF aims to maximize the quality and impact of PMD registry data. Ongoing work to align variables and frameworks such as OMOP and SDTM, share lessons with the broader community, and build an aggregated, industry-accessible database will drive further progress. Ultimately, our collective commitment is to ensure that these harmonized data and collaborative methodologies catalyze the development of more effective, patient-centered therapies that deliver meaningful improvements in outcomes and quality of life for all individuals and families living with PMD.

Abbreviations

POLG / POLG1
DNA Polymerase Gamma (gene)
TAZ / TAFAZZIN

Tafazzin gene (causative in Barth Syndrome)
TP
Thymidine Phosphorylase
ARS
Aminoacyl tRNA Synthetase
GDF-15
Growth Differentiation Factor 15
FGF-21
Fibroblast Growth Factor 21
CSF
Cerebrospinal Fluid
PDC
Pyruvate Dehydrogenase Complex
VO_2-max
Maximum Oxygen Consumption
OLE
Open-Label Extension
6MWT
6-Minute Walk Test
12MWT
12-Minute Walk Test
PPAR-δ
Peroxisome Proliferator-Activated Receptor Delta
PROMIS
Patient-Reported Outcomes Measurement Information System
COA
Clinical Outcome Assessment
PRO
Patient-Reported Outcome
ObsRO
Observer-Reported Outcome
ClinRO
Clinician-Reported Outcome
MIDD
Model-Informed Drug Development
NDA
New Drug Application (implied/contextual)
C-Path / Cpath
Critical Path Institute
RDCA-DAP
Rare Disease Cures Accelerator – Data and Analytics Platform
NAMDC
North American Mitochondrial Disease Consortium
NORD
National Organization for Rare Disorders
MseqDR
Mitochondrial Disease Sequence Data Resource
HmtVar
Human Mitochondrial Variants (database)
ICIMD
International Classification of Inherited Metabolic Disorders
CFR
The Champ Foundation Registry
CureARS
CureARS MAPS Registry (Aminoacyl tRNA Synthetase)
CRID
Clinical Research ID
GUID
Global Unique Identifier
SME

Subject Matter Expert

Glossary of Terms

Term	Definition
Primary mitochondrial diseases (PMD/PMDs)	Genetic disorders caused by dysfunctional mitochondria due to pathogenic variants in nuclear DNA (nDNA) or mitochondrial DNA (mtDNA), typically affecting oxidative phosphorylation and high-energy organs.
Secondary mitochondrial dysfunction (SMD)	Mitochondrial dysfunction arising from non-mitochondrial genetic defects or acquired factors (for example, neurodegenerative diseases, metabolic syndromes, environmental exposures) that indirectly impair mitochondrial function.
nDNA (nuclear DNA)	Nuclear genome encoding many mitochondrial proteins; pathogenic variants in these genes can cause primary mitochondrial diseases.
mtDNA (mitochondrial DNA)	Mitochondrial genome encoding key components of oxidative phosphorylation; pathogenic variants cause a significant subset of primary mitochondrial diseases.
Pathogenic variant	Disease-causing change in a gene, inherited or de novo, that contributes to mitochondrial dysfunction and clinical disease manifestations.
Oxidative phosphorylation	Mitochondrial process that generates ATP via the electron transport chain and ATP synthase; disruption underlies many clinical features of PMDs.
Point prevalence	Proportion of individuals in a population who have a disease at a specific point in time; PMDs are reported with minimum point prevalence around 1 in 4,000–1 in 5,000 individuals in cited studies.
Median survival	Age by which 50% of affected individuals have died; for 74% of classical PMD syndromes, reported as less than 10 years in referenced literature.
Leigh syndrome	Genetically complex primary mitochondrial disease with over 110 identified pathogenic variants, associated with severe neurological impairment and challenges for targeted treatment development.
Alpers syndrome	PMD due to multiple POLG gene mutations, characterized by seizures, liver degeneration, and progressive developmental regression (“classical triad”).
Autosomal Dominant Optic Atrophy (ADOA)	PMD mainly caused by OPA1 mutations (and others such as SPG7, MFN2) affecting mitochondrial dynamics, leading to progressive vision loss and associated neurological features.
Barth syndrome	X-linked PMD caused by TAZ (TAFAZZIN) mutations, leading to cardiomyopathy, neutropenia, skeletal myopathy, growth delay, and characteristic facial features
Chronic Progressive External Ophthalmoplegia (CPEO)	PMD associated with large-scale mtDNA deletions or nuclear/mtDNA mutations, presenting with bilateral ptosis, ophthalmoplegia, proximal myopathy, dysphagia, and ataxia.
Kearns-Sayre syndrome (KSS)	PMD caused by large-scale mtDNA deletions or rearrangements, featuring CPEO, pigmentary retinopathy, cardiac conduction defects, endocrine abnormalities, and neurologic involvement.
Leber Hereditary Optic Neuropathy (LHON)	PMD due to specific mtDNA point mutations (for example, m.3460G>A, m.11778G>A, m.14484T>C), causing bilateral painless subacute visual loss and possible additional neurological features (“LHON plus”).
Outcome measures	Clinical, functional, or biomarker endpoints used to assess treatment efficacy in trials; traditional measures have recently failed in PMD programs, motivating disease-specific tools.
Endpoint development	Development, validation, and regulatory qualification/acceptance of outcome measures suitable for clinical trials in a given disease area
Data integration	Combining data from multiple sources (registries, natural history studies, clinical trials, etc.) into a harmonized structure to enable analysis and model development.
Data standardization	Applying common data formats, terminologies, and structures across datasets to support interoperability, pooling, and regulatory-grade analyses.
FDA-approved treatment	Therapy is formally approved by the U.S. Food and Drug Administration for a specific indication, following review of safety and efficacy data.
Critical Path Institute (C-Path)	Independent, non-profit organization leading collaborative programs to accelerate drug development through data integration, model development, and regulatory science tools.
Rare Mitochondrial Diseases Task Force / Primary Mitochondrial Diseases Task Force	C-Path-led collaborative initiative (launched January 2024) focusing on accelerating therapeutic development in PMDs via comprehensive data integration, standardization, and endpoint development.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

DMD declared employment with employee of Astellas until October 2024. SZ is currently an employee of AstraZeneca and owns AstraZeneca stock and stock options. All other authors declare that they have no competing interests.

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Authors' contributions

AB and DMD contributed to the conception and design of the work, acquisition, analysis, and interpretation of data, and drafting and revising the manuscript. RB and SZ contributed to the analysis and interpretation of data and participated in drafting and revising the manuscript. ER contributed to drafting and revising the manuscript. RLW contributed to the design of the work, acquisition, analysis, and interpretation of data, and drafting and revising the manuscript. VW contributed to drafting and revising the manuscript. All authors read and approved the final manuscript.

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Clinical trial number

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Figures

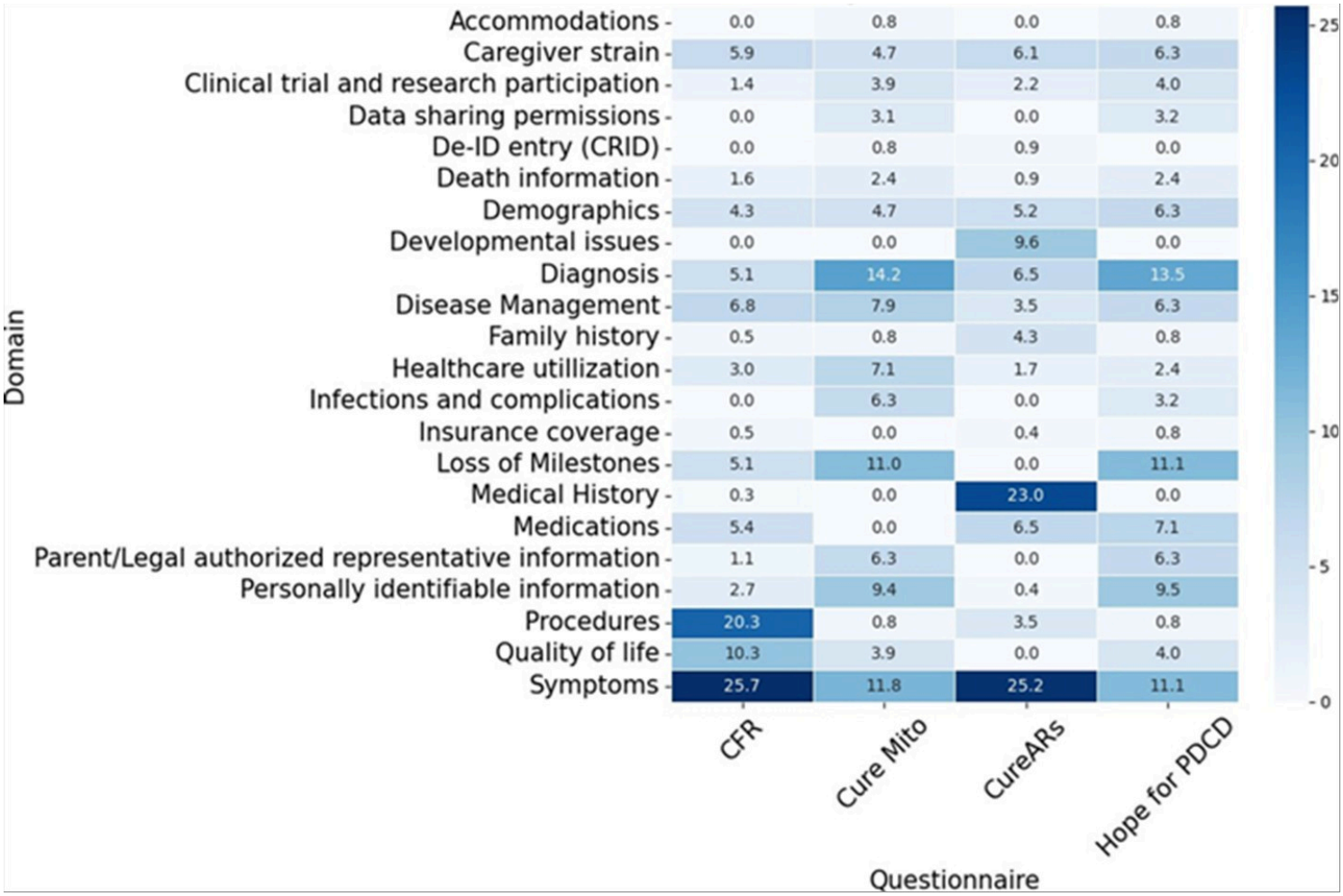


Figure 1

Domain Coverage across Questionnaires (%)

Percentage of questions covering each domain in the questionnaires

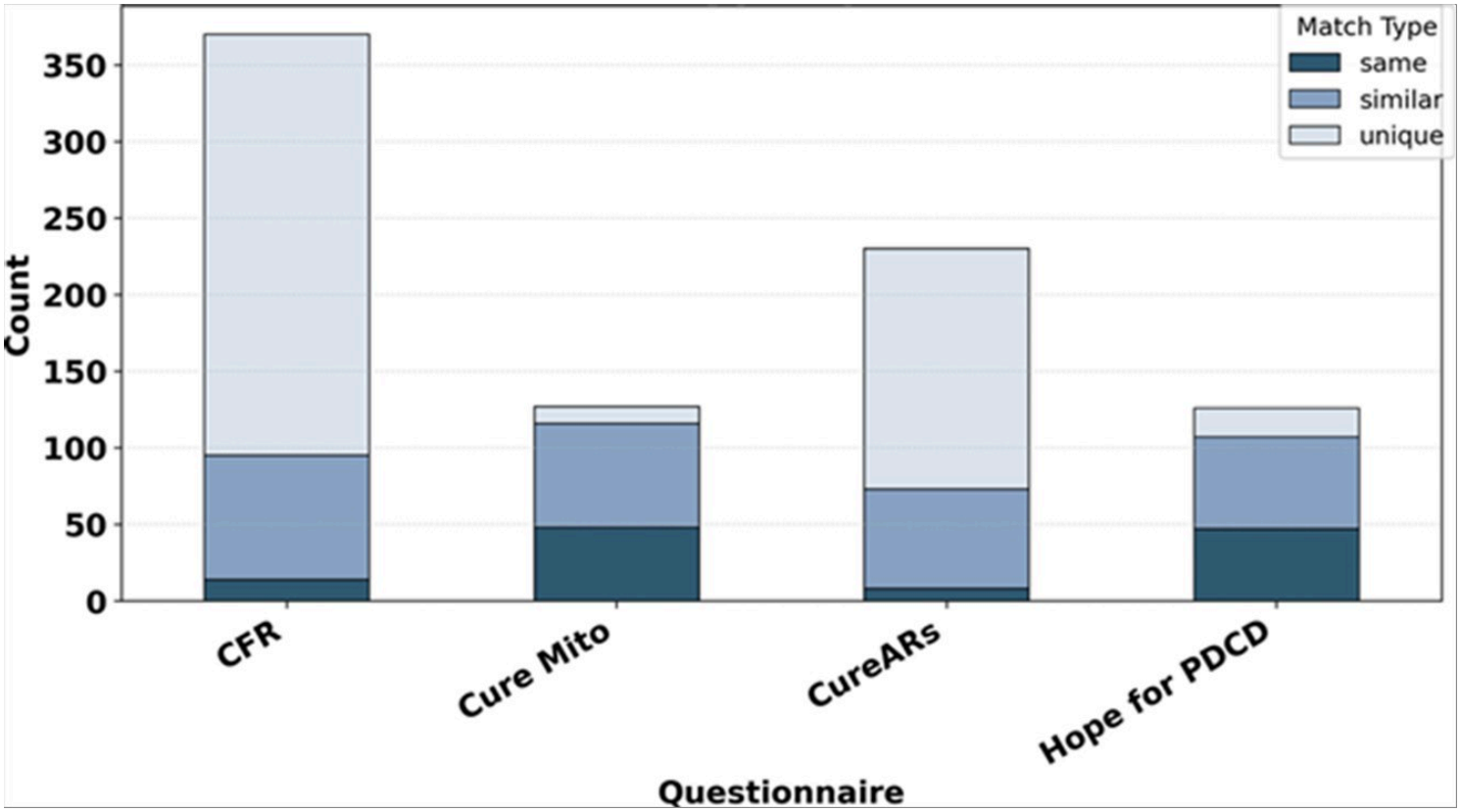


Figure 2

Question Match Type Per Questionnaire

Distribution of match type i.e. same, similar or unique questions per questionnaire

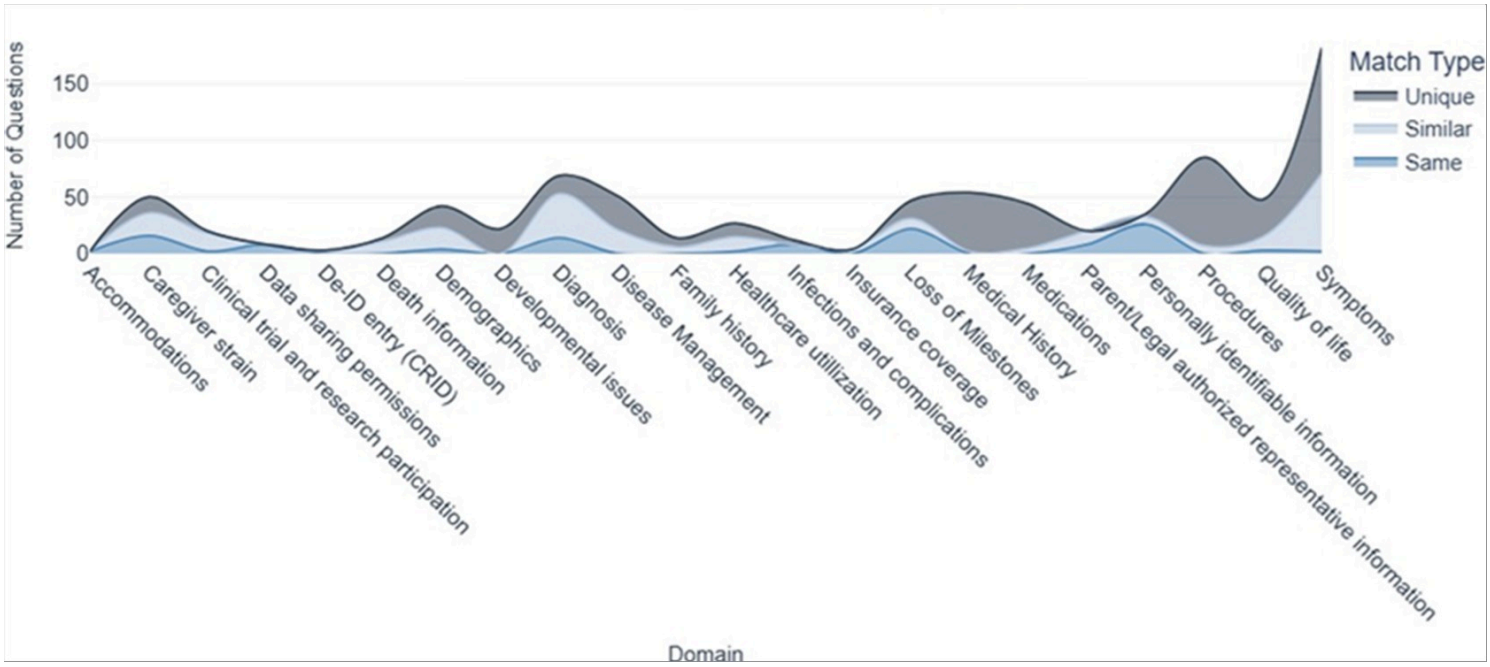


Figure 3

Distribution of Question Types by Domain

Distribution of question match type for each domain