A Review of Natural History Studies in Polymerase Gamma (POLG) Disease to Identify Potential Knowledge Gaps and Clinical Trial Endpoints for Future Studies

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OBJECTIVE

A literature review of nine natural history studies (NHS) in patients with polymerase gamma (POLG) disease was conducted to identify common data elements and knowledge gaps that could inform future natural history and interventional clinical studies.

INTRODUCTION

POLG (polymerase gamma) mediated mitochondrial disorders are a group of rare mitochondrial diseases caused by mutations in the *POLG* gene. They are progressive, multisystemic disorders driven by impaired energy production. They are also debilitating neurodegenerative diseases with high morbidity and early mortality. Mitochondrial DNA (mtDNA) depletion is the underlying pathology leading to symptoms impacting all age groups.

POLG disease is considered one of the most common inherited mitochondrial disorders. While the clinical spectrum is extremely broad, symptoms strongly correlate with age of onset:

- Childhood-Onset (prior to age 12 years): Features a severe prognosis characterized by liver involvement, cognitive regression, and early-onset seizures.
- Juvenile/Adult-Onset (Ages 12-40 years): Often presents with ataxia, peripheral neuropathy, and seizures.
- Late-Onset (After age 40 years): Predominantly featuring progressive external ophthalmoplegia (PEO), ptosis, and myopathy.

There are currently no disease modifying treatments for POLG disease.

Natural history studies play an important role in understanding any disease because they follow patients over time to define how the disease develops and changes without experimental treatment intervention. For rare diseases like POLG disease, natural history studies are foundational because many aspects of the disease are still poorly understood. Natural history studies also help create and define clinical trial outcome measures, including biomarkers, which are pertinent to the disease, regulators, and industry.

METHODS

A literature review of nine natural history studies (NHS) in patients with POLG disease was conducted to identify common data elements and knowledge gaps that could inform future natural history and interventional clinical studies. Of these nine studies, five have already reported results in peer-reviewed journals (four retrospective and one prospective), while four are ongoing (all prospective), with study designs available but results not published. This literature review focused on NHS, and although there are real world evidence and case studies that also provide valuable information, they were not included in this review.

STUDIES REFERENCED

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RESULTS

Across all nine studies, the most frequently used clinical outcome measure was the Scale for the Assessment and Rating of Ataxia (SARA), which appeared only in prospective studies. In all prospective studies (one published and four ongoing), SARA was used to quantify ataxia progression (Table 1).

The most commonly collected biomarkers were liver function tests (LFTs) (6/9), followed by lactate (5/9), MRI (4/9), and growth differentiation factor 15 (GDF15) (3/9). Emerging biomarkers, neurofilament light chain (NfL) and circulating cell-free mitochondrial DNA, were included in one study each (Table 1).

Common Patient Reported Outcomes (PROs), regardless of age of onset, included seizure frequency (5/9) and the PROMIS (Patient-Reported Outcome Measurement Information System) and the Mitochondrial Fatigue Scale (3/9). PROs Zarit Caregiver Burden and SF-36 were included in one study each (Table 1).

Pediatric Onset	Adolescent and Adult Onset
Survival / Age at Death	Rate of Ataxia Progression (SARA/ICARS)
Seizure Onset & Status Epilepticus	Gait & Mobility Decline
Liver Dysfunction / Liver Failure	Peripheral Neuropathy
Developmental Regression / Plateau	Ophthalmoplegia / Ptosis
Feeding Dependence (NG/G -tube)	Epilepsy Emergence (later onset)
Growth Failure / Failure to Thrive (FTT)	Loss of Independence / ADLs
	Quality-of-Life Measures

High priority Lower priority

Table 2: Clinical Outcomes Measures by Age of Disease Onset

Data from the published studies suggest age of disease onset influences disease course and clinical outcomes and therefore determines the most relevant clinical endpoints. In pediatric onset patients, key outcomes included survival, seizure onset, and liver involvement, whereas in adult and adolescent onset patients, ataxia was the predominant clinical outcome (Table 2).

	Clinical Outcome Measures				Biomarkers							Patient Reported Outcomes (PROs)			
NHS Reference	SARA	NMDAS NPMDS	MM-COAST	INAS	LFTs	Lactate	MRI	GDF 15	Nfl	Circulating cell-free mDNA	Nerve Conduction	Seizure Frequency	PROMIS or Mito Fatigue Scale	Zarit Caregiver Burden	SF 36
1	–	–	–	–	✓	✓	✓	–	–	–	–	✓	–	–	–
2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
3	–	–	–	–	✓	✓	✓	–	–	–	–	✓	–	–	–
4	✓	–	–	✓	–	–	✓	–	–	–	✓	–	–	–	–
5	–	–	–	–	✓	–	–	–	–	–	–	✓	–	–	–
6 EU	✓	✓	–	–	–	–	–	–	–	–	–	–	–	–	–
7 CHOP	✓	–	✓	–	✓	✓	–	✓	–	–	–	✓	✓	–	–
8 SPAIN	✓	–	–	–	✓	✓	✓	✓	✓	✓	–	–	✓	–	–
9 UMDF PIONEER	✓	✓	–	–	✓	✓	–	✓	✓	✓	–	✓	✓	✓	✓
Total Count	5	2	1	1	6	5	4	3	2	2	1	5	3	1	1

Table 1: Frequency of Clinical Outcome Measures, Biomarkers, and Patient Reported Outcomes Cited in NHS Referenced

CONCLUSIONS

- It is essential to integrate insights from both retrospective and prospective NHS of POLG disease and to engage regulatory agencies regarding the most meaningful clinical outcome measures across different age groups.
  - For infants and children, priorities are survival, seizure control, and liver function.
  - For adolescents and adults, the consistent focus on ataxia suggests it is a critical symptom for assessment and should be incorporated into clinical trial designs.
- Systematic collection of patient reported outcomes (PROs) related to fatigue is important, although a single scale has yet emerged as the standard in the field.

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