

Endpoint Retention in Public POLG Deoxycytidine-Deoxythymidine Trial Reports

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Abstract

Background: POLG-related disease is caused by pathogenic variants in the gene encoding DNA polymerase gamma, but a clinical endpoint story cannot be inferred merely because several public endpoints move in a favorable direction. Public deoxycytidine/deoxythymidine reports now include a 2024 six-month interim POLG trial report and a 2026 longer-term report from the same trial family, creating a specific endpoint-retention problem rather than a generic mitochondrial-treatment question.

Objective: The selected question was whether longitudinal Newcastle Mitochondrial Disease Scale (NMDS), growth differentiation factor 15 (GDF-15) and quality-of-life endpoints in public POLG deoxycytidine/deoxythymidine reports support sustained endpoint concordance, or whether deaths, withdrawals, missing biomarker windows and single-arm cohort overlap make concordance non-identifiable.

Methods: Complete public primary texts and indexed primary records were inspected for two POLG dC/dT trial-family reports, two POLG-relevant preclinical nucleoside sources, one non-POLG/non-TK2 dC/dT clinical report and one 2026 POLG biomarker cohort. A source-comparison pilot coded endpoint class, follow-up window, denominator or event caveat and claim boundary. No patient-level data, private platform inputs, pooled effect size, treatment ranking, survival model or clinical recommendation was generated.

Results: Six public endpoint rows from two overlapping POLG trial-family reports were coded across NMDS, GDF-15, EEG and quality-of-life classes; five rows had favorable reported directions and four rows were retention- or measurement-limited. The 2024 first-ten report recorded NMDS and GDF-15 improvement over six months, while the 2026 expanded report recorded 25 starters, five deaths, five withdrawals, improved NMDS through reported windows, early GDF-15 improvement and quality-of-life improvement at selected timepoints. The same evidence also preserved open-label single-arm design, cohort overlap, changing timepoint support, missing GDF-15 windows and upper-limit biomarker constraints. Preclinical nucleoside studies supported biological plausibility and endpoint-transfer caution, not clinical rescue.

Conclusions: Public POLG dC/dT reports support endpoint-specific favorable signals under important retention conditions, not a demonstrated same-participant concordant clinical rescue claim. The analysis is non-causal, non-pooled and hypothesis-generating: future POLG dC/dT interpretation should require matched participant/time windows, event and withdrawal accounting, biomarker censoring rules, genotype/onset strata and comparator or natural-history anchoring before endpoint concordance is treated as identifiable.

Keywords: POLG; DNA polymerase gamma; deoxycytidine; deoxythymidine; NMDS; GDF-15; endpoint retention; mitochondrial DNA depletion

1 Introduction

POLG encodes the catalytic subunit of mitochondrial DNA polymerase gamma, and pathogenic POLG variants produce heterogeneous neurologic, hepatic, neuromuscular and multisystem disease. The current public deoxycytidine/deoxythymidine (dC/dT) literature is scientifically important because the intervention has a plausible nucleotide-support rationale and because the reported clinical directions are encouraging. The unresolved problem is narrower: favorable aggregate directions across NMDS, GDF-15 and quality-of-life endpoints do not by themselves show that the

same participants, same windows and same event accounting support concordant rescue [1,2].

The competing interpretation is straightforward. One account reads repeated favorable NMDS, GDF-15 and quality-of-life directions as a coherent POLG treatment response. The selected account instead treats those directions as endpoint-specific signals that remain conditioned on retention, missingness, timepoint support, biomarker censoring and open-label single-arm design. These accounts make different same-condition predictions. If concordant rescue is identifiable from public aggregate text, endpoint classes should

remain directionally aligned without material denominator or assay-limit caveats. If the retention-conditioned account is correct, favorable endpoint rows should coexist with deaths, withdrawals, missing windows or other qualifiers that block same-participant concordance inference.

The question is POLG-specific because the focal clinical reports enrolled people with POLG-related disorders and biallelic pathogenic or likely pathogenic POLG variants, and because the preclinical rationale concerns DNA polymerase gamma-dependent mitochondrial DNA maintenance rather than a generic mitochondrial intervention [1-4]. The same analysis cannot simply be applied to any mitochondrial disorder: it depends on the overlap structure of NCT04802707 POLG reports, POLG-specific genotype inclusion, the NMDS/GDF-15 endpoints used in those reports, and preclinical POLG/TWNK/DGUOK nucleotide-transfer limits.

2 Methods

Primary records were verified against PubMed, PMC or publisher pages on 11 October 2026. The central clinical sources were the 2024 EClinicalMedicine interim report and the 2026 Neurotherapeutics longer-term report from the same POLG dC/dT trial family [1,2]. Preclinical transfer-boundary sources were Dombi et al. 2024 and Bulst et al. 2012 [3,4]. Current adjacent clinical and biomarker context was checked through a 2025 non-POLG/non-TK2 dC/dT report and a 2026 POLG biomarker cohort [5,6]. Trial-family overlap was preserved; the two POLG trial reports were not counted as independent cohorts.

The public source-comparison pilot coded endpoint class, follow-up window, reported direction, direct public count, retention limitation and caveat count. Endpoint rows were coded only from public aggregate reporting. Preclinical mtDNA quantity, red-signal, imaging, culture-cell and myotube findings were used to bound transfer claims, not as surrogates for patient benefit. Figure 1 summarizes the public workflow from fixed POLG question through source verification, endpoint coding, sensitivity checks and bounded synthesis.

Three sensitivity checks were declared. The same-trial-family check was decision-changing because it prevented double-counting the 2024 and 2026 reports as independent replication. The retention-limited-row check was a robustness check because it asked whether favorable directions remained attached to denominator or measurement constraints. The endpoint-harmonization check was exploratory because exact-label and harmonized endpoint grouping can change row support and should not be interpreted as biology. No pooling was performed because the public evidence comprises overlapping single-arm reports, not independent randomized cohorts or released patient-level longitudinal data.

The public bundle includes manuscript source, endpoint-retention matrix, evidence table, source-data JSON, analysis summary, analysis code, figures, figure geometry measurements, biological-audit supplements, QA record, Gemini review and checksums. A supplementary biological audit ledger records exact

manuscript anchors, source identifiers, source excerpts, source-version hashes and unresolved assumptions. The ledger checks quotation and manuscript-location integrity only; it is not proof of biological truth, clinical efficacy or guideline suitability.

3 Results

3.1 Evidence synthesis

The source-comparison pilot coded six endpoint rows across NMDS, GDF-15, EEG and quality-of-life classes. Five of six rows had favorable reported directions, and four of six rows were retention- or measurement-limited. In the 2024 first-ten report, NMDS sections 1-3 improved from a mean of 27.3 at baseline to 20.7 at six months, mean GDF-15 decreased from 1031 to 729 pg/ml, and EEG improved in five of eight participants with abnormal baseline EEG [1]. In the 2026 longer-term report, 25 individuals started dC/dT; the public abstract reported five deaths and five withdrawals, NMDS improvement across reported windows through 24 months, early GDF-15 improvement and quality-of-life improvement at selected follow-up windows [2].

Table 1 preserves the central evidence and its interpretive limits. The table intentionally separates clinical aggregate endpoint behavior from preclinical transfer-boundary evidence and from adjacent non-POLG/non-TK2 or observational biomarker context.

Figure 2 shows the discriminating structure. Favorable endpoint directions are present in the public POLG trial-family reports, but they are accompanied by open-label single-arm design, trial-family overlap, deaths, withdrawals, changing timepoint support, missing GDF-15 values and upper-limit biomarker constraints. Under these conditions, public aggregate reporting supports endpoint-specific favorable signals but does not identify same-participant longitudinal concordance.

3.2 Evidence-coded sensitivity analysis

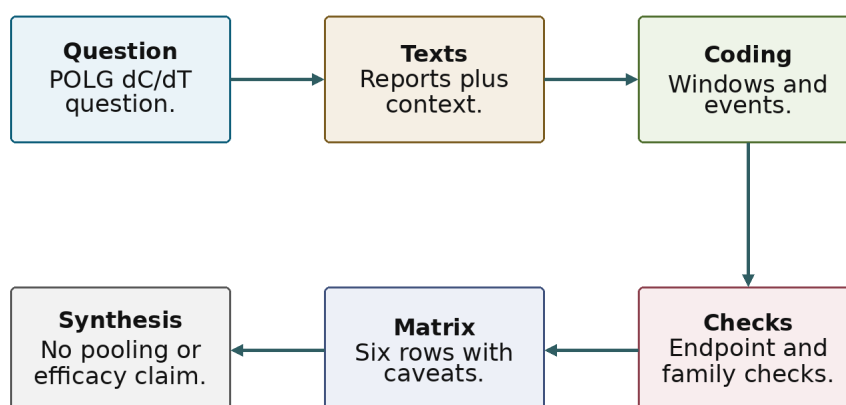
The decision-changing same-family sensitivity check retained two public POLG reports as overlapping trial-family evidence rather than independent cohorts. The robustness check retained four retention-limited endpoint rows, so the claim boundary did not depend on dismissing favorable results. The exploratory endpoint-harmonization check found that NMDS and GDF-15 recur across both POLG reports, while quality-of-life appears in the longer-term report; this pattern supports a future endpoint-availability request but does not create a pooled clinical effect.

The preclinical sources motivate biological plausibility while sharpening the boundary. Dombi et al. tested fifteen deoxynucleoside combinations across fibroblast models including POLG-related cells and reported mtDNA-content responses in culture contexts [3]. Bulst et al. reported nucleotide-mixture responses in myotube and transdifferentiated-fibroblast models, with gene- and model-specific behavior [4]. These studies concern cell-system mtDNA or imaging endpoints. They do not validate NMDS, GDF-15 or quality-of-life concordance in an open-label human POLG cohort.

Table 1. Public POLG dC/dT endpoint evidence and transfer-boundary context.

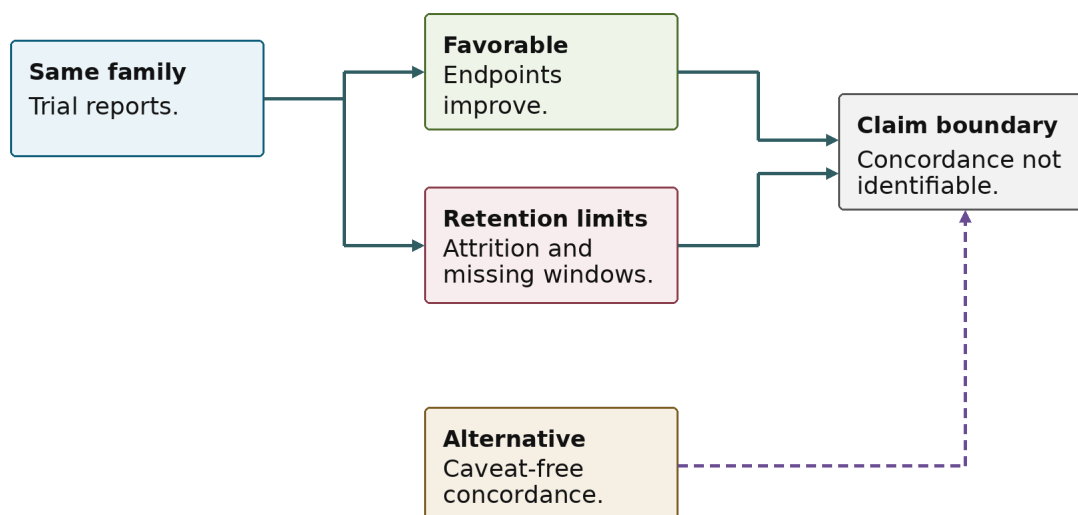
ID	Model and perturbation	Key finding	Interpretive limitation
[1]	Open-label single-arm phase 2 POLG-related disorder report; first 10 children.; Enteral deoxycytidine/deoxythymidine for 6 months.	NMDS sections 1-3 improved from mean 27.3 to 20.7; GDF-15 mean decreased from 1031 to 729 pg/ml; EEG improved in 5 of 8 with abnormal baseline EEG.	No control arm, no formal sample-size calculation, descriptive interim design and biomarker ceiling/normal-baseline issues prevent causal endpoint-concordance inference.
[2]	Expanded open-label POLG-related disorder report from the same NCT04802707 trial family; 25 starters.; Enteral deoxycytidine/deoxythymidine with longer follow-up.	Five deaths and five withdrawals were reported; NMDS improved through 24 months, GDF-15 improved early, and quality-of-life scores improved at selected windows.	The 2024 and 2026 reports are not independent cohorts; changing timepoint support, missing biomarker samples and open-label design condition the interpretation.

ID	Model and perturbation	Key finding	Interpretive limitation
[3]	POLG/TWINK/DGUOK fibroblast high-content imaging and isotope-labelling source.; Fifteen deoxynucleoside combinations in replicating and quiescent culture states.	Some nucleoside combinations increased mtDNA-content measurements in POLG model cells.	Cell imaging endpoints, red-signal measurements and retained cell counts do not validate patient efficacy or clinical endpoint concordance.
[4]	Patient myotube and MyoD-transdifferentiated fibroblast models of mitochondrial DNA depletion.; Variable deoxynucleoside monophosphate mixtures and NRTI-induced depletion.	POLG and DGUOK cell models showed mtDNA-copy responses to selected nucleotide mixtures.	Cell-type, genotype and biochemical-threshold differences limit transfer to human longitudinal NMDS, GDF-15 or quality-of-life endpoints.
[5]	Open-label dC/dT report in non-POLG and non-TK2 mitochondrial DNA depletion disorders.; Enteral deoxycytidine/deoxythymidine in a genetically different MDDS cohort.	The study broadens clinical dC/dT reporting beyond POLG and TK2.	Different genes and cohort composition cannot be used as direct POLG endpoint-concordance evidence.
[6]	Confirmed pathogenic POLG-variant cohort with biomarker assessment.; Observational clinical and biomarker characterization, not dC/dT treatment.	GDF15 and neurofilament light were evaluated as nonspecific candidate biomarkers in POLG-related disease.	Biomarker usefulness for diagnosis or monitoring does not make GDF-15 a treatment-response surrogate in a single-arm dC/dT trial.



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Figure 1. Public source-comparison workflow for the POLG endpoint-retention analysis. The workflow fixes the POLG dC/dT question, verifies complete public primary sources, codes endpoint windows and denominators, applies same-family and retention sensitivity checks, and produces a bounded synthesis without private inputs or clinical efficacy inference.



Solid connectors indicate source-coded relationships; dashed connector marks the competing interpretation.

Figure 2. Concept summary for retention-conditioned endpoint concordance. Favorable NMDS, GDF-15 and quality-of-life directions are interpreted together with trial-family overlap, deaths, withdrawals, missing biomarker windows and assay constraints; the dashed connector shows the competing coherent-rescue account that would require concordance without material caveats.

4 Discussion

The principal finding is evidentiary rather than therapeutic. Public POLG dC/dT reports contain favorable endpoint directions, but the public aggregate evidence does not show that NMDS, GDF-15 and quality-of-life changes are concordant for the same participants across matched windows after deaths, withdrawals, missing

biomarker windows and assay constraints are preserved. The result therefore supports a retention-conditioned interpretation of endpoint behavior.

This contribution differs from the two clinical trial reports because it does not re-report safety or efficacy outcomes and does not treat the reports as independent cohorts [1,2]. It differs from the

preclinical nucleoside studies because it does not infer clinical rescue from mtDNA quantity, high-content imaging or myotube endpoints [3,4]. It also differs from broad biomarker or non-POLG dC/dT context because it keeps the POLG genotype inclusion, trial-family overlap and endpoint windows central [5,6].

The contribution is also distinct from the closest current Mito Map portfolio papers. The POLG astrocyte assay-state paper asks whether induced mitophagy, basal autophagy-lysosome signal and reactive/co-culture endpoints remain separable in human astrocyte-lineage models; this paper asks whether public human POLG dC/dT clinical endpoints remain concordant after deaths, withdrawals and missing windows are preserved. The POLG liver-vulnerability paper asks whether genotype, primary liver mtDNA maintenance and regeneration-stress endpoints discriminate hepatic injury mechanisms; this paper does not analyze liver stress, VPA exposure or regeneration endpoints. The TWNK optical-tweezers paper audits whether a public Twinkle workbook preserves trace identifiers for pause-persistence inference; this paper uses no TWNK workbook or single-molecule kinetics and instead codes aggregate POLG clinical endpoint retention. Those comparisons leave the present paper's new contribution as the source-bound endpoint-retention matrix for overlapping POLG dC/dT trial-family reports.

The practical research decision is concrete. Future POLG dC/dT interpretation should request or report same-participant endpoint matrices, death and withdrawal handling, GDF-15 censoring rules, genotype and onset strata, baseline severity, follow-up windows and comparator or natural-history anchoring. Without these elements, endpoint concordance remains hypothesis-generating even when several aggregate endpoints move in favorable directions.

5 Limitations

The analysis used public aggregate reports and archived public source text only. It did not access patient-level trial data, individual longitudinal trajectories, unpublished adverse-event tables, genotype-specific response tables or sponsor-held trial datasets. It cannot estimate treatment efficacy, survival benefit, clinical utility, optimal dose, mechanism, variant-specific response or patient-level prognosis.

The 2024 and 2026 POLG reports were treated as overlapping trial-family evidence, so the analysis is intentionally conservative about replication. The coding used deposited measurement labels and public text; it did not reinterpret GDF-15 as a validated treatment-response surrogate or convert quality-of-life summaries into blinded clinical endpoints. Current searches did not identify a randomized controlled POLG dC/dT primary report, and that absence is a limitation rather than evidence against efficacy.

6 Conclusions

Public POLG dC/dT reports support endpoint-specific favorable signals under important retention and measurement constraints. They do not presently identify sustained same-participant endpoint concordance across NMDS, GDF-15 and quality-of-life endpoints. A future claim of concordant clinical rescue should be anchored to matched participant windows, event accounting, biomarker censoring rules, genotype/onset strata and comparator logic.

Declarations

Data and code availability. The public bundle includes endpoint-retention data, an evidence table, source-data JSON, analysis code, figure geometry measurements, biological-audit supplements, QA outputs and checksums. Manuscript-quality and concept-impact grades are available at <https://precisionmito.com/paper-grades>; these grades do not establish scientific validation. Private selection files, source snapshots, raw biological-audit inputs, portfolio context and

outreach planning files are retained locally and excluded from public manifests.

Ethics statement. This working paper used public literature and aggregate public trial reporting only. It used no identifiable patient data and required no new human-participant or animal research approval.

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