J Biochem Technol (2026) 17(4): 14-22
https://doi.org/10.51847/yqvph3fbT7
ISSN: 0974-2328

Defining Durability in Somatic Gene Therapy: A Conceptual Framework Separating Vector Persistence, Transgene Expression, Cellular Turnover, and Maintenance of Therapeutic Function

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Received: 13 August 2026 / Received in revised form: 13 September 2026, Accepted: 16 September 2026, Published online: 27 October 2026

Abstract

Durability has become a central descriptor of somatic gene-therapy performance, yet the term is frequently applied to biologically different observations. Persistent vector DNA, continued transgene expression, long-lived corrected cells, and sustained therapeutic function can coincide, but none is an automatic surrogate for the others. This conceptual framework separates these layers and examines the biological and measurement conditions under which each can support a claim of durable therapeutic effect. Evidence from adeno-associated virus gene transfer, hematopoietic stem and progenitor cell gene therapy, retinal treatment, skeletal-muscle expression, and other somatic-cell platforms indicates that durability depends on vector fate, transcriptional competence, immune pressure, cell turnover, lineage contribution, tissue renewal, disease progression, and the choice and timing of longitudinal endpoints. The framework therefore treats durability as a multidimensional longitudinal property rather than a single binary state. A therapy can remain molecularly detectable while losing clinically relevant output, or retain functional benefit despite changes in one molecular proxy. Durable therapeutic function is most defensibly inferred when the biological layer being measured, the tissue and cellular substrate, the observation interval, and plausible alternative explanations are stated explicitly. This separation provides a basis for interpreting longitudinal gene-therapy outcomes without equating persistence of a component with persistence of benefit.

Keywords: Somatic gene therapy, Durability, Vector persistence, Transgene expression, Cellular turnover, Longitudinal endpoints

Introduction

Durability is one of the most consequential claims made about somatic gene therapy because a major part of the therapeutic proposition is that a single or limited administration may produce benefit over an extended interval. Yet "durable" is used to describe observations at several biological levels. In recombinant adeno-associated virus (rAAV) therapy, long-term expression depends on vector-genome fate, transcriptional activity, target-tissue biology, immune responses, and the stability of the cells containing the vector. These determinants can vary independently, making persistence of therapeutic output a compound biological phenomenon rather than a property of the vector alone (Muhuri *et al.*, 2022).

Clinical evidence reinforces this heterogeneity. Across rAAV trials, durability is reported using different molecular, biochemical, physiological, and clinical endpoints, with substantial variation in vector serotype, dose, target organ, disease, immune status, assay selection, and follow-up duration (Shen *et al.*, 2022). The same label can therefore refer to persistent circulating protein activity in one study, retained visual function in another, or continued detection of vector-derived material in a third. Such observations may each be valid within their own measurement domains while answering different scientific questions.

Long-term interpretation also depends on study architecture. Gene-therapy follow-up extends across periods in which patient retention, assay practice, supportive care, disease progression, treatment standards, and clinically relevant outcomes can change. Statistical and practical approaches to long-term follow-up are consequently part of the evidentiary basis for durability claims rather than administrative details external to them (Rohde *et al.*, 2024). A five-year observation is scientifically informative only in relation to what was measured, when it was measured, how missingness was handled, and whether the selected endpoint remains an appropriate proxy for the biological process of interest.

Measurement itself can introduce further ambiguity. Anti-AAV binding and neutralizing-antibody assays, for example, differ in design, sensitivity, biological interpretation, and relevance to distinct stages of gene transfer (Schulz *et al.*, 2023). An immune measurement can identify a potential modifier of vector performance without directly establishing loss of transgene expression or therapeutic effect. More broadly, a molecular assay should not be interpreted as though it measured a downstream clinical state merely because both change over time.

The central argument developed here is that durability in somatic gene therapy should be decomposed into at least four analytically separable longitudinal properties: persistence of vector or genetically modified material; persistence of transgene expression;

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persistence of the corrected cellular substrate or its functional progeny; and persistence of therapeutic function. These properties interact, but they need not share the same time course or failure mechanism. The purpose of this framework is therefore not to impose a universal durability threshold. It is to identify which layer has actually been demonstrated, which mechanisms could account for change, and what additional evidence would be needed before persistence at one level can be interpreted as persistence at another.

Materials and Methods

Conceptual Ambiguities in the Definition of Gene Therapy Durability

The strongest empirical reason to separate durability layers is that vector material, RNA production, protein output, and clinical function can be measured independently. In liver biopsies obtained after AAV5-mediated factor VIII gene therapy, vector DNA, transgene RNA, and protein-related evidence did not behave as interchangeable quantities across individuals (Fong *et al.*, 2022). Such observations show why the statement "the vector persists" cannot, by itself, establish that transcription remains stable, that therapeutically relevant protein continues to be produced at the same level, or that a clinical effect is being maintained. Each inference requires a measurement capable of addressing its own biological layer.

Immune responses add another source of non-equivalence. Longitudinal analysis in valoctocogene roxaparvovec recipients demonstrates that humoral and cellular immune responses can accompany treatment and must be considered when interpreting expression trajectories (Long *et al.*, 2024). However, immunity should be treated as a conditional modifier rather than a default explanation for every change in transgene output. Hepatocyte state, episomal vector behavior, transcriptional regulation, vector design, assay variability, and individual biological context may contribute to the same observed pattern. The conceptual task is therefore to distinguish a plausible mechanism from a mechanism actually supported by the available longitudinal evidence.

Multi-year hemophilia A studies illustrate why time alone does not resolve this problem. Factor VIII activity may remain measurable for several years after AAV-mediated transfer, yet individual trajectories can differ and expression can change during follow-up (Pasi *et al.*, 2020; George *et al.*, 2021; Ozelo *et al.*, 2022). A later time point can demonstrate that some therapeutic output remains, but it does not specify whether the underlying vector genomes are unchanged, whether transcription per persisting vector genome is stable, or whether the relationship between circulating factor activity and clinical protection has remained constant. Durability is therefore better represented by a trajectory and its biological interpretation than by the mere presence of a positive value at an arbitrarily late visit.

Evidence from hemophilia B provides an important comparison without implying that different products share identical kinetics. Etranacogene dezaparvovec can sustain factor IX activity and clinically meaningful bleeding protection over longitudinal follow-up (Pipe *et al.*, 2023). Earlier AAV5-mediated factor VIII work similarly established the feasibility of sustained expression after a single administration while also revealing substantial between-patient variation (Rangarajan *et al.*, 2017). Taken together, these studies support a general distinction between persistent expression and durable therapeutic function, but they do not justify transferring quantitative expectations from one transgene, vector construct, disease, or target population to another.

The four principal meanings of durability can therefore be separated according to what is actually measured and what that measurement can legitimately establish.

Table 1 summarizes distinct biological meanings of durability in somatic gene therapy and the measurements required to support each inference.

Table 1. Distinct biological meanings of durability in somatic gene therapy and the measurements required to support each inference

Durability layer	Biological object that must persist	Measurements that directly address the layer	What persistence at this layer can establish	What it cannot establish by itself	Major context modifiers
Vector-material persistence	Vector genomes, integrated vector sequence, or genetically modified cellular material	Vector-copy analysis, tissue DNA assays, integration-site analysis where applicable	Continued presence of treatment-derived genetic material	Continued transcription, stable protein output, preserved target-cell function, or clinical benefit	Vector class, integration status, tissue sampling, cell division, genome loss, clonal replacement
Transgene-expression persistence	Therapeutically relevant RNA and/or encoded protein	RNA quantification, protein measurement, biochemical activity attributable to the transgene	Continued biological output from the therapeutic construct	Persistence of every original vector genome, stability of the corrected cellular population, or maintained patient-level benefit	Promoter activity, transcriptional regulation, immune pressure, protein turnover, assay sensitivity
Corrected-cell persistence	Long-lived corrected cells, stem/progenitor cells, or functionally	Lineage-resolved gene marking, integration-site tracking, cellular phenotyping, longitudinal clonal analysis	Continued contribution of genetically modified cells to the relevant compartment	Equivalent contribution across all lineages or preservation of downstream organ function	Cell identity at treatment, self-renewal, differentiation, selection, tissue renewal, conditioning

	relevant descendants				
Therapeutic-function persistence	Disease-relevant physiological or clinical function	Validated functional tests, disease biomarkers, event rates, organ-specific outcomes, treatment-independence measures	Continued clinically or physiologically meaningful benefit	Mechanistic persistence of the vector, RNA, protein, or original corrected cell population	Disease progression, compensatory biology, concomitant care, organ reserve, endpoint responsiveness

The distinction becomes still clearer outside hepatic factor replacement. In RPE65-mediated inherited retinal disease, voretigene neparvovec produced measurable functional improvement in a controlled trial (Russell *et al.*, 2017). That observation supports persistence of a therapeutically relevant visual effect over the measured interval, but a functional test does not directly quantify retinal vector genomes or transcriptional activity. Ocular gene therapy further illustrates how the target compartment itself affects interpretation: retinal cell type, local immune environment, disease-associated degeneration, vector tropism, and route of administration all shape the relationship between molecular persistence and functional outcome (Wang *et al.*, 2024). A durability definition that ignores tissue context would therefore erase precisely the biology needed to interpret the result.

Post-mitotic skeletal muscle represents a different persistence environment. Long-term AAV9-mediated DOK7 overexpression in mice demonstrates that sustained transgene expression can be achieved in a tissue in which many target cells are relatively long lived (Huang *et al.*, 2023). That finding is informative about the compatibility of a post-mitotic cellular substrate with prolonged expression, but it does not establish a universal human duration or eliminate the influence of species, vector, promoter, disease, and immune context. Tissue stability can make one failure mechanism less likely while leaving others intact.

A further ambiguity arises when structural and functional outcomes diverge. After voretigene neparvovec treatment, improvement in full-field stimulus testing has been observed in the same broader clinical context in which chorioretinal atrophy can develop (Stingl *et al.*, 2023). Such discordance does not automatically mean that one measurement is invalid. It indicates that function, tissue structure, disease evolution, and treatment-associated biological processes may occupy different longitudinal trajectories. The relevant question becomes which therapeutic function is being maintained, in which tissue state, and by which biological substrate.

These distinctions lead to a more restrictive use of the word durability. A durability claim should identify the persisting entity, the level at which it is observed, and the time interval over which persistence has been demonstrated. It should also specify whether the observation is direct or inferred from a downstream proxy. Vector retention, expression, corrected-cell persistence, and maintained therapeutic function should be treated as connected but non-identical states. A therapy is most convincingly described as functionally durable when sustained benefit is demonstrated with endpoints appropriate to the disease while the molecular and cellular observations used to explain that benefit are interpreted within their own measurement limits.

The resulting relationships are summarized in **Figure 1**. The figure treats durability as a longitudinal inference problem in which different biological layers can remain coupled, become partially uncoupled, or diverge under tissue-specific and measurement-specific conditions.

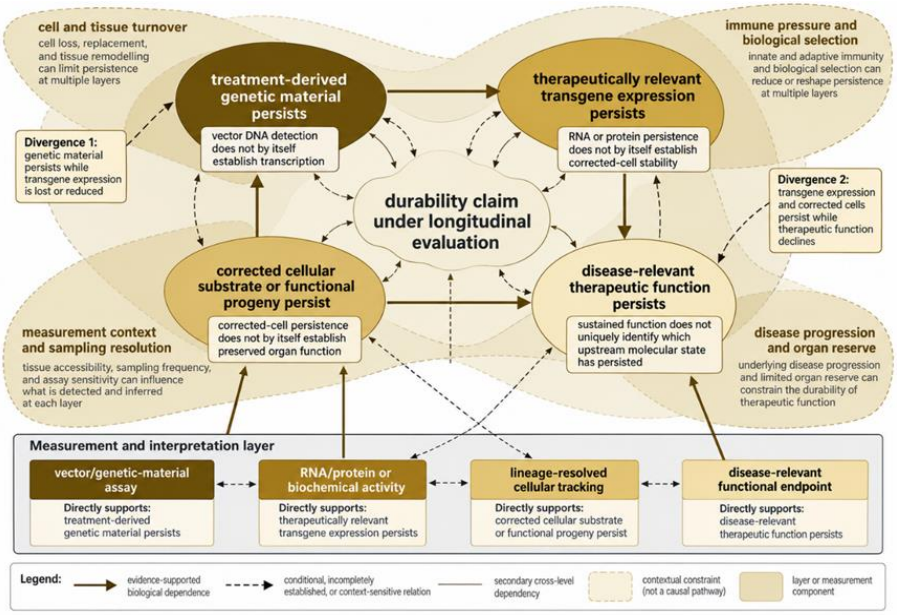


Figure 1. Divergent persistence layers that determine what a durability claim can mean in somatic gene therapy

Vector Persistence and Maintenance of Transgene Expression

The distinction between vector persistence and maintained expression becomes especially important when comparing non-integrating AAV approaches with gene-modified hematopoietic stem and progenitor cell therapies. In Wiskott-Aldrich syndrome, lentiviral HSPC gene therapy has produced long-term corrected hematopoiesis and clinical benefit over extended follow-up (Magnani *et al.*, 2022). In such a system, therapeutic persistence depends less on retention of an episomal vector within one long-lived differentiated cell and more on durable engraftment and output from genetically modified progenitors. The relevant biological object is therefore a self-renewing cellular population and its descendants, not simply persistence of a vector genome in a static tissue compartment.

Metachromatic leukodystrophy further demonstrates that cellular and functional durability can operate on different spatial and temporal scales. Lentiviral HSPC gene therapy can establish durable genetically modified hematopoiesis and sustained arylsulfatase A delivery while neurological outcomes depend on treatment timing, disease stage, migration or replacement of relevant myeloid populations, and the amount of irreversible tissue damage present before therapy (Fumagalli *et al.*, 2022). Persistent corrected blood-cell production is consequently important but cannot be interpreted as an immediate or complete measure of central nervous system function.

Even within the hematopoietic compartment, the starting cellular population influences long-term reconstruction. Comparative analysis of bone-marrow-derived and mobilized-peripheral-blood HSPCs used for Wiskott-Aldrich syndrome gene therapy showed differences in the composition and early dynamics of reconstitution while genetically engineered grafts could persist over follow-up (Scala *et al.*, 2023). This observation highlights a general durability principle: equivalent evidence of successful transduction at treatment does not imply that the modified cells have equivalent long-term self-renewal, lineage contribution, or selective behavior.

Longitudinal clonal studies provide stronger resolution of this problem. Tracking vector integration sites in patients receiving HSC gene therapy shows that durable hematopoiesis is produced by large populations of persisting clones whose lineage contributions vary with disease and biological context. Long-term ADA-SCID studies likewise demonstrate that corrected-cell persistence can coexist with sustained immune or metabolic benefit while remaining analytically separable from event-free survival and late safety outcomes (Calabria *et al.*, 2024; Migliavacca *et al.*, 2024; Booth *et al.*, 2025). Thus, a stable bulk gene-marking value can conceal changes in which clones are contributing, which lineages they supply, and whether the distribution of corrected cells remains appropriate for therapeutic function.

Length of follow-up does not, however, compensate for weak causal identification. A pilot report of HSC gene therapy in three patients with advanced symptomatic juvenile metachromatic leukodystrophy described persistent arylsulfatase A activity and longitudinal neurological observations over several years (Zhang *et al.*, 2025). Subsequent critical appraisal argued that the small uncontrolled cohort and limitations in the available neurological evidence substantially restrict strong claims of clinical improvement in advanced disease (Schoenmakers *et al.*, 2025). This disagreement is methodologically important for durability research: a long observation interval can establish persistence of a measured biochemical or cellular feature without automatically establishing durable therapeutic efficacy.

A similar distinction applies when hematopoietic gene correction is intended to modify disease in another organ. In cerebral adrenoleukodystrophy, lentiviral HSPC gene therapy links long-term corrected hematopoietic output to neurological and imaging outcomes that evolve on a different biological time scale (Eichler *et al.*, 2024). The therapeutic mechanism requires more than persistence of modified peripheral cells; it depends on their capacity to generate relevant progeny, reach or influence the diseased compartment, and do so before irreversible neurological injury exceeds the therapy's capacity to preserve function.

Recent β-thalassemia work shows how multiple layers can be measured within the same treatment program. In a small pilot study of children with β0/β0 transfusion-dependent β-thalassemia, vector marking, transgene expression, cellular engraftment and clinically relevant transfusion outcomes were evaluated longitudinally using complementary molecular and cellular methods (Li *et al.*, 2024). The strength of such multidimensional measurement is not that every endpoint should move in parallel. Its value is that a later loss of benefit could, in principle, be localized to engraftment, lineage contribution, transcription, protein production or a downstream disease process instead of being described only as a generic loss of durability.

Long-term observation of other gene-modified somatic cell populations provides the same conceptual lesson. Large-scale follow-up of lentiviral- and gammaretroviral-modified T-cell therapies demonstrates that persistence of genetically modified cells can itself be monitored as a long-term property while safety and therapeutic outcomes are assessed separately (Jadlowsky *et al.*, 2025). T-cell kinetics should not be transferred directly to HSPCs or AAV-transduced tissues, but the comparison reinforces the need to define the cellular substrate whose continued presence is being claimed.

Across these systems, vector persistence and maintenance of transgene expression are therefore inseparable from the biology of the cells that carry the therapeutic material. In relatively stable post-mitotic tissues, persistence may depend heavily on retention and transcriptional competence within long-lived cells. In self-renewing systems, the crucial question may instead be whether long-term repopulating cells were modified and whether their descendants continue to populate the therapeutically relevant compartment. In tissues undergoing disease-related degeneration, function can decline despite continued molecular evidence of treatment. A durability analysis must consequently identify the tissue's renewal logic before it assigns meaning to the persistence of a vector, transcript, protein or corrected-cell population.

Table 2 summarizes tissue and cell-state determinants that alter the expected persistence path after somatic gene transfer.

Table 2. Tissue and cell-state determinants that alter the expected persistence path after somatic gene transfer

Somatic context	Renewal or persistence logic	Therapeutic material whose persistence is most informative	Dominant mechanisms that can weaken durability	Longitudinal observation that best localizes the problem	Transfer boundary
Hepatic AAV factor expression	Long-lived hepatocytes with possible cell loss or replacement; non-integrating vector material generally depends on persistence within transduced cells	Hepatic vector material plus sustained transgene RNA/protein activity	Loss or dilution of vector genomes, transcriptional change, immune-mediated effects, hepatocyte turnover, disease-related liver change	Parallel molecular and biochemical measurements across repeated time points	Factor-expression kinetics in liver should not be extrapolated quantitatively to retina, muscle or stem-cell systems
Retinal AAV therapy	Target-cell longevity may support persistence, while inherited degeneration can continue independently	Local transgene function together with disease-relevant visual performance	Progressive retinal degeneration, local structural change, immune or surgical effects, expression loss	Functional testing combined with structural retinal follow-up	Preserved visual function does not directly quantify local vector genomes or transcription
Skeletal-muscle AAV expression	Predominantly long-lived post-mitotic fibers create a different persistence environment from rapidly renewing tissues	Persistent transgene expression within muscle fibers	Vector loss after cell damage or regeneration, immune pressure, promoter or expression change	Molecular expression plus relevant neuromuscular function	Preclinical muscle persistence cannot define human durability in another tissue
Hematopoietic stem/progenitor cell gene therapy	Long-term function depends on modification and self-renewal of repopulating cells and continued production of appropriate descendants	Corrected HSC clones and lineage-resolved progeny	Failure to modify durable stem cells, lineage bias, clonal loss, inadequate engraftment, disease-specific selection	Longitudinal clonal tracking with lineage-specific gene marking and functional assays	Bulk blood marking does not establish equivalent correction across lineages or organs
HSPC-mediated treatment of neurological disease	Corrected hematopoiesis must generate cells or products capable of affecting the nervous system over a delayed interval	Persistent corrected hematopoietic output plus organ-level neurological function	Late treatment, irreversible tissue damage, inadequate tissue replacement or enzyme delivery, disease progression	Combined hematopoietic, biochemical, imaging and neurological follow-up	Peripheral correction cannot be interpreted as immediate CNS correction
Gene-modified mature immune-cell therapy	Persistence depends on survival, expansion, differentiation and contraction of the modified cellular population	Gene-modified cell population and its functionally relevant subsets	Cellular exhaustion, contraction, selection, host environment, treatment-specific biology	Long-term cellular persistence assessed separately from efficacy and safety	Mature T-cell persistence kinetics are not a substitute for HSC or tissue-specific durability

Cellular Turnover, Tissue Renewal, and Loss of Therapeutic Capacity

Cellular persistence cannot be inferred reliably from a single bulk measurement. In hematopoietic gene therapy, integration-site tracking permits longitudinal reconstruction of the clones contributing to circulating lineages and therefore distinguishes durable cellular contribution from transient gene marking (Pais *et al.*, 2023). Such analyses address a different question from measuring vector copy number in bulk blood: they ask whether the same or related corrected cellular populations continue to participate in tissue maintenance over time.

The identity of the cells modified at treatment is equally important. CD90-targeted lentiviral approaches illustrate that only a fraction of phenotypically broad CD34-positive populations possesses the

long-term repopulating properties expected of true hematopoietic stem cells (Berckmueller *et al.*, 2023). Consequently, strong early transduction of short-lived progenitors could produce substantial initial expression without equivalent long-term cellular durability. Conversely, successful modification of self-renewing cells may preserve corrected output even while the relative abundance and lineage contribution of individual clones change.

This distinction extends beyond hematopoiesis. Tissue renewal can progressively replace initially modified cells, disease processes can destroy treated cells, and regenerative episodes can alter the fraction of cells carrying therapeutic material. Functional decline under such circumstances does not necessarily imply that the remaining transgene has become transcriptionally inactive. Likewise, persistent expression in surviving cells does not guarantee that enough corrected cells remain to sustain organ-level benefit. Cellular turnover therefore constitutes an independent durability axis connecting molecular persistence to tissue-level therapeutic capacity.

Longitudinal interpretation is strongest when the measured endpoint can localize the level at which change occurs. Clonal tracking, lineage-specific gene marking, molecular expression assays, structural measurements, and disease-relevant functional outcomes answer complementary questions. Their combination permits a decline in therapeutic effect to be evaluated as possible loss of corrected cells, altered lineage contribution, reduced expression within surviving cells, progressive tissue pathology, or another downstream process instead of being assigned automatically to "loss of gene therapy durability."

The distinction between these possibilities leads to an endpoint structure in which each longitudinal measurement is tied to the biological claim it can directly support.

Table 3 summarizes longitudinal endpoint classes for separating persistence of therapeutic material from persistence of therapeutic benefit.

Table 3. Longitudinal endpoint classes for separating persistence of therapeutic material from persistence of therapeutic benefit

Longitudinal endpoint class	Biological quantity primarily observed	Persistence claim directly supported	Discordance that would require additional explanation	Important interpretive boundary
Vector or therapeutic DNA measurement	Treatment-derived genetic material	Continued molecular presence of therapeutic material	DNA remains detectable while RNA, protein, corrected-cell contribution, or function declines	Molecular detection alone does not establish active therapeutic output
Transgene RNA or encoded-protein measurement	Expression from the therapeutic construct	Continued transcriptional or protein-level output	Expression persists while clinical or physiological benefit decreases	Expression assays do not identify every mechanism governing downstream function
Bulk gene marking or vector-copy measurement	Fraction of sampled cells containing therapeutic sequence	Continued presence of genetically modified cells within the sampled compartment	Bulk marking appears stable while lineage composition or clonal contribution changes	Bulk values can conceal population restructuring
Lineage-resolved clonal tracking	Contribution of corrected stem/progenitor clones and descendants	Persistence and distribution of corrected cellular lineages	Individual clones contract or expand while aggregate correction remains similar	Clone abundance does not itself measure therapeutic efficacy
Structural or organ-state measurement	Disease-relevant tissue integrity	Persistence or progression of anatomical state	Structure deteriorates while a functional measure remains improved, or vice versa	Structural and functional trajectories may differ
Disease-relevant functional endpoint	Physiological or clinical performance	Maintenance of therapeutic benefit	Function changes without a parallel change in the measured molecular proxy	Functional persistence does not uniquely identify the upstream mechanism

A Multidimensional Framework for Evaluating Functional Durability

The evidence supports treating durability as a set of linked longitudinal state variables rather than a single scalar property. At minimum, interpretation should specify the status of therapeutic genetic material, transgene expression, corrected-cell or lineage persistence, and disease-relevant function. These dimensions should be considered together with tissue turnover, disease progression, immune context, and the assay used to observe each layer.

The framework is therefore diagnostic rather than numerical. It does not assign a durability score or establish a universal threshold. Instead, it asks which layer remains demonstrably persistent and which competing mechanisms could explain discordance between layers. Integration-site analysis can help determine whether an apparent decline reflects changing clonal contribution (Pais *et al.*, 2023), whereas molecular assays may localize loss to transcription or protein production. Functional measurements address the final therapeutic consequence but cannot uniquely identify the upstream cause.

Attempts to maximize persistence also face biological constraints. High systemic AAV exposure can produce serious immunotoxicity, showing that greater vector exposure cannot be treated as an unqualified route toward greater durability (Duan, 2023). Persistence must therefore be interpreted alongside safety, target-organ biology, and the possibility that increasing one determinant of exposure may introduce another mechanism of failure.

Contemporary AAV engineering can modify capsid behavior, genome configuration, expression characteristics, tropism, and host interaction (Suarez-Amaran *et al.*, 2025). Such advances can alter the probability that molecular persistence will be achieved, but they do not remove the dependence of therapeutic durability on cell survival, tissue renewal, immune biology, disease progression, and downstream functional reserve. Vector design occupies one level of the system rather than determining the entire longitudinal outcome.

A useful durability claim should consequently be falsifiable. Persistent vector DNA accompanied by falling RNA or protein would challenge an explanation based only on vector loss. Stable expression accompanied by decreasing corrected-cell abundance would direct attention toward population turnover. Preserved molecular output with worsening organ function would require examination of disease progression or insufficient biological effect. These discordant trajectories are scientifically informative because they distinguish rival explanations instead of collapsing them into a single declaration of treatment success or failure.

Results and Discussion

Longitudinal Evaluation, Endpoint Selection, and Clinical Interpretation

The practical implication is that follow-up schedules should match the biological time scale of the durability layer being evaluated. Long-term surveillance is essential, but observation duration alone is insufficient (Rohde *et al.*, 2024). Sampling must be capable of detecting the mechanisms expected to operate in the relevant tissue, whether these involve loss of vector material, altered expression, cellular replacement, clonal restructuring, progressive organ damage, or delayed functional change.

Endpoint selection should therefore follow the biological claim. Vector DNA, RNA, protein activity, corrected-cell abundance, tissue structure, and clinical function are complementary measurements rather than interchangeable surrogates. The coexistence of improved retinal function and structural change after ocular gene therapy illustrates why an apparently conflicting longitudinal signal should trigger mechanistic interpretation rather than automatic rejection of one endpoint (Stingl *et al.*, 2023). Similar caution applies to HSPC therapy, in which corrected hematopoiesis and organ-level benefit can emerge on different time scales.

Clinical interpretation should explicitly state which layer has been demonstrated. Persistent factor activity supports durable transgene output; lineage-resolved gene marking supports durable cellular contribution; sustained disease-relevant function supports durable therapeutic effect. None alone proves persistence of every upstream component. This discipline is particularly important when molecular sampling is limited or when investigators infer mechanism from a downstream clinical outcome.

The framework also limits inappropriate transfer between tissues. Retinal cells, hepatocytes, skeletal muscle fibers, HSCs, their differentiated progeny, and mature gene-modified lymphocytes differ in renewal, compartmentalization and functional organization. A persistence pattern established in one system can identify a plausible mechanism in another, but it should not supply a quantitative durability expectation without direct evidence.

Durability should therefore be reported as an evidence-bounded longitudinal interpretation: what persisted, where it persisted, how it was measured, over what interval, and which alternative mechanisms remain compatible with the observation. Such reporting would make apparently discordant findings easier to reconcile and would allow future studies to test specific failure mechanisms instead of treating durability as a binary label.

Conclusion

Durability in somatic gene therapy is not a single biological state. Vector persistence, continued transgene expression, persistence of corrected cells, and maintained therapeutic function occupy related but separable levels of analysis. Their trajectories can converge or diverge according to vector biology, cellular turnover, tissue renewal, immune context, disease progression, and measurement design. A defensible durability claim should therefore identify the layer actually demonstrated and avoid treating persistence of one component as proof of all others. This multidimensional interpretation provides a more precise basis for longitudinal evaluation and for locating the biological mechanism when therapeutic effects change over time.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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