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Review Article

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Delayed Safety Outcomes After Therapeutic Genome Editing: A Scoping Review of Clonal Dynamics, Genomic Alterations, Follow-Up Duration, and Adverse-Event Attribution in Clinical Translation

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ABSTRACT

Therapeutic genome editing now spans ex vivo hematopoietic stem-cell products, engineered immune cells, and in vivo organ-directed treatment. Clinical outcomes can improve before rare or delayed genomic consequences become detectable. To distinguish observed delayed outcomes from mechanistic safety signals, and to examine how editing modality, clonal behavior, surveillance duration, sampling, and competing causes condition clinical interpretation. A PRISMA-ScR-aligned evidence-map design was specified around therapeutic genome editing and delayed genomic or clinical safety. Published clinical and translational reports were examined to establish the charting structure. A reproducible, enumerated database search and full-text selection ledger have not yet been completed; consequently, a final included-study denominator, evidence distribution, and PRISMA count are unavailable. Clinical studies document treatment activity and adverse events over defined follow-up periods; preclinical studies identify on-target structural lesions, editing-associated cellular responses, and modality-dependent changes in hematopoietic clonal persistence. These sources use non-equivalent assays and observational horizons. Long-term safety assessment requires longitudinal measurement of genomic lesions, clone identity, clinical outcomes, and competing exposures. The present manuscript remains a provisional evidence-mapping draft until the selection ledger and complete study-level extraction are verified.

Key words: *Therapeutic genome editing, CRISPR–Cas9, Clonal hematopoiesis, On-target structural variation, Long-term surveillance, Adverse-event attribution*

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INTRODUCTION

Programmable editing of DNA has advanced from ex vivo manipulation of hematopoietic stem and progenitor cells (HSPCs) to infusion of edited cellular medicines and delivery of editing reagents directly to patients. The same term, *genome editing*, encompasses nuclease-mediated disruption, homology-directed repair, base editing, and related technologies with different DNA lesions, cellular selection pressures, and exposure patterns. The promise and translational complexity of these products have been described in broad reviews of therapeutic editing [1]. Their pharmaceutical identity also differs from transient drug exposure: an intended genomic alteration can

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persist in self-renewing cells or their descendants, while an in vivo intervention may distribute across multiple tissues [2].

Delayed safety has at least three distinguishable meanings. A genomic change may arise during the editing procedure but be detected later; an edited clone may expand or contract over time; and a clinically apparent event may occur after a latency interval. Evidence of one is not automatically evidence of the others. In experimental cell systems, nuclease-induced double-strand breaks have produced large on-target deletions and complex rearrangements that short amplicon assays may miss [3]. CRISPR manipulation can trigger a p53-dependent DNA-damage response [4]. In human pluripotent stem cells, p53 activity has also been implicated in selection under editing conditions [5]. These observations establish mechanistic concerns without providing a patient-level incidence of late malignancy.

Precision beyond conventional nuclease editing does not eliminate the need for product-specific genomic characterization. Base- and prime-editing systems can generate unwanted genetic outcomes in experimentally edited HSPCs [6]. Long-term rhesus macaque comparisons have demonstrated that CRISPR/homology-directed repair and lentiviral transduction can have markedly different engraftment and clonal trajectories [7]. These findings motivate a review that records the exact experimental system, assay, time origin, and cell population rather than pooling all reported 'off-target effects' or 'long-term safety' into a single endpoint.

Review rationale, objectives, and research questions

A useful delayed-safety map must distinguish *persistence of intended edit*, *clonal persistence*, *structural genomic integrity*, and *clinical adverse-event attribution*. Barcoded tracking of long-term hematopoietic engraftment illustrates why an edited-cell fraction at product release cannot describe the eventual repertoire of contributing clones [8]. Initial reports of CRISPR-edited cells in hemoglobinopathies [9] and in vivo transthyretin editing [10] established important therapeutic feasibility but did not, by themselves, settle much later risks. Preclinical correction models for severe immunodeficiency and chronic granulomatous disease contribute biological feasibility and assay evidence that must remain separate from post-treatment human outcomes [11]. Clinical translation additionally varies with cell source and repair strategy [12]. Therapeutic base-editing experiments introduce still another molecular exposure profile [13].

The primary question is: How are delayed genomic alterations, edited-clone dynamics, clinical adverse events, follow-up intervals, and causal attribution measured and linked in therapeutic genome-editing research? Subsidiary questions address which technologies and populations are observed, what surveillance and sequencing methods are used, when samples are collected, what adverse events are reported, and what competing causes are considered. The analysis prioritizes differences that could reverse a safety interpretation: pre-existing clones, transplantation and conditioning toxicity, underlying disease, donor biology, assay blind spots, and attrition. A temporal event after treatment is insufficient to assign the event to the edit.

MATERIALS AND METHODS

Scoping review design and reporting framework

The intended design is a scoping review using the PRISMA extension for scoping reviews (PRISMA-ScR) [14]. Mapping is appropriate because the relevant literature spans clinical trials, longitudinal observation, animal experiments, genomic-assay validation, and distinct treatment modalities. The current evidence collection is preliminary. It can support a draft charting dictionary and source-specific observations, but it is not yet an executed exhaustive scoping-review selection process. No critical-appraisal score or pooled safety estimate is reported.

Protocol and registration, if applicable

No prospective protocol registration or deposited protocol has been verified for this review. The eligibility logic below therefore describes the intended review protocol and must not be represented as prospectively registered. Deviations from any subsequently finalized protocol should be dated and disclosed.

Eligibility criteria using Population–Concept–Context

Population: recipients of therapeutic programmable-genome editing in human clinical translation, with directly relevant animal or human-cell models assigned to separate translational strata. Concept: genomic integrity, clonal expansion or loss, sustained editing, delayed clinical adverse events, ascertainment methods, or attribution of potentially late effects. Context: ex vivo edited HSPCs and immune-cell products, in vivo organ-targeted

interventions, and associated preclinical evaluation. Studies limited to viral gene addition, naturally occurring clonal hematopoiesis, general CRISPR technology, or unrelated molecular systems serve as contextual comparators unless they directly address a defined eligible editing question. There is no minimum follow-up threshold created solely for this manuscript; observed durations are charted as published. Q1 journal status is not an eligibility criterion for evidence units.

Information sources and search strategy

An initial discovery search used internet-indexed journal and PubMed records on 9 October 2026. Example executed keyword logic included `CRISPR editing hematopoietic stem cells genome stability long term clonal`, `base prime editing genotoxic effects human hematopoietic stem cells`, and `genome editing clonal dynamics structural variants safety`. These discovery queries were not captured as complete enumerated database exports. Their returned documents establish traceable candidates, not a verified number of identified records. A final report needs reproducible platform-specific strings, execution dates, retrieval counts, exports, and citation-chaining records.

Evidence selection procedures

The candidate DOI inventory is not equivalent to title/abstract screening of an exported search result. Record-level deduplication, independent eligibility decisions, full-text retrieval status, standardized exclusion reasons, and multiple-report linkage remain undocumented. Consequently, this draft makes no claims about reviewer agreement or a final population of included publications. A defensible review flow would require identification → deduplication → screening → full-text assessment → eligible evidence, with every transition reconciled to actual records.

Data-charting process and variables

A study-level charting specification was prepared for edit chemistry, target locus, ex vivo versus in vivo delivery, cell or tissue source, disease, recipient or model, conditioning and concomitant treatment, comparator, genomic assay, sampled compartment, time from editing or infusion, observation length, clone-identification approach, reported lesion or adverse event, and investigator attribution. Each observation must retain its numerator/denominator, assay detection boundaries, and source-specific time origin when reported. The current descriptions below were checked against selected publication records; they are not presented as a fully extracted included-study dataset.

Evidence categorization and synthesis approach

Four analytical strata are retained: human clinical observations, longitudinal translational models, molecular genotoxicity experiments, and contextual comparator evidence. Observed association, experimentally induced alteration, inferred mechanism, and clinically adjudicated causation are recorded separately. Because study selection is unfinished and endpoints are heterogeneous, no formal evidence-frequency map, cumulative adverse-event estimate, or meta-analysis is appropriate in the current draft. The critical comparison is whether a method can detect a biologically plausible harm and whether the observations support assigning that harm to the editing step.

The intended eligibility and extraction distinctions are operationalized in **Table 1**. In particular, a patient's clinical event, a product-level structural variant, and a later clonal change must remain separate data entities until an empirical connection is demonstrated.

Table 1. Scoping-review eligibility and charting boundaries for delayed genome-editing safety

Review unit or measurement	Eligible evidence boundary	Fields requiring direct reporting	Interpretation protected against
Human recipient	Therapeutic programmable editing, ex vivo or in vivo	Indication; editing locus; product or delivery route; conditioning; follow-up origin	Treating concomitant therapy toxicity as editing-specific
Edited-cell or animal model	Mechanistically relevant translational evidence, separately classified	Model; cell lineage; assay; serial sampling; edit persistence	Generalizing experimental lesions to patient event incidence

On-target integrity	Structural or sequence-level assay of edited locus	Genomic assay and detection scope; lesion class; sampled tissue	Equating small-amplicon negativity with intact genomes
Off-target assessment	Prespecified or discovered candidate loci with documented method	Nomination technique; assay sensitivity; sample and time point	Calling an untested locus free of editing
Clonal trajectory	Serial evidence able to distinguish cell contributions	Barcode, edit identity, integration or lineage tracer, as applicable	Mistaking edited fraction for clonal diversity
Delayed adverse event	Defined clinical outcome at a reported interval	Event definition; onset; censoring; baseline risks; attribution	Treating temporal association as established causality

RESULTS AND DISCUSSION

Characteristics of included therapeutic genome-editing evidence

The heading denotes the planned domain of an eventual included-study synthesis; the currently described publications are verified illustrative clinical records, not a completed eligible-study set. Ex vivo HSPC approaches introduce genetic changes into a product that can be characterized before infusion, yet patient-level observation then depends on engraftment, clonal contribution, and further exposures. In the 2024 exagamglogene autotemcel sickle cell report, autologous CD34-positive HSPCs underwent BCL11A enhancer editing followed by busulfan conditioning and infusion [15]. A related β-thalassemia trial applied the same therapeutic principle in a different disease population [16]. The ex vivo product characterization and the clinical adverse-event record answer connected but different questions.

Off-target evaluation for exagamglogene autotemcel has been described using nominated loci and complementary assay approaches [17]. This addresses specified detectable editing outcomes within tested cell material. It cannot by itself establish the absence of every unusual structural event in every surviving recipient clone. Conversely, absence of a malignancy at a prespecified clinical cutoff is an observation about the cohort and surveillance window, not a proof that experimental genotoxic mechanisms occurred clinically.

In vivo interventions have different ascertainment limits because the edited organ is not available as an entire released cell product. Early clinical reports include targeting of the kallikrein pathway in hereditary angioedema [18] and a patient-specific lipid-nanoparticle-delivered editing intervention for carbamoyl-phosphate synthetase 1 deficiency [19]. The latter report described seven weeks of observation after initial dosing, explicitly requiring longer follow-up. Edited immune-cell studies add heterogeneous expansion, malignant-disease background, and concomitant therapies [20]. A 2026 study of CD33-deleted allogeneic HSC transplantation in high-risk myeloid malignancy combined an edited graft with conditioning and gemtuzumab ozogamicin maintenance [21]. Its observed transplant complications cannot be assigned to one exposure solely from their chronological order. Cas12a promoter editing for β-thalassemia extends the clinical modality range [22].

Table 2 sets these identifiable clinical contexts alongside their distinct safety observation units. It does not assert a denominator of all eligible trials or a comparative safety ranking.

Table 2. Selected clinical genome-editing reports and the unit in which safety can be observed

Published clinical setting	Editing and therapeutic compartment	Co-intervention or clinical context	Reported observation scope	Delayed-safety inference limit
Severe sickle cell disease, 2024	Ex vivo CRISPR–Cas9 BCL11A enhancer editing of autologous HSPCs	Busulfan myeloablation and transplantation	44 infused; median follow-up 19.3 months	No cancer by cutoff does not establish lifetime incidence
Transfusion-dependent β-thalassemia, 2024	Ex vivo CRISPR–Cas9 BCL11A enhancer editing of autologous HSPCs	Busulfan myeloablation and transplantation	52 infused; median follow-up 20.4 months	Clinical surveillance and genomic assay coverage differ
Patient-specific metabolic disease, 2025	In vivo lipid-nanoparticle-delivered base editing	Neonatal metabolic instability and supportive care	One treated infant; seven weeks after initial infusion in report	Cannot infer delayed event frequencies

High-risk AML/MDS, 2026	CRISPR–Cas9 CD33-deleted allogeneic hematopoietic graft	Conditioning, graft biology, gemtuzumab ozogamicin maintenance	30 transplanted; phase 1/2 report	Competing transplant and cancer causes require adjudication

Evidence on delayed genomic and clinical safety outcomes

The earliest signal may be molecular. Large deletions and complex on-target rearrangements were experimentally demonstrated after nuclease-induced DNA breaks, including in progenitor-cell contexts [3]. Editing-associated DNA-damage responses and selective disadvantages can affect which cells remain measurable [4]. The cellular consequences of base and prime editing depend on molecular design and target context; comparative experimentation has documented unexpected genomic outcomes that standard small-variant assays may overlook [6]. These findings justify structural-genome assays without quantifying the frequency of future patient cancers.

Clonal dominance is also ambiguous until the mechanism of selection is known. A reduced number of contributing clones after transplantation can reflect editing-induced cellular stress, differing stem-cell fitness, bottlenecks, conditioning, disease biology, or assay sampling. Work on CRISPR/HDR in nonhuman primates illustrates marked changes in clone composition compared with viral gene addition [7]. In experimental HSPCs, CRISPR–Cas9/AAV6-mediated editing has been linked to senescence and inflammatory responses [23]. A 2025 examination of structural variation and genome integrity emphasizes that molecular surveillance must account for more than classical off-target site prediction [24]. Neither result should be phrased as an observed delayed patient adverse event.

The clinical reports described above document early and intermediate safety outcomes at their respective cutoffs, including conditions that can arise from conditioning and transplantation. Attribution should retain the investigators' event classification while allowing reanalysis if the same clone or lesion is later traced across archived product material and clinical samples. Without patient-linked longitudinal genomic evidence, structural lesions detected in an assay and a subsequent clinical diagnosis remain distinct observations.

Follow-up practices, surveillance duration, and outcome detection

Follow-up length has meaning only with a specified starting point, outcome, sample compartment, and ascertainment schedule. The 2024 sickle cell study reported median follow-up after exagamglogene autotemcel infusion of 19.3 months, with a range of 0.8 to 48.1 months, and no cancers at the analyzed cutoff [15]. For β-thalassemia, the analogous report recorded 20.4 months median follow-up, range 2.1 to 48.1, with no cancers or deaths at that cutoff [16]. These medians summarize different recipient populations; neither is a universal duration for genome-editing safety follow-up. They also do not specify by themselves how comprehensively rare genomic lesions were tested in vivo.

Longitudinal clonal analysis requires serial specimens and a stable marker that allows clone identity to be reconstructed. Lentiviral gene-addition studies have provided detailed lineage tracking over several years, but their integration-site markers and vector-associated risks differ from targeted genome editing [25]. Follow-up of lentiviral- or gammaretroviral-modified T-cell products likewise informs surveillance design, without constituting direct evidence of CRISPR product incidence [26]. Where a baseline clone is not sampled or the affected tissue is inaccessible, negative findings may reflect observability rather than biological absence.

Surveillance procedures should connect release-stage genomic characterization with later accessible compartments, clinical malignancy monitoring, and event-triggered sequencing where feasible. Quantifying surveillance completeness requires reporting the enrolled denominator, living and evaluable recipients at each time point, specimen availability, assay changes, and whether clinical endpoints were actively ascertained. **Table 3** preserves these observation-specific differences; unavailable elements are explicitly marked instead of filled by assumptions.

Table 3. Observation time, specimen access, and interpretation of delayed safety signals in identified evidence

Evidence setting	Temporal information directly reported	Safety or clonal observation	What cannot be concluded from the report alone
Exagamglogene autotemcel: sickle cell disease	Median 19.3 months; range 0.8–48.1 months	No cancers at trial data cutoff	Lifetime cancer risk or genome-wide absence of structural lesions

Exagamglogene autotemcel: β-thalassemia	Median 20.4 months; range 2.1–48.1 months	No cancers or deaths at trial data cutoff	Long-latency incidence after the observation window
Patient-specific in vivo base editing	Seven weeks after first dose in the published report	No serious adverse events reported in that early interval	Rare late toxicity or durable organ-wide genomic specificity
Rhesus macaque HSPC competitive transplantation	Longitudinal study; precise interval not transcribed in current dossier	Strong difference in clonal retention between CRISPR/HDR and lentiviral-modified cells	Human comparative malignancy incidence
Lentiviral HSC gene addition comparator	Follow-up up to eight years in published cohort	Integration-site-based long-term lineage commitment	Equivalent clonal measurement or identical hazard mechanisms for targeted editing

Adverse-event attribution and competing explanations

A late event in a treated person may follow editing without being caused by it. Attribution requires a chain of observations: the abnormality must be detected, characterized in a defined cellular compartment, linked where possible to an archived product or earlier specimen, and interpreted against other exposures. Clone-resolved analysis illustrates this logic. Single-cell expansion can reveal both intended corrections and large deletions within individual experimentally edited HSC clones [27]. A clone's presence at release does not establish a later illness mechanism. An archived pre-edit sample can distinguish introduced alterations from pre-existing variants; the infused product can establish whether an alteration was present at release; serial patient samples can test persistence; and lesion-matched event tissue can connect genomic identity to phenotype. When one of these compartments is unavailable, attribution confidence falls without necessarily changing the biological probability of harm.

A separate problem concerns background risk. Underlying disease, transplantation and prior cytotoxic treatment may also contribute to malignancies. Reviews of vector genotoxicity explain why insertional oncogenesis must be considered in integrating-vector products while preserving mechanistic differences from nuclease editing [28]. Deep profiling of somatic mutations reveals selection among unedited cells across human tissues [29]. In sickle cell disease, inflammatory HSC states and lineage bias have also been associated with variable engraftment after *lentiviral gene addition*, a relevant biological comparator rather than direct evidence of CRISPR harm [30].

Figure 1 separates therapy-associated genomic findings, clonal trajectories, clinical outcomes, and competing pathways of selection. Attribution requires longitudinal lineage or lesion tracing and consideration of plausible alternative causes.

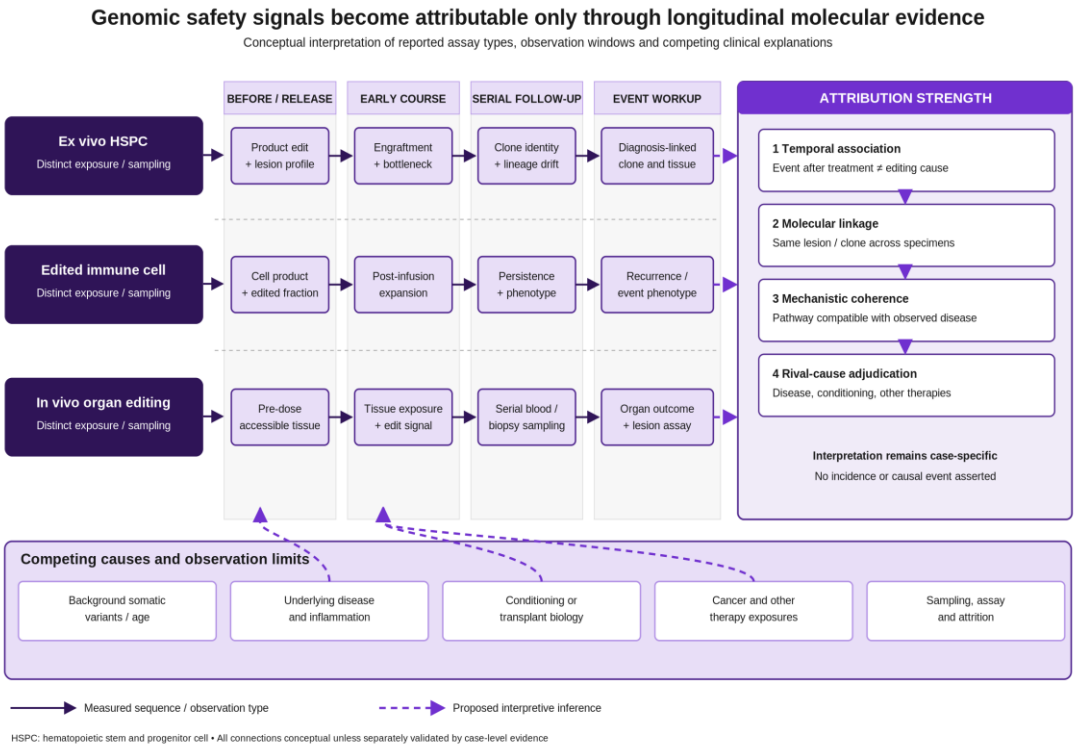


Figure 1. Delayed safety attribution requires genomic continuity, longitudinal observation, and rival-cause assessment

Evidence distribution and research gaps

The currently assembled sources illuminate different stages of the evidence chain, but cannot establish proportions of study designs or frequencies of adverse events because complete search screening is unfinished. Clinical reports contain patient-level endpoints and defined observation windows, while mechanistic studies provide higher-resolution genomic characterization in cells or animal systems. Naldini's translational account situates HSC editing within this distinction between therapeutic cell manufacture and post-infusion biology [31]. Bone-marrow-targeted nanoparticle editing has been explored experimentally across multiple hematopoietic populations [32]; liver studies similarly show that spatial and developmental heterogeneity affect the fate of gene-engineered cells [33]. Engineered HSC niches reveal how culture conditions can affect maintenance of long-term repopulating populations [34]. These themes are not counted eligible-study categories.

Table 4 identifies missing attribution measurements without estimating their prevalence.

Table 4. Missing observations that prevent progression from editing-related signals to delayed-event attribution

Attribution question	Available observation type in identified evidence	Critical missing linkage	Prospective discriminating observation
Did an edit-associated lesion precede clone growth?	Release-stage on-target/off-target or structural-variant profiles	Same-lesion tracking across later independent specimens	Matched pre-dose, product and serial lineage-resolved sequencing
Does clone dominance indicate an editing effect?	Engraftment and clone-frequency trajectories in models	Baseline clone prevalence and treatment-specific fitness effects	Clone identity, pre-existing somatic drivers and matched comparator context
Can organ-edited cells be monitored over time?	Tissue or accessible-blood assays in in vivo editing studies	Representative sampling of inaccessible edited compartments	Defined tissue coverage and repeatable surrogate–tissue concordance
Is a late malignancy attributable to editing?	Clinical adverse-event ascertainment and targeted molecular workup	Causal connection between the edit, oncogenic pathway and event tissue	Tumor sequencing, archival product matching and independent clinical adjudication
How does follow-up loss affect reassurance?	Trial-reported follow-up windows	Specimen-available and outcome-ascertained denominators at each interval	Time-point-specific retention and active/passive ascertainment reporting

A safety claim changes meaning as it moves across biological levels. Manufacturing quality, persistent function and patient safety require different measurements. Immunodeficiency editing models illustrate functional rescue under controlled conditions [35]. RAG1 correction studies likewise support therapeutic feasibility and assessment of engineered cells, without yielding general late-event rates in recipients [36]. These experiments cannot replace patient surveillance.

Selection is particularly important. Experimental multiplex CD33/HBG base editing has demonstrated persistence and drug-associated enrichment of engineered populations in preclinical systems [37]. Transient reporter selection can enrich intended edits within an HSC product [38]. Neither approach licenses an assumption that favorable selection at one stage excludes later unintended selection. The question is which clones persist and remain identifiable over time.

Product specifications and longitudinal surveillance should therefore use compatible assay identifiers, sample provenance and sequence-level definitions, while separating intended variants, small off-target changes, structural alterations and putative pre-existing driver mutations. Suspected malignancy requires independent adjudication of alternative causes. Their prevalence cannot currently be estimated across trials. Clinical case review should record the treating team's assessment alongside independent molecular adjudication, with indeterminate outcomes retained. Negative assays should be interpreted within validated detection limits, especially when rare events emerge after trials reduce specimen collection. Surveillance systems must be capable of reopening earlier causal judgments when new molecular evidence becomes available.

Future surveillance and research priorities

First, prospective protocols should prespecify observation starting points, clinical endpoints, specimen windows and retention denominators. Second, archive release-stage profiles for reanalysis of structural events. Third, validate serial clone identifiers and blood-to-tissue representativeness.

In vivo editing adds delivery and compartment challenges. Experimental durable HSPC editing using targeted nanoparticles in humanized mice provides proof of principle, while leaving human tissue coverage and long-latency follow-up unresolved [39]. Epitope-editing approaches developed for less genotoxic transplantation conditioning also shift the balance among graft selection, therapeutic exposure and monitoring, but preclinical efficacy cannot be converted into clinical event-free survival [40]. Each product requires assay-specific surveillance and detection limits.

Plan suspected-event investigations in advance with banked samples, tissue sequencing escalation and adjudication categories of demonstrated, provisional or indeterminate causation.

Review limitations

This manuscript is a provisional evidence-mapping draft, not a completed scoping-review results report. Searches conducted during initial discovery did not produce an auditable record-level export and full-text eligibility ledger. Thus the final study denominator, deduplication totals, PRISMA-ScR flow values and evidence-category distributions cannot be stated. The tables are illustrative, not exhaustive. The candidate bibliography is DOI-anchored; some full author strings, pagination and journal-quartile checks remain incomplete. Experimental and clinical sources cannot yield a common adverse-event incidence estimate.

CONCLUSION

The available clinical and mechanistic literature indicates that delayed genome-editing safety is a longitudinal attribution problem involving genomic lesions, cell selection, surveillance completeness and competing risks. Persistent benefit or an event-free interim cutoff provides useful information, but neither resolves the possibility of rare long-latency events. More defensible conclusions require molecular continuity between pre-treatment, product or early specimens and later clinical events, supported by surveillance that explicitly reports its own limits. The present draft cannot quantify the distribution of these practices without a completed review-selection ledger.

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