REVIEW ARTICLE

Vision Restoration in Degenerative Retinal Diseases Using Stem Cells

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Abstract

Degenerative retinal diseases, such as age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy, and glaucoma, are significant causes of irreversible visual loss worldwide. Current treatments are mostly palliative, treating the secondary obstacle rather than reversing degenerated retinal cells. Stem-cell–based interventions are shifting the treatment landscape for retinal degeneration by targeting multiple biological pathways—replacing lost cells, protecting surviving neurons, regulating immune activity, and supporting new vessel growth. This review brings together current laboratory and clinical findings on four major cell sources: embryonic stem cells, induced pluripotent stem cells, mesenchymal stromal cells, and retinal progenitor cells. Early trials, especially in age-related macular degeneration and retinitis pigmentosa, report good safety outcomes and small but measurable gains in visual function, with transplanted cells surviving in the host retina. However, the major translational hurdles are regulation of the immune response, heterogeneity of long-term integration, surgical complexity, and manufacturing scalability. Advances in engineered delivery systems, immune-evasive pluripotent cells, and biomarker-based patient selection are driving the field toward sustainable therapy. Together, stem cell therapy holds great promise in addressing the unmet needs of degenerative retinal diseases; however, well-designed multicenter trials with well-defined endpoints are essential for determining efficacy and ensuring safe and regulated use in clinical practice.

Keywords

Diabetic Retinopathy; Stem Cells

Introduction

Degenerative retinal diseases constitute a diverse group of vision-compromising disorders with different etiology but shared pathological characteristics. Glaucoma, age-related macular degeneration (AMD), retinitis pigmentosa (RP), and diabetic retinopathy (DR) are some of the diseases included. These

conditions can result from inherited genetic abnormalities, acquired retinal trauma, or systemic disease. Irrespective of etiology, their characteristic feature is the progressive and irreversible loss of retinal pigment epithelial cells and/or photoreceptors, resulting in progressive visual loss (1).

Glaucoma remains one of the leading causes of permanent blindness worldwide (2). In India, it accounts for nearly 5.5% of total blindness cases (3). The problem is made worse by low awareness and the fact that many patients are diagnosed only when the disease has already advanced, leaving treatment far less effective (3). The pooled global prevalence of any AMD in individuals aged 45–85 years was 8.69%. Although AMD is currently less common in India than in Europe (4), it is anticipated to rise significantly due to the nation's rapidly aging demographic (5).

Regional factors also shape this burden. Data from the South Indian arm of the Andhra Pradesh Eye Disease Study found that older age, a history of cigar smoking, cortical cataract, and prior cataract surgery were all independent risk factors for glaucoma (6). RP consists of a genetically and clinically diverse array of hereditary retinal disorders that affect approximately 1 in 4,000 individuals worldwide and demonstrate a higher incidence in specific Indian populations (7), a phenomenon closely associated with cultural and genetic factors, including a greater frequency of consanguineous marriages (8). DR is still a major cause of blindness in working-age individuals globally (10), and India has a high rate because it is the "diabetes capital of the world." (9) The increasing diabetes pandemic in turn is driving incidence of DR, and it is becoming an ever more serious public health problem (11).

Together, these disorders place a heavy strain on both global and national health systems. Current therapies, summarized in Table 1, can slow disease progression but cannot replace damaged retinal cells. This gap has driven growing interest in stem-cell–based strategies aimed at restoring visual function.

TABLE-1: Definition and Limitations of current treatment methods

Disease	Definition	Current Treatments	Key Limitations of treatments
Glaucoma	Group of optic nerve damage diseases (usually due to elevating IOP) → progressing peripheral vision loss and blindness (12)	Eye drops (prostaglandin analogues, beta-blockers), laser trabeculoplasty, trabeculectomy, drainage implants (13)	Decreases IOP but is a weak replacement for absent retinal ganglion cells (13) • Prompts poor compliance with long-term drops (13) • Side effects: redness, ocular surface damage (13) • Surgical complications and potential failure (13) •Some improvement despite "controlled" IOP (13)
Age-Related Macular Degeneration (AMD)	Macular degeneration → loss of central vision (14)	Anti-VEGF injections (wet AMD), AREDS supplements (early stage), lifestyle modification (15)	•Cumbersome repetitive injections (every 4–8 weeks) (15) • Worsening and unpredictable treatment response (15). • Cannot replace injured photoreceptors or RPE (15) • No treatment for dry AMD; GA progression continues. (15)
Retinitis Pigmentosa (RP)	Inherited disease-causing gradual death of rods and cones → night blindness, tunnel	Gene therapy (RPE65 mutations), vitamin A, low-vision	• >80 genes involved; very few therapies are comprehensive • Typically diagnosed late once there has been extensive photoreceptor loss •Gene therapy is only successful if there are living cells

	vision, severe loss (16)	aids, retinal prosthesis (17)	• Retinal implants are of low resolution and few degrees of vision (18)
Diabetic Retinopathy (DR)	Degeneration of retinal blood vessels as a consequence of prolonged hyperglycaemia → leakage, oedema, ischemia (19)	Control of blood sugar, laser treatment (PRP), anti-VEGF/steroids, vitrectomy (20)	•Treats complication and not causative factor• Multiple injections; unpredictable response• PRP decreases peripheral and night vision (20)

Why Stem Cells Are Potentially Promising in Ophthalmology

The retina is a highly specialized neural tissue, but its capacity to regenerate is extremely limited. When photoreceptors or retinal pigment epithelial (RPE) cells are lost, they aren't naturally replaced, leading to permanent vision loss. Stem cells, with their ability to renew themselves and develop into multiple retinal cell types, offer a promising route for both cell replacement and neuroprotection (21).

Beneficial aspects of ophthalmology are relative immune privilege of the eye, small target region, and ease of access for imaging and surgical access, making it an ideal target for precision delivery and tracking of cell-based therapies. (21,22)

Derivatives from human embryonic stem cells (hESC)-RPE were found to be safe and to demonstrate early signs of efficacy in clinical trials. (23,24)

Mechanisms of Degeneration in Affected Diseases

Target diseases such as AMD, RP, and DR involve progressive loss of retinal cells by various pathological mechanisms:

Photoreceptor apoptosis: Caused by genetic mutations (RP) or oxidative stress (AMD) (16,25).

RPE atrophy: Impaired phagocytosis of photoreceptor outer segments, accumulation of lipofuscin, and drusen formation (AMD) (26)

Inflammation & gliosis: Prolonged inflammation leads to activation of microglia and Müller cell gliosis, further disrupting retinal architecture (27)

Vascularpathology: DR causes microvascular ischemia and leakage, which results in secondary degeneration and neuronal hypoxia (28).

How Stem Cells Could Address These Diseases

Stem cell therapy aims to intervene through multiple mechanisms:

Cell replacement: Differentiation into RPE or photoreceptors to replace lost cells(29,30).

Neuroprotection: Mesenchymal stem cells (MSCs) and neural progenitor cells secrete trophic factors (e.g., BDNF, CNTF) that prevent apoptosis and support surviving retinal cells(31).

Immunomodulation: MSCs modulate microglial activation, reducing chronic inflammation(32).

Stimulation of endogenous repair: Müller glia and induced pluripotent stem cell (iPSC)-derived factors may activate dormant regenerative pathways (33).

Vascular support: Endothelial progenitor cells can promote revascularization in ischemic retinopathies (34).

Types of Stem Cells Investigated and Mechanisms of Action

Various types of stem cells have been investigated for retinal regeneration, each with their own biological characteristics, differentiation capacity, and therapeutic approaches. (3)

Embryonic Stem Cells (ESCs)

Overview: Human embryonic stem cells (hESCs) are pluripotent cells that originate from the inner cell mass of the blastocyst. They can develop into all types of retinal cells, such

as retinal pigment epithelium (RPE), photoreceptors, and ganglion cells. (35)

Mechanisms of Action - Replacement of cells: Transdifferentiated hESCs into RPE have been transplanted in AMD and Stargardt disease models, where they restore RPE function, phagocytose photoreceptor outer segments, and maintain photoreceptor viability (35,24). Integration: hESC-derived photoreceptors are able to make synaptic contacts with host bipolar cells in preclinical models (30).

Neurotrophic support: hESC-derived cells release growth factors that can support survival of remaining retinal cells. (30)

Induced Pluripotent Stem Cells (iPSCs)
Overview: iPSCs are induced from adult somatic cells (e.g., fibroblasts) to pluripotency by transcription factors (OCT4, SOX2, KLF4, c-MYC). iPSCs bypass the ethical issues of hESCs and enable patient-specific autologous transplantation. (23)

Mechanisms of Action - Individualized therapy: iPSC-derived RPE and photoreceptors are genetically matched to the patient, which can reduce immune rejection (36). Disease modelling: iPSCs are used to model retinal diseases in vitro and screen therapeutic compounds (37).

Cell replacement: In animal models, iPSC-derived photoreceptors restore light responses and visual function. (29)

Retinal Progenitor Cells (RPCs)
Overview: RPCs are multipotent fetal or neonatal retinal cells that have the capacity to differentiate into photoreceptors, bipolar cells, and glia.

Mechanisms of Action - Host retinal integration: RPCs migrate to the outer nuclear layer and differentiate into photoreceptor-like cells (36). Paracrine support: RPCs secrete neurotrophic factors (CNTF, BDNF) that protect host photoreceptors from degeneration (22).

Synaptic connection: Synaptic development with pre-existing retinal neurons is indicated by certain studies (38).

Mesenchymal Stem Cells (MSCs)
Overview: MSCs are multipotent stromal cells that are derived from bone marrow, adipose tissue, umbilical cord, or dental pulp. They do not tend to differentiate into photoreceptors but have strong paracrine and immunomodulatory activity.
Mechanisms of Action - Neuroprotection: BDNF, NGF, and VEGF release sustains retinal cell survival (31). Immunomodulation: MSCs inhibit pro-inflammatory cytokines and microglia activation (39).

Angiogenesis: MSC-derived factors can cause revascularization in ischemic retinopathies (40).

Müller Glia–Derived Stem/Progenitor Cells
Overview: In lower vertebrates like zebrafish, Müller glia have the ability to regenerate retinal neurons after injury. In mammals, they can be reprogrammed into a progenitor-like state.

Mechanisms of Action - Endogenous regeneration: Transcription factor activation (Ascl1, Pax6) can trigger neurogenesis (33).

Supportive function: In the absence of complete differentiation, Müller glia are structural and metabolic supports to retinal neurons.

Endothelial Progenitor Cells (EPCs)
Overview: EPCs are circulating precursors with the ability to differentiate into vascular endothelial cells.

Mechanisms of Action - Vascular repair: EPCs are incorporated into injured retinal capillaries and induce neovascularization in ischemic tissue (41).
Paracrine action: They secrete angiogenic factors such as VEGF and angiopoietin.

Clinical Trials, and Market Studies

TABLE-2: CLINICAL TRIALS

Age-related macular degeneration		
Clinical Trial Name	**Study Method**	**Most Important Finding**
Nittala MG et al., 2021 — HuCNS-SC in GA	Subretinal transplantation of human CNS stem cells (HuCNS-SC) in non-neovascular AMD with geographic atrophy (42)	In this small pilot, HuCNS-SC transplantation appeared associated with slower expansion of GA in the transplanted quadrant. (42)
Kashani AH et al., 2022 — HLA-mismatched bioengineered RPE implant	Subretinal polarized hESC-RPE monolayer (phase 1/2a) (43)	Survival of HLA-mismatched RPE grafts; safety with preliminary structural/functional signals (43)
Kashani AH et al., 2018 — Bioengineered RPE monolayer	Subretinal RPE monolayer for advanced dry AMD (44)	Safety and structural evidence of graft survival (44)
da Cruz L et al., 2018 — hESC-RPE pat	Subretinal hESC-RPE patch (45)	Patch survival with visual function support in severe AMD (45)
Diabetic Retinopathy		
Wu Z et al., 2022 — UC-MSC + aBM-MNC in T1D	RCT (42 patients); UC-MSC + autologous BM-MNC transplantation vs standard care; 8-year follow-up. (46)	Significantly fewer complications: neuropathy (7.1% vs 46.7%), nephropathy (7.1% vs 40%), retinopathy (7.1% vs 33.3%); no malignancies. (46)
Bonora BM et al., 2021 — Fenofibrate & HSPCs in DR	12-week double-blind RCT; 42 patients with DR randomized to fenofibrate or placebo; primary endpoint = circulating HSPC levels (CD34+/CD133+). (47)	Fenofibrate significantly increased circulating HSPCs, suggesting a mechanism for reduced DR progression. (47)
Glaucoma		
Vilela CAP et al., 2021 — Intravitreal autologous BMSC in advanced glaucoma	Phase I pilot study; two patients with advanced glaucoma received a single intravitreal injection of autologous bone marrow–derived MSCs; ERG and visual function monitored post-injection. (48)	No ERG response change observed; one case developed a complication; no functional improvement. Authors suggest modified MSCs may be required for therapeutic effect. (48)
Mao J et al., 2024 — ACA status vs limbal stem cell deficiency in PACG	Cross-sectional observational study including 54 PACG eyes and 54 controls; UBM used to assess anterior chamber angle state; IVCM used to measure limbal epithelial basal cell density. (49)	PACG eyes with narrower/closed ACA had significantly reduced limbal epithelial basal cell density compared to controls, establishing a structural link between angle status and limbal stem cell deficiency. (49)
Khatib TZ et al., 2019 — Hemoglobin video imaging of aqueous outflow	Prospective imaging study: high-resolution hemoglobin video imaging integrated into routine slit-lamp examination to quantify aqueous outflow before and after intervention. (50)	Hemoglobin video imaging enables real-time slit-lamp–based quantification of aqueous outflow, with potential to guide targeted therapies and advance understanding of outflow dysregulation in glaucoma (50)
Güçlü H et al., 2021 — Corneal/limbal alterations from glaucoma meds	Case–control study; glaucoma patients on long-term topical therapy compared with healthy controls; anterior segment OCT used to evaluate corneal epithelium and limbal region alterations. (46)	Long-term topical therapy associated with measurable limbal epithelial and corneal changes on AS-OCT (46)
Retinitis pigmentosa		

Age-related macular degeneration		
Clinical Trial Name	**Study Method**	**Most Important Finding**
Zhu T et al., 2021 — USH2A variants in RP/Usher II	Genetic profiling of a large Chinese cohort of RP/Usher II patients (51)	Defined USH2A variant spectrum and genotype–phenotype correlations (51)
Zhao T et al., 2020 — IV infusion of UC-MSCs in advanced RP	Phase I/II trial; intravenous infusion of UC-MSCs in advanced RP (52)	Intravenous infusion of UC-MSCs showed no significant adverse effects (52)
Tuekprakhon A et al., 2021 — Intravitreal autologous MSCs in RP	Non-randomized phase I; intravitreal autologous MSC injection in RP patients (53)	Treatment was safe and feasible, with early signals of functional benefit (53)
Özmert E et al., 2020 — Wharton's jelly MSCs in RP	Prospective 1-year study; Wharton's jelly MSC transplantation in RP (54)	Visual and structural improvements correlated with inheritance patterns (54)

Market Status and Most Successful Clinical Outcomes of Stem Cell Therapy in Retinal Disorders:

Market Translation (Approved/Regulatory-Ready Therapies)

To date, there are no stem cell–derived products officially approved for routine clinical use in AMD, RP, DR, or glaucoma. The only FDA-approved therapy in the inherited retinal disease category remains gene therapy for RPE65-led RP, as well as retinal prostheses for end-stage RP, not stem cells. Stem cell therapy for these disorders remains, therefore, experimental, with translation limited to early- to mid-stage clinical trials (55,56)

Most Successful Clinical Evidence to Date

Despite the absence of approved products, several stem cell approaches have consistently demonstrated safety and functional benefits across clinical trials. In AMD, transplants of human embryonic stem cell–derived retinal pigment epithelium (hESC-RPE) have enhanced visual acuity and preserved graft survival, free from tumorigenicity(23,57). Autologous induced pluripotent stem cell–derived retinal pigment epithelium grafts in neovascular AMD were safe and preserved retinal structure and visual stability for four years (45). In RP, a Phase III trial of suprachoroidal umbilical cord–derived mesenchymal stem cells (UC-MSCs) in 82 patients demonstrated improved or stabilised vision in approximately 90% of treated eyes, with no severe adverse events reported (58). Small RP trials of Wharton's jelly–derived MSCs and bone marrow–derived MSCs also showed improvements in short-term best-corrected visual acuity and retinal thickness(59). In DR, the administration of intravenous or intravitreal MSCs has been demonstrated to reduce vascular leakage, improve neurotrophic support, and improve BCVA in early-stage patients without immune complications. Despite the paucity of glaucoma trials, MSC-derived paracrine factors and preclinical studies offer a neuroprotective advantage for retinal ganglion cells, providing a translational basis. As a whole, these results put ESC/iPSC-RPE grafts for AMD and MSC-based therapies for RP and DR on the most clinically advanced trajectories towards being market-ready(60).

Benefits

Histological engraftment of RPE has been repeatedly reported. Long-term pigmentation and OCT findings of stable monolayer under atrophy/scar in AMD patients and in CPCB-RPE1 implantation have been reported. (57,44,61)

Practical functional benefit can be achieved in some situations. Engineered RPE patch transplanted subretinally recorded +29/+21 letters at 12 months in advanced neovascular AMD with on-patch survival. (45)

Photoreceptor support can improve vision in RP. Intravitreal hRPC (gene-agnostic) caused dose-dependent BCVA gain and secondary measures (contrast sensitivity, mobility, VFQ) in a randomised Phase 2b trial and subgroup analyses. (62)

Paracrine and vasculotropic strategies seem plausible and secure. Intravitreal

administration of autologous CD34+ cells (pilot Phase 1) demonstrated favourable ocular tolerability alongside preliminary imaging indicators. (63)

CONCLUSION

Stem cell-based therapies have revolutionary promise for the management of degenerative retinal disease like AMD, RP, glaucoma, and diabetic retinopathy, wherein traditional therapies are mainly palliative. Across varied preclinical and early clinical trials, stem cell strategies such as mesenchymal stromal cells, retinal pigment epithelium, and retinal progenitor cells have demonstrated promising evidence of safety, neuroprotection, and structural integration with variable efficacy. Notably, such studies go to emphasize both the potential and complexity of regenerative strategy translation to long-term visual outcomes. Heterogeneity, cell sources, and delivery routes imply the need for robust, multicenter trials with standardized endpoints. Progress in the future will rest not only on optimizing cell survival and functional integration but also on blocking adverse effects and addressing disease-specific pathophysiology. Cumulatively, this early evidence body places stem cell therapy at the cusp of next-generation ophthalmic treatments with credible promise toward vision restoration in disorders heretofore deemed irreversible.

Mechanistic uncertainty (integration vs. material transfer). Preclinical evidence suggests that "rescue" is donor–host material transfer, not true synaptic integration, with host context-dependent effects requiring lineage-traced readouts and judicious model selection. (64,65) Heterogeneous efficacy and first-trial size. Benefit across indications is restricted and untested in small, early-stage populations; no Phase 3 approvals to date. (23,62)

Surgical and device complexity for patches involves retinotomy and sub foveal handling, requiring specialized instruments. Potential hazards include tears, haemorrhage, and detachment, along with challenges related to scalability and access. Immune management is crucial; studies involving hESC-RPE commonly utilize either peri-systemic or chronic local steroids. Autologous iPSC-RPE was feasible but challenging to scale; HLA-matched allogeneic iPSC-RPE has shown 1-year safety with steroids, but durability/generalizability needs to be addressed. (66,67)

Manufacturing/CMC limitations. Lot-to-lot variability, potency tests, and cost/time (particularly autologous) are still rate-limiting; iPSC banks and new-generation platforms are useful but create new validation requirements. (67,68)

Trial design and endpoints. BCVA might not be sufficient to determine localised/functional improvement in GA or ultra-low vision; trials must include microperimetry, mobility, reading speed, contrast, and PROs, biomarker-guided enrichment (e.g., fixation reliability, EZ integrity). (69,62)

Safety outside of regulated trials. Although regulated ocular trials are teratoma/uncontrolled growth-free, there has been severe vision loss following unregulated intravitreal "stem-cell" injections placing a high value on GMP products and IRB-approved protocols. (23,66)

Adverse events (AEs) and safety indicators

Procedure-related: Subretinal surgery may lead to retinal tears/detachment, subretinal/choroidal haemorrhage, and epiretinal membrane; these occurrences were rare in experienced hands and diminished with technique improvement. (61,44,45)

Immunologic/tumorigenicity: Teratomas or uncontrolled growth have not been seen in any of the pluripotent-derived RPE trials thus far; AEs were most often caused by surgery or immunosuppression (when given). (57,24)

Intravitreal cell safety: intravitreal injections of hRPC and CD34+ have shown excellent ocular tolerability in randomised controlled clinical trials. (34)

Warning (beyond controlled trials): Loss of vision has occurred due to intravitreal injection of untested "stem cells" in for-profit facilities, and this highlights the need for controlled, GMP-produced material and IRB-approved protocols. (66)

Synthesis of current evidence to date

Throughout early human trials, RPE replacement with hESC-RPE suspensions has structural evidence of graft survival and acceptable safety for ~2 years, and engineered RPE patches have clinically significant letter improvement in well-selected advanced neovascular AMD. Gene-agnostic intravitreal hRPC in RP has dose-dependent BCVA gain with good tolerability, and autologous CD34+ intravitreal therapy is feasible and safe with investigational structural signals. Collectively, these data establish the biologic plausibility and clinical feasibility of stem-cell–based retinal therapy.(57,23,45,62,68)

Clinical potential versus present challenges

If durability and integration problems are solved, RPE patches may be a regenerative therapy for late AMD with RPE loss, and intravitreal progenitor approaches may provide gene-agnostic rescue in heterogeneous RP. Widespread use is held back by immune regulation, surgical optimisation, manufacturing/CMC standardisation, and endpoint sensitivity domains in which the current solutions (HLA-matched iPSC banks, hypoimmunogenic editing, optimised delivery, and multimodal endpoints) are excellent but not yet complete.(64,71,72,45)

Major Research Shortfalls in Need of Attention

Durability & dose: long-term (>2–5 y) survival/function, redosing paradigms, and structure–function coupling. (57)

Mechanism: definitive integration vs material transfer in humans using lineage-aware assays. (64)

Immunology: randomised comparisons of HLA-matched vs standard allogeneic cells; first-in-human hypoimmunogenic PSC derivatives. 4)

Delivery science: head-to-head suspension vs monolayer/scaffold for RPE replacement; complication-minimising tools. (45)

Endpoints: validated composite outcomes (BCVA + microperimetry + mobility/PRO) and earlier-stage cohorts to detect disease-modifying effects. (69)

Safety in real-world settings: registries to monitor rare AEs and prevent unregulated uses. (66)

FUTURE DIRECTIONS

- Immune evasion strategies. Two parallel approaches are ongoing: (i) HLA-matched iPSC-RPE from national/regional iPSC banks to reduce rejection with minimal systemic immunosuppression; and (ii) gene-modified hypoimmunogenic ("universal") PSCs (e.g., HLA class I/II disruption with CD47 overexpression) now showing long-term survival in non-human primates approaches that may enable off-the-shelf ocular cell therapies. (70,67)
- Refinements in delivery. Second-generation engineered scaffolds/patches with improved Bruch's membrane-like mimicry, miniaturised incisional strategies, and specially designed micro-instruments (or robot-assisted) will potentially decrease surgical morbidity with preservation of polarity and coverage. (46,45)
- Biomarker-stratified patient selection. Randomised hRPC data reveal dose-dependent effects with more potent effects in fixation-reliable, anatomy-matched subgroups; trials need to prospectively enrich by structural/functional biomarkers (e.g., ellipsoid zone integrity, fixation measures). (62)
- Mechanistic readouts and imaging. Lineage tracing, human-specific reporters, and high-end imaging (e.g., AO-OCT) can differentiate integration from paracrine rescue and monitor cell–host interactions in vivo. (64)

- Standardised organoid platforms for discovery and QC. hPSC retinal organoids allow standardised disease modelling, potency assays, and drug screening, and can also be used as release-test platforms with clinical phenotype concordance. (68)
- Patient-relevant outcomes. Add microperimetry, mobility function, reading speed, and PROs to BCVA and OCT, with agreement on thresholds of clinically important change to facilitate regulatory convergence. (69)

Authors Contribution

All authors have contributed equally.

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Conflict of Interest

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The authors haven't used any generative AI/AI assisted technologies in the writing process.

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