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Regenerative and Physical Energy-Based Therapies Across Ophthalmic Disease: An Umbrella Review of Systematic Reviews and Meta-Analyses of Human Studies

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Abstract

Background: Regenerative approaches to eye disease now span cells, cell-free secretome products, blood derivatives, amniotic membrane and biomaterials, regenerative-intent gene-cell products, and physical energy-based modalities applied with explicit endogenous-repair or neuroprotective intent, yet review-level evidence has never been synthesized across the whole eye. The closest comparable ophthalmic overview was restricted to dry eye and judged only 26 of 71 eligible reviews (37%) reliable [6], and the closest photobiomodulation umbrella review reported no ophthalmic outcome among its moderate-certainty endpoints [7]. The objective is to map, appraise and interpret systematic reviews of human studies across six ophthalmic condition families, separating patient benefit from anatomical signal and marketing authorization.

Methods and Findings: This overview is designed for reporting against PRIOR [1] and PRISMA 2020 [2], with the systematic review as the unit of searching, inclusion and analysis. Eight databases are prespecified for the formal search: MEDLINE/PubMed, Embase, Scopus, Web of Science, the Cochrane Database of Systematic Reviews with CENTRAL, Epistemonikos and LILACS, with PROSPERO and [ClinicalTrials.gov](https://clinicaltrials.gov) to be consulted for unpublished work. A structured evidence map assembled to 7 September 2026 informs this manuscript draft.

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Methodological confidence will be rated with AMSTAR 2 [3], certainty will be collected as reported and assessed de novo only where data permit, and overlap will be quantified as corrected covered area [5]. Registration: [PROSPERO number pending]. Flow counts, final included number, AMSTAR 2 distribution, corrected covered area and inter-rater agreement: [to be completed after dual independent screening and appraisal]. In the mapped evidence, the highest certainty identified was moderate: intense pulsed light versus no treatment in meibomian gland dysfunction, Ocular Surface Disease Index mean difference –16 points (95% CI –20 to –12) [36], and pterygium recurrence at 6 months with conjunctival autograft versus amniotic membrane, risk ratio 0.53 (95% CI 0.33 to 0.85) [24]. Limbal transplantation converges on 67% to 69% anatomical success across independent syntheses while resting on zero randomized trials [8,9,10]. Photobiomodulation for macular degeneration yields discordant meta-analyses on an overlapping trial pool: +1.76 ETDRS letters (95% CI 0.04 to 3.48) against a stated minimal clinically important difference of 6.8 letters [33] versus a null standardized mean difference of –0.30 (95% CI –0.85 to 0.26) [34]. Serious harms were rare within controlled research, whereas irreversible bilateral blindness has followed unregulated intravitreal adipose cell injection [45]. An overview cannot exceed the certainty or product characterization of its constituent reviews.

Conclusions: Ocular regenerative medicine is evidence-rich but certainty-poor. Modest, clinically interpretable benefit is best supported for intense pulsed light in meibomian gland dysfunction, amniotic membrane in defined surface indications and blood-derived eye drops in dry eye, all at low to moderate certainty. Cell and cell-free therapies for retina and optic nerve remain investigational and are dominated by single-arm pre-post pooling; in glaucoma and corneal endothelial disease, meta-analytic support is animal-only or confined to single embedded studies. Effects below accepted minimal clinically important differences should not be reported as clinical benefit.

Keywords

Regenerative medicine; Ophthalmology; Umbrella review; Photobiomodulation; Mesenchymal stromal cells; Evidence certainty.

Introduction

Vision loss from corneal surface failure, dry eye disease, retinal degeneration and optic nerve injury shares one biological problem: the affected tissues have limited or absent spontaneous regenerative capacity, so conventional therapy stabilizes rather than restores. The resulting therapeutic field is unusually heterogeneous: autologous serum eye drops prepared in a hospital blood bank, ex vivo expanded limbal epithelial cell sheets holding a European marketing authorization, and light-emitting diode arrays delivering multiwavelength retinal irradiation are promoted under one regenerative banner on evidence differing by orders of magnitude in volume, design quality and regulatory status.

For this overview, regenerative medicine denotes interventions whose declared therapeutic intent is restoration of ocular tissue structure and function through one of four mechanisms: replacement of a deficient cell or tissue compartment; delivery of trophic, matrix-derived or secretome-derived signals that redirect wound healing toward restoration; provision of a scaffold that supports host tissue reconstruction; or stimulation of endogenous repair, cytoprotective and neuroprotective pathways in surviving host tissue. The first three mechanisms define the biological platforms conventionally labeled regenerative. The fourth is why physical and energy-based modalities are included, and inclusion is deliberately conditional: photobiomodulation, transcorneal and transorbital electrical stimulation and intense pulsed light qualify because each is applied with an explicit endogenous-repair or neuroprotective rationale and is evaluated against outcomes of tissue structure and function rather than an ablative endpoint. Where that rationale rests only on preclinical work, the limitation is stated rather than treated as clinical support.

Procedurally adjacent interventions are treated as boundaries. Standard destructive laser

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photocoagulation, standard incisional and lamellar corneal or vitreoretinal surgery, acupuncture, optical and pharmacological myopia control, and routine thermal pulsation for gland clearance do not meet the regenerative-intent criterion, because their mechanisms are ablative, mechanical, expressive or refractive rather than restorative. Thermal pulsation is nevertheless discussed where it calibrates energy-based device claims [38], and amniotic membrane for pterygium is retained not as a regenerative claim about pterygium biology but because it generates the only high-certainty and moderate-certainty estimates in this field [24,25].

An overview of reviews is the appropriate design now because primary-study synthesis has already been repeated within narrow silos, leaving review-level questions: which nodes converge, which are discordant on overlapping trial pools, and which have no human synthesis. The one existing ophthalmic overview showed that review quality is itself rate-limiting, with 62% of its unreliable set lacking a comprehensive search and 40% using inappropriate meta-analytic methods, but was restricted to dry eye [6], while the comparable photobiomodulation umbrella review was modality-restricted [7]. No overview identified to 7 September 2026 spans cellular, cell-free, blood-derived, biomaterial and energy-based modalities across cornea, ocular surface, retina and optic nerve together.

The objectives are to map the tier of human review-level evidence for nine modality families across six condition families; to appraise methodological confidence and certainty; to quantify primary-study overlap; to separate anatomical from functional and patient-reported outcomes and test pooled effects against stated minimal clinically important differences; to synthesize safety signals, including under-reporting as a finding; and to define the evidence voids where no credible human synthesis exists.

Methods

Design, reporting and registration

This is an umbrella review, that is, an overview of systematic reviews, in which the systematic review is the unit of searching, inclusion, appraisal and analysis. Design and reporting follow PRIOR, comprising 27 main items and 19 sub-items with a dedicated flow diagram [1], and additionally PRISMA 2020, which the target journal requires for reviews [2]. Prospective PROSPERO registration is planned before screening begins, absence of which would itself constitute an AMSTAR 2 critical-domain flaw [3]: [PROSPERO registration number pending].

Eligibility criteria

Population. Humans of any age in six condition families: cornea and ocular surface disease, including persistent epithelial defects and neurotrophic keratopathy; dry eye disease and meibomian gland dysfunction; limbal stem cell deficiency; retinal degenerative and retinal vascular disease, including age-related macular degeneration, retinitis pigmentosa, Stargardt disease, diabetic retinopathy and retinal vascular occlusion; optic nerve disease and glaucoma; and other degenerative or inflammatory surface conditions, including pterygium, acute ocular burns, Stevens-Johnson syndrome and keratoconus.

Interventions. Nine modality families: limbal and oral mucosal epithelial cell therapy; mesenchymal stromal and pluripotent-cell-derived therapy; corneal endothelial cell therapy; cell-free secretome, extracellular vesicle and exosome products; blood-derived products, including serum of autologous,

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allogeneic or umbilical cord origin, platelet-rich plasma and platelet lysate; amniotic membrane, biomaterials and tissue-engineered scaffolds; regenerative-intent gene-cell products; photobiomodulation, low-level light therapy and intense pulsed light; and non-light physical energy, comprising electrical and magnetic stimulation, therapeutic ultrasound and thermal pulsation.

Comparators and outcomes: Eligible comparators are sham or placebo, artificial tears or standard medical therapy, an alternative modality or surgical technique, or no treatment; reviews pooling only single-arm pre-post change are analyzed separately and never presented as comparative efficacy. Primary efficacy outcomes are best-corrected visual acuity and condition-specific anatomical success, defined as stable corneal epithelialization without progressive conjunctivalization, corneal healing time, drusen volume and geographic atrophy area, or visual-field detection accuracy; the primary patient-reported outcome is the Ocular Surface Disease Index or equivalent; and primary safety outcomes are serious or vision-threatening adverse events plus modality-specific harms such as rejection, intraocular pressure elevation, retinal detachment, infection and tumorigenicity. Secondary outcomes are tearing break-up time, Schirmer score, corneal staining, endothelial cell density, electroretinography, retinal nerve fiber layer and central macular thickness, recurrence, quality of life and durability at 12 months or longer.

Design: Eligible are systematic reviews, with or without meta-analysis, explicitly described as systematic, reporting a reproducible search of at least two databases and including at least one human study and one eligible modality and outcome, in English, Portuguese or Spanish full text or with numerically extractable English abstracts, published to 7 September 2026. Excluded from the core synthesis are narrative reviews, scoping reviews, animal-only reviews, protocols without results, duplicate publications, and reviews of pharmacotherapy or standard destructive laser and surgery except as comparators; animal-only and scoping syntheses are retained in a labeled contextual annex and never merged with human estimates. Following the approach that classified 45 of 71 dry eye reviews as unreliable, reviews failing a comprehensive-search criterion or using inappropriate meta-analytic methods are labeled unreliable and reported separately [6], and reviews with unretrievable full text or unverifiable indexing status are flagged for manual resolution and, if unresolved, restricted to sensitivity analysis.

Information sources and search strategy

The formal search will cover each source from inception to 7 September 2026: MEDLINE via PubMed, Embase, Scopus, Web of Science Core Collection, the Cochrane Database of Systematic Reviews with CENTRAL, Epistemonikos and LILACS, together with PROSPERO for ongoing or unpublished overviews, ClinicalTrials.gov for registered but unreported trials, and grey literature through the first 200 Google Scholar hits per modality block. The PubMed strategy combines a publication-type and title-abstract filter for systematic reviews, meta-analyses, network meta-analyses and overviews of reviews with a condition block and an intervention block covering regenerative medicine, stem cell transplantation, mesenchymal, pluripotent and embryonic stem cells, limbal and oral mucosal epithelial cells, retinal pigment epithelium and progenitors, corneal endothelial cells, extracellular vesicles, exosomes, platelet-rich plasma, platelet lysate, autologous and cord blood serum, amnion, tissue engineering, gene therapy, photobiomodulation, intense pulsed light, electrical and magnetic stimulation, ultrasonic therapy and thermal pulsation. Equivalent strategies will be mapped to Emtree and to TITLE-ABS-KEY and TS operators with document-

type refinement. The final supplement will report line-by-line strategies, dates and hit counts, and language exclusions will be documented at full-text stage.

Selection, extraction and handling of duplicate reviews

Dual independent screening, extraction, AMSTAR 2 rating and certainty assessment, each with a third adjudicator and a calibration exercise on 10% of records, are required for this overview and have not yet been executed. Agreement will be reported as Cohen kappa: [kappa to be reported after dual screening]. No selection decision described here should be read as the product of completed dual review until those values are supplied. Duplicate and overlapping reviews are handled by three prespecified rules: successive versions of one review are deduplicated to the most recent, with the superseded version recorded; where several reviews by one group address the same trial pool, one is selected per outcome node by most recent search date, then broadest population, then highest AMSTAR 2 rating; and estimates are never re-pooled, the range of pooled estimates being reported alongside the most credible estimate per node and the reason for that choice.

Overlap assessment

For each modality-by-condition node, a review-by-primary-study citation matrix is constructed and the corrected covered area computed as the frequency of repeated occurrences of index publications across reviews divided by the product of index publications and reviews minus the number of index publications; the reported median across published overviews is 4.0, and overlap reporting is required of a well-conducted overview [5]. Node-level and overall values are reported once the matrix is complete: [corrected covered area values to be computed]. Four high-overlap clusters are anticipated a priori: the autologous serum trial pool across serum and platelet reviews [17], the photobiomodulation trials across the two discordant macular degeneration meta-analyses [33,34], the stimulation trials across stimulation syntheses [39], and the non-randomized limbal transplantation case-series pool across every limbal stem cell deficiency synthesis [9].

Methodological quality and certainty of evidence

Each included review is rated with AMSTAR 2 across its 16 items, with attention to the seven critical domains: prior registration, search adequacy, justification of exclusions, risk of bias in included studies, appropriateness of meta-analytic methods, use of risk of bias in interpretation, and publication bias. Overall confidence is high, moderate, low or critically low, and item scores are not summed [3]. Distribution of ratings: [AMSTAR 2 rating distribution to be reported]. Certainty follows the PRIOR distinction between collecting and assessing [1]. Where authors report GRADE, the rating is collected verbatim and labeled as collected, which applies to amniotic membrane [22,23], autologous serum [15,16], pterygium surgery [24,25], thermal pulsation [38], intense pulsed light [36] and electrical stimulation [39]. Where GRADE is absent, the outcome is labeled not assessed by review authors, and de novo assessment is undertaken only where two reviewers can access sufficient underlying data, applying the four certainty categories and the five downgrading and three upgrading domains [4]. Collected and de novo ratings are never merged in one column.

Synthesis approach

Synthesis is structured, tabular and narrative, with no quantitative re-pooling. Each modality-by-condition

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node receives an evidence tier: meta-analytic human evidence with pooled between-group or pooled-proportion estimates; meta-analytic evidence limited to single-arm pre-post change; systematic-review evidence without pooling; preclinical or contextual evidence only; and no credible evidence identified. Estimates are reported with 95% confidence intervals and heterogeneity where available and interpreted against stated minimal clinically important differences, anatomical, functional and patient-reported outcomes are reported in parallel and never substituted for one another, and discordance between reviews sharing a trial pool is analyzed rather than averaged. Safety is synthesized by modality family, with absent or heterogeneous reporting recorded as a finding, and evidence voids are reported as explicit negative findings.

Results

Flow of records, number of reviews in the core synthesis, number classified as unreliable and reasons for exclusion at each stage: [PRISMA 2020 and PRIOR flow counts to be completed after database export and dual screening]. Final number of included systematic reviews: [to be completed]. What follows is the evidence map assembled during protocol development, with every estimate individually sourced.

Cornea, ocular surface and limbal stem cell deficiency

Limbal stem cell deficiency is the most mature ocular cell-therapy node and the clearest case of high-volume, low-design-quality evidence. Cultivated limbal epithelial cells on amniotic membrane, pooled across 18 articles and 572 eyes, achieved 67% success (95% CI 0.59 to 0.75, I^2 60%) with no autograft-versus-allograft difference [8]. The largest synthesis, 40 studies and 2202 eyes of 1999 patients, reported 67.4% overall success (95% CI 62.1 to 72.3) and 74.5% ocular surface improvement (95% CI 69.3 to 79.2), and identified no randomized clinical trials in the literature [9]; that absence was reproduced in a further 17 studies, which pooled simple limbal epithelial transplantation success at 79.08% (95% CI 74.10 to 84.07) [11]. Across 22 non-comparative case series and 1023 eyes, anatomical and functional success were 69% and 60% at a median of 1.75 years, with a technique gradient favoring simple limbal epithelial transplantation and conjunctival limbal autograft over cultivated grafts ($p = 0.0048$) (10).

Graft source remains discordant. Two syntheses found no autologous-versus-allogeneic difference [8,11], whereas the largest reported 83.2% success for autologous direct transplantation against 53.9% for allogeneic, with cultivated autologous grafts intermediate (**Table 2**) [9]. Because these reviews share much of the same case-series pool, overlap-based adjudication is required. A broader review of 42 articles on clinical regenerative medicine for the cornea reported median surface reconstruction of 74.1% and visual recovery of 54.5% after autologous cultivated limbal transplantation with 0% immunologic rejection, against 71.4% and 71.4% with 7.1% rejection after allogeneic transplantation; it also contains the only synthesized human corneal endothelial cell-therapy data identified, a single bullous keratopathy study in which corrected acuity improved in 82% [12].

Dry eye disease and blood-derived products

Blood derivatives form the densest node and the clearest example of large sample size failing to raise certainty. A Cochrane review of 5 randomized trials, 92 participants and 149 eyes did not pool, reported symptom improvement of -12.00 points (95% CI -20.16 to -3.84), graded certainty low versus artificial

tears and very low versus saline, and documented one stored serum sample growing mixed organisms including yeast [15]. Across 19 randomized trials and 729 patients, serum eye drops improved tear break-up time and symptoms at 2 to 6 weeks but not Schirmer score or fluorescein staining, no clear difference persisted at 2 to 12 months, and certainty was very low to low (**Table 2**) [16]. The largest autologous serum meta-analysis, 12 randomized trials and 1112 participants, reproduced those directions with tighter intervals and reported fewer adverse events than artificial tears (risk ratio 0.36, 95% CI 0.13 to 0.99) [17].

A network meta-analysis of 16 randomized trials and 898 patients compared platelet-rich plasma drops and injections, umbilical cord serum, allogeneic serum, deproteinized calf blood extract, autologous whole blood and autologous serum against artificial tears. Several active products beat artificial tears on selected endpoints, yet no significant difference emerged between any two active products, and indication-based selection was proposed [18]. Platelet-rich plasma monotherapy across 19 studies, 10 comparative and 9 before-after, produced moderate standardized effects on symptoms (0.81, 95% CI 0.25 to 1.37) and corneal staining (0.72, 95% CI 0.14 to 1.30), with an adverse-effect rate of 2.6% (95% CI 0.5 to 4.7) and heterogeneity of 67% to 85% [19]. A review of 38 clinical studies of platelet drops, lysates and gels concluded that the field cannot be evaluated coherently until platelet products are characterized [20].

Cell and cell-free products for dry eye rest largely on within-group change. A 2026 meta-analysis of mesenchymal stromal cells and their exosomes in 6 studies and 131 patients reported Schirmer improvement of 4.70 mm (95% CI 4.18 to 5.22) and reduced corneal staining, without serious treatment-related adverse events but with heterogeneous safety reporting and limited follow-up [13]. A companion synthesis in Sjögren-associated and refractory disease pooled 5 studies and 114 patients, reporting symptom improvement of -15.10 points (95% CI -18.65 to -11.56) that persisted at 12 months while the Oxford staining score was unchanged (-0.20, 95% CI -0.85 to 0.45); critically, effects were pooled as within-group pre-post change, and harms were procedural [14].

Amniotic membrane, biomaterials and corneal nerve regeneration

Amniotic membrane provides the field's sharpest outcome-tier contrast: across 18 studies, 385 patients and 390 eyes, corneal epithelial healing reached 97% (95% CI 0.94 to 0.99) while visual improvement reached only 53% (95% CI 0.42 to 0.65), with significant differences between single-layer inlay, multilayer inlay and sandwich techniques [21]. In infectious keratitis, adjuvant transplantation pooled from 4 randomized trials and 209 eyes shortened healing by 4.08 days (95% CI -6.27 to -1.88) and improved 1-month uncorrected acuity by 0.26 logMAR (95% CI -0.50 to -0.02) without increasing adverse events, at very low to low certainty [22]. In acute ocular burns, 2 randomized trials and 128 burns showed a visual-acuity advantage in moderate burns (mean difference -0.32, 95% CI -0.55 to -0.09) but no benefit in severe burns, with no adverse events in any arm and certainty very low to low [23].

The boundary indication of pterygium yields the highest certainty in the evidence map. Conjunctival autograft reduced recurrence relative to amniotic membrane at 6 months (risk ratio 0.53, 95% CI 0.33 to 0.85, 10 studies, 1021 participants, moderate certainty) but not at 3 months, across 20 randomized trials and 1866 participants [24]. Across 12 randomized trials and 1144 participants, conjunctival autograft with mitomycin C reduced recurrence at high certainty (risk ratio 0.12, 95% CI 0.02 to 0.63), amniotic

membrane versus conjunctival autograft recurrence was indeterminate, and amniotic membrane produced fewer adverse events (risk ratio 0.46, 95% CI 0.22 to 0.95) [25].

Corneal nerve regeneration is an emerging node with two uncontrolled human syntheses. Pooled complete healing across 20 studies and 571 patients with neurotrophic keratopathy was 92% (95% CI 86 to 98) for autologous serum, 86% (95% CI 78 to 94) for amniotic membrane and 99% (95% CI 95 to 103) for neurotization, against 23% (95% CI 14 to 32) for non-specific treatment ($p < 0.001$); only nerve growth factor and amniotic membrane improved acuity, and two intervals exceed 100% (26). Corneal neurotization across 17 studies and 232 eyes improved acuity by 0.44 logMAR (95% CI -0.66 to -0.21) and corneal sensitivity by 32.42 mm (95% CI 27.45 to 37.38), alongside gains in nerve fiber density, without reported safety data or certainty rating [27].

Retinal degeneration

Retinal cell therapy is where review-level discordance is most consequential. A three-level meta-analysis of 18 studies and 224 eyes, drawn from 39 eligible reports, found improvement in logMAR acuity overall for age-related macular degeneration (Hedges g -0.47 , 95% CI -0.91 to -0.03), driven by neovascular disease (-1.74 , 95% CI -2.91 to -0.58), while the atrophic subgroup carrying most of the clinical burden was non-significant (-0.26 , 95% CI -0.73 to 0.22 , $p = 0.29$); Stargardt disease (-0.36 , 95% CI -0.61 to 0.01) and retinitis pigmentosa (-0.33 , 95% CI -0.48 to -0.17) improved, severe adverse events were infrequent, and primary-study quality scored 6 to 9 of 9 on the JBI quasi-experimental checklist [28]. A separate meta-analysis of 10 studies and 102 patients with atrophic disease reported extreme relative benefit at 6 months (risk ratio 17.00, 95% CI 6.08 to 47.56) and 12 months (risk ratio 11.00, 95% CI 2.36 to 51.36), with 4 related ocular adverse events and none systemic [29]. These conclusions are incompatible for the same indication despite a shared primary-study base, the difference reflecting outcome metric, effect measure and uncontrolled data rather than new patients.

A larger synthesis with outcome prediction across 43 studies and 666 eyes, comprising 147 atrophic and 9 neovascular macular degeneration, 422 retinitis pigmentosa and 88 Stargardt eyes, reported 6-month adjusted logMAR values by cell type, including 0.65 (95% CI 0.57 to 0.72) for adipose-derived cells and 0.49 (95% CI 0.33 to 0.65) for embryonic stem cell-derived retinal pigment epithelium in atrophic disease, and 0.50 (95% CI 0.28 to 0.73) for Wharton jelly cells in retinitis pigmentosa. Its adverse-event catalogue is the most complete available and includes tractional retinal detachment, vitreous hemorrhage, osseous metaplasia, choroidal neovascular and epiretinal membrane, and retinal pigment epithelial detachment, with no systemic events; primary-study quality scored 6 to 9 on the Newcastle-Ottawa Scale, and reliance on case reports and short follow-up could overestimate effect [30]. No review in this node reports a sham-controlled pooled estimate of patient-important vision gain.

Optic nerve and glaucoma

This is the largest true void in human synthesis. The only human meta-analysis pooled 7 reports of mesenchymal stromal cell therapy across glaucomatous, ischemic, inflammatory, compressive, toxic, hereditary and traumatic optic neuropathy, analyzing 62 of 66 reported eyes treated by seven different delivery routes. Visual acuity changed from 0.90 to 0.65 logMAR ($p < 0.001$) and retinal nerve fiber layer thickness from 77.56 to 82.55 μm without reaching significance, but there was no comparator group and

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no confidence intervals were reported; overall quality was moderate on the Mixed Methods Appraisal Tool and long-term safety was not assessed [31]. For glaucoma specifically, meta-analytic support exists only in animals: 19 animal randomized studies pooled intraocular pressure reduction at week 4 (-1.29 mmHg, 95% CI -1.61 to -0.96), retinal ganglion cell count at week 2 (23.06, 95% CI 18.22 to 27.89), brain-derived neurotrophic factor (0.75, 95% CI 0.67 to 0.83) and nerve fiber layer thickness (10.69, 95% CI 9.44 to 11.94), with no systemic adverse events [32]. These animal estimates establish plausibility and must not be transferred to patients.

Photobiomodulation and light-based modalities

Photobiomodulation for age-related macular degeneration produces the field's most instructive contradiction. Across 3 randomized sham-controlled trials and 247 eyes treated with light-emitting diodes at 590, 660 and 850 nm, pooled acuity improved by 1.76 ETDRS letters (95% CI 0.04 to 3.48, I^2 77%) and drusen volume fell by 0.12 mm^3 , with no effect on geographic atrophy area. The same review specified minimal clinically important differences of 6.8 letters and 0.39 mm^3 , rated all three trials at high risk of bias, and concluded that the statistical gains do not amount to clinical benefit [33]. A second meta-analysis of 6 randomized trials, 5 pooled, covering 360 patients and 477 eyes, found no effect on acuity (standardized mean difference -0.30 , 95% CI -0.85 to 0.26), drusen volume, central subfield thickness or microperimetry, with adverse events unchanged overall and fewer within 6 months (risk ratio 0.48, 95% CI 0.29 to 0.82), concluding that there is no significant clinical benefit [34]. Indication specificity is decisive: a phase 2 randomized trial of home 670 nm photobiomodulation in 135 eyes with center-involved diabetic macular edema found a central subfield thickness difference of $-2 \text{ }\mu\text{m}$ (95% CI -20 to 16) and was reported as not effective [35].

Light-based treatment of the ocular surface performs better and holds the only moderate-certainty energy-based estimate. In a health-technology-assessment-grade synthesis of 13 studies, intense pulsed light versus no treatment improved symptoms by 16 points (95% CI -20 to -12 , 280 participants, moderate certainty), whereas adding it to standard treatment produced a 7-point improvement (95% CI -12 to -3) at very low certainty, with mild transient adverse events in 4 of 10 trials analyzed for safety across 746 participants [36]. Across 12 studies of low-level light therapy combined with intense pulsed light, symptoms improved substantially and signs modestly, but heterogeneity of 97.5% to 98.6% renders those pooled means barely interpretable; the same review reports the key negative structural signal in this literature, meibomian gland area loss improving initially but worsening at 6 months or later ($+5.9\%$, 95% CI 1.8 to 10.0, $p = 0.005$), with long-term safety not evaluated [37]. Thermal pulsation, the calibrating comparator, did not outperform other thermostatic devices on symptoms across 13 trials and 1155 participants, no trial reported intervention-related vision-threatening events, and certainty was low or very low [38].

Electrical and other physical modalities

The most rigorous stimulation synthesis pooled 13 randomized sham-controlled trials and 441 adults across repetitive transorbital alternating current, transpalpebral and transcorneal electrical stimulation, and transcranial random noise and direct current stimulation, across mixed retinal, optic nerve and cerebral causes of vision loss. No benefit was demonstrated for acuity at 1 month or earlier (-0.02

logMAR, 95% CI -0.08 to 0.04), detection accuracy, mean sensitivity or quality of life; minor adverse effects were not increased (risk ratio 1.24, 95% CI 0.99 to 1.54) and no serious events occurred. Certainty was low for early acuity and moderate for later outcomes and safety, and any improvement was judged of uncertain clinical relevance [39]. Therapeutic ultrasound has no human evidence: a systematic review of 37 animal studies from 2002 to 2022 identified no clinical trial or human study, could not pool because of heterogeneity, and documented pervasive dosimetry under-reporting, with 29 of 37 studies omitting peak negative pressure and 23 of 37 omitting temperature assessment against ophthalmic exposure limits [40].

Extracellular vesicle and exosome evidence

No human systematic review of extracellular vesicle therapy for retinal disease was identified. Ocular extracellular vesicle evidence is preclinical across all indications reviewed, and only five ocular extracellular vesicle trials are registered worldwide, three in dry eye and one each in retinitis pigmentosa and refractory macular hole [41]. The only human meta-analytic signal comes from exosome-treated participants embedded within a mesenchymal stromal cell dry eye synthesis, in which products were not analyzed separately [13]. Regulatory status is unambiguous: no exosome product is approved by the United States Food and Drug Administration, and regenerative products are explicitly not approved for macular degeneration or blindness [44].

Safety synthesis

Within controlled research settings serious harm was uncommon in every modality family, but the pattern is platform-specific. Ocular surface cell therapy carries technique-dependent risk: no serious donor-eye events occurred across 1023 eyes [10], while recipient events include persistent erosion, infectious keratitis, corneal melt, rejection and raised intraocular pressure [9], with rejection of 7.1% after allogeneic versus 0% after autologous cultivated transplantation [12]. Retinal cell therapy harms are structural and procedure-related rather than systemic [30]. Blood derivatives are comparatively benign, with fewer adverse events than artificial tears (risk ratio 0.36, 95% CI 0.13 to 0.99) [17], a platelet-rich plasma adverse-effect rate of 2.6% [19] and a contamination signal favoring strict preparation and storage standards [15]. Energy-based modalities show no vision-threatening intervention-related events [38,39], qualified by delayed meibomian gland area worsening after combined light therapy [37].

Under-reporting is itself a result: safety reporting was heterogeneous in cell therapy for dry eye [13], long-term safety was not evaluated for combined light therapy [37] or optic neuropathy cell therapy [31], and ultrasound dosimetry was largely unreported [40]. The harm profile outside regulated research is categorically different: bilateral intravitreal injection of autologous adipose cells in platelet-rich plasma at a commercial clinic produced vision loss to no light perception or hand motions at 1 year in three patients, with intraocular pressures of 66 and 59 mmHg, lens dislocation, vitreous hemorrhage, retinal detachment and proliferative vitreoretinopathy [45].

Translational maturity

Only one ocular cell therapy holds a European marketing authorization: ex vivo expanded autologous corneal epithelial cells containing stem cells, authorized conditionally on 17 February 2015 for adults with moderate to severe limbal stem cell deficiency after physical or chemical ocular burns and converted to a

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standard marketing authorization on 22 February 2024, supported by successful outcomes in 75 of 104 patients (72%) at 1 year [42]. One photobiomodulation device holds a United States De Novo authorization granted on 14 December 2023 for improving visual acuity in atrophic macular degeneration with acuity between 20/32 and 20/70, supported by a pivotal trial of 100 subjects and 148 eyes in which the treatment difference was 2.6 letters at month 13 ($p = 0.0548$, not significant) and 4.3 letters at month 24 (95% CI 1.5 to 7.2), with no data beyond 54 treatments per eye and no non-White subjects treated [43]. Blood derivatives, amniotic membrane and intense pulsed light are in routine practice without product-level authorization, retinal and endothelial cell therapies are early-phase and single-arm dominated, extracellular vesicles are registered but unreported, and ultrasound and stem cells for glaucoma remain preclinical.

Tables

Modality family	Cornea, ocular surface and LSCD	Dry eye and MGD	Retinal degeneration	Optic nerve and glaucoma	Boundary and other conditions
Limbal and oral mucosal epithelial cell therapy	M (8,9,10,11); S for oral mucosal grafts (12)	0	0	0	S, burns as dominant etiology (10)
Mesenchymal stromal and pluripotent-derived cells	S (12)	M, partly single-arm (13,14)	M (28,29,30)	M without comparator for optic neuropathy (31); P only for glaucoma (32)	0
Corneal endothelial cell therapy	S, one study within a broader corneal review (12)	0	0	0	0
Extracellular vesicles and secretome	P (41)	M only as an unseparated subset (13)	P, 0 human synthesis (41)	P (41)	0
Serum and blood-derived drops	M for neurotrophic keratopathy (26)	M (15,16,17,18)	0	0	0
Platelet-rich plasma and platelet derivatives	S, characterization deficit (20)	M (18,19)	0	0	0
Amniotic membrane and biomaterials	M (21,22)	S, within surface indications (21)	0	0	M for pterygium (24,25) and acute burns (23)
Photobiomodulation and low-level light	M as combined light therapy (37)	M (37)	M but discordant (33,34); negative trial in diabetic macular edema (35)	0	0
Intense pulsed light and thermal pulsation	M as combined light therapy (37)	M (36,37,38)	0	0	0
Electrical stimulation and ultrasound	0	0	S and M within mixed-condition pooling (39); P for ultrasound (40)	M within mixed-condition pooling (39)	0

Table 1: Evidence map: highest available tier of human review-level evidence by modality family and condition family. M denotes meta-analytic human evidence with pooled between-group or pooled-proportion estimates; S denotes systematic-review human evidence without pooling; P denotes preclinical or contextual evidence only; 0 denotes no credible human review-level evidence identified to 7 September 2026.

Modality and condition	Representative pooled estimate (95% CI)	Certainty as reported	Principal limitation	Source
Limbal transplantation, LSCD	Overall success 67.4% (62.1 to 72.3); autologous 83.2% vs allogeneic 53.9%	Not reported	No randomized trial among 40 studies and 2202 eyes	Le 2020
Cultivated limbal cells on amniotic membrane, LSCD	Success 67% (0.59 to 0.75); two-line acuity gain 62% (0.57 to 0.66)	Not reported	Autograft versus allograft indeterminate; I ² 60%	Zhao 2015
Autologous serum drops, dry eye	TBUT 2.68 s (1.33 to 4.03); OSDI -11.17 (-16.58 to -5.77) at 2 to 6 weeks	Low for TBUT and OSDI; very low for Schirmer and staining	No clear difference beyond 2 to 12 months	Franchini 2019
Autologous serum drops, dry eye	Schirmer 2.35 (1.45 to 3.24); OSDI -10.54 (-13.31 to -7.77); adverse events RR 0.36 (0.13 to 0.99)	Not reported (risk of bias assessed)	Substantial trial-level heterogeneity in concentration and regimen	He 2024
Blood components, dry eye (network)	Active products superior to artificial tears on selected endpoints; no difference between active products	Not reported	Indirect comparisons only; no head-to-head superiority	Zhang 2024
Platelet-rich plasma, dry eye	Symptoms SMD 0.81 (0.25 to 1.37); staining SMD 0.72 (0.14 to 1.30)	Not reported	Nine of 19 studies uncontrolled; I ² 67% to 85%	Akowuah 2024
MSC and exosomes, dry eye	Schirmer 4.70 mm (4.18 to 5.22); OSDI -11.44 (-22.71 to -0.17)	Not reported (RoB 2 and ROBINS-I applied)	Six studies, 131 patients; products not analyzed separately	Chen 2026
MSC, Sjögren-associated dry eye	OSDI -15.10 (-18.65 to -11.56); Schirmer 3.87 (1.93 to 5.81)	Not reported	Within-group pre-post pooling; no between-group comparison	Zhang 2026
Amniotic membrane, corneal ulceration	Epithelial healing 97% (0.94 to 0.99); vision improvement 53% (0.42 to 0.65)	Not reported	Anatomical and functional outcomes diverge sharply	Liu 2019
Adjuvant amniotic membrane, infectious keratitis	Healing -4.08 days (-6.27 to -1.88); UDVA -0.26 logMAR (-0.50 to -0.02)	Very low for healing, UDVA, adverse events; low for CDVA	Only 4 randomized trials, 209 eyes; no herpetic or acanthamoebic data	Ting 2021
Conjunctival autograft vs amniotic membrane, pterygium	Recurrence at 6 months RR 0.53 (0.33 to 0.85)	Moderate at 6 months; very low at 3 months	Recurrence definitions and follow-up vary across 20 trials	Clearfield 2016
Conjunctival autograft with mitomycin C, pterygium	Recurrence RR 0.12 (0.02 to 0.63)	High	Not a regenerative claim; included as certainty benchmark	Taher 2022
Specific therapies, neurotrophic keratopathy	Complete healing: serum 92% (86 to 98); neurotization 99% (95 to 103); NGF 75% (46 to 104)	Not reported	Uncontrolled pooling; two intervals exceed 100%	Roumeau 2022
Corneal neurotization	BCVA -0.44 logMAR (-0.66 to -0.21); sensitivity 32.42 mm (27.45 to 37.38)	Not reported	No comparator; I ² 88.7% for acuity	Molinari 2025
Cell therapy, retinal degeneration	AMD g -0.47 (-0.91 to -0.03); atrophic AMD -0.26 (-0.73 to 0.22)	Not reported (JBI 6 to 9 of 9)	Atrophic subgroup null; quasi-experimental designs	Soltani Khaboushan 2024
Cell therapy, atrophic AMD	Acuity improvement RR 17.00 (6.08 to 47.56) at 6 months	Not reported	102 patients, one randomized trial; implausible precision	Li 2022
MSC, optic neuropathy	Acuity 0.90 to 0.65 logMAR (p < 0.001); RNFL 77.56 to 82.55 μ m (not significant)	Moderate on MMAT	No comparator group; no confidence intervals reported	Chaibakhsh 2024
Photobiomodulation, AMD	BCVA +1.76 ETDRS letters (0.04 to 3.48) against stated MCID 6.8 letters	Not graded; all 3 trials at high risk of bias	Statistically significant but below the review's own MCID	Rassi 2024

Photobiomodulation, AMD	BCVA SMD -0.30 (-0.85 to 0.26); drusen SMD -0.08 (-0.52 to 0.37)	Not reported (Cochrane tool, generally low risk)	Directly discordant with the estimate above on an overlapping pool	Chen 2025
Intense pulsed light vs no treatment, MGD	OSDI -16 points (-20 to -12)	Moderate	Add-on effect much smaller and very low certainty	Peira 2025
Combined low-level light and IPL, MGD	OSDI -22.8 (-29.1 to -16.5); gland area loss +5.9% (1.8 to 10.0) at 6 months or later	Not reported	I ² 97.5% to 98.6%; delayed anatomical worsening	Chan 2025
Thermal pulsation, dry eye	OSDI 4.59 (1.23 to 7.95) favoring other thermostatic devices	Low to very low	Boundary modality; 7 of 13 trials at high risk of bias	Pucker 2024
Non-invasive electrical stimulation, mixed	Acuity -0.02 logMAR (-0.08 to 0.04); detection accuracy SMD 0.09 (-0.58 to 0.77)	Low for early acuity; moderate for later outcomes and safety	Mixed conditions pooled; clinical relevance uncertain	Navarro 2023
Stem cells, glaucoma	IOP -1.29 mmHg (-1.61 to -0.96); RGC count 23.06 (18.22 to 27.89)	Not applicable to humans	Animal randomized studies only; not transferable to patients	Wu 2025

Table 2: Representative pooled estimates by modality and condition, with certainty as reported and principal limitation. Certainty is collected as reported by the review authors; entries marked not reported were not graded by those authors and are not graded de novo in this draft.

Modality family	Key safety signal from review-level evidence	Translational position
Limbal and oral mucosal epithelial cell therapy	No serious donor-eye events across 1023 eyes [10]; recipient rejection 7.1% allogeneic vs 0% autologous, infectious keratitis 12.0% vs 4.6% [12].	Authorized product for burn-related LSCD, standard EU authorization since 22 February 2024, based on 72% success in 104 patients [42].
Serum and blood-derived drops	Fewer adverse events than artificial tears, RR 0.36 (0.13 to 0.99) [17]; stored-serum microbial contamination [15].	Routine practice without product authorization; certainty low to very low [16].
Platelet derivatives	Adverse-effect rate 2.6% (0.5 to 4.7) [19]; product characterization identified as the limiting deficiency [20].	Routine practice; no demonstrated superiority over other blood derivatives [18].
Amniotic membrane and biomaterials	Adverse events not increased versus antimicrobials, RR 0.80 (0.46 to 1.38) [22]; none reported in burn trials [23]; fewer events than conjunctival autograft, RR 0.46 (0.22 to 0.95) [25].	Established surgical adjunct; certainty very low to moderate [24].
Retinal and optic nerve cell therapy	Structural events including tractional detachment, vitreous hemorrhage, osseous metaplasia and RPE detachment, without systemic events [30]; long-term safety not assessed in optic neuropathy [31]	Early-phase, single-arm dominated; no sham-controlled pooled functional benefit [28].
Extracellular vesicles	No human review-level safety data; no approved exosome product and no approval for macular degeneration or blindness [44]	Registered but essentially unreported; five ocular trials worldwide [41].
Photobiomodulation and light-based therapy	Adverse events not increased, RR 1.04 (0.51 to 2.12), and fewer within 6 months, RR 0.48 (0.29 to 0.82) [34]; mild transient events in 4 of 10 IPL trials [36]; delayed gland-area worsening [37]	One device authorized for atrophic AMD via De Novo pathway with dosing limits and a non-diverse pivotal population [43]
Thermal pulsation (boundary)	No intervention-related vision-threatening events in any of 13 trials [38].	Marketed device; certainty low or very low [38]
Electrical stimulation	No serious adverse events; minor effects RR 1.24 (0.99 to 1.54) [39]	Investigational; benefit of uncertain clinical relevance [39]

Therapeutic ultrasound	Dosimetry unreported in most studies, including peak negative pressure in 29 of 37 [40]	Preclinical only; no human study identified [40]
Unregulated cell products	Irreversible bilateral vision loss with intraocular pressures of 66 and 59 mmHg, retinal detachment and proliferative vitreoretinopathy [45]	Outside acceptable practice; explicitly unapproved for these indications [44]

Table 3: Safety signals and translational maturity by modality family.

Discussion

Synthesis points

Evidence volume and evidence certainty are dissociated. The highest certainty identified anywhere was moderate, for intense pulsed light versus no treatment [36], pterygium recurrence at 6 months [24] and later outcomes after electrical stimulation [39], with the only high rating attaching to a non-regenerative surgical adjunct [25]. The flagship cell platforms sit at low or ungraded certainty, so publication volume is not a proxy for confidence in this literature.

A licensed cell therapy can rest on non-randomized evidence. Ex vivo expanded limbal epithelial cells hold a standard European marketing authorization [42], while the largest meta-analysis of limbal transplantation found no randomized trial among 40 studies and 2202 eyes [9], reproduced in a second synthesis [11]. This is defensible in an orphan indication without alternatives, but the effect size in routine practice derives from case series.

Convergence across independent syntheses is a usable quality signal, and technique matters more than graft source. Three syntheses with different search dates converge on 67% to 69% anatomical success [8,9,10]. The technique gradient favoring simple limbal epithelial transplantation and conjunctival limbal autograft over cultivated grafts [10] is more actionable than the graft-source question, which two syntheses found null and one strongly non-null; because these reviews share primary studies, adjudication requires overlap analysis, not a fourth pooled estimate.

Photobiomodulation for macular degeneration is the clearest divergence between statistical significance, clinical importance and regulatory decision. An overlapping trial pool yields +1.76 ETDRS letters in one meta-analysis [33] and a null standardized effect in another [34], while device authorization rested on a month-24 difference of 4.3 letters [43]. All three values fall below the 6.8-letter minimal clinically important difference specified by the first review itself [33].

Class claims for light-based therapy are indefensible because indication specificity dominates. The contested signal in atrophic macular degeneration does not extend to center-involved diabetic macular edema, where a randomized trial found a central subfield thickness difference of $-2\ \mu\text{m}$ and a 0.4-letter acuity difference [35]. Photobiomodulation must be evaluated indication by indication, with wavelength, irradiance, fluence, spot area, schedule and sham fidelity specified each time.

Blood derivatives are the most trial-dense modality and remain low-certainty because of product heterogeneity, not sample size, and no active product has been shown superior to another. Nineteen randomized trials in 729 patients [16], 12 in 1112 participants [17] and a 16-trial network meta-analysis

in 898 patients [18] still resolve to low or very low certainty [15], and the deficiency named by the platelet literature itself is product characterization [20]. Because active products beat artificial tears but not each other [18], selection should follow preparation feasibility, storage and contamination control rather than claims of comparative superiority [15].

Anatomical and functional success diverge systematically, which argues for paired core outcomes. Amniotic membrane achieves 97% epithelial healing but 53% visual improvement [21], limbal transplantation 74.5% surface improvement against 67.4% clinical success [9], and neurotization large nerve-morphology gains with a more modest acuity gain [27]. Single composite success rates obscure this gap.

Single-arm pre-post pooling is the dominant methodological failure mode in ocular cell therapy. Within-group change was pooled without between-group comparison in Sjögren-associated dry eye [14]; the optic neuropathy meta-analysis had no comparator and no confidence intervals [31]; the retinal prediction analysis acknowledged that reliance on case reports could overestimate effects [30]. AMSTAR 2 item 11 on appropriateness of meta-analytic methods is a critical domain and should drive most downgrades here [3].

Implausible precision is a recurring red flag. Complete-healing estimates with upper limits above 100% [26], a risk ratio of 17.00 for acuity in 102 patients [29] and heterogeneity of 97.5% to 98.6% around pooled symptom means [37] indicate that the pooled quantity is not estimating a stable effect and must not ground clinical advice.

Glaucoma, corneal endothelial disease and ocular extracellular vesicle therapy are the largest voids, and in two of them synthesis lags practice. Meta-analytic support for stem cells in glaucoma exists only in animals [32]; human corneal endothelial cell therapy appears at synthesis level only as a single embedded study [12]; ocular extracellular vesicle therapy has five registered trials worldwide and no human systematic review [41]; and therapeutic ultrasound has no human study at all [40].

Safety asymmetry, not efficacy, is the strongest justification for a tiered clinical policy. Energy-based modalities produced no vision-threatening intervention-related events [38] and no serious events across 13 stimulation trials [39], whereas unregulated intravitreal cell injection produced irreversible bilateral blindness [45]. A defensible ordering is: modest benefit with acceptable safety at low to moderate certainty for intense pulsed light, amniotic membrane and blood derivatives; safe but unproven for photobiomodulation and electrical stimulation; investigational-only for retinal, optic nerve and corneal endothelial cell therapy; and unacceptable outside registered trials for direct-to-consumer intraocular cell and exosome products.

Regulatory context

Regulatory decisions have run ahead of certainty in both directions. In Europe, the only authorized ocular cell therapy moved from conditional authorization in February 2015 to standard authorization in February 2024 on a 72% success rate in 104 patients, in a defined burn-related indication requiring residual undamaged limbus, with eye pain, corneal epithelial defects, conjunctival hemorrhage and blepharitis as

common adverse events [42]. In the United States, a photobiomodulation device received De Novo authorization in December 2023 for a narrow atrophic macular degeneration population, with an acuity gain that missed significance at month 13, no evidence beyond 54 treatments per eye, and no non-White subjects in the pivotal trial [43], while the same regulator states that no exosome product is approved and that regenerative products are not approved for macular degeneration or blindness [44]. Counseling should present authorization status, effect size relative to a minimal clinically important difference, and the authorized dosing envelope as three separate items.

Standardized platform reporting requirements

Certainty stalls at low largely because interventions are inadequately specified, which prevents pooling and forbids transfer of evidence between products, so a platform-specific minimum reporting set should be mandatory. Cell therapies should report source tissue, autologous or allogeneic status, culture and carrier system, manufacturing and release controls, dose, route, immunosuppression and follow-up [12]. Extracellular vesicle products should report parent cell, isolation and characterization method, particle count and dose, route, storage and release criteria, none of which is recoverable from current ocular human evidence [41]. Blood derivatives should report cellular content, activation status, volume, concentration, preparation system and schedule, precisely the deficiency the platelet literature identifies in itself [20], with microbiological control for serum products [15]. Biomaterials should report composition, preservation state, layer configuration and fixation, since configuration differences produced significant pooled outcome differences [21]. Energy-based devices should report wavelength or frequency, irradiance, fluence, spot area, pulse structure, site, schedule, cumulative exposure limits, device identity and sham fidelity, and never treat a preset or peak power figure as a validated dose; the ultrasound literature shows how completely such reporting fails [40] and the light-based literature shows why cumulative exposure matters [37].

Research agenda

Five priorities follow. First, sham-controlled or actively controlled randomized trials with masked assessment are required in retinal and optic nerve cell therapy, since no node there provides a controlled pooled estimate of patient-important vision change [28,31]. Second, head-to-head trials of characterized blood derivatives with prespecified minimal clinically important differences should replace further placebo-controlled trials of uncharacterized preparations [18,20]. Third, light-based therapy requires dose-ranging, indication-specific trials with follow-up beyond 12 months and prespecified anatomical safety endpoints [33,37]. Fourth, early-phase trials with rigorous product characterization, rather than further preclinical work, are the next step for ocular extracellular vesicles [41] and for cell-based neuroprotection in glaucoma [32]. Fifth, a core outcome set pairing anatomical, functional, patient-reported and durability endpoints is needed, with registry-based surveillance for authorized products whose pivotal exposure envelopes are narrow [43].

Limitations

Five limitations apply. An overview inherits the deficiencies of its constituent reviews, and where reviews did not grade certainty this manuscript reports that absence rather than substituting an unverified rating. Primary-study overlap means several apparently independent estimates describe the same patients, and

until corrected covered area is computed per node the inflation is unquantified [5]. Flow counts, the final number of included reviews, AMSTAR 2 ratings, agreement statistics and registration remain outstanding, so this is an evidence-mapped draft rather than a completed overview. Several source records were incomplete at extraction, two candidate reviews having unretrievable full text, one appearing in an outlet of unverifiable indexing status, and several reporting outcomes without pooled values; those nodes are reported as unresolved rather than negative. Finally, restriction to reviews with English, Portuguese or Spanish full text or numerically extractable English abstracts may under-represent trials published in other languages, notably the Chinese-language trials populating several serum and light-therapy pools [17].

Clinical interpretation

For the ocular surface, the evidence supports amniotic membrane as an adjunct in defined indications with modest, mostly anatomical benefit at very low to low certainty [22,23], and blood-derived drops as a second-line option in refractory dry eye with short-term benefit at low certainty and a favorable safety profile [16,17]. For meibomian gland dysfunction, intense pulsed light offers the largest and best-graded symptom benefit as monotherapy against no treatment, with a considerably smaller add-on effect [36]. For limbal stem cell deficiency, technique selection is better supported than graft-source selection [10], and an authorized product exists for a narrow burn-related indication [42]. For retinal degeneration, optic neuropathy and glaucoma, cell and cell-free therapies belong inside registered clinical trials, and patients should be told explicitly that commercial intraocular cell products have caused irreversible blindness [45] and are not approved for these indications [44].

Conclusion

Across cornea and ocular surface disease, dry eye and meibomian gland dysfunction, limbal stem cell deficiency, retinal degeneration and optic nerve disease, regenerative and physical energy-based therapies have generated a large review-level literature whose certainty is at best moderate and more often low, very low or ungraded. Modest, clinically interpretable benefit is best supported for intense pulsed light in meibomian gland dysfunction, amniotic membrane in specified surface indications and blood-derived eye drops in refractory dry eye. Anatomical success consistently exceeds functional success, statistically significant effects for retinal photobiomodulation fall below the minimal clinically important difference stated in the very review reporting them, and cell therapy for retina and optic nerve is dominated by uncontrolled pre-post pooling. Glaucoma, corneal endothelial disease and ocular extracellular vesicle therapy are genuine synthesis voids. The route to higher certainty is not more publications but better specified products and devices, adequately controlled and masked trials, paired anatomical and functional core outcomes, longer safety follow-up, and separation of authorization status from clinical magnitude. No clinical recommendation in this field can exceed the certainty of the reviews on which it rests.

Declarations

Ethics approval

Not applicable. This perspective article involved no human participants, human material or identifiable human data.

Consent for publication

Not applicable.

Availability of data and materials

All normative instruments, guidance documents, court decisions and published studies discussed are publicly available at the URLs given in the reference list.

Competing interests

The authors denied any relationship with manufacturers of orthobiologic devices, energy-based platforms, cell-processing systems or advanced therapy products, and any role in professional-society regulatory advocacy.

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References

1. Gates M, Gates A, Pieper D, et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. *BMJ*. 2022;378:e070849.
2. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
3. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
4. GRADE Working Group. GRADE Handbook for grading quality of evidence and strength of recommendations. GRADEpro GDT.
5. Pieper D, Antoine SL, Mathes T, Neugebauer EAM, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol*. 2014;67(4):368-75.
6. McCann P, et al. Interventions for dry eye: an overview of systematic reviews. *JAMA Ophthalmol*. 2024;142(1):58-74.
7. Son Y, Lee H, Yu S, Kim HJ, Park J, Woo S, et al. Effects of photobiomodulation on multiple health outcomes: an umbrella review of randomized clinical trials. *Syst Rev*. 2025;14(1):160.
8. Zhao Y, Ma L. Systematic review and meta-analysis on transplantation of ex vivo cultivated limbal epithelial stem cell on amniotic membrane in limbal stem cell deficiency. *Cornea*. 2015;34(5):592-600.
9. Le Q, Chauhan T, Yung M, Tseng CH, Deng SX. Outcomes of limbal stem cell transplant: a meta-analysis. *JAMA Ophthalmol*. 2020;138(6):1-11.
10. Shanbhag SS, Nikpoor N, Rao Donthineni P, Singh V, Chodosh J, Basu S. Autologous limbal stem cell transplantation: a systematic review of clinical outcomes with different surgical techniques. *Br J Ophthalmol*. 2020;104(2):247-53. doi:10.1136/bjophthalmol-2019-314081.

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DOI: [https://doi.org/10.52793/JCPMCR.2026.3\(1\)-37](https://doi.org/10.52793/JCPMCR.2026.3(1)-37)

11. Ganger A, Singh A, Kalaivani M, Gupta N, Vanathi M, Mohanty S, Tandon R. Outcomes of surgical interventions for the treatment of limbal stem cell deficiency. *Indian J Med Res.* 2021;154(1):51-61.
12. Oie Y, Komoto S, Kawasaki R. Systematic review of clinical research on regenerative medicine for the cornea. *Jpn J Ophthalmol.* 2021;65(2):169-83.
13. Chen KY, Chan HC, Chan CM. Efficacy and safety of stem cell therapy for dry eye disease: a systematic review and meta-analysis. *Stem Cell Res Ther.* 2026. Online ahead of print.
14. Zhang J, Wang W, Li C. Stem cell therapy for Sjögren-associated dry eye disease: a systematic review and meta-analysis. *Front Immunol.* 2026;17:1834453.
15. Pan Q, et al. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev.* 2017;CD009327.
16. Franchini M, Cruciani M, Mengoli C, et al. Serum eye drops for the treatment of ocular surface diseases: a systematic review and meta-analysis. *Blood Transfus.* 2019;17(3):200-9.
17. He CZ, Zeng ZJ, Liu JQ, Qiu Q, He Y. Efficacy and safety of autologous serum eye drops for dry eye: a systematic review and meta-analysis. *Front Med.* 2024;11:1430785.
18. Zhang Y, Li N, Ge Z, Li F. Blood component therapy for dry eye disease: a systematic review and network meta-analysis. *Front Med.* 2024;11:1500160.
19. Akowuah PK, Obinwanne CJ, Owusu E, et al. Platelet-rich plasma for treating dry eye disease: a systematic review and meta-analysis. *Cont Lens Anterior Eye.* 2024;47(1):102091.
20. You J, et al. Human platelets and derived products in treating ocular surface diseases: a systematic review. 2020. PMID 33116370.
21. Liu J, Li L, Li X. Effectiveness of cryopreserved amniotic membrane transplantation in corneal ulceration: a meta-analysis. *Cornea.* 2019;38(4):454-62.
22. Ting DSJ, Henein C, Said DG, Dua HS. Amniotic membrane transplantation for infectious keratitis: a systematic review and meta-analysis. *Sci Rep.* 2021;11:13007.
23. Clare G, et al. Amniotic membrane transplantation for acute ocular burns. *Cochrane Database Syst Rev.* 2022;CD009379.
24. Clearfield E, et al. Conjunctival autograft for pterygium. *Cochrane Database Syst Rev.* 2016;CD011349.
25. Taher NO, Alnabih AN, Hersi RM, et al. Amniotic membrane transplantation and conjunctival autograft combined with mitomycin C for the management of primary pterygium: a systematic review and meta-analysis. *Front Med.* 2022;9:981663.
26. Roumeau S, Dutheil F, Sapin V, et al. Efficacy of treatments for neurotrophic keratopathy: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol.* 2022;260(8):2623-37.
27. Molinari ME, Huntermann R, Chavez MP, Lopes SC, Camacho AOC. Corneal neurotization: a systematic review and meta-analysis. *Ann Plast Surg.* 2025;95(6):672-9.
28. Soltani Khaboushan A, Ebadpour N, Johari Moghadam MM, Rezaee Z, Kajbafzadeh AM, Majidi Zolbin M. Cell therapy for retinal degenerative disorders: a systematic review and three-level meta-analysis. *J Transl Med.* 2024;22:227.
29. Li L, Yu Y, Lin S, Hu J. Improvement of best-corrected visual acuity after stem cell transplantation in patients with dry age-related macular degeneration: a systematic review and meta-analysis. *Stem Cell Res Ther.* 2022;13(1):237.
30. He HL, Chen XY, Du MX, Li YH, Wang YH, Jin ZB. Long-term predictive outcomes of stem cell therapy in degenerative retinal disease. *Eye ENT Res.* 2025;2(4):247-63.
31. Chaibakhsh S, Azimi F, Shoaee-Hassani A, et al. Mesenchymal stem cell therapy in optic neuropathy: a systematic review and meta-analysis. *BMC Ophthalmol.* 2024;24:316.
32. Wu D, Liu Y, Zhang X, et al. Stem cell therapy for glaucoma: a systematic review and meta-analysis of preclinical randomized studies. *Front Pharmacol.* 2025;16:1587440.
33. Rassi TNO, Barbosa LM, Pereira S, Novais EA, Penha F, Roisman L, Maia M. Photobiomodulation efficacy in age-related macular degeneration: a systematic review and meta-analysis of randomized clinical trials. *Int J Retina Vitreous.* 2024;10:54.
34. Chen KY, Lee HK, Chan HC, Chan CM. Efficacy and safety of multiwavelength photobiomodulation therapy in age-related macular degeneration: a systematic review and meta-analysis. *Ophthalmol Ther.* 2025;14(5):969-87.
35. Kim JE, et al. Randomized trial of photobiomodulation therapy for center-involved diabetic macular edema with good visual acuity (DRCR Retina Network Protocol AE). *Ophthalmol Retina.* 2021;6(4):298-307.
36. Peira N, Mohammed Ali E, Kenan Modén N, Fjellgren E, Lennmarken C, Hultcrantz M. Intense pulsed light for meibomian gland dysfunction-related dry eye disease: a systematic review and assessment of certainty of evidence. *Acta Ophthalmol.* 2025;103(4):371-9.
37. Chan KE, Lau BSR, Lim BXH, et al. Low-level light therapy and intense pulsed light in meibomian gland dysfunction: a systematic review and meta-analysis. *Cont Lens Anterior Eye.* 2025;48(2):102344.
38. Pucker AD, Yim TW, Rueff E, Ngo W, Tichenor AA, Conto JE. LipiFlow for the treatment of dry eye disease. *Cochrane Database Syst Rev.* 2024;CD015448.

39. Navarro PA, Contreras-Lopez WO, Tello A, Cardenas PL, Vargas MD, Martinez LC, Yepes-Nuñez JJ. Non-invasive electrical stimulation for vision restoration: a systematic review and meta-analysis of randomized controlled trials. *Neuroophthalmology*. 2023;48(2):93-110.
40. Rad IJ, Chapman L, Tupally KR, et al. Ultrasound-mediated ocular drug and gene delivery: a systematic review of preclinical evidence. *Theranostics*. 2023;13(11):3582-638.
41. Tseng AM, Kandoi S, Heur M, Lee SY. Cell free regenerative extracellular vesicle therapy for ocular diseases. *Curr Eye Res*. 2025;50(12):1297-311.
42. European Medicines Agency. Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells): European public assessment report. Amsterdam: European Medicines Agency.
43. United States Food and Drug Administration. De Novo classification request DEN230083, Valeda Light Delivery System: decision summary. 14 December 2023.
44. United States Food and Drug Administration. Consumer alert on regenerative medicine products including stem cells and exosomes. 22 July 2020.
45. Kuriyan AE, Albin TA, Townsend JH, et al. Vision loss after intravitreal injection of autologous "stem cells" for age-related macular degeneration. *N Engl J Med*. 2017;376(11):1047-53.