Electronic Supplementary Material — Online Resource 1

Temporal Response Architecture Following Laser-Based Iris Pigment Modification: An Integrative Mechanistic Review

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Supplementary Methods

Evidence identification was organized around predefined TRA response domains. Direct reports of iris-directed laser exposure were considered alongside relevant experimental evidence on trabecular, aqueous-outflow, inflammatory, and cellular processing pathways. The synthesis preserved the distinction between direct procedural findings and mechanistic or measurement parallels.

Study observations were mapped by source model, exposure, measured outcome, and response domain. Clinically discordant findings were retained. Reported posterior-segment events were distinguished by whether an anterior-segment pressure/perfusion connection was described or a different injury route was implicated.

Review articles were used primarily for background, terminology, and citation chaining rather than as primary evidence for mechanistic conclusions.

Additional targeted literature verification examined chemokine-mediated outflow signaling, ECM regulation, CD5L/AIM-related cellular clearance, objective anterior-chamber flare measurement, corneal endothelial morphometry, and iris/angle structural imaging.

Supplementary Table S1. PubMed Search Strategy

Database: PubMed. Coverage: database inception through 30 September 2026.

Search A — Direct iris-directed laser evidence

("laser iris depigmentation"[Title/Abstract] OR "iris depigmentation"[Title/Abstract] OR "cosmetic iridoplasty"[Title/Abstract] OR "iris color change"[Title/Abstract] OR "iris colour change"[Title/Abstract] OR "iris pigment modification"[Title/Abstract] OR "iris pigmentation"[Title/Abstract]) AND (laser*[Title/Abstract] OR Nd:YAG[Title/Abstract] OR "selective laser trabeculoplasty"[Title/Abstract] OR SLT[Title/Abstract])

Purpose: To identify human clinical reports and direct preclinical studies involving intentional laser modification of iris pigmentation.

Search B — Pigment–trabecular and aqueous-outflow interaction

(pigment*[Title/Abstract] OR "pigment dispersion"[Title/Abstract] OR "pigmentary glaucoma"[Title/Abstract]) AND ("trabecular meshwork"[Title/Abstract] OR "aqueous outflow"[Title/Abstract] OR "outflow facility"[Title/Abstract]) AND (phagocyt*[Title/Abstract] OR migration[Title/Abstract] OR contract*[Title/Abstract] OR cytoskeleton[Title/Abstract] OR "intraocular pressure"[Title/Abstract])

Purpose: To identify evidence concerning the effects of pigment exposure on trabecular cellular behavior and conventional aqueous outflow.

Search C — Laser-associated inflammatory and remodeling responses

("selective laser trabeculoplasty"[Title/Abstract] OR "laser trabeculoplasty"[Title/Abstract] OR SLT[Title/Abstract]) AND (inflammation[Title/Abstract] OR inflammatory[Title/Abstract] OR cytokine*[Title/Abstract] OR "interleukin-1"[Title/Abstract] OR "IL-1"[Title/Abstract] OR "tumor necrosis factor"[Title/Abstract] OR TNF[Title/Abstract] OR "anterior chamber"[Title/Abstract])

Purpose: To identify mechanistically relevant inflammatory, cellular, and matrix-remodeling responses following anterior-segment laser exposure.

Search D — Cellular processing, macrophages, and clearance

("trabecular meshwork"[Title/Abstract] OR "aqueous outflow"[Title/Abstract]) AND (macrophage*[Title/Abstract] OR monocyte*[Title/Abstract] OR phagocyt*[Title/Abstract] OR clearance[Title/Abstract] OR debris[Title/Abstract]) AND (laser[Title/Abstract] OR pigment*[Title/Abstract] OR iridotomy[Title/Abstract])

Purpose: To identify mechanistic evidence concerning particulate processing, phagocytosis, monocyte/macrophage recruitment, and recovery of conventional aqueous outflow.

Supplementary identification: Reference lists of eligible primary studies and relevant reviews were manually screened for additional publications addressing the predefined response domains.

Supplementary targeted evidence domains

Focused source verification and citation tracking addressed MCP-1/CCL2–CCR2, MMPs, TGF-β2, ECM stiffness, CD5L/AIM/CD36, laser flare photometry, specular microscopy, and anterior-segment OCT. These sources were incorporated to inform mechanistic links and prospective measurement design, rather than to create a pooled comparative outcome estimate.

Supplementary Table S2. Study-Level Evidence Map

Study, model and exposure	Observation and TRA response domain
Yildirim et al., 2016 [Category B] Rabbit iris Frequency-doubled Nd:YAG iris exposure	Pigment reduction with transient AC cells/flare and no significant IOP change in the reported protocol TRA domain: Target interaction; inflammatory response
Basoglu & Celik, 2018 [Category A] Human; sectoral heterochromia 532-nm SLT-platform iris treatment	Human iris-directed treatment using a gradual zonal/staged approach TRA domain: Target interaction
Grimaldos Ruiz, 2021 [Category A] Human; 1176 eyes Protocol-specific 532-nm Q-switched Nd:YAG	Cosmetic pigment change; reported longitudinal IOP behavior and inflammatory findings in a subset TRA domain: Target interaction; IOP response
Ning et al., 2022 [Category A] Human case Cosmetic iris-lightening laser	Secondary pigment dispersion following treatment TRA domain: Pigment redistribution
Ong et al., 2023 [Category A] Human case Cosmetic iris laser	Refractory secondary pigmentary glaucoma TRA domain: Pigment redistribution; IOP response
Swampillai et al., 2023 [Category A] Human case Cosmetic iris color-change laser	Secondary pigmentary glaucoma TRA domain: Pigment redistribution; IOP response
Liu et al., 2023 [Category A] Human case Multiple cosmetic iris-laser sessions	Severe pigmentary glaucoma with marked bilateral IOP elevation, free-floating pigment and PAMM reported after multiple sessions TRA domain: Pigment redistribution; IOP response; associated retinal endpoint

Study, model and exposure	Observation and TRA response domain
Jaber et al., 2026 [Category A] Human cases Procedures described as LID	Marked IOP elevation following cosmetic iris laser treatment TRA domain: IOP response
Matsumoto & Johnson, 1997 [Category C] Human trabecular tissue Phagocytic assessment	Active phagocytic capacity of trabecular meshwork cells TRA domain: Trabecular biology
Epstein et al., 1986 [Category C] Living monkey model Experimental pigment infusion	Acute reduction in outflow facility followed by recovery and particulate uptake TRA domain: Outflow disturbance; recovery
Dang et al., 2018 [Category C] Experimental pigmentary-glaucoma model Pigment exposure	IOP elevation preceding later reduction in trabecular phagocytic activity TRA domain: Outflow response; temporal relationship
Wang et al., 2019 [Category C] Trabecular-meshwork cellular model Pigment exposure	Reduced migration and phagocytosis with cytoskeletal and contractile changes TRA domain: Pigment–trabecular interaction
De Keyser et al., 2017 [Category C] Human SLT Selective laser trabeculoplasty	Early anterior-chamber cellular response and transient IOP changes TRA domain: Inflammatory response
Bradley et al., 2000 [Category C] Laser-trabeculoplasty model Laser exposure	Early IL-1β/TNF-α signaling and matrix-remodeling responses TRA domain: Inflammatory signaling
Alvarado et al., 2010 [Category C] SLT-related experimental/human outflow work Selective laser trabeculoplasty	Monocyte/macrophage recruitment and modulation of conventional outflow TRA domain: Cellular processing; recovery
Nemoto et al., 2023 [Category C] Mouse laser-iridotomy model and TM cells Laser iridotomy	Pigment/debris accumulation, phagocytic processing, and association between clearance and IOP recovery TRA domain: Cellular processing; recovery
Tsuboi et al., 2012 [Category C] Perfused porcine eyes; Schlemm-canal endothelial cells Experimental MCP-1/CCL2–CCR2 exposure	MCP-1 modified conventional outflow facility and endothelial-barrier properties TRA domain: Chemokine/outflow interaction
De Groef et al., 2013 [Category C] Trabecular-meshwork literature MMP-related outflow regulation	MMPs contribute to ECM remodeling and conventional-outflow regulation TRA domain: ECM remodeling
Keller & Peters, 2022 [Category C] Trabecular-meshwork ECM review Glaucoma/outflow biology	Summarizes cellular–matrix regulation of outflow resistance TRA domain: ECM/outflow interaction
Li et al., 2022 [Category C] Human trabecular-cell model TGF-β2 and controlled matrix stiffness	TGF-β2/ECM stiffness modulate YAP/TAZ and contractile responses TRA domain: ECM and mechanotransduction
Tugal-Tutkun & Herbort, 2010; Swampillai et al., 2024 [Category C] Clinical laser-flare photometry literature	Objective quantification of aqueous flare during anterior-segment inflammation and glaucoma procedures TRA domain: Inflammatory assessment
Chaurasia & Vanathi, 2021 [Category C] Clinical specular-microscopy review	ECD, cell-size variability and endothelial morphology support quantitative corneal assessment TRA domain: Structural observation
Triolo et al., 2021 [Category C] Clinical AS-OCT review Iridocorneal-angle imaging	AS-OCT measures angle opening and iris architecture in relevant clinical contexts TRA domain: Structural observation

Direct human, preclinical iris, and mechanistically related studies mapped to TRA response domains.

Evidence categories: A — direct human procedural evidence; B — direct preclinical iris evidence; C — mechanistically analogous evidence; D — integrative inference. Categories describe proximity to the clinical question.

Molecular and imaging studies are categorized as related biological or measurement evidence. They do not represent direct measurements after the iris-laser protocols reviewed here.

Supplementary Table S3. Contextual and Related Literature

Source and classification	Contribution to the review
Imesch et al., 1997 Background biology	Iris morphology and pigmentation
Sturm & Larsson, 2009 Background biology	Iris pigmentation and phenotype
D'Oria et al., 2022 Contextual review	Background on eye-color modification techniques; citation chaining
D'Oria & Alio, 2025 Contextual review	Updated procedural context and citation chaining
Ferrari, 2021 Scope boundary	Demonstrates reported structural iris injury
Flores-Márquez et al., 2023 Scope boundary	Demonstrates posterior-segment laser-associated injury
Wisdorf et al., 2025 Scope boundary	Demonstrates lamellar macular-hole/epiretinal changes
Mete, L-SAFE, 2026 Related conceptual framework	Clinical state and safety-oriented trajectory interpretation
Mete, L-OAT, 2026 Related conceptual framework	Multimodal measurement and iris phenotyping
Tugal-Tutkun & Herbort, 2010; Swampillai et al., 2024 Clinical measurement context	Laser flare photometry for quantitative anterior-chamber activity
Chaurasia & Vanathi, 2021 Corneal measurement context	Specular endothelial cell density and morphometry
Triolo et al., 2021 Anterior-segment imaging context	AS-OCT angle and iris structural parameters

Sources contributing background biology, procedural context, and related conceptual perspectives.

Related frameworks: L-SAFE addresses clinical safety staging; L-OAT addresses iris architectural phenotyping; TRA organizes temporal anterior-segment response.