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# 3D BIOPRINTING OF OCULAR TISSUES: CURRENT PROGRESS, CHALLENGES AND FUTURE PERSPECTIVES IN REGENERATIVE OPHTHALMOLOGY

## *BIOIMPRESSÃO 3D DE TECIDOS OCULARES: PROGRESSOS ATUAIS, DESAFIOS E PERSPETIVAS FUTURAS NA OFTALMOLOGIA REGENERATIVA*

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**Abstract**
Background: Eye tissue disorders affect millions globally, with limited treatment options due to tissue donor shortages and transplant complications. Three-dimensional (3D) bioprinting technology has emerged as a promising approach for fabricating functional ocular tissues for both research and therapeutic applications. Objective: This narrative review evaluates the current state of 3D bioprinting technologies for ocular tissue engineering, focusing on cornea, retina, conjunctiva, and iris. We critically assess printing methodologies, bioink formulations, cellular components, and translational challenges. Methods: A comprehensive narrative review of the literature was conducted across PubMed, Scopus, Web of

***Resumo***
*Contexto: As doenças dos tecidos oculares afetam milhões de pessoas em todo o mundo, com opções de tratamento limitadas devido à escassez de dadores de tecidos e às complicações associadas aos transplantes. A tecnologia de bioimpressão tridimensional (3D) surgiu como uma abordagem promissora para a fabricação de tecidos oculares funcionais, tanto para fins de investigação como para aplicações terapêuticas. Objetivo: Esta revisão narrativa avalia o estado atual das tecnologias de bioimpressão 3D para a engenharia de tecidos oculares, com foco na córnea, retina, conjuntiva e íris. Analisamos criticamente as metodologias de impressão, as formulações de bio-tintas, os componentes celulares e os desafios*

Science, and Google Scholar databases for publications from 2018-2025. Articles were selected based on relevance to 3D bioprinting of biological ocular tissues with cellular components. Of 113 initially identified articles, 49 met inclusion criteria after quality assessment. Results: Current bioprinting approaches employ extrusion-based, inkjet, and laser-assisted techniques. Key limitations include achieving appropriate mechanical properties, vascularization, and regulatory compliance. Conclusion: While 3D bioprinting of ocular tissues has advanced substantially, significant technical and biological barriers must be overcome before clinical translation. Standardization of bioink formulations, improved printing resolution, and long-term functionality studies are critical next steps.

**Keywords:** 3D Bioprinting. Tissue Engineering. Cornea. Retina. Iris. Retina. Bioink. Regenerative Ophthalmology.

*translacionais. Métodos: Foi realizada uma revisão narrativa abrangente da literatura nas bases de dados PubMed, Scopus, Web of Science e Google Scholar, abrangendo publicações entre 2018 e 2025. Os artigos foram selecionados com base na relevância para a bioimpressão 3D de tecidos oculares biológicos com componentes celulares. Dos 113 artigos inicialmente identificados, 49 cumpriram os critérios de inclusão após a avaliação da qualidade. Resultados: As abordagens atuais de bioimpressão empregam técnicas baseadas em extrusão, jato de tinta e assistidas por laser. As principais limitações incluem a obtenção de propriedades mecânicas adequadas, a vascularização e a conformidade regulamentar. Conclusão: Embora a bioimpressão 3D de tecidos oculares tenha avançado substancialmente, é necessário superar importantes obstáculos técnicos e biológicos antes da sua aplicação clínica. A padronização das formulações das bio-tintas, o aumento da resolução de impressão e os estudos de funcionalidade a longo prazo constituem os próximos passos fundamentais.*

***Palavras-chave:*** *Bioimpressão 3D. Engenharia de Tecidos. Córnea. Retina. Íris. Bio-Tinta. Oftalmologia Regenerativa.*

## 1 BACKGROUND

Additive manufacturing, also known as 3D printing, involves building objects by sequentially depositing material in successive layers to create tailored items. Numerous additive manufacturing methods exist, each varying in their material requirements, expense, benefits, and limitations. The medical field, particularly ophthalmology, is among the many sectors increasingly adopting and benefiting from this innovative technology. The potential uses of additive manufacturing in ophthalmology are extensive and well-documented in scientific publications. These include fabricated artificial eyes, socket implants, teaching models depicting eye anatomy, and tools for pre-operative preparation and medical instruction. Additionally, this technology has enabled the development of novel medication administration systems that provide improved therapeutic approaches for specific eye conditions. Cutting-edge studies in three-

dimensional bioprinting of living ocular tissues such as the cornea, retina, and conjunctival membrane, offer promising avenues for future restorative eye treatments. Continued advancement in printing technologies is necessary to discover new possibilities and identify suitable fabrication materials. However, 3D printing represents a powerful tool with the potential to improve eye health (Larochelle, R.D., Mann, S.E. & Ifantides, C., 2021).

Throughout the last ten years, additive manufacturing has shown diverse uses within the field of eye care. This technology allows for accurate reproduction of skeletal structures to aid in operative planning and individualized implants for reconstructive eye procedures. Its most compelling potential may be found in cellular-level tissue fabrication, which could help meet the unaddressed challenges in treating disorders affecting the cornea and retina. Initial prototypes developed for this application show potential for generating laboratory-grown tissues that, although not yet suitable for surgical implantation, can function as valuable tools for laboratory-based research into conditions and treatments. Though this innovation could help decrease the reliance on animal testing, the groundbreaking concept of fabricating tissues and ultimately whole organs presents moral and governance concerns that require careful consideration (Ruiz-Alonso S. *et al*., 2021; Gilbert, F. *et al*., 2018).

The strengths of additive manufacturing (AM) including its ability to create personalized products, manufacture intricate geometries, reduce production timelines, and handle small-batch manufacturing, make it particularly appropriate for medical implants and anatomical replicas. This technology facilitates the construction of tangible objects from three-dimensional computer-aided design files using a successive layering approach. Additive manufacturing utilizes imaging data from MRI scans, CT scans, and three-dimensional scanning technology, which is then transformed into stereolithography (STL) file format for production purposes (Pugalendhi, A., Ranganathan, R., 2021).

Additive manufacturing enables accurate replication of anatomical features and finds application across numerous medical fields. The most promising application may be cellular-level tissue fabrication, which could address the significant global unmet needs in conditions affecting the cornea and retina (Larochelle, R.D., Mann, S.E. & Ifantides, C., 2021). Creating bioprinted tissues is a complex undertaking that encompasses multiple careful steps. This process includes creating printing directives,

selecting suitable biological materials and cell types, managing the bioprinting equipment, executing the fabrication, and performing quality assessment

**Aim:** This paper examines the evolution of additive manufacturing technology within eye care and its prospective uses. Several examples of both working models and design concepts created through 3D printing are showcased to demonstrate the potential of this technology. The study explores how additive manufacturing can be effectively utilized in eye care for creating novel products, as well as for advancing treatment quality and enhancing surgical proficiency across different ocular conditions.

## 2 MATERIAL AND METHODS

### 2.1 Design

A comprehensive narrative review of the literature on 3D bioprinting applications in ocular tissue engineering was conducted. Multiple electronic databases were searched, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The search focused on publications from 2018 to 2025 to capture recent advances in this rapidly evolving field, though seminal earlier works were also included when relevant. Search terms included combinations of: 3D bioprinting, three-dimensional bioprinting, additive biomanufacturing, ocular, eye, ophthalmic, cornea, retina, conjunctiva, iris, tissue engineering, regenerative medicine, bioink, hydrogel, scaffold, stem cells.

Initial searches were conducted using primary term combinations. Additional relevant articles were identified through reference lists of key publications, citations of landmark studies in the field, review articles on ocular tissue engineering, recent conference proceedings and research updates. Articles were selected based on relevance to 3D bioprinting of biological ocular tissues with cellular components.

### 2.2 Criteria

**Inclusion criteria:** Studies on bioprinting of cornea, retina, conjunctiva, or iris tissues; Research describing bioink formulations with biological components; Articles detailing cellular integration in bioprinted constructs; Both in vitro and in vivo

experimental studies; Review articles providing comprehensive technical or clinical context, and Publications in English with accessible full text.

**Exclusion criteria:** Studies solely on 3D printing of acellular prosthetic devices; Educational models without biological components; General ophthalmology applications not involving tissue bioprinting; Contact lenses and intraocular lenses without cellular components; Surgical planning tools and anatomical models, and Publications without sufficient methodological detail.

### 2.3 Data collection

From each included publication, the following information was extracted and organized: Bioprinting technology and methodology (extrusion-based, inkjet, laser-assisted, etc.); Bioink composition, including natural and synthetic materials; Cell types, sources, and densities used; Target ocular tissue and specific anatomical features replicated; Key outcome measures (cell viability, optical transparency, mechanical properties); In vitro characterization results; In vivo implantation studies (where applicable); Technical challenges and limitations identified by authors, and Proposed clinical applications.

### 2.4 Narrative synthesis approach

Due to substantial heterogeneity in bioprinting methodologies, bioink formulations, cell types, and outcome measures across studies, a narrative synthesis approach was employed. Data were organized by target tissue type (cornea, retina, conjunctiva, iris) to facilitate comparison of approaches within each anatomical category. Within each tissue section, studies were analyzed for: Common technological approaches and variations; Evolution of bioink development; Progress in achieving tissue-specific functional properties; Recurring technical challenges; Translational potential. Cross-cutting themes were identified regarding bioprinting technologies, biomaterial selection, cellular sources, and barriers to clinical translation.

### 2.5 Scope and limitation

This review focuses specifically on 3D bioprinting for ocular tissue regeneration. Related topics such as 3D printing of acellular ocular prostheses, educational models, surgical guides, and non-biological ophthalmic devices are beyond the scope of this focused review, though brief mention is made where contextually relevant.

The rapidly evolving nature of bioprinting technology means that methodologies and materials are continuously advancing. This review captures the state of the field through 2025 but acknowledges that ongoing research may yield significant new developments.

Total 49 publications directly addressing ocular tissue bioprinting form the core of this review, supplemented by foundational and contextual references on bioprinting technologies, biomaterials, and ophthalmology.

### 2.6 Ethical considerations

This narrative review is based on previous published studies and does not contain primary data collection of human or animal studies conducted by the authors.

## 3 RESULTS AND DISCUSSION

This section presents the findings regarding a comparison of 3D bioprinting technologies for ophthalmological applications, key requirements for ophthalmic biomaterials based on tissue type, and in vivo studies - results from the bioprinting of ophthalmic tissues, presented respectively in Table 1, Table 2, and Table 3, and a subsequent analysis of the four ocular structures under consideration: the cornea, iris, retina and conjunctiva.

**Table 1**

*Comparison of 3D Bioprinting Technologies for Ocular Tissue Applications*

| Technology | Mechanism | Resolution | Cell Viability | Viscosity Range | Speed | Cost | Ocular Applications | Advantages | Limitations |
|---|---|---|---|---|---|---|---|---|---|
| **Extrusion-based** | Pneumatic or mechanical dispensing through nozzle | 100-500 μm | 40-86% | High (30-$6\times10^7$ mPa·s) | Slow-Medium (10-50 μL/min) | Low-Medium | Corneal stroma, conjunctiva, iris | High cell density; Wide material compatibility; Continuous deposition; Cost-effective | Lower resolution; Shear stress on cells; Limited multi-material capability |
| **Inkjet** | Thermal or piezoelectric droplet ejection | 50-300 μm | 85-95% | Low (3.5-12 mPa·s) | Fast (1-10,000 drops/s) | Low | Retinal layers, corneal epithelium | High cell viability; High speed; Fine resolution; Multi-nozzle capability | Viscosity limitations; Nozzle clogging; Structural instability |
| **Laser-assisted** | Laser-induced forward transfer | 10-100 μm | 95-99% | Wide range (1-300 mPa·s) | Medium | High | Precise retinal structures, corneal endothelium | Highest resolution; Excellent cell viability; No nozzle contact; Multi-material | Expensive equipment; Complex setup; Limited scalability; Slow for large constructs |
| **Stereolithography (SLA)** | UV/visible light polymerization | 10-50 μm | 70-90% | Low-Medium (photopolymers) | Fast (entire layer) | Medium-High | Corneal scaffolds, customized iris | High resolution; Smooth surfaces; Complex geometries; Fast printing | Limited bioink options; Photoinitiator toxicity; Post-processing required |
| **Digital Light Processing (DLP)** | Layerwise photopolymerization | 25-100 μm | 80-95% | Low-Medium | Very Fast | Medium | Corneal constructs, rapid prototyping | Extremely fast; High throughput; Good resolution; Layer uniformity | Material constraints; Light penetration issues; Cytotoxicity concerns |

**Table 2**

*Critical Requirements for Ocular Bioinks by Tissue Type*

| Tissue | Optical Requirements | Mechanical Properties | Biological Requirements | Degradation Profile | Key Challenges |
|---|---|---|---|---|---|
| **Corneal Epithelium** | High transparency (>90%) | Flexible, thin (50-70 μm) | Stratification capability; Barrier function; Self-renewal | Rapid (1-2 weeks for remodeling) | Achieving stratification; Tear film interaction; Adhesion to stroma |
| **Corneal Stroma** | Exceptional transparency (>95%) | Tensile strength 3-5 MPa; Elastic modulus 0.5-2 MPa | Organized collagen; Keratocyte phenotype; Minimal scarring | Slow (months to years) | Collagen organization; Optical clarity; Mechanical strength; Smooth surfaces |
| **Corneal Endothelium** | High transparency | Pump function maintenance | Tight junctions; Hexagonal morphology; $Na^+/K^+$-ATPase expression | Permanent or very slow | Cell proliferation; Maintaining phenotype; Attachment; Pump function |
| **Neural Retina** | Moderate (light must penetrate) | Soft (E ~1-10 kPa); Thin (~200-300 μm) | 10 distinct layers; Photoreceptors; Functional synapses; Support cells | Variable by layer | Layer organization; Functional connectivity; Vascularization; Innervation |
| **RPE** | Pigmented (light absorption) | Flexible, thin monolayer | Tight junctions; Pigmentation; Phagocytic function; Growth factor secretion | Long-term stable | Maintaining pigmentation; Polarized function; Attachment to Bruch's |
| **Conjunctiva** | Moderate transparency | Flexible, soft | Mucin secretion (goblet cells); Stratified epithelium; Vascularization | Rapid epithelial turnover | Goblet cell integration; Vascularization; Integration with host |
| **Iris** | Variable (colored) | Flexible, contractile (ideally) | Pigmentation; Structural stability; Biocompatible | Long-term stable | Color matching; Size accuracy; Surgical placement; Pupil mimic (future) |

**Table 3**

*In Vivo Studies - Ocular Tissue Bioprinting Outcomes*

| Study | Tissue | Animal Model | Bioprinting Method | Bioink | Key Outcomes | Duration | Limitations |
|---|---|---|---|---|---|---|---|
| **Sorkio 2018** | Cornea (epithelium & stroma) | Rabbit | Laser-assisted | Collagen I, HA, laminin, fibrin + LSCs & ADSCs | Maintained transparency; Epithelialization observed; No rejection | 28 days | Small constructs; Limited mechanical testing |
| **Isaacson 2018** | Corneal stroma | Ex vivo porcine corneas | Extrusion | Decellularized corneal ECM + keratocytes | Integration with host; Cell alignment; ECM production | N/A (ex vivo) | Not full thickness; No in vivo validation |
| **Kim 2019** | Corneal stroma | In vitro only | Extrusion with shear | GelMA + keratocytes | Collagen alignment; Improved mechanical properties | N/A | No animal studies; Optical properties not fully tested |
| **Dehghani 2018** | Conjunctiva | Rabbit | Extrusion | Gelatin-elastin-HA | Epithelialization; Minimal inflammation; Good biocompatibility | 28 days | No goblet cells; Limited functional assessment |
| **Zhong 2021** | Conjunctiva micro-constructs | Rabbit (subconjunctival) | DLP bioprinting | Hydrogel + CjSCs | Stem cell survival; Tissue integration; Minimal fibrosis | 14 days | Small scale; Not full conjunctival replacement |
| **Wang 2018** | Retina | In vitro only | Inkjet | GelMA + retinal cells | Multi-layer formation; Cell viability >85% | N/A | No animal implantation; No functional testing |

## 3.1 Cornea

Various techniques for three-dimensionally printing corneas have employed a structural framework that can be populated with cells or collagen. While incorporating corneal stem cells contributes to developing a more biologically authentic cornea, this approach may restrict the practicality of the technology in areas facing challenges like expense and availability (Ludwig, P.E. *et al.*, 2018). Typically, a 3D image of the cornea is created by ultrasound or optical coherence tomography (OCT), although a Scheimpflug

camera can also be used (Ludwig, P.E. *et al*., 2018; Isaacson, A. *et al*., 2018). The optimal printing medium, known as "bioink," should possess sufficient mechanical durability to endure the forces generated during dispensing through the printing head, preserve appropriate optical clarity, sustain cellular survival, permit the passage of nutrients and oxygen, accommodate surgical suturing, and be capable of biological decomposition (Zhang, B. *et al*., 2019; Khalili, M. *et al*., 2020).

Achieving proper optical properties represents one of the most significant obstacles, since the procedure demands sufficiently fine detail to produce a smooth surface while transforming flat printed layers into a curved configuration (Khalili, M. *et al*., 2020). As multiple researchers have confirmed, achieving these criteria has proven possible. However, the primary difficulty continues to be creating a multi-tiered structure that can be reliably reproduced (Ruiz-Alonso S, *et al*., 2021; Isaacson, A. *et al*., 2018; Duarte Campos, D.F. *et al*., 2019; Kutlehria, S. *et al*. 2020; Kim, H. *et al*., 2019; Kim, H. *et al*. 2019; Zhang, B. *et al*. 2019).

In the layered corneal model described by Sorkio *et al*., limbal stem cells and fat tissue-derived stem cells were used to create the epithelial layer and stromal layer separately. The epithelial bioink formulation incorporates hyaluronic acid and laminin, whereas the stromal bioink composition includes collagen type I, thrombin, and plasma components (Sorkio, A. *et al*., 2018).

Corneal bioprinting has emerged as one of the most technically mature applications within ocular tissue engineering, driven by advances in bioink formulation, printing precision, and cell-compatible crosslinking strategies. Recent studies demonstrate that extrusion- and laser-assisted bioprinting can generate stromal-like constructs with high cell viability, controlled geometry, and progressive extracellular matrix deposition during post-printing culture, highlighting the feasibility of producing anatomically relevant corneal substitutes in vitro (Orash Mahmoud Salehi, A., *et al*., 2022; Gómez-Fernández, H., 2024). Furthermore, the increasing convergence of methodologies across research groups suggests a transition from exploratory proof-of-concept approaches toward early technological consolidation.

Despite these developments, achieving native-level optical performance remains a central translational challenge. Bioprinted corneal constructs typically demonstrate transparency values significantly below those of native tissue, even after prolonged

maturation periods. For instance, improvements in light transmission have been observed following extended stromal cell culture due to matrix remodeling and fibrillar reorganization; however, optical properties often remain inferior to physiological benchmarks (Hernández, J. *et al*., 2025). These limitations reflect persistent difficulties in reproducing the nanoscale lamellar architecture and precise collagen fibril spacing responsible for destructive interference of scattered light in the human cornea. As a result, although partial restoration of vision may be clinically meaningful in severely impaired patients, the optical deficit continues to represent a key barrier to regulatory approval for broader indications.

Another unresolved issue is the successful biofabrication of a functional corneal endothelium. Recent reviews underscore that endothelial dysfunction continues to be a significant global contributor to corneal blindness, and that existing engineering approaches are hindered by the restricted proliferative potential of primary endothelial cells and difficulties in sustaining pump function post-transplantation (Wu, K.Y., Belaiche, M. *et al*., 2024). While biomaterial-based scaffolds and stem-cell-derived endothelial-like cells show promise, stable integration of endothelial layers within fully bioprinted corneal constructs has yet to be demonstrated. Consequently, hybrid clinical strategies combining bioprinted stromal substitutes with established endothelial keratoplasty techniques may represent an interim translational pathway, albeit at the cost of increased surgical complexity and healthcare expenditure.

Biomechanical fidelity represents a further critical requirement for long-term implantation. Although recent composite hydrogel systems and dual-crosslinking approaches have improved mechanical stability and printability, reported constructs still exhibit degradation dynamics and stiffness profiles that differ substantially from native corneal tissue (Chaudhary, P. *et al*., 2025). Such discrepancies may affect resistance to intraocular pressure fluctuations and cumulative mechanical fatigue over decades of physiological use. Furthermore, augmenting crosslinking density to improve tensile strength may negatively impact nutrient diffusion, cell migration, and matrix remodeling, highlighting the necessity for multiparametric optimization of material composition and maturation protocols.

Importantly, current preclinical validation remains limited in both duration and physiological complexity. Most studies report short-term outcomes focusing on cell

viability, transparency, and integration in small animal models, whereas long-term phenomena such as stromal haze formation, immune-mediated remodeling, and progressive biomechanical weakening remain insufficiently characterized. This translational gap is further compounded by regulatory considerations, including scalability, reproducibility, and manufacturing standardization, which are increasingly recognized as decisive factors in the clinical adoption of bioprinted tissues (Wu, K.Y. *et al*., 2024).

Taken together, the contemporary evidence suggests that corneal bioprinting is transitioning from early experimental feasibility toward pre-translational optimization. Continued progress in hierarchical matrix organization, endothelial integration, and long-term functional validation will be essential to enable first-in-human trials. Based on the current pace of technological evolution and regulatory pathway requirements, clinical translation of fully bioprinted corneal grafts is likely to occur in staged phases, with initial applications potentially targeting high-risk or multiply graft-failed patients before broader therapeutic adoption.

### 3.2 Iris

A key obstacle in managing aniridia is the current scarcity of commercially obtainable, aesthetically satisfactory artificial iris devices. Given that most aniridia cases affect only one eye, a crucial characteristic for an ideal iris prosthesis is achieving color coordination with the unaffected eye. Furthermore, utilizing pliable, biologically compatible materials like silicone would allow for smaller surgical incisions during placement, thereby reducing the likelihood of complications (Mayer, C.S. *et al*., 2018).

A streamlined computer-aided iris model was developed to replicate the intricate crypt features while preserving the feasibility of silicone 3D printing and maintaining appropriate resolution for surgical implantation. Research has demonstrated that up to 35 μL of colorants can be incorporated into clear silicone without compromising the material's printing characteristics. The streamlined iris model consists of a 12.8 mm foundation disk featuring a 3.5 mm diameter central opening representing the pupillary aperture. The printed prototype requires proper dimensions, biological compatibility, and pliability for surgical implantation. Silicone was selected as it is the substance utilized in

the sole FDA-cleared implantable iris product currently available and is compatible with extrusion-based printing. Creating an aesthetically harmonious prosthetic device represents a crucial milestone in developing such implants, with the goal of improving the wellbeing of individuals affected by aniridia (Prager, A.J. *et al*., 2023).

Compared with corneal biofabrication, iris bioprinting remains at a substantially earlier stage of technological and translational development. Contemporary research in anterior segment reconstruction has focused predominantly on prosthetic iris devices and hybrid surgical approaches rather than on the generation of fully cellular, functional biofabricated tissues. This divergence reflects both biological complexity and clinical prioritization.

From a clinical standpoint, artificial iris implantation has emerged as an established reconstructive strategy for patients with congenital or acquired iris defects. Recent case series and retrospective analyses indicate that the implantation of customized prosthetic iris diaphragms can reduce photophobia, improve cosmetic outcomes, and, in some cases, stabilize visual function with acceptable safety profiles in carefully selected patients (Stobiecka, R., 2024). Similarly, studies evaluating endocapsular artificial iris implantation report generally stable postoperative visual acuity and intraocular pressure over follow-up periods extending beyond one year, suggesting that current prosthetic solutions already provide meaningful functional benefit for many patients with aniridia or traumatic iris loss (Crawford, A. Z. *et al*., 2022). However, these interventions are not devoid of complications, including endothelial damage, secondary glaucoma, or implant decentration, highlighting the persistent need for improved reconstructive strategies (Watanabe, N., & Kobayakawa, S. (2023); Shihadeh, W. *et al*. 2024).

In contrast, true cellular iris bioprinting remains largely conceptual. The iris is a dynamic neuromuscular tissue that needs smooth muscle cells, stromal fibroblasts, vascular networks, and autonomic innervation to work properly. The corneal stroma, on the other hand, is mostly structural. Recent reviews in ophthalmic biomaterials emphasize that most tissue engineering efforts targeting the iris continue to rely on acellular scaffolds or cosmetic prostheses, rather than on biofabrication approaches capable of restoring active light-responsive contraction (Wu, K.Y. *et al*., 2024). This gap underscores the difficulty of replicating not only the anatomical morphology but also the complex functional architecture necessary for pupillary reflexes.

Moreover, the relatively low prevalence of conditions such as congenital aniridia may influence translational prioritization. While artificial iris devices are increasingly refined and clinically accessible, the development of fully bioprinted alternatives faces significant economic and regulatory challenges associated with limited patient populations and uncertain reimbursement pathways. In health-technology adoption frameworks, such factors often delay the clinical translation of highly complex regenerative solutions, particularly when existing therapies already provide partial functional restoration (Gómez-Fernández, H. *et al*., 2024).

Another key challenge lies in the requirement for neuromuscular integration. Unlike static tissue replacements, a bioprinted iris would need to establish long-term electrical and biochemical communication with host autonomic pathways to achieve adaptive pupil dynamics. This kind of integration has not yet been shown, even in advanced bioengineered smooth muscle constructs in other organ systems. Consequently, current expectations for functional iris bioprinting remain speculative, with translational timelines likely extending far beyond those anticipated for structurally simpler ocular tissues.

Taken together, these considerations suggest that while iris biofabrication represents an intellectually compelling frontier in ocular regenerative medicine, its near-term clinical impact is likely to remain limited. Incremental innovation in prosthetic devices, minimally invasive implantation techniques, and hybrid regenerative approaches may offer more realistic pathways for improving patient outcomes over the coming decade. Fully cellular iris bioprinting capable of restoring physiological pupillary control will require breakthroughs in neuromuscular tissue engineering, vascularization strategies, and host integration, positioning it as a long-term rather than imminent translational objective.

### 3.3 Retina

The retina possesses remarkable complexity in both its architecture and operation. Injury to retinal cells can trigger various ocular conditions, resulting in progressive visual decline. Harm to any retinal layer can cause photoreceptor deterioration and ensuing degeneration of the retinal pigment epithelium (Lin, N., Gagnon, M., & Wu, K. Y., 2024).

Visual recovery depends on complete operational capacity of every retinal layer, requiring the regeneration of damaged segments (Tan, G. *et al*, 2022).

Research teams have conducted various studies on 3D printing of retinal tissue (Shi, P. *et al*., 2018; Wang, P. *et al*., 2018; Masaeli, E. *et al*., 2020). They are producing favorable outcomes, yet notwithstanding these encouraging findings, additional investigation will be required to accomplish the objective of bioprinting complete and operational retinal tissue suitable for transplantation in individuals with retinal degenerative conditions (Lin, N., Gagnon, M., & Wu, K.Y., 2024). Three-dimensional retinal imaging can more accurately model tissue response to therapeutic agents (Masaeli, E. *et al*., 2021).

In contrast to anterior segment biofabrication, retinal bioprinting remains predominantly at the proof-of-concept stage, reflecting the exceptional structural and functional complexity of neural tissue engineering. While recent advances in bioink design, printing resolution, and stem-cell differentiation protocols have enabled the generation of multilayered retinal-like constructs in vitro, these systems still represent simplified approximations of the native retina rather than faithful anatomical or functional replicas (Masaeli, E. *et al*., 202; Wu, K.Y., Osman. *et al*., 2024).

A central limitation concerns architectural fidelity. Most reported bioprinted retinal tissues reproduce only one to three cellular layers, falling far short of the highly organized lamination characteristic of the human retina. Importantly, this shortfall is not solely attributable to technical constraints in spatial resolution. Rather, it reflects deeper biological uncertainties regarding the optimal spatial arrangement of diverse retinal cell populations and the mechanisms governing layer-specific differentiation and stabilization during development and regeneration. Contemporary studies emphasize that replicating the instructive biochemical and mechanical cues required for laminar organization remains a major challenge in retinal tissue engineering, even in non-printed stem-cell-derived systems (Zerti, D. *et al*., 2023). Consequently, the translation of developmental principles into reproducible bioprinting workflows remains an unresolved objective.

Beyond anatomical organization, the absence of functional neuronal connectivity represents a critical translational barrier. To date, no bioprinted retinal construct has demonstrated robust synaptic integration between photoreceptors, bipolar cells, and ganglion cells sufficient to support electrical signal propagation. Reviews of retinal

regenerative techniques typically note that vision restoration involves not just cell viability and spatial structure but also the creation of proper synaptic circuits and suitable electrophysiological development (Mandai, M., 2023). To get this kind of connectivity, neurons need to differentiate in a coordinated way over long periods of time in culture, express ion channels and neurotransmitter receptors that are specific to their cell type, and avoid bad synaptic wiring. These requirements make retinal biofabrication one of the hardest problems in regenerative medicine, going beyond what current layer-by-layer printing methods can do.

Vascularization further constrains translational progress. Unlike the cornea, the inner retina depends on dense microvascular networks to meet its high metabolic demand. Recent bioengineering literature emphasizes that diffusion limits restrict the thickness and long-term viability of avascular retinal constructs, particularly beyond approximately 200 μm (Vajda, J. *et al*., 2021). Although strategies such as sacrificial printing and endothelial co-culture have shown promise in other tissues, functional vascular integration has yet to be demonstrated in bioprinted retinal models. This limitation effectively confines current applications to thin constructs suitable primarily for laboratory research rather than therapeutic implantation.

Cell sourcing represents an additional unresolved challenge. Many experimental platforms rely on immortalized retinal cell lines due to their reproducibility and ease of culture; however, such models lack clinical relevance and fail to recapitulate mature neuronal phenotypes. Induced pluripotent stem cell-derived retinal organoids have emerged as a more physiologically representative alternative, demonstrating spontaneous lamination and photoreceptor differentiation under optimized conditions (Cowan, C.S. *et al*., 2020). Nevertheless, integrating these organoids with printed scaffolds while keeping effective signal processing remains an unanswered challenge. The complexity of coordinating scaffold mechanics, biochemical gradients, and neuronal maturation suggests that hybrid approaches combining self-organized organoid biology with biofabrication technologies may ultimately prove more viable than purely printed constructs.

Taken together, current evidence indicates that therapeutic retinal bioprinting faces a considerably longer translational trajectory than structurally simpler ocular tissues. Some investigators have proposed that restoring meaningful visual function

through biofabricated retinal implants may require fundamental paradigm shifts, including the incorporation of bioelectronic interfaces or the transplantation of pre-organized organoid tissues without extensive printing-based patterning (Bellapianta, A. *et al*., 2022). Within this framework, the most feasible near-term impact of retinal bioprinting lies in the development of improved in vitro disease models and drug screening platforms. Indeed, bioprinted retinal tissues offer regulated spatial organization and scalability advantages that may boost reproducibility in pharmacological testing and mechanistic studies of retinal degeneration (Wu, K.Y., Osman. *et al*., 2024). While these contributions are scientifically valuable, they represent a more incremental translational outcome than initially envisioned for regenerative retinal therapies.

Overall, retinal bioprinting illustrates both the promise and the limitations of current biofabrication technologies when applied to highly specialized neural tissues. Future progress will likely depend on integrating insights from developmental neurobiology, stem-cell engineering, vascular biofabrication, and neuroprosthetics, rather than relying on incremental improvements in printing resolution alone.

### 3.4 Conjunctiva

Conjunctival tissue is vulnerable to numerous inflammatory and autoimmune conditions, along with various forms of trauma, including cuts, heat or chemical damage, and foreign body injuries. Conventional management for these injuries involves surgical intervention and transplantation using either the patient's own tissue or donor tissue (Elkhenany, H. *et al*., 2022; Ashena, Z. *et al*., 2021).

However, these standard treatment approaches also carry drawbacks such as infection risk, tissue clouding, negative immunological reactions to transplanted material, and depletion of mucin-producing goblet cells (Witt, J. *et al*., 2018).

In response to these potential concerns, 3D bioprinting of conjunctival-like tissue was performed by Dehghani *et al*. 2018 (Dehghani, S. *et al*., 2018). However, comparatively limited studies have addressed this topic to date. Researchers created a membrane through extrusion-based additive manufacturing utilizing gelatin, elastin, and hyaluronic acid as fabrication materials. Biological characteristics were evaluated regarding cellular compatibility, adhesion properties, and cell growth in laboratory

settings, as well as epithelial formation, inflammatory response, scarring development, and granulation tissue presence in living organisms. Favorable outcomes were achieved concerning cellular compatibility, attachment, and proliferation in laboratory conditions. Results from living organism studies were equally encouraging. These findings suggest that this methodology is appropriate for creating membranes designed to restore injured conjunctival tissue (Ruiz-Alonso, S. *et al*., 2021). However, additional investigation is necessary to confirm the effectiveness of additive manufacturing techniques for conjunctival membrane restoration.

Stem cell-based treatment offers a promising therapeutic approach for ocular surface disorders, and in 2021 Zhong and colleagues investigated this potential by initially culturing rabbit-sourced conjunctival stem cells (CjSCs) in laboratory conditions and then incorporating them into hydrogel microstructures. Stem cell and hydrogel structures are manufactured through digital light processing (DLP) technology for accelerated bioprinting to maintain their biological function and cell survival (Zhong, Z. *et al*., 2021; Zhong, Z. *et al*., 2022). Given this context, it is logical to anticipate that additional studies will be conducted in the coming years regarding the use of additive manufacturing for conjunctival tissue restoration.

Conjunctival bioprinting occupies an intermediate position within the broader landscape of ocular biofabrication, reflecting a balance between biological feasibility and translational necessity. Compared with neural retinal tissue engineering, conjunctival reconstruction does not require restoration of synaptic connectivity or electrophysiological signal transmission, substantially reducing functional complexity. At the same time, conjunctival substitutes are subject to fewer optical performance constraints than corneal constructs, allowing greater tolerance for variability in scaffold transparency and microstructural organization. These factors collectively position conjunctival biofabrication as a potentially tractable target for translational innovation.

Recent advances in ocular surface tissue engineering demonstrate increasing feasibility in generating stratified epithelial constructs with supportive stromal components using bioprinting and related biofabrication approaches. Contemporary reviews emphasize that biomaterial-based conjunctival equivalents can achieve favorable epithelial cell viability, controlled geometry, and early integration in preclinical models, supporting the concept of printed mucosal substitutes for surface reconstruction (Salehi,

A.O.M. *et al*., 2022; Wu, K.Y. *et al*., 2024). Nevertheless, these constructs remain simplified representations of native conjunctival tissue, lacking key functional elements required for long-term physiological performance.

A critical limitation concerns the absence of goblet cells in most reported biofabricated conjunctival models. Goblet cells play a central role in maintaining tear film stability through mucin secretion and are essential for ocular surface homeostasis. Recent literature highlights persistent challenges in differentiating and maintaining functional conjunctival goblet cells in vitro, particularly within three-dimensional scaffold environments (Schwebler, J. *et al*., 2023). Without adequate mucin production, engineered conjunctival tissues may fail to support long-term lubrication and epithelial protection, thereby limiting their therapeutic durability.

Vascularization represents another unresolved challenge. The conjunctiva is among the most vascularized ocular surface tissues, enabling rapid immune surveillance, metabolic support, and wound healing responses. While biofabrication strategies incorporating endothelial cells or angiogenic biomolecules have shown promise in other mucosal tissues, functional vascular network formation has not yet been convincingly demonstrated in conjunctival bioprinted constructs (Vajda, J. *et al*., 2021). This limitation may constrain graft thickness, survival, and integration, particularly in inflammatory or cicatricial disease settings.

Importantly, translational momentum in conjunctival bioprinting is also shaped by clinical context. Current reconstructive approaches (including amniotic membrane transplantation, conjunctival autografting, and oral mucosal grafts) provide acceptable outcomes in many patients with ocular surface disorders. Systematic reviews suggest that these techniques can restore epithelial integrity and reduce inflammation in conditions such as pterygium recurrence or symblepharon formation, thereby reducing immediate pressure for disruptive regenerative solutions (Taher, N.O. *et al*., 2022). Consequently, conjunctival bioprinting may initially find application in niche indications, including severe cicatricial disease, large surface defects, or cases with limited autologous tissue availability.

Taken together, these considerations indicate that conjunctival bioprinting represents a biologically plausible yet clinically incremental innovation. Its translational trajectory will likely depend less on achieving extreme architectural precision and more

on restoring key functional attributes, particularly mucin secretion and vascular integration. Future progress may therefore require hybrid strategies combining stem-cell differentiation protocols, pro-angiogenic scaffold design, and immunomodulatory biomaterials. In this context, conjunctival biofabrication may emerge not as a paradigm-shifting therapy but as a complementary tool within a broader armamentarium of ocular surface reconstruction technologies.

### 3.5 Benefits, risks, ethical issues

Recent progress in three-dimensional ocular bioprinting has created novel possibilities for constructing eye tissues with prospective biomedical uses, and currently it appears certain that this domain will continue expanding and advancing in the coming years. Nevertheless, significant obstacles remain to be addressed before ocular bioprinting and additive biofabrication in general can become a practical clinical alternative (Ruiz-Alonso S. *et al*., 2021).

The most frequently cited advantage throughout all research is the possible reduction in time achieved through implementing a digital workflow incorporating additive manufacturing (AM). Additive manufacturing is gaining increasing attention for fabricating orbital and ocular prosthetic devices, offering benefits including decreased manual work, which reduces manufacturing duration, minimizes patient discomfort, enhances precision, and enables reproduction of components when required subsequently. Constraints on the application of additive manufacturing requiring additional investigation include material biological compatibility, and the necessity for eye care specialists and prosthetists to receive instruction in computer-aided design programs and 3D scanning protocols (Chaudhary, P. *Et al*., 2025).

From an ethical standpoint, the distinct benefit of this technology relates to utilizing additively bio-manufactured ocular structures or tissues for educational or scientific purposes (Ruiz-Alonso S. *et al*., 2021).

However, potential hazards and ethical considerations require attention, particularly when 3D bioprinting technology is intended for tissue engineering applications. In these instances, the formulation of biological printing materials presents certain concerns, encompassing not only the safety of transplanted constructs but also

questions regarding the biological source of these cells (Bova, L., Billi, F., Cimetta, E., 2020).

While 3D bioprinting technology holds substantial promise for clinical tissue engineering applications, the risk-benefit evaluation must be assessed similarly to other advanced therapeutic approaches including cellular and genetic therapies (Ruiz-Alonso S. *et al*., 2021).

An additional ethical issue regarding the implementation of 3D bioprinting technology in routine clinical settings stems from the planning and execution of clinical studies for individualized treatment. The permanent nature of grafts placed through bioprinting technology prevents patient discontinuation from the study following implantation should adverse events occur (Cubo-Mateo, N., 2020).

When addressing healthcare and economic resources, it is logical to anticipate ethical dilemmas. In this regard, the technological capability to bioprint and transplant particular organs or tissues as an alternative approach for managing late-stage disease conditions may create societal divisions. From this perspective, while bio-ink manufacturing and 3D bioprinting are not costly materials, the collaborative nature of the entire process along with its supervision makes it an expensive procedure. Consequently, its adoption would not be available to all societal groups, but rather limited to a particular segment of the population with sufficient financial means (Ruiz-Alonso S. *et al*., 2021).

Further domains requiring investigation to advance toward the adoption of additive manufacturing for orbital and ocular prosthetic devices concern the education and skill development of prosthetists.

Based on the reviewed literature, a dedicated regulatory framework for the clinical use of 3D bioprinting technology in medical contexts remains absent. While some regulatory provisions exist, they primarily address the application of these technologies for educational and scientific objectives or for creating cell-free ophthalmic products, such as eyewear or corrective lenses (Ruiz-Alonso S. *et al*., 2021).

### 3.6 Concluding perspective

Ocular tissue bioprinting has progressed from speculative concept to demonstrated proof-of-principle over approximately 7-10 years - a relatively rapid

evolution. The field has successfully shown that cells can be bioprinted while maintaining viability, that multi-layered constructs approximating native tissue architecture can be created, and that these constructs can integrate into living tissue without catastrophic rejection.

However, significant gaps persist between current capabilities and clinical requirements. The field would benefit from tempered optimism: acknowledging progress while honestly confronting remaining challenges. Overpromising timelines risks disillusionment and funding withdrawal if expectations are unmet.

The most valuable contribution of this review may be its candid assessment of both achievements and limitations. By clearly identifying gaps (transparency deficit in cornea, absent neural connectivity in retina, lack of vascularization broadly, and short-term validation only) we provide a roadmap for future research priorities.

Ultimately, ocular tissue bioprinting is a promising long-term method to solving unmet clinical requirements in ophthalmology. Whether it becomes a transformational therapeutic reality or remains purely a research tool will be determined by the field's ability to overcome fundamental biological and technological barriers over the next 10-20 years. Continued rigorous science, realistic expectations, and sustained investment are essential for realizing bioprinting's therapeutic potential.

## 4 CONCLUSION

The field of 3D bioprinting for ocular tissue regeneration has experienced remarkable growth over the past decade, evolving from theoretical concepts to functional tissue constructs demonstrated in preclinical models. This review has critically reviewed the current status of bioprinting for cornea, retina, conjunctiva, and iris, analyzing technological approaches, bioink formulations, cellular sources, and the major challenges that remain before clinical translation can be realized.

Future directions for 3D printing in eye care involve addressing existing challenges related to attainable structural complexity, biologically compatible materials, limited standardization, and economic viability. As additive manufacturing technology and investigation continue advancing, the availability of beneficial solutions for patients requiring treatment will increase rapidly. It is essential to acknowledge the importance of

3D printing technology in this intricate and continuously evolving field, which represents a matter of critical significance to ophthalmology.

In conclusion, recent developments in 3D bioprinting, especially concerning eye tissue engineering, have shown significant promise for prospective biomedical uses. However, it is crucial to recognize the numerous obstacles that must still be addressed before these technologies can be effectively implemented in clinical settings.

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