Mastering the Eye: Clinical Paradigm Shifts from Optical Restoration to Genomic Correction

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Xiulan Zhang, Fei Li, Tin Aung, Dennis S.C. Lam and Robert N. Weinreb are authors of the randomized trials of angle-closure surgery discussed in this article (Lin et al., 2025; Lin et al., 2026; Song et al., 2025).

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Abstract

Historically, the main operation for cataract was couching, and the interior of the living eye could not be examined until Hermann von Helmholtz introduced the ophthalmoscope in 1851. Since the mid-twentieth century, seven advances have reshaped ophthalmic care. Harold Ridley implanted the first intraocular lens in 1949, and the ophthalmologist Charles Kelman and the engineer Anton Banko developed phacoemulsification, reported in 1967. Robert Machemer performed the first pars plana vitrectomy in 1970, while David Huang and colleagues described optical coherence tomography in 1991. Endothelial keratoplasty, developed by Gerrit Melles and others between 1998 and 2006, replaced only the failing corneal endothelium instead of the full thickness of the cornea. Anti-VEGF therapy followed the purification of VEGF by Napoleone Ferrara and colleagues in 1989 and the approval of ranibizumab in 2006. Minimally invasive glaucoma surgery has spread since 2012, and in 2017 voretigene neparvovec became the first approved gene therapy for an inherited retinal disease. Five of these advances enabled a new type of intervention, whereas endothelial keratoplasty and minimally invasive glaucoma surgery made existing operations safer. For each advance we summarize the best available evidence of benefit to patients and its certainty, which is high for some, such as anti-VEGF therapy, and low for others, such as the effect of imaging on patient outcomes. Each advance created new burdens, from chronic injections to dependence on donor tissue, and routine adoption depended on manufacturing, regulation, cost, reimbursement, and health-system capacity.

Introduction

Historically, the main operation for cataract was couching, in which the opaque lens is displaced into the vitreous. The interior of the living eye could not be examined in detail until Hermann von Helmholtz introduced the ophthalmoscope in 1851(von Helmholtz, 1851). Even after the fundus became visible, the means to enter, measure or repair the inside of the eye remained limited for another century. Those limits began to change in the middle of the twentieth century.

Each advance overcame a specific obstacle. These were aphakia after cataract extraction, corrected only by thick and vision-distorting spectacles; a posterior segment that could not be operated on in a controlled way; retinal layers that could not be resolved in the living eye; endothelial failure that could be treated only by replacing the full thickness of the cornea; the absence of a targeted drug for neovascular retinal disease; the gap in glaucoma care between lifelong eye drops and high-risk filtration surgery; and the absence of any disease-modifying treatment for inherited retinal disease. Some advances introduced a new level of intervention: an operation, a measurement or a drug that had not existed before. Others lowered the risk of an existing intervention enough to change when, and for whom, it is used. The article is organized around that distinction.

Seven advances are set out in approximate historical order (Figure 1): cataract surgery with phacoemulsification and the intraocular lens, pars plana vitrectomy, optical coherence tomography, endothelial keratoplasty, anti-VEGF therapy, minimally invasive glaucoma surgery, and gene therapy for inherited retinal disease. Whereas five introduced a new level of intervention, two advances (endothelial keratoplasty and minimally invasive glaucoma surgery) made established operations safer. For each, we describe the obstacle, the change, the evidence of benefit to patients and its certainty, and the new burdens it created (Tables 1 and 2). The seven illustrate the pattern. The selection is not exhaustive.

This article is a perspective rather than a systematic review. Advances that met three conditions were included: they addressed a major cause of visual loss or a major limit of earlier care; they had reached routine clinical use at scale or, for gene therapy, regulatory approval; and they represented a distinct kind of change in clinical practice. Several other advances meet some of

these conditions. Refractive laser surgery is a major change in the correction of refractive error, but it treats eyes without disease, and we have focused on diseases that cause visual loss. Biologic therapy for non-infectious uveitis makes an existing treatment safer. In randomized trials, adalimumab halved the risk of treatment failure and reduced dependence on corticosteroids (Jaffe et al., 2016; Nguyen et al., 2016). Endothelial keratoplasty and MIGS are the examples used for this type of change. Corneal cross-linking is discussed in Section 4, and laser trabeculoplasty in Section 6. Other candidates, such as retinal prostheses, have not yet reached routine use.

1. Cataract surgery: from large-incision extraction to phacoemulsification and microincision with foldable intraocular lens (IOL) implants

Although cataract surgery is one of the oldest operations in recorded medicine, for roughly two millennia it was performed by couching, a small-incision displacement of the opaque lens. Couching remained the main operation for cataract until 18 September 1750, when Jacques Daviel performed a planned extracapsular extraction of the lens in Cologne and announced his new technique in the Gazette de Cologne four days later(Leffler, Schwartz and Grzybowski, 2026). For about a century after Daviel's extraction of 1750, cataract surgery was done without anesthesia. General anesthesia came into use in the 1840s(Leffler et al., 2025a), but effective local anesthesia became available only in 1884, when Carl Koller introduced topical cocaine(Koller, 1884). The wound was usually left open. Before antisepsis, a suture was a contaminated foreign body, and corneoscleral suturing was not practical with the instruments of the time(Leffler et al., 2020). Henry Willard Williams of Boston described suturing the corneal flap in the mid-1860s(Leffler et al., 2020). Closing the cataract wound became standard only from the end of the nineteenth century(Roper, 1954). In the first half of the twentieth century, both intracapsular and extracapsular extraction were large-incision procedures. They needed several corneoscleral sutures(Davis, 1950; Stallard, 1938; Verhoeff, 1927) and a long recovery, and they carried a risk of expulsive hemorrhage and retinal detachment(Davis, 2016; Welch, Spaeth and Benson, 1988). The opacity could be removed, but predictable, routine optical rehabilitation of the eye typically was not achieved. Patients did not receive an IOL and were left aphakic,

depending on thick, highly distorting spectacles; there was limited visual quality, anisometropia, and a constricted field of view(Linebarger et al., 1999).

Two complementary advances made this transition possible: intraocular lens (IOL) implantation and phacoemulsification. On 29 November 1949, Harold Ridley performed the first intraocular lens implantation after cataract surgery at St Thomas' Hospital, London, and the lens was left permanently in place at a second operation on 8 February 1950(Apple and Sims, 1996; Leffler et al., 2025b). Common adoption of this approach took a further two decades, accompanied by many modifications and improvements in IOL technology. Phacoemulsification was developed by the ophthalmologist Charles Kelman and the engineer Anton Banko. After they met on 13 July 1965, they added ultrasonic energy, of the kind used in dental scalers, to a cutting tool with irrigation and aspiration. Kelman first tested an ophthalmic phacoemulsifier on 27 August 1965 and reported the technique in 1967(Kelman, 1967; Leffler, Banko and Schwartz, 2026). Instead of removing the intact lens nucleus through a large incision, ultrasonic energy emulsified it within the closed eye, enabling aspiration through a millimeter-scale incision. The decisive engineering advance lay in operating within a pressurized, closed globe; the smaller incision was a consequence of that control. Continuous irrigation and aspiration maintained anterior-chamber stability throughout the procedure. Ophthalmic viscosurgical devices provided further support by maintaining chamber depth, protecting the corneal endothelium, and stabilizing intraocular tissues during phacoemulsification and IOL implantation(Arshinoff, 1999; Borkenstein, Borkenstein and Malyugin, 2021). Phacoemulsification was therefore conceived as a small-incision technique, rather than evolving gradually from large-incision extraction, and subsequent refinements enabled sub-2-mm microincision surgery.

Evidence and clinical adoption confirmed the crossing. Controlled studies showed that, compared with extracapsular extraction, phacoemulsification yielded better visual outcomes and lower complication rates, although at higher cost(de Silva, Riaz and Evans, 2014). In resource-limited settings, extracapsular surgery still retains a role because it helps maximize surgical volume. Where phacoemulsification is unaffordable, manual small-incision cataract surgery gives similar corrected visual acuity at much lower cost(Riaz, de Silva and Evans, 2013). Indeed, microincision surgery and the foldable lens were inseparable advances. Rigid polymethyl methacrylate lenses,

used from Ridley's first implant onwards, still required a large incision for insertion. The foldable IOL was the optical partner that completed this transition: because a full-power optic could now pass through the same small wound, a technically elegant microincision became clinically transformative, allowing sutureless optical rehabilitation in a single sitting(Apple and Sims, 1996).

Success brought new expectations. The burdens now familiar to us include refractive expectations and dysphotopsia after premium multifocal IOLs, posterior capsule opacification, corneal endothelial cell loss, and the financial and regulatory complexity of the premium IOL market. Cataract surgery has frequently become a refractive procedure, placing patient expectations and visual quality at the center of what counts as surgical success(Srinivas et al., 2025; Susanna, Ferguson and Randleman, 2025). Here the conceptual shift outran the technical one. Phacoemulsification and the foldable IOL redefined the operation itself: cataract surgery ceased to be the mere extraction of an opaque tissue and became the optical reconstruction of a closed globe.

2. Pars plana vitrectomy: opening the posterior segment to controlled surgery

Before closed vitreous surgery, the posterior segment had no controlled surgical access. Surgery for posterior segment disease relied almost entirely on ab externo approaches: the surgeon could only indent and buckle the sclera from outside the eye, approaching the lesion indirectly through compression and cryotherapy. In the late nineteenth and early twentieth centuries, surgeons including Albrecht von Graefe, Eugen von Hippel and Rudolph Deutschmann had already cut vitreous membranes through the pars plana for vitreous hemorrhage and tractional retinal detachment(Deutschmann, 1895; von Graefe, 1863; von Hippel, 1915). These procedures were not reliable enough to become standard practice. Vitreous loss during anterior segment surgery was regarded as a catastrophe. Complex retinal detachment, proliferative vitreoretinopathy, vitreous hemorrhage, and macular traction all lacked any reliable mechanical treatment. David Kasner demonstrated in 1968 that the vitreous could be safely removed through an open-sky approach, but the method required simultaneous lens removal and offered no controlled manipulation of the posterior pole(Kasner et al., 1968).

Robert Machemer, at the Bascom Palmer Eye Institute, changed this. On 20 April 1970, using a vitreous infusion suction cutter developed with the engineer Jean-Marie Parel, he performed the first pars plana vitrectomy. The procedure established a fundamentally new operative principle: the vitreous could be entered, manipulated, and excised through a small pars plana incision while the eye remained closed and pressurized. The first patient treated, for vitreous hemorrhage, improved from 6/60 to 6/15. O'Malley and Heintz followed in 1975 with the three-port 20-gauge system, dedicating ports to the cutter, infusion, and illumination, an architecture that became the foundation of all subsequent vitreoretinal surgery. As instrument gauge progressively narrowed to 25- and 27-gauge, surgery became more precise, faster and less traumatic, and in most cases sutureless(Machemer et al., 1971; Mohamed, Claes and Tsang, 2017; O'Malley and Heintz, 1975).

The impact extended far beyond technical refinement. Vitreoretinal surgery became an independent subspecialty with its own instruments, training, and academic community(Chen et al., 2025; Ruamviboonsuk et al., 2025). Diseases once considered untreatable, including complex retinal detachment with proliferative vitreoretinopathy, macular hole, diabetic tractional retinal detachment, and endophthalmitis, all became surgically manageable. Less visible but perhaps most far-reaching, mastery of controlled access to the posterior segment created a surgical platform that later made subretinal gene therapy and cell delivery feasible.

Access came with its own intraoperative dependencies: the complexity of intraocular tamponade with gas or silicone oil, the risk of recurrent proliferative vitreoretinopathy, the requirement for prolonged postoperative positioning, and the difficulty of removing tamponade agents. The subspecialty also created a new category of high expectations for surgical success: patients whose preoperative prognosis had once been considered hopeless now confronted a definite surgical outcome. These complications are the price of entry. By breaching the barrier to the posterior segment, vitrectomy turned a space that could only be watched from afar into an anatomical compartment open to direct repair.

3. Optical coherence tomography: micrometer-precision 3D imaging

Before optical coherence tomography, the posterior pole could be inspected, photographed, and, through fluorescein angiography, interrogated indirectly for leakage and perfusion. However, the images were two-dimensional, providing very limited depth information through stereoscopic viewing. The internal layers of the living retina could not be visualized. Edema, traction, photoreceptor disruption, and retinal nerve fiber loss could be suspected, but could not be accurately quantified.

These limitations were overcome in 1991, when Huang and colleagues described optical coherence tomography (OCT), a noninvasive imaging method that uses low-coherence interferometry to generate cross-sectional images of internal tissue microstructure at micrometer-scale resolution (Huang et al., 1991). Subsequent technical advances increased acquisition speed, enabled volumetric assessment, and improved retinal layer visualization, converting OCT from a laboratory demonstration into a routine clinical platform (Fujimoto, Swanson and Huang, 2023).

OCT achieved a diagnostic breakthrough. It replaced vague clinical impressions of disease activity with quantifiable structural measurements. In doing so, OCT became the substrate on which later therapeutic advances depended. In macular diseases, intraretinal fluid, subretinal fluid, pigment epithelial detachment, retinal thickness, and outer retinal integrity became measurable targets for making treatment decisions and monitoring response (Murthy et al., 2016). In glaucoma, OCT provided objective structural measurements of the optic disc rim, peripapillary retinal nerve fiber layer(Townsend, Wollstein and Schuman, 2009), and macular ganglion cell complex(Tan et al., 2009), complementing functional testing and strengthening detection and monitoring of disease (Dong, Wollstein and Schuman, 2016). Most consequentially, although OCT is not itself therapeutic, it made anti–vascular endothelial growth factor (anti-VEGF) therapy operational. The same measures supplied the endpoints on which retreatment decisions and individualized dosing came to depend, allowing retinal vascular disease to be managed by objective response rather than symptoms alone (Freund et al., 2015). The evidence that OCT improves patient outcomes is, however, indirect. No randomized trial has compared care with and without OCT, and its benefit rests on diagnostic accuracy and on its role in guiding treatment: in CATT, as-

needed ranibizumab guided largely by OCT gave visual acuity similar to monthly treatment with about 7 rather than 12 injections in the first year(Martin et al., 2011).

Technological advances have allowed the speed of OCT imaging to increase in an exponential fashion, from 100 Hz axial scan repetition in the first commercial clinical product in 1996, to over 200 kHz today, representing a 2000-fold increase. This has enabled an ever-wider field of view as well as novel contrasts such as Doppler OCT(Wang et al., 2007), OCT angiography(Jia et al., 2015), and OCT optoretinography(Chen, Huang and Jonnal, 2025). These novel imaging modalities now allow clinical quantifications of retinal function as well as structure. OCT is also moving into the operating room and the home. In the DISCOVER study, microscope-integrated intraoperative OCT acquired images in 98% of 837 eyes. Surgeons reported that it changed their surgical decisions in 43% of anterior segment cases, mostly endothelial keratoplasty, and in 29% of posterior segment cases(Ehlers et al., 2018). Whether this improves patient outcomes has not been tested in randomized trials. In 2024, a patient-operated home OCT device received US marketing authorization for monitoring neovascular AMD between clinic visits (Notal Vision Home OCT System). In a prospective study, patients performed a mean of 5.7 scans per week, and home and clinic scans agreed on fluid status in 96% of cases(Liu, Holekamp and Heier, 2022). Home OCT could allow anti-VEGF retreatment to be timed by disease activity rather than by fixed visits. Evidence that it improves visual outcomes or reduces treatment burden is so far limited to small studies.

Quantification brought its own costs. OCT increased imaging workload, entrenched dependence on expensive devices that remain unevenly distributed, and introduced new sources of diagnostic ambiguity through artifacts and segmentation error (Bazvand and Ghassemi, 2020). As with the other crossings considered here, the burden shifted, rather than disappearing: from limited visualization to the clinical interpretation of super-abundant 3D imaging information. Routine adoption has also depended on equipment cost, maintenance capacity, and access to trained image acquisition and interpretation. Compact lower-cost platforms may broaden access(Dsouza et al., 2018).

4. Endothelial keratoplasty: from full-thickness replacement to selective replacement

The corneal endothelium is a single layer of cells that do not divide in vivo. They keep the stroma transparent by pumping fluid out of it. When the layer fails, as in Fuchs endothelial corneal dystrophy or after intraocular surgery, the cornea swells, vision becomes cloudy, and painful epithelial bullae may follow. No drug restores endothelial function. Eduard Zirm performed the first successful human corneal transplant in Olomouc on 7 December 1905. For a century after that transplant, the only effective treatment was penetrating keratoplasty, which replaces the full thickness of the central cornea(Moffatt, Cartwright and Stumpf, 2005; Zirm, 1906). By replacing every corneal layer to treat a disorder of a single cell monolayer, penetrating keratoplasty requires a 360-degree sutured wound and a visual rehabilitation period of a year or more. High or irregular astigmatism is common, the globe remains permanently vulnerable to traumatic wound rupture, and endothelial rejection remains a leading cause of graft failure(Tan et al., 2012).

Later work replaced only the diseased layer. In 1998, Melles and colleagues described posterior lamellar keratoplasty(Melles et al., 1998). A disc of donor posterior stroma and endothelium was inserted through a small incision and held against the recipient cornea by an air bubble, without corneal sutures. Stripping the recipient Descemet membrane simplified the operation(Price and Price, 2005). Preparing the donor with an automated microkeratome, an instrument borrowed from refractive surgery, made the graft reproducible and allowed eye banks to supply pre-cut tissue. That preparation gave Descemet stripping automated endothelial keratoplasty (DSAEK)(Gorovoy, 2006). In 2006, Melles and colleagues introduced Descemet membrane endothelial keratoplasty (DMEK)(Melles et al., 2006). DMEK transplants only Descemet membrane and its endothelium, without donor stroma, and restores near-normal corneal anatomy. Rather than introducing an entirely new category of intervention, endothelial keratoplasty lowered the surgical risk and recovery burden of corneal transplantation enough to change when, and to whom, surgery is offered. Just as phacoemulsification and pars plana vitrectomy had earlier transformed cataract and vitreoretinal surgery, selective endothelial

replacement converted corneal transplantation from an open-sky, multi-sutured operation into a small-incision procedure within a closed globe.

Clinical uptake was rapid. In the United States, endothelial keratoplasty has been the most common form of keratoplasty since 2012, based on the Eye Bank Association of America's 2019 Eye Banking Statistical Report. Endothelial disease, mainly Fuchs dystrophy and corneal edema after cataract surgery, has become the leading indication for corneal transplantation(Park et al., 2015). Corneal edema after cataract surgery is itself a burden created by the first advance described in this article. The outcome evidence is strongest for comparisons between endothelial techniques. It is weaker for comparisons with penetrating keratoplasty, which rest mainly on cohort data. In a single-center cohort using the same corticosteroid regimen, the cumulative probability of an immunological rejection episode at 2 years was 1% after DMEK(Anshu, Price and Price, 2012). It was 12% after Descemet stripping endothelial keratoplasty (DSEK) and 18% after penetrating keratoplasty. In the patient- and outcome-assessor-masked DETECT trial, DMEK gave 1.4 lines better best spectacle-corrected visual acuity than ultrathin DSAEK at 12 months(Chamberlain et al., 2019). Vision-related quality of life improved to a similar extent in both groups(Ang et al., 2019). A Dutch multicenter randomized trial found no significant difference in mean visual acuity between DMEK and ultrathin DSAEK(Dunker et al., 2020). More DMEK eyes reached 20/25, but adverse events were more common, mainly graft detachment requiring re-bubbling. A Cochrane review rated the visual advantage of DMEK over DSAEK as low-certainty evidence(Stuart et al., 2018). The certainty of evidence is moderate for the faster recovery and lower rejection risk of endothelial keratoplasty compared with penetrating keratoplasty. Those comparisons rest on consistent cohort data. It is low for the additional benefit of DMEK over DSAEK.

Whereas endothelial keratoplasty lowered the surgical trauma of corneal transplantation, a second corneal advance reduced the need for transplantation altogether by halting disease progression. Corneal collagen cross-linking with riboflavin and ultraviolet-A light, introduced in 2003, became the first treatment capable of arresting ectatic progression in keratoconus(Wollensak, Spoerl and Seiler, 2003). Keratoconus affects adolescents and young adults and had been a major indication for penetrating keratoplasty. After cross-linking was

introduced nationwide in the Netherlands, the number of corneal transplants performed for keratoconus fell by about 25%(Godefrooij et al., 2016).

Selective replacement brought burdens of its own. The thin graft must be unfolded and positioned inside the eye, and it depends on an air or gas bubble to attach. Partial graft detachment requiring further air injection is the most common complication of DMEK. Across published series the mean rate was 28.8%, and the rate falls with surgeon experience(Deng et al., 2018). Postoperative positioning, steroid-related rises in intraocular pressure and continuing endothelial cell loss remain part of care. Above all, dependence on donor tissue remains the principal bottleneck, as every conventional endothelial keratoplasty still requires a one-to-one donor cornea. A global survey estimated that 12.7 million people were awaiting corneal transplantation, with only one donor cornea available for every 70 needed and 53% of the world's population lacking access altogether(Gain et al., 2016). Endothelial keratoplasty did not eliminate that supply ceiling; rather, it shifted the clinical burden from managing a full-thickness sutured wound to the preparation, intraocular attachment, and global supply of donor tissue.

The next step is to replace the cells themselves. In 2018, Kinoshita and colleagues injected cultured human corneal endothelial cells supplemented with a ROCK inhibitor into the anterior chamber of 11 eyes with bullous keratopathy. At 24 weeks, all eyes had regained corneal transparency, with central endothelial cell densities above 500 cells/mm²(Kinoshita et al., 2018). This suspension-based cell therapy (neltependocel; Vyznova) received regulatory approval in Japan in March 2023, allowing a single donor cornea to be expanded in vitro to treat multiple patients. In the cornea, cell replacement has already moved from proof of concept to approved treatment, a step that retinal cell therapy has yet to take (see Outlook).

5. Anti-VEGF therapy: from tissue destruction to targeted molecular modulation

Before targeted drugs, the main treatments for retinal vascular disease destroyed tissue and had limited efficacy. Laser photocoagulation had already transformed the management of proliferative diabetic retinopathy, diabetic macular edema, retinal tears, and some neovascular conditions, and was itself a major therapeutic advance. Its limitation was mechanistic rather than clinical: laser reduced risk by ablating tissue or closing vessels, leaving the underlying angiogenic

drive untouched. Verteporfin photodynamic therapy likewise offered selective vascular occlusion for predominantly classic neovascular lesions, but could not arrest the underlying disease activity.

The shift in therapeutic mode arose from recognizing VEGF as the principal driver of pathological intraocular neovascularization, a process to which ophthalmic research contributed original discoveries rather than merely borrowing from oncology. In particular, Napoleone Ferrara and colleagues at Genentech purified and cloned VEGF in 1989(Ferrara and Henzel, 1989; Leung et al., 1989) and subsequently developed the first anti-VEGF antibodies; bevacizumab was first developed as a full-length antibody for oncology, whereas ranibizumab was engineered as an ocular-specific antibody fragment for intravitreal use(Ferrara et al., 2006). Ranibizumab changed the prognostic expectation for neovascular age-related macular degeneration: in the MARINA trial, the great majority of treated patients avoided moderate vision loss as the patient outcome measured at one year, and a substantial proportion gained vision, an outcome that earlier destructive or occlusive strategies could not achieve(Rosenfeld et al., 2006). The subsequent landmark trials consolidated rather than reshaped the paradigm: ANCHOR established its superiority over photodynamic therapy in predominantly classic lesions; CATT showed that off-label bevacizumab was non-inferior to ranibizumab for visual acuity, with important implications for access(Brown et al., 2006; Martin et al., 2011). Aflibercept, and more recently faricimab and high-dose aflibercept, aimed to extend treatment intervals and address residual disease activity(Lai et al., 2025; Zou et al., 2025). In practice, what sustained the anti-VEGF era was not the drugs alone but the OCT-guided management described above. By making retinal fluid and structural response visible over time, OCT allowed treatment to be adjusted according to tissue response, making pro re nata (PRN) and treat-and-extend regimens clinically practical(Freund et al., 2015). The non-inferiority of bevacizumab also had important economic implications, because its substantially lower acquisition cost expanded the range of affordable anti-VEGF options(Hutton et al., 2014; Rosenfeld et al., 2018). Biosimilar entry may further reduce acquisition costs in health systems where patients pay directly for treatment(Chakraborty et al., 2026).

The effect on disease trajectory was revolutionary: neovascular age-related macular degeneration, diabetic macular edema, and retinal vein occlusion were converted from conditions carrying a high risk of progressive vision loss into manageable diseases in which vision could be maintained or improved over years in a substantial proportion of patients. The new burdens were proportional to this success: repeated intravitreal injections, monitoring visits, and individualized regimens requiring a vast global care infrastructure. Real-world outcomes consistently fall short of trial results, reflecting undertreatment, missed injections, and inequities in access(Ciulla et al., 2020; Wykoff et al., 2024). For this reason, laser photocoagulation is still used. In proliferative diabetic retinopathy, intravitreal ranibizumab was non-inferior to panretinal photocoagulation (PRP) for visual acuity at 2 years in the DRCR Retina Network Protocol S trial. At 5 years, mean visual acuity was about 20/25 in both groups, and ranibizumab caused less vision-impairing macular edema and less visual field loss. Only 61% of eyes completed the 5-year visit(Gross et al., 2018). In the CLARITY trial, aflibercept gave better visual acuity than PRP at 52 weeks(Sivaprasad et al., 2017). An individual participant data meta-analysis of 12 trials found no clinically meaningful visual benefit of anti-VEGF therapy over PRP at 1 year, although anti-VEGF therapy reduced the risk of macular edema(Simmonds et al., 2025). In a retrospective cohort of 76 eyes lost to follow-up for 6 months or more, eyes treated with anti-VEGF injections alone had worse outcomes, including more tractional retinal detachment, than eyes treated with PRP(Obeid et al., 2019). PRP, alone or combined with injections, remains a standard option for patients who may not be able to attend regularly. Long-term cohort studies, such as the seven-year SEVEN-UP follow-up, documented a mean decline in visual acuity relative to the original trial baseline, and a larger decline relative to the peak acuity achieved during the trials(Rofagha et al., 2013). This burden in turn drove the next wave of development. Sustained-release platforms, including the ranibizumab port delivery system, and new gene therapy strategies designed for continuous intraocular anti-VEGF expression are explicit attempts to address the injection burden. Yet these approaches show again that clinical burden is redistributed rather than erased: the port delivery system cut injection frequency at the cost of implant-related complications, complex refill exchanges, and a temporary recall for redesign(Sharma et al., 2023). Once retinal vascular care moved from intermittent tissue destruction to chronic suppression of a molecular signal, durability and delivery became the central clinical problems.

6. The minimally invasive turn: glaucoma as a case of a cross-disciplinary surgical principle

The development of minimally invasive surgery is not unique to ophthalmology. Across many surgical fields, including orthopedics, general surgery, and cardiovascular intervention, the past four decades have seen a systematic shift toward smaller incisions, less tissue disruption, faster recovery, and earlier rehabilitation(Siddaiah-Subramanya, Tiang and Nyandowe, 2017). Within ophthalmology, cataract surgery and vitreoretinal surgery had already completed their own minimally invasive transitions; minimally invasive glaucoma surgery (MIGS) extended the same principle to glaucoma.

Before this, the main choices were long-term topical medication and filtration surgery (trabeculectomy or tube shunt implantation). Filtration surgery was high risk and traumatic. Laser trabeculoplasty was the only procedure between those two. Argon laser trabeculoplasty was introduced in 1979(Wise and Witter, 1979). Selective laser trabeculoplasty (SLT), which targets pigmented trabecular cells with less thermal damage, followed in 1995(Latina and Park, 1995). In the LiGHT trial of 718 patients with newly diagnosed open-angle glaucoma or ocular hypertension, 69.8% of eyes treated first with SLT remained at target pressure without drops or surgery at 6 years. Compared with initial eye drops, SLT-first treatment led to less disease progression (19.6% vs 26.8%) and fewer trabeculectomies (13 vs 32 eyes), with no serious laser-related adverse events(Gazzard et al., 2023; Gazzard et al., 2019). Laser trabeculoplasty is an alternative to lifelong drops. It does not replace surgery when greater pressure lowering is needed.

Trabeculectomy remains the benchmark procedure for lowering intraocular pressure, but it carries potential risks, including bleb-related infection, hypotony, surgical failure, and permanent alteration of the conjunctival tissue that may be needed for later surgery. Catastrophic complications such as suprachoroidal hemorrhage and malignant glaucoma have long haunted every glaucoma surgeon. Before MIGS, the main advance within incisional glaucoma surgery was the tube shunt. Anthony Molteno described a tube draining aqueous to an equatorial plate in 1969(Molteno, 1969). The Baerveldt implant(Lloyd et al., 1994) and the valved Ahmed

implant(Coleman et al., 1995) followed in the early 1990s. In eyes with previous cataract or glaucoma surgery, the Tube Versus Trabeculectomy Study found a 5-year cumulative failure rate of 29.8% with the Baerveldt implant and 46.9% with trabeculectomy with mitomycin C(Gedde et al., 2012). In eyes without previous surgery, the Primary Tube Versus Trabeculectomy Study found no significant difference in failure at 5 years (42% vs 35%), although complete success without medication was more frequent after trabeculectomy(Gedde et al., 2022). In pooled 5-year data from the Ahmed Baerveldt Comparison and Ahmed Versus Baerveldt studies, failure was less frequent with the Baerveldt implant (37% vs 49%), but hypotony was more common(Christakis et al., 2017). Among US Medicare beneficiaries, trabeculectomy declined from its peak in 1996, while tube shunt implantation grew until the two procedures were performed in similar numbers(Arora et al., 2015; Boland, Corcoran and Lee, 2021). Tube shunts remain a mainstay of glaucoma surgery, particularly after failed trabeculectomy and in neovascular and uveitic glaucoma. However, they do not avoid disrupting the conjunctiva, and also have complications, including tube exposure, diplopia and loss of corneal endothelial cells.

MIGS was introduced to fill this middle ground. Ab interno microincision procedures aim to restore or augment physiological aqueous outflow while preserving the conjunctiva and avoiding the risks of filtration surgery. A separate class of ab externo bleb-associated procedures establishes a new subconjunctival outflow pathway through a micro-drainage device, replacing traditional filtration surgery in a more controlled manner. Over the past decade or so, dozens of MIGS procedures and devices have emerged, rapidly reshaping the therapeutic landscape between medication and filtration surgery. The field also continues to broaden. For example, bio-interventional cyclodialysis with scleral allograft reinforcement, which enhances uveoscleral rather than trabecular outflow, was introduced into United States practice in 2025, illustrating the continuing proliferation of distinct minimally invasive approaches(Ianchulev et al., 2024).

In glaucoma, lowering intraocular pressure surgically has long been achievable; the real barrier has been the surgical risk required to achieve it. The minimally invasive turn changed this threshold(Wang et al., 2025). By preserving the conjunctiva, reducing tissue disruption, and combining with cataract surgery, angle-based and microincision procedures changed the point at which surgical intervention can reasonably enter the treatment pathway.

In practice, these procedures fall into two broad classes. Device or implant-based methods, such as the iStent, iStent inject, and Hydrus Microstent, employ a microstructure to bypass or support flow in the trabecular meshwork and Schlemm canal. Tissue-based methods incise, excise, or dilate conventional outflow structures without leaving a permanent foreign body. In randomized studies combining these procedures with cataract surgery, both classes have shown reduced intraocular pressure and a lower medication burden(Samuelson et al., 2019a; Samuelson et al., 2019b). Cochrane reviews rate the evidence that adding the Hydrus microstent to cataract surgery increases the proportion of medication-free eyes as moderate certainty, but the evidence for the iStent as very low certainty, and none of the iStent trials measured quality of life(Le et al., 2019; Otarola et al., 2020). Overall, MIGS has an excellent safety profile; however, it is associated with a smaller magnitude of IOP lowering than trabeculectomy. Although individual devices have been studied in numerous randomized trials, most have compared them with cataract surgery alone or with one another rather than with trabeculectomy; randomized trials comparing MIGS directly head-to-head with trabeculectomy remain few, and this is itself a notable evidence gap(Lavia et al., 2017).

A clinically important special case is primary angle-closure glaucoma, where this minimally invasive logic takes a distinctive form. The subtype is especially prominent as a cause of glaucoma blindness in East and Southeast Asian populations and is estimated to account for nearly half of bilateral glaucoma blindness worldwide, despite being less prevalent than open-angle disease(Quigley and Broman, 2006; Tham et al., 2014). In China, it accounts for an estimated 91% of bilateral glaucoma blindness(Foster and Johnson, 2001). Its traditional treatment is peripheral iridotomy, supplemented, when necessary, by trabeculectomy or by phacotrabeculectomy. Here the transformation wrought by phacoemulsification extends well beyond the cataract itself: removing the lens deepens the anterior chamber and relieves lens-related crowding, so that lens extraction has become an important and even first-line intervention for angle-closure disease, as established by the EAGLE trial(Azuara-Blanco et al., 2016).

On this anatomical basis, the logic of combined treatment comprises three distinct layers that must not be conflated. Lens extraction addresses the crowding just described. Goniosynechialysis

(GSL) then mechanically reopens a synechially closed angle, a separate surgical step. Finally, once the synechial angle has been opened, angle-based trabecular incision (goniotomy) can further enhance trabecular outflow, provided the angle anatomy is adequate. Two randomized trials have compared these procedures with filtration surgery in advanced primary angle-closure glaucoma. In eyes with cataract, phacogoniotomy was non-inferior to phacotrabeculectomy for IOP reduction at 2 years (difference -0.5 mmHg; 97.5% CI -1.7 to 0.8), and the result persisted at 3 years(Lin et al., 2026; Song et al., 2025). In eyes without cataract, surgical peripheral iridectomy with GSL and goniotomy was non-inferior to trabeculectomy for IOP at 12 months, with fewer postoperative interventions but a lower rate of complete success (60.5% vs 82.2%)(Lin et al., 2025). That trial specifically compared minimally invasive angle surgery with standard trabeculectomy in patients aged over 45 years with advanced PACG who retained good central visual acuity despite severe visual field loss; the lens was preserved because extracting a clear lens in eyes with good visual acuity remains controversial(Azuara-Blanco et al., 2016; Lin et al., 2025). Neither procedure requires an implant (non-device-based), which may matter in resource-limited settings(Chan et al., 2024). Surgical costs were similar to those of filtration surgery(Lin et al., 2025; Song et al., 2025). However, both trials were conducted in a single country, with unmasked surgeons and a non-inferiority margin of 4 mmHg. Because phacoemulsification was performed in both arms, the cataract trial cannot show how much of the benefit came from goniotomy rather than from lens extraction, although smaller randomized trials suggest that adding a trabecular incision to phacoemulsification lowers IOP further(El Sayed et al., 2024; Paik et al., 2025; Shokoohi-Rad et al., 2021). Longer follow-up, replication in other populations and trials with a lens-extraction comparator are needed before these procedures can be considered alternatives to filtration surgery outside experienced centers.

The limitations of this low-risk strategy are equally important. For many conventional MIGS procedures, particularly in open-angle glaucoma or refractory disease, the magnitude of IOP lowering may not match that of trabeculectomy. The steady proliferation of devices with uneven evidence bases has made clinical decision-making more complex. Despite these limitations, the minimally invasive turn has moved the threshold for surgical decision-making earlier; in selected cases of angle-closure disease, it may also reduce the need to use filtration surgery as a first

surgical choice. In the United States, reimbursement changes were followed by measurable shifts in glaucoma procedure selection, illustrating how payment policy may influence clinical adoption(Williams et al., 2024).

7. Gene therapy: from phenotypic management to molecular intervention

Inherited retinal diseases are a highly heterogeneous group of conditions caused by pathogenic variants in more than 280 genes affecting photoreceptors, the retinal pigment epithelium, and associated structures, and it constituted one of the oldest therapeutic nihilisms in ophthalmology(Wong et al., 2024). Identification of pathogenic variants began with the cloning of a retinitis pigmentosa gene around 1990(Dryja et al., 1990) and accelerated in the genomic era, transforming diagnosis while leaving prognosis unchanged for decades. Genetic counseling and low-vision rehabilitation largely remain the standard of care. The eye, however, has several features that make it an ideal pioneer organ for gene therapy: a small target volume; relative immune privilege conferred by the blood-ocular barrier; surgical accessibility of both subretinal and intravitreal delivery; and the capacity for precise, non-invasive functional and structural monitoring.

The turning point came with evidence that gene augmentation could restore meaningful visual function. Building on early phase 1 and 2 trials of AAV2-mediated *RPE65* gene replacement, the pivotal phase 3 trial of voretigene neparvovec showed improved functional mobility in *RPE65* biallelic mutation–associated retinal dystrophy, an effect that depends on surviving, functional retinal cells(Maguire et al., 2019). Pooled long-term follow-up of voretigene-treated eyes has since indicated that the gain in functional vision is durable over several years, although the eventual ceiling of effect remains under study and may be constrained by ongoing photoreceptor loss(Leroy et al., 2023). Voretigene neparvovec received US FDA approval in December 2017 for patients with confirmed biallelic *RPE65* mutations and viable retinal cells, becoming the first FDA-approved ophthalmic gene therapy and a milestone in the treatment of monogenic disease(FDA, 2017; Russell et al., 2017).

The field under investigation has since broadened beyond *RPE65*-associated retinal dystrophy to other monogenic eye diseases. In particular, gene therapy for Leber hereditary optic neuropathy

(LHON) caused by the m.11778G>A *MT-ND4* variant has shown encouraging late-stage clinical results, extending the field conceptually from inherited retinal diseases to mitochondrial optic neuropathies(Yu-Wai-Man et al., 2020). Next-generation AAV capsids with improved tissue tropism, alternative delivery routes, and in vivo genome editing (exemplified by the BRILLIANCE trial of EDIT-101, a CRISPR-Cas9 strategy for CEP290-associated Leber congenital amaurosis) have extended the mechanistic repertoire from gene augmentation to genome correction. BRILLIANCE provided the first proof of concept for in vivo CRISPR-Cas9 editing in the human retina; enrollment was subsequently paused because of the limited size of the eligible population, a reminder that mechanistic feasibility and sustainable clinical development are two different thresholds. Intraocular genome editing remains investigational and should be regarded as a future-facing extension rather than a current clinical standard(Pierce et al., 2024).

This paradigm remains constrained in several important respects. The gene therapies that currently hold regulatory approval or late-stage evidence cover only a small fraction of the genes noted above. Efficacy requires the target cells to remain viable, limiting its value in advanced disease. Manufacturing complexity, immunogenicity, delivery risk, very high cost, and uncertain long-term durability together constrain access; and for diseases in which vision is a late and insensitive measure, endpoint development remains methodologically challenging. Ethical and practical questions surrounding trial access, durability, retreatment, and affordability remain unresolved. Gene therapy for inherited retinal disease is therefore an emerging paradigm shift, not yet a completed one. Even so, by acting on the causative mutation instead of its downstream phenotype, it reaches the deepest biological level of the seven advances. More notably, gene-level intervention is rapidly expanding beyond inherited retinal diseases, signaling the deeper development of this paradigm. First, mutation-agnostic strategies are no longer confined to a single causative gene: long-acting IOP-lowering gene therapy that genetically modulates aqueous production pathways such as carbonic anhydrase II in the ciliary epithelium, for example, may offer a single-dose, sustained-control option for glaucoma, and is currently preclinical(Jiang et al., 2024). Second, intraocular gene therapy using AAV to sustain anti-VEGF protein expression has entered human trials, aiming to replace repeated intravitreal injections with a single dose, directly echoing the injection burden described in Section 5. Third, next-generation capsids, in

vivo editing, and base and prime editing are expanding the treatable disease spectrum from a few monogenic conditions to a broader range of inherited and multifactorial retinal and optic nerve diseases. Together these directions show that the boundary of gene therapy continues to advance, rather than halting at the few approved indications.

A unifying pattern and its limits

Across these seven advances, a common structure emerges. Five of the seven advances supplied a level of intervention missing from clinical practice. The limit was the absence of that level, not insufficient intensity within a method already in use. The missing level differed in each case: operating within a closed eye, controlled access to the posterior segment, micrometer-scale measurement of the living retina, a molecular drug acting on the correct target, and causal, genome-level intervention. The other two advances made an existing intervention safe enough to change its use. Endothelial keratoplasty replaced only the failing endothelium instead of the full-thickness cornea. MIGS offered a surgical option calibrated between the insufficiency of eye drops and the trauma of filtration surgery (Figure 2).

Taken together, these advances trace a clear escalation in the depth of clinical action. The five boundary-crossing innovations moved successively from optical rehabilitation of the globe, to controlled surgical entry into the posterior segment, to micrometer-scale measurement of living tissue, to pharmacological blockade of a molecular signal, and finally to repair of the genetic defect itself. Endothelial keratoplasty and MIGS stripped away the surgical trauma of established operations. Whether by opening a new level of intervention or by lowering the risk threshold of an existing one, each advance changed what clinicians can attempt, when they intervene, and which patients they can reasonably treat.

A second shared feature was the application of cross-disciplinary knowledge (Figure 3). Phacoemulsification applied ultrasonic fragmentation; vitrectomy applied engineering concepts to closed-eye instrumentation; OCT translated low-coherence interferometry and biomedical optics into clinical imaging; endothelial keratoplasty drew on microkeratome engineering from refractive surgery and, in its cell-based form, on cell culture from regenerative medicine; anti-VEGF therapy converged with angiogenesis research; MIGS drew on device and stent concepts

from interventional medicine; and gene therapy used vectors developed in basic virology. Progress in ophthalmology has rarely arisen wholly from within. Cross-disciplinary discovery was only one part of translation; industrial engineering, scalable manufacturing, regulatory development, and distribution were also required to bring these advances into clinical practice. Commercial incentives, in turn, influenced which technologies were developed, how they were priced, and where they first became available. Whether the same pattern extends to other fields of medicine remains an open question.

A third feature, recurrent yet often underestimated, is that each advance brought new burdens: dysphotopsia and refractive expectations; tamponade dependence and proliferative vitreoretinopathy; imaging workload and artifact interpretation; graft detachment and dependence on donor tissue; the chronic injection burden and its real-world undertreatment; device-related safety concerns; and the genotype restrictions and prohibitive cost of gene therapy. Medical progress rarely abolishes clinical problems outright; instead, it trades old limitations for a new class of management challenges. The evidence that these advances benefit patients differs widely in strength (Table 2). It is high for anti-VEGF therapy and for macular hole closure after vitrectomy, both supported by randomized trials against sham treatment or observation(Parravano et al., 2015; Solomon et al., 2019). For anti-VEGF therapy, population data also show that the incidence of legal blindness from AMD in Denmark halved after its introduction(Bloch, Larsen and Munch, 2012). The evidence is moderate for phacoemulsification, endothelial keratoplasty, MIGS and gene therapy. For these, randomized trials exist but are small, compare one technique with another, or measure surrogate outcomes such as IOP rather than visual function or quality of life. It is low for OCT, whose benefit for patients has not been tested directly. For several advances, clinical use spread before the evidence was strong. Certainty in Table 2 was rated with predefined criteria adapted from GRADE by two authors independently. Disagreements were resolved by discussion. Where a published GRADE assessment exists, its rating was adopted.

A fourth shared feature is that technical capability does not ensure routine clinical adoption. Whether an expanded level of clinical action reaches patients depends on manufacturing, regulation, affordability, reimbursement, and delivery capacity. These conditions have been met

unevenly across the seven advances. Anti-VEGF therapy illustrates the point most clearly. Efficacy was established in the pivotal trials, yet treatment in practice has depended on acquisition cost and on the availability of lower-priced options. Undertreatment persists where cost, travel, and monitoring capacity limit injection frequency, particularly in low- and middle-income settings(Sam-Oyerinde and Patel, 2023). Gene therapy raises the same issue in a more acute form. Published cost-effectiveness estimates for voretigene neparvovec vary by nearly an order of magnitude according to the assumptions adopted(Farris, Goodall and De Abreu Lourenco, 2023; Huygens et al., 2021). The value of a single administration therefore remains less settled than its biological rationale. Glaucoma surgery provides a related example, as reimbursement changes have been followed by measurable shifts in procedure selection(Williams et al., 2024). These considerations do not constitute a further paradigm shift. They identify an implementation boundary within the same framework, one that determines whether an established capability becomes routine care.

The pattern described here is necessarily retrospective and selective, drawn from challenges that have already been overcome, and should not be interpreted as evidence that all limitations will eventually fall. Any such retrospective account is shaped by survivorship bias: we see the breakthroughs that endured, not the many plausible technologies that stalled in translation or failed to deliver lasting benefit. Several of the most critical challenges in ophthalmology have resisted decades of effort such as regeneration of the optic nerve and retinal ganglion cells, durable neuroprotection in glaucoma, reversal of late degeneration such as geographic atrophy, and the global shortage of donor corneal tissue. These impasses are a reminder that the trajectory sketched above is a record of solved problems, not a guarantee that the unsolved ones are merely technical.

Outlook

If gene therapy represents the shift from phenotypic management to molecular causal intervention, the next boundary may lie in repair after the loss of a cellular substrate. Cell therapy, replacing degenerated photoreceptors or retinal pigment epithelial cells with pluripotent stem cell–derived equivalents, and optogenetics, conferring light sensitivity on

surviving inner retinal neurons through AAV-mediated opsin delivery, are leading candidates at this stage. Proof of concept for optogenetics has reached the clinic, with early reports of partial visual recovery in patients with end-stage retinitis pigmentosa(Sahel et al., 2021). Both approaches are at an earlier stage of development than the first *RPE65* gene therapy trials were.

A different frontier concerns clinical decision-making itself. At present, artificial intelligence functions primarily as an implementation amplifier, improving screening, diagnosis, treatment planning, and workflow(Lim et al., 2024). However, increasingly autonomous diagnostic systems and predictive foundation models may move artificial intelligence toward a distinct decision-making boundary if they demonstrate reliable clinical autonomy and improved patient outcomes(Jin et al., 2026; Zhou et al., 2023). Regulatory authorization and implementation pathways for autonomous diabetic retinopathy screening are already developing alongside technical validation, while CPT 92229 provides a dedicated billing and reimbursement pathway for autonomous retinal imaging(Grzybowski et al., 2026; Wolf et al., 2024).

Each candidate, cell therapy, optogenetics, and increasingly autonomous artificial intelligence, will face the same evaluative questions posed by the seven advances described here: Does it cross an existing clinical or therapeutic barrier? Does it open a previously untreatable disease spectrum? Does it reshape clinical practice? For cell therapy and optogenetics, there is still insufficient evidence. Whether the most important limitations facing current therapy will, in retrospect, prove to be technical, or fundamental and biological, is precisely the question that the next generation of discoveries and inventions will answer.

Conclusion

Modern ophthalmology was not built by incremental refinement alone. Its defining trajectory since the middle of the twentieth century has been a series of decisive leaps across long-accepted limits, turning what once seemed anatomical or biological fate into a problem that could be measured, reached, or repaired. Five of the advances examined here opened entirely new optical, surgical, diagnostic, molecular, or genomic planes of action; the other two advances made established operations safer and hence soon became more widely used. Progress along

this path was never inevitable, and every breakthrough created clinical and economic burdens of its own. Yet the historical pattern is clear: transformative care arrives either by making the impossible doable, or by making the doable safe, quantifiable, and durable enough for routine practice. Which of today's remaining impasses are merely technical barriers, and which are hard biological limits, is the question left to the next generation of discovery.

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Figure Captions

Graphical abstract: Seven crossings and the expansion of clinical agency in modern ophthalmology
The staircase shows seven boundary crossings: optical reconstruction through cataract extraction and intraocular-lens implantation; controlled posterior access through vitrectomy; objective structural measurement through optical coherence tomography; selective replacement of the corneal endothelium through endothelial keratoplasty; molecular inhibition through anti-vascular endothelial growth factor therapy; lower-risk procedural intervention through minimally invasive glaucoma surgery; and genotype-directed treatment through ocular gene therapy. Five of these crossings introduced a new kind of intervention. Endothelial keratoplasty and minimally invasive glaucoma surgery primarily lowered the risk of an existing intervention, and the threshold at which it is used. Each advance also created new burdens. Entry into routine care depended on manufacturing, regulation, affordability, reimbursement and durable clinical benefit. The final column marks regenerative cell replacement in the retina as a possible future crossing, not an inevitable next step. Abbreviations: EK, endothelial keratoplasty; IOL, intraocular lens; MIGS, minimally invasive glaucoma surgery; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.

Figure 1. Selected landmark advances in modern ophthalmology
The timeline highlights seven boundary-crossing developments that expanded or extended clinical agency. Optical reconstruction emerged with Harold Ridley's introduction of the intraocular lens in 1949–1950. Surgical access advanced through Kelman's preliminary report of phacoemulsification in 1967, Kasner's open-sky vitrectomy in 1968 and Machemer's pars plana vitrectomy in 1970. Optical coherence tomography introduced cross-sectional optical imaging in 1991; the original report included imaging of ex vivo human retina, preceding in vivo human retinal imaging. The molecular era developed from the isolation and cloning of vascular endothelial growth factor in 1989 to the approval of pegaptanib in 2004 and ranibizumab in 2006. Voretigene neparvovec became the first US Food and Drug Administration-approved ocular gene therapy in 2017 for patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy and viable retinal cells. Endothelial keratoplasty developed from posterior lamellar keratoplasty in 1998 through Descemet stripping endothelial keratoplasty in 2005 to Descemet membrane endothelial keratoplasty in 2006, lowering the risk of corneal transplantation by replacing only the diseased endothelium. From 2012 onward, minimally invasive glaucoma procedures lowered the intervention threshold for selected patients, including device-based procedures and tissue-based angle surgery. Dates represent selected milestones rather than an exhaustive history or exclusive claims of priority. Dashed extensions indicate developments beyond 2026. Abbreviations: DMEK, Descemet membrane endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; FDA, US Food and Drug Administration; GSL, goniosynechialysis; IOL, intraocular lens; MIGS, minimally invasive glaucoma surgery; OCT, optical coherence tomography; PACG, primary angle-closure glaucoma; RPE65, retinoid isomerohydrolase RPE65 gene; SPI, surgical peripheral iridectomy; VEGF, vascular endothelial growth factor.

Figure 2. A framework for clinical paradigm shifts in ophthalmology
Panel A shows a boundary-crossing cycle that begins when an existing clinical ceiling limits what clinicians can observe, access or treat. A principle or platform, often imported from another discipline, creates a categorical advance and makes a previously inaccessible clinical action tractable. The resulting intervention generates new burdens that may, but do not inevitably, define a subsequent clinical ceiling. The cycle is therefore contingent and subject to survivorship bias rather than a claim of predetermined

technological progress. In Panel B, selected advances are arranged by category of clinical agency and by illustrative risk or procedural burden relative to the standard of care that they displaced. The vertical axis is categorical and does not represent a hierarchy or rank order; horizontal positions are conceptual rather than quantitative estimates. Endothelial keratoplasty and minimally invasive glaucoma surgery extend existing procedural capabilities by lowering their risk threshold rather than creating an entirely new category of agency. Open circles denote displaced standards of care. Abbreviations: IOL, intraocular lens; IOP, intraocular pressure; MIGS, minimally invasive glaucoma surgery; OCT, optical coherence tomography; PPV, pars plana vitrectomy; SPI, surgical peripheral iridectomy; VEGF, vascular endothelial growth factor; RPE65, retinoid isomerohydrolase RPE65 gene.

Figure 3. Selected enabling relationships among advances in clinical ophthalmology

The diagram traces four examples in which an external principle or platform enabled an earlier crossing, created a clinically actionable capability and supported a later crossing. First, closed-system instrument engineering and pars plana vitrectomy established controlled posterior access, which is required for the approved subretinal delivery of voretigene neparvovec; this relationship is specific to the depicted subretinal route and does not apply to intravitreal delivery. Second, low-coherence interferometry enabled optical coherence tomography and objective structural endpoints, supporting response-guided monitoring and retreatment in the anti-vascular endothelial growth factor era. The expansion of anti-vascular endothelial growth factor treatment subsequently increased the installed base, workload and clinical dependence on optical coherence tomography, producing a mutually reinforcing operational relationship. Third, phacoemulsification with foldable intraocular-lens implantation can deepen the anterior chamber and relieve lens-related crowding, facilitating angle-closure management. Phacogoniotomy applies to eyes with cataract, whereas lens-sparing surgical peripheral iridectomy combined with goniosynechialysis and goniotomy applies to eyes without cataract; these procedures remain anatomically and conceptually distinct. Fourth, cataract surgery provided an established procedural and regulatory platform for the adoption of trabecular micro-bypass devices, although stand-alone angle surgery demonstrates that intervention need not remain bundled with lens extraction. Solid arrows indicate route-specific enabling relationships, dashed arrows indicate facilitating but non-necessary relationships, and double-headed arrows indicate mutually reinforcing relationships. The convergence node distinguishes approved sustained ocular anti-VEGF drug delivery from investigational gene-based anti-VEGF expression. Abbreviations: GSL, goniosynechialysis; IOL, intraocular lens; MIGS, minimally invasive glaucoma surgery; OCT, optical coherence tomography; PPV, pars plana vitrectomy; SPI, surgical peripheral iridectomy; VEGF, vascular endothelial growth factor.