

Applications of SMILE-extracted lenticules in ophthalmology

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Abstract

• **AIM:** To review recent innovations, challenges, and applications of small incision lenticule extraction (SMILE) extracted lenticule for treating ocular disorders.

• **METHODS:** A literature review was performed in the PubMed database, which was last updated on 30 December 2021. There was no limit regarding language. The authors evaluated the reference lists of the collected papers to find any relevant research.

• **RESULTS:** Due to the simplicity and accuracy of modern femtosecond lasers and the extensive development of SMILE surgery, many healthy human corneal stromal lenticules were extracted during surgery, motivating some professionals to investigate the SMILE lenticule reusability in different ocular disorders. In addition, new approaches had been developed to preserve, modify, and bioengineer the corneal stroma, leading to the optimal use of discarded byproducts such as lenticules from SMILE surgery. The lenticules can be effectively re-implanted into the autologous or allogenic corneas of human subjects to treat refractive errors, corneal ectasia, and corneal perforation and serve as a patch graft for glaucoma drainage devices with better cosmetic outcomes.

• **CONCLUSION:** SMILE-extracted lenticules could be a viable alternative to human donor corneal tissue.

• **KEYWORDS:** small incision lenticule extraction; corneal lenticule implantation; keratoconus; corneal perforation; femtosecond laser; stromal keratophakia

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INTRODUCTION

Small incision lenticule extraction (SMILE) was developed as a novel method of flapless femtosecond laser-assisted corneal refractive surgery for myopia and myopic astigmatism correction in 2008^[1-2]. In this technique, an intrastromal lenticule is made using a femtosecond laser that is manually extracted with a 3-4 mm incision^[3]. Approximately six million SMILE surgeries have been performed worldwide^[4]. As a result of this process, a considerable number of corneal stromal lenticules are removed intactly, which has encouraged some experts to consider reshaping and modifying SMILE-extracted biological lenticules for excimer laser intrastromal reimplantation in recent years^[5]. The lenticules have been transplanted successfully into autologous or allogenic human corneas in a variety of conditions like hyperopia treatment^[6], keratoplasty^[7], and tissue engineering studies^[8-11]. This review will summarize recent studies investigating the use of SMILE-extracted lenticules for managing ocular disorders, tissue engineering, and xenograft studies.

DATA SOURCE

A comprehensive systematic search was conducted in a number of international databases, including Web of Science, PubMed, Scopus, Embase, and Google Scholar to find articles relevant to the SMILE lenticule. Keywords including “small incision lenticule extraction (SMILE)”, “lenticule”, “reuse”, “eye bank”, “keratoplasty”, “patch graft”, “glaucoma tube implants”, “corneal tissue engineering”, “xenograft”, “animal study”, “corneal ectasia”, “hyperopia correction”, and “presbyopia correction” were used in a variety of conceptual combinations. We only included studies that included an English full-text or abstract.

Keratoplasty

Keratoplasty in corneal thinning and perforation Corneal thinning and perforation may result in permanent vision loss, and immediate surgical intervention is needed to prevent catastrophic consequences such as endophthalmitis^[12]. Temporary therapies for this situation including corneal gluing^[13-15], bandage contact lenses^[16-19], amniotic membrane transplantation^[20-22], scleral graft, and conjunctival flap^[23-26] have unsatisfactory long-term results. Furthermore, tectonic lamellar or penetrating keratoplasty (PK) is the most recommended treatment for most patients with extensive corneal lesions^[27-28]. Lamellar keratoplasty has grown in popularity due to fewer surgical complications like lower rates of graft rejection and secondary glaucoma compared to PK^[29]. Due to the limited access to donor corneas in many developing countries^[30-32], some researchers are investigating the use of SMILE-extracted lenticule to treat corneal thinning and perforation.

Pant *et al*^[12] studied the outcome of tectonic keratoplasty using SMILE-extracted lenticules in 18 eyes with corneal thinning and perforation due to different ocular pathologies such as corneal ulcer, recurrent pterygium, limbal dermoid, *etc.* This procedure was successful in 16 of the 18 patients in the first surgery. Moreover, two patients required lenticule reimplantation and conjunctival grafting, respectively. The corneal integrity was successfully reconstructed and vision improved (especially in cases with perforation) in all patients with no complications. Additionally, the patients with infratemporal lesions experienced the most significant improvement in visual acuity. For deep, extensive, and complex corneal lesions, the authors advised the use of double-layer lenticules instead of single-layer lenticules. They also reported successful treatment and satisfactory visual outcomes of this method in two pediatric patients with corneal perforation secondary to severe Demodex-induced blepharokeratoconjunctivitis^[33].

Jacob *et al*^[34] reported successful treatment of multiple corneal macroperforations in a case of complicated pseudopterygium excision with deep intracorneal extension using a SMILE-extracted lenticule with fibrin glue as a patch graft. They showed that this method could provide a complete leak-proof seal with a good long-term visual outcome and graft survival [corrected distance visual acuity (CDVA) was 20/30 and the donor graft remained clear]. In addition, Pant *et al*^[35] reported the excellent outcome of lamellar keratoplasty using SMILE-extracted lenticule in case of recurrent pterygium complicated by a thin cornea. After eight months, the transplanted lenticule remained intact with a good CDVA (20/30) without any signs of pterygium recurrence.

Yang *et al*^[7] showed that tectonic keratoplasty using the SMILE-extracted lenticule to repair microperforations or partial-thickness corneal defects was highly effective. They

performed successful corneal patch grafts using SMILE-extracted lenticules in 17 eyes with corneal perforation or severe thinning caused by infectious and noninfectious causes. The perforations were patched in all patients without complications such as graft displacement, aqueous leakage, or immune rejection. They also reported significant CDVA improvement in 8 out of 17 eyes because of peripheral cornea involvement while 9 eyes did not experience any significant visual acuity change due to central cornea involvement. Abd Elaziz *et al*^[36] found similar results in a study of 7 patients with corneal perforation who were successfully treated with lamellar keratoplasty using a single layer of SMILE-extracted lenticule with an overlying amniotic membrane as an adjuvant to provide nourishment and growth factors for better corneal healing. At a one-year follow-up, visual acuity improved in patients with peripheral corneal lesions, and the graft remained clear with no signs of ulcerative corneal disease or perforation. Wan *et al*^[37] reported the successful results of SMILE-extracted lenticule-assisted corneal patch graft for treating limbal dermoid in a case series of 3 patients without any significant complications. The limbal dermoid was removed, and a tectonic patch graft with a SMILE-extracted lenticule was placed. In the final follow-up visit, they observed that the patients' astigmatism decreased and their visual acuity improved. Additionally, considering the absence of significant differences in corneal thickness between the surgical and normal fields, the authors suggested that the transplanted intrastromal lenticule could play a crucial role in tectonic keratoplasty. Jacob *et al*^[38] reported similar outcomes with good cosmetic and refractive results in a case series of 3 patients with limbal dermoid treated with sutureless fibrin glue-assisted tectonic grafts using SMILE-extracted lenticules. Zhao *et al*^[39] reported a successful combined PK to remove the corneal opacity and immediate autologous lenticule transplant obtained from a SMILE procedure in a patient with partial corneal flap loss and opacity after laser-assisted *in situ* keratomileusis (LASIK). The graft remained clear, visual acuity improved, and central corneal thickness increased in the 2-year follow-up visit. Table 1^[7,12,33-42] summarizes clinical studies on the role of SMILE-extracted lenticules in keratoplasty and glaucoma drainage surgery. In conclusion, several studies have proven that tectonic keratoplasty using SMILE-extracted lenticule is an efficient and trustworthy treatment for ocular defects and LASIK flap problems.

Keratoplasty in corneal ectasia treatment Keratoconus is a progressive ectatic disease that causes corneal thinning and steeping, leading to visual impairment and blindness in the late stages^[43]. In more advanced stages, when spectacles or contact lenses are ineffective at restoring proper visual function, surgical approaches such as full thickness or lamellar

Table 1 Published papers on SMILE's lenticule-assisted patch graft in corneal defects and glaucoma drainage exposure

Author (y)	Study design	Indication of surgery	n (eyes)	Follow-up (mo)	Outcome
Pant <i>et al</i> (2020) ^[32]	Retrospective	Corneal thinning and perforation	18	9-19	Globe integrity in 16 patients in the first attempt; Visual acuity improvement in 38.9% and unchanged at 61.1% at the final follow-up; A greater visual gain in corneal perforation and infratemporal area.
Yang <i>et al</i> (2020) ^[7]	Case series	Corneal thinning and perforation	17	6	Successful anatomical integrity and graft survival in all 17 eyes; Visual acuity improvement in 47%; No evidence of infection, relapse, or perforation in any eye.
Wan <i>et al</i> (2020) ^[37]	Case series	Limbal dermoid excision	3	3	No significant difference among BCVA and astigmatism before and after limbal dermoid removal with smile lenticules keratoplasty; Successful lenticule graft without complications and adverse reactions for at least 3mo; No immune rejection or perforation in any patient; There was no significant difference in corneal thickness between the surgical and normal fields, suggesting that the intrastromal lenticule obtained from SMILE as a corneal patch graft can play an important role in tectonic keratoplasty.
Jacob <i>et al</i> (2019) ^[34]	Case report	Corneal thinning and perforation	1	18	Visual acuity improvement from 6/18 to 20/30 within 3mo and unchanged until final follow-up; Refractive and topographic cylinders were 3 and 2 diopters; Good integration of the lenticule through the overlying cornea.
Pant <i>et al</i> (2019) ^[33]	Case report	<i>Demodex</i> -induced blepharo keratoconjunctivitis and corneal perforation in two pediatric patients	2	9 and 18	The globe's integrity was preserved, and the optical result was satisfying; This technique is safe and effective in corneal perforation caused by blepharokeratoconjunctivitis.
Pant <i>et al</i> (2018) ^[35]	Case report	Recurrent pterygium with a thin cornea	1	8	Graft remained clear with no sign of rejection; No sign of pterygium recurrences.
Zhao <i>et al</i> (2018) ^[39]	Case report	Partial LASIK flap loss	1	24	Improved uncorrected and corrected acuity in this patient with flap loss after LASIK; The lenticule remained translucent, with a clear demarcation line at the final follow up.
Song <i>et al</i> (2018) ^[40]	Case series	Two patients with Ahmed valve exposure and one patient with bullous keratopathy	3	3-8	Patients with tube exposure were treated successfully with good CDVA and controlled IOP in the last follow-up visit without any sign of conjunctival erosion and tube exposure; In a patient with bullous keratopathy, the treated eye was stable, without displacement or melting of the lenticule graft at the final visit.
Jacob <i>et al</i> (2017) ^[38]	Case series	Limbal dermoid excision and sutureless fibrine glue-assisted tectonic keratoplasty	3	12-25	The procedure is simple, fast, and efficient, with good cosmetic and refractive results; It maintains tectonic integrity and reduces the chance of intraoperative complications.
Abd Elaziz <i>et al</i> (2017) ^[36]	Prospective interventional study	Corneal perforations	7	12	All patients' corneal perforations had been successfully sealed, with no signs of re-perforation or infection.
Wang <i>et al</i> (2019) ^[41]	RCT	Patch graft for glaucoma drainage implant surgery	262	6-20	No conjunctival erosion and drainage tube extrusion and better cosmetic appearance in the SMILE lenticule graft group compared with the scleral patch graft.
Wang <i>et al</i> (2021) ^[42]	RCT	Patch graft in glaucoma drainage implantation surgery	335	6-33	Two layers of lamellar corneal tissue (240-300 μm) may be the most suitable thickness for reducing tube exposure; Three layers of lamellar corneal tissue are required in rare cases such as nystagmus or inferior placements of the drainage plate.

SMILE: Small incision lenticule extraction; RCT: Randomized controlled trial; BCVA: Best-corrected vision acuity; LASIK: Laser-assisted *in situ* keratomileusis; CDVA: Corrected distance visual acuity; IOP: Intraocular pressure.

keratoplasty may be the only option for improving the visual acuity (approximately 15%–28% of the patients)^[44-46]. Prof. José Ignacio Barraquer introduced stromal keratophakia, or tissue additive keratoplasty, in 1949^[47]. However, it was first rejected since it was inaccurate, and reactive wound healing along the borders of the incisions caused further opacities and many postoperative complications. The development of femtosecond laser technology made it possible to perform accurate, simple, and quick lenticule extraction from a donor and prepare an intrastromal pocket in a host (where the lenticule is re-implanted). Apart from its simplicity, keratophakia may provide a greater immunological advantage

compared to deep anterior lamellar keratoplasty or PK, because the implanted lenticule is placed in the corneal stroma and concealed from the limbal lymphatic vessels, cytokines, and immune cells in the tear fluid and aqueous humor^[48]. In addition, this innovative approach may restore normal corneal structures in individuals with advanced keratoconus, making refractive correction possible^[49]. The hyperopic algorithm for SMILE surgery creates negative meniscus-shaped lenticules, which are thicker at the periphery and thinner in the center^[50-51]. These lenticules can be implanted into the stroma, resulting in central corneal flattening and increasing stromal thickness, which is beneficial in the treatment of keratoconus^[52].

Jiang *et al*^[53] introduced a novel method of lamellar keratoplasty (tuck-in keratoplasty) using the SMILE-extracted lenticule to treat post-LASIK ectasia. In this technique, the SMILE-extracted lenticule was placed on the cone region between the LASIK flap and the stromal bed after the LASIK flap was gently lifted. The LASIK flap was then placed back into its previous position. During the 12-month follow-up, all the grafts remained clear, and the corneal thickness and keratometry values improved. In addition, the corneal biomechanical profile showed that the corneal deformation amplitude (DA value) was within the healthy cornea range. Similarly, Li *et al*^[54] described the successful treatment of two patients with post-LASIK corneal ectasia and thin cornea (central corneal thickness less than 400 μm) using tuck-in keratoplasty with SMILE-extracted lenticule. The first case was a 29-year-old patient with a refraction of $-13.50/-6.00 \times 10^\circ$ in the left eye and contact lens intolerance. An allogeneic hyperopic SMILE-extracted lenticule was implanted under the LASIK flap. After 10mo, refraction changed to $-3.25/-1.50 \times 10^\circ$ with a CDVA of 20/40. Moreover, front corneal keratometry values also improved. The second case was a 26-year-old patient with post-LASIK ectasia and extremely thin corneas (395 μm in the right eye and 324 μm in the left eye) that treated using the same technique as in the previous case^[55]. At 30-month follow-up, the lenticule integrated well with the adjacent corneal stroma, CDVA improved, corneal power and elevation remained constant, and corneal thickness increased significantly compared to baseline. These studies showed that tuck-in lamellar keratoplasty using SMILE-extracted lenticule might be an effective alternative to conventional treatment for severe cases of post-LASIK ectasia with thin cornea.

In an *ex vivo* model of the ectatic human cornea in 34 cases, Pedrotti *et al*^[55] evaluated the effectiveness of intrastromal lenticule insertion to restore the normal corneal structure. Seventeen corneas were thinned at the posterior surface with two sequential ablations in the inferotemporal corneal quadrant using an excimer laser. To expose the ectatic apex, the intracameral pressure was increased to 100 mm Hg and then brought back to 25 mm Hg to make an *ex vivo* ectasia model (recipient corneas). Using a femtosecond laser, the remaining 17 donor corneas were shaped to form biconvex stromal lenticules and placed into an intrastromal pocket inside the ectatic recipient corneas. Corneal topography and anterior segment optical coherence tomography (AS-OCT) were used to assess corneal architecture and profile changes. The intervention resulted in a significant increase in corneal thickness, a significant decrease in the maximal posterior elevation from best-fitted toric ellipsoid, and flattening of the posterior K1 and K2. There were no significant differences

in anterior and posterior astigmatism, anterior and posterior asphericity, or spherical aberration.

Jin *et al*^[56] compared the efficacy of small-incision femtosecond laser-assisted intracorneal concave lenticule implantation (SFII) and PK in 31 patients with progressive keratoconus. The results showed long-term graft stabilization and visual improvement in both groups. Maximum central keratometry reduced after concave lenticule implantation, which was more significant than other studies^[57-58]. However, visual improvement was better in the SFII group compared to the PK group. The implanted lenticule remained stable with no dislodging, as confirmed by AS-OCT, and contained fewer dendritic and inflammatory cells with no obvious change in the endothelial cells, which resulted in faster recovery of the corneal endothelium function and quicker resolution of the graft edema in SFII group, suggesting that SFII can be a safe and effective surgical technique for progressive keratoconus and is less invasive and time-consuming than PK as it does not need sutures and many surgical instruments, which reduces the surgical time^[59]. Moreover, it does not require intraocular manipulations, since all surgical manipulations are performed inside a pocket in the recipient's cornea.

Doroodgar *et al*^[60] investigated the benefits of keratoconus surgical treatment using customized myopic SMILE-extracted lenticule implantation in 22 patients with advanced keratoconus. The extracted lenticules were formed into 120° necklace-and-ring shapes using biopsy punches to mimic the effect of intra corneal ring segment implantation by flattening the central cornea and increasing the thickness of the thinnest point. The results showed a marked visual improvement [CDVA increased from 0.70 (range: 0.4–1) to 0.49 (range 0.3–0.7) at six months], decreased aberrations and keratometry (from 54.68 ± 2.77 to 51.95 ± 2.21 D), and transparent grafts in all cases. The corneal densitometry and thickness improved significantly, and there were no signs of inflammation caused by the newly implanted lenticules on confocal biomicroscopy during the follow-up period.

Li *et al*^[61] treated 8 post-LASIK ectasia patients with SMILE derived lenticules. First, they lifted the recipient's corneal flap and inserted the hyperopic SMILE-extracted lenticule into the exposed stromal bed (5 cases used cryopreserved lenticules and 3 cases used fresh lenticules). Finally, the flap was repositioned. Over three years, visual acuity, refraction, corneal topography, and *in vivo* confocal microscopy were used to evaluate changes in the lenticules and recipient corneas. The results showed elongated, deformed keratocyte nuclei in the implanted lenticules one year after surgery, suggesting repopulation and partial morphological recovery of keratocytes in the lenticules, ensuring corneal health maintenance in the long term. No subbasal nerve fibers were discovered

in recipient's central cornea in the first week after surgery. However, some thick, tortuous nerve fibers were apparent in all of the examined eyes during the three years of postoperative visits. In one case, nerve fibers were detected in the implanted lenticules three years after surgery, which could be due to keratoconus progression, as several studies have shown neural density and morphology changes in keratoconus corneas^[62-64]. There was no significant difference in the wound healing process between cryopreserved and fresh lenticules. The results showed a gradual improvement in the density and morphology of keratocytes and the re-growth of subbasal nerves. In a similar study, Mastropasqua *et al*^[65] evaluated 10 patients with advanced keratoconus for 12mo after undergoing femtosecond laser-assisted negative meniscus-shaped stromal lenticules addition keratoplasty. The results showed that stromal lenticule addition keratoplasty caused a transitory reduction in nerve plexus density and a minor inflammatory response that resolved quickly during the first month. Additionally, there was no sign of rejection or stromal opacification.

In a systematic review of the clinical outcomes of lenticule implantation for keratoconus treatment, Riau *et al*^[49] reported the efficacy of femtosecond laser-assisted stromal keratophakia. They found that various factors, including the lenticule shape, corneal cross-linking, and implantation depth could be related to visual improvement. The implantation of different-shaped lenticules appeared to improve the stromal volume, keratometric measurements, and visual acuity in advanced keratoconus patients, with the greatest effects for concave shaped lenticules. Before implantation, lenticules can be reshaped with an excimer laser to achieve the desired refractive status^[5]. The implantation depth is crucial since a depth of 110 μm provides 66%–78% of the desired refractive correction. In comparison, an implantation depth of 160 μm results in only 42%–50% of the desired correction^[66].

Cross-linking the entire cornea with the implanted lenticule may reduce refractive regression over time. A review study by Fasolo *et al*^[67] found that stromal keratophakia with SMILE-extracted lenticule provided biomechanical support to the ectatic cornea and restored stromal volume and pachymetry to normal values in advanced keratoconus. Additionally, the reuse of waste materials such as SMILE-extracted lenticules and unsuitable donor corneas for lamellar or penetrating keratoplasty has been made possible by novel methods for lenticule preservation, modification, and cellular therapy.

The results of a review study by El Zarif *et al*^[68] showed that using planner lenticules^[57,69-71] resulted in a more significant increase in corneal thickness compared to allogenic SMILE-extracted lenticule corneal inlay with or without collagen cross-linking^[72-73], and negative meniscus- or donut-shaped lenticules were appropriate only for pure central cones since

they could produce excessively high aberrations around the visual axis in eccentric cones. Visual acuity enhancement with negative meniscus lenticules is marginally superior to planar laminas^[57,72-73]. Customized lenticules that combine the benefits of planar (higher increase in corneal thickness and better results for eccentric cones) and negative meniscus-shaped lenticules (greater flattening effect) may be more beneficial for treating keratoconus patients and produce better anatomical and visual outcomes.

In summary, stromal lenticule addition keratoplasty with SMILE-extracted lenticules is clinically effective for improving the corneal structure and vision in patients with keratoconus. Nevertheless, the results of the above studies should be interpreted with caution since they are prone to bias due to their small sample sizes. However, all of the studies included in this review initially seemed to be theoretically helpful for advanced keratoconus care, and there was no evidence of rejection or inflammation in the treated corneas in the studies. Additional research may be required to increase the number of cases and evaluate the efficacy of these corneal procedures in keratoconus patients during longer follow-up periods. We recommend investigating recellularized customized SMILE-extracted lenticules (which combine the benefits of planar and negative meniscus-shaped lenticules) with mesenchymal stem cells in a large number of advanced keratoconus patients, as multiple studies have shown the feasibility of regenerating the corneal stroma using autologous adipose-derived adult stem cells^[57,69,71]. Table 2^[49,53-56,60-61,65,67,74] summarizes clinical studies investigating SMILE-extracted lenticule applications in corneal ectasia treatment.

Patch Graft for Glaucoma Tube Implants Wang *et al*^[41] compared the efficacy of SMILE-extracted lenticules and the sclera as patch graft to prevent glaucoma drainage tube exposure. In this study, 131 patients (135 eyes) were grafted using the three layers of allogeneic SMILE-extracted lenticules with a diameter of 7 mm and thickness of 100-150 μm as patch graft to achieve an adequate thickness while 124 patients (127 eyes) received scleral allograft. Although there was no statistically significant difference between the two groups, surgical complications including conjunctival melting (no patient in the cornea group and 2 eyes in the scleral group) and graft thinning (3 eyes in the cornea group and 7 eyes in the sclera group) were less frequent in the SMILE-extracted lenticule group. The cosmetic results were also better in the SMILE lenticule group. Unlike another study^[75] in which the corneal lenticule was harvested from a previous Descemet's endothelial keratoplasty or a whole corneal graft button, there were no cases of tube exposure or corneal lenticule melting in this study due to the suitable graft thickness or better lenticule quality. The authors concluded that the SMILE-extracted

Table 2 Published papers on SMILE's lenticule applications in corneal ectasia treatment

Author (y)	Study design	Indication of surgery	n (eyes)	Follow-up (mo)	Outcome
Jiang <i>et al</i> (2017) ^[53]	Case series	Post-LASIK ectasia	3	13	Safe surgical approach for the treatment of post-LASIK ectasia, especially for severe cases with cornea thickness less than 400 μm .
Li <i>et al</i> (2018) ^[54,74]	Case report	Post-LASIK ectasia	2	10 and 30	Refraction and CDVA improved significantly.
Pedrotti <i>et al</i> (2019) ^[55]	Experimental	<i>Ex vivo</i> model of ectatic human corneas	34	-	Corneal thickness was significantly increased, posterior keratometric values significantly flattened after the procedure; Anterior and posterior astigmatism, anterior and posterior asphericity and spherical aberration did not differ significantly after the procedure; Femtosecond laser-assisted stromal lenticule addition effectively improves the corneal thickness and normalizes posterior corneal elevation in ectatic areas.
Jin <i>et al</i> (2019) ^[56]	Prospective interventional study	Compare lenticule implantation and PK in progressive keratoconus	31	24	In this long-term study, both SFII and PK achieved stable corneal volume and increased visual acuity. In comparison to PK, SFII was less invasive and more effective.
Doroodga <i>et al</i> (2020) ^[60]	Prospective interventional study	Customized lenticule implantation in advanced keratoconus	22	12	Customized SMILE lenticule implantation using a femtosecond laser effectively treated advanced keratoconus, resulting in improved vision, topography, and refraction in advanced keratoconus.
Li <i>et al</i> (2020) ^[61]	Prospective interventional study	Confocal microscopic changes in lenticule implantation for post-LASIK ectasia	8	36	Lenticules are repopulated with recipient keratocytes, and lenticule keratocytes gradually return to their natural morphology; Gradual increase in the density of the recipient cornea subbasal nerve plexus, but lenticules lacked nerve fibers.
Mastropasqua <i>et al</i> (2020) ^[65]	Prospective interventional study	Confocal microscopic changes in lenticule implantation for advanced keratoconus	10	12	Transient decrease in nerve plexus density and a slight inflammatory reaction that recovers quickly with no evidence of stromal opacification or rejection in the long term.
Riau <i>et al</i> (2021) ^[49]	Systemic review and Meta-analysis	Stromal keratophakia for keratoconus	-	-	Stromal keratophakia is an effective method for correcting refractive aberrations and visual acuity improvement, increasing corneal volume, and normalizing corneal curvature.
Fasolo <i>et al</i> (2021) ^[67]	Systemic review	Stromal keratophakia for keratoconus	-	-	Femtosecond laser-assisted stromal keratophakia is an effective therapeutic alternative for treating advanced keratoconus by providing biomechanical support and restoring pachymetry to near normal values.
El Zarif <i>et al</i> (2021) ^[68]	Review	Human clinical studies in keratoconus treatment	-	-	Allogenic SMILE lenticules have been reported to initially successfully treat advanced keratoconus without long-term complications.

SMILE: Small incision lenticule extraction; LASIK: Laser *in situ* keratomileusis; CDVA: Corrected distance visual acuity; SFII: Small-incision femtosecond laser-assisted intracorneal concave lenticule implantation; PK: Penetrating keratoplasty.

lenticule-assisted patch graft could effectively prevent drainage tube exposure. It is also simple to obtain and less expensive and improves the patient's cosmetic appearance. Wang *et al*^[42] compared the effect of different SMILE lenticule thicknesses on the tube exposure and surgical success rate in glaucoma drainage implant surgery. Group A received one layer of lamellar corneal tissue from one donor; group B received two layers of lamellar corneal tissue from one donor, and group C received three layers of lamellar corneal tissue from two donors. The results showed no conjunctival melting or tube exposure in group C. However, drainage tubes were exposed in three eyes in group A and one eye in group B (a rare case of Peter's abnormality with nystagmus in whom the plate was placed infratemporally). The authors suggested that two layers of lamellar corneal tissue (approximately 300 μm) were adequate to prevent drainage tube exposure, and that three layers of lamellar corneal tissue (approximately 450 μm) might be required in some unique circumstances. However, using

one layer (approximately 150 μm) was not recommended due to the chance of complications in the future. Similar to the previous studies, Song *et al*^[40] reported the successful surgical outcome of patch grafts with SMILE-extracted lenticules in a case series of three patients (two patients with glaucoma drainage exposure and one case of bullous keratopathy) with visual acuity and ocular symptoms improvement as well as intraocular pressure control in the final follow-up visit. In conclusion, the SMILE-extracted lenticule effectively prevents drainage tube exposure. Moreover, it is less expensive and easier to obtain and improves the patient's cosmetic appearance in comparison with the sclera.

Corneal Tissue Engineering and Animal Studies
Angunawela *et al*^[76] studied the possibility of re-implanting previously removed stromal lenticules in an animal model for the first time and found that it might be a novel method for restoring corneal stromal volume. Since then, various animal models have shown the effectiveness and safety

of this method^[77-81]. Various conditions such as infections, ectatic disorders, and trauma can cause irreversible corneal damage requiring keratoplasty with healthy tissue for visual rehabilitation. However, there is a considerable shortage of allogenic donor corneas worldwide, and there are many disadvantages to transplantation methods, such as immunological rejection, graft failure, secondary glaucoma, and postoperative astigmatism due to sutures^[82-84]. Corneal bioengineering seems ideal, and various biological and synthetic materials can provide a scaffold for epithelial cell expansion^[85-86]. However, therapeutic uses are limited due to progressive biodegradability, exogenous contamination, and possible inflammatory reactions. Decellularized corneal scaffolds made from natural ocular tissue have gained popularity since they lower the rejection rate by removing the cornea's major immunogenic cellular components while maintaining the integrity of the extracellular matrix^[87-90]. Briefly, to decellularize the stromal lenticules, the donor corneal lenticule is washed at room temperature with phosphate-buffered saline and placed in a 1% sodium dodecyl sulfate solution containing a protease inhibitor cocktail and antibiotic-antimycotic agents in an orbital shaker for 24h (75 rpm). The lenticule is washed and incubated in phosphate-buffered saline with DNase (Benzonase Nuclease 6.5 U/mL) at 37°C for 72h. The decellularized lenticule acts as an excellent biological scaffold and can be recellularized by injecting stem cells or human keratocytes into it^[9,70,91]. There are reports of the great therapeutic capacity of decellularized SMILE-extracted lenticule scaffolds with or without recellularization by pluripotent mesenchymal stem cells with various origins^[89,92-93]. This bioengineered scaffold provides a new source of corneal tissue for tissue engineering regenerative medicine. Hong *et al*^[94] integrated a decellularized human corneal lenticule inside compressed collagen to create a limbal epithelial stem cell carrier for treating limbal stem cell deficiency, which resulted in a new biocomposite with high suture retention strength and higher resistance to enzymatic degradation. The transplantation of this biocomposite carrying rabbit limbal epithelial stem cells into the corneas of rabbits with limbal epithelial stem cell deficiency showed adequate support for developing and stratifying limbal epithelial stem cells and producing differentiated corneal epithelial cells, which confirmed its clinical efficacy for the ocular surface reconstruction.

Fernández-Pérez *et al*^[91] effectively synthesized decellularized porcine corneal scaffolds that easily supported epithelial cell proliferation and innervation *in vitro*. They also recellularized these scaffolds with human keratocytes and compared their therapeutic effects in animal models. They found no significant differences between decellularized and recellularized scaffolds

after three months, suggesting that recellularization with human keratocytes might not be advantageous. El-Massry *et al*^[95] reported the great therapeutic potential and safety of decellularized porcine corneal lenticules in patients with advanced keratoconus and post-LASIK ectasia during 12mo. Visual acuity and corneal structures improved significantly in most eyes, and the results suggested that decellularized corneal lenticule could be a viable option for keratoplasty.

Zhao *et al*^[81] investigated the efficacy of SMILE-extracted lenticule allotransplantation in six rabbits. At six months, slit-lamp microscopy revealed that the lenticules had successfully merged with the underlying tissue and confocal microscopy showed the regenerated branches of the corneal nerves and increased central corneal thickness in corneal topography. In another study^[96], the authors extended their research by evaluating the morphologic and histopathologic changes of allogenic SMILE-extracted lenticule implantation in six monkey corneas for two years. The corneal transparency improved according to the corneal densitometry findings. Additionally, slit-lamp biomicroscopy showed excellent graft-host integration and confocal microscopy revealed nerve fiber reinnervation in the lenticule layer. The maximum central thickness ($70.5 \pm 14 \mu\text{m}$) of the implanted lenticules measured by AS-OCT did not show a significant difference after two years compared to the corneal thickness at six months ($69 \pm 11 \mu\text{m}$), indicating that the corneal thickness can increase effectively and remain stable six months after an allogenic SMILE-extracted lenticule transplantation. The total corneal refractive power decreased significantly at two years ($1.83 \pm 1.36 \text{ D}$) compared to six months ($3.27 \pm 1.2 \text{ D}$) with no significant changes in posterior corneal curvature. This regression trend may be due to many factors such as the small diameter of refractive lenticule, wound healing, measurement error, lenticule decentration due to poor fixation during surgery, and epithelial remodeling. These findings suggest that allogenic SMILE-extracted lenticule transplantation is a viable and effective method for corneal reshaping; however, the process of histopathologic alteration and the long-term refractive stability need further investigation.

Aghamollaei *et al*^[9] evaluated the safety of recellularized human SMILE-extracted lenticule grafting with Wharton's jelly-derived mesenchymal stem cells in an experimental animal model. The results showed excellent biointegration in histopathological analysis with minimal collagen bundle destruction and no signs of graft rejection. However, in comparison to the decellularized group, recellularized grafts had a higher expression level of keratocyte-specific markers, indicating the potential of recruiting Wharton's jelly-derived mesenchymal stem cells as keratocyte progenitor cells, which could improve corneal remodeling and healing. This

finding was consistent with the results of a study by Alió del Barrio *et al*^[70] who reported the great therapeutic potential of recellularized corneal lenticules with mesenchymal stem cells for corneal stroma architecture restoration in advanced keratoconus. However, Alió del Barrio *et al*^[70] found minimal difference in stem cell recruitment in a human clinical study, perhaps due to corneal microstructural disruption during the decellularization procedure, which warrants further investigation. Qin *et al*^[89] successfully transformed human induced pluripotent stem cells (iPSC) with urothelial origins into corneal epithelial-like cells with coherent stratified epithelial sheets using decellularized human SMILE-extracted lenticule as a scaffold. Differentiated human iPSC produced a stratified epithelial layer without inducing the immune system on the decellularized scaffold, suggesting that these cells are a potential source for treating various corneal disorders with a high risk of immune rejection, including limbal stem cell deficiency. Decellularized human stromal lenticules containing human iPSC did not induce immunogenicity and therefore did not require immunosuppression for a long time, making them an excellent potential source for keratoplasty. Chen *et al*^[93] evaluated the ability of mesenchymal stem cells (MSCs) originating from embryonic stem cells to transform into corneal epithelial cells after seeding them on fresh and decellularized SMILE-extracted lenticules. The results showed that SMILE-extracted lenticules efficiently increased the proliferation of MSCs without significant difference between fresh and decellularized lenticules. According to the authors, one possible reason may be that MSCs seeded on the acellular corneal matrix expressed many growth factors that promoted cellular growth. On the other hand, the decellularization techniques used in this research affected some of the extracellular matrix ultrastructure, which may impair proliferation. In addition, the keratocytes that remained in the freshly formed lenticules could act as a barrier to MSC adhesion and migration. Analysis of corneal epithelial cell marker expression (CK3 specific marker and unspecific markers including CK8 and CK18) revealed a significant difference in the expression of CK3 between MSCs seeded on fresh (5-fold) and decellularized lenticules (18-fold), while the expression of CK8 and CK18 was similar in control and fresh lenticule groups. In contrast, the expression of these markers was decreased in the decellularized group. These differences showed that decellularized SMILE-extracted lenticules were superior to fresh ones for MSCs to differentiate into pure terminally corneal epithelial cells.

Gu *et al*^[97] used induced pluripotent stem-conditioned medium and femtosecond laser intrastromal lenticule obtained during the SMILE procedure for myopic correction as an alternate scaffold for the replacement of the Bruch's membrane to create an engineered functional retinal pigment epithelium (RPE)

layer. They found that engineered RPE sheets cultured in the induced pluripotent stem-conditioned medium in conjunction with the femtosecond laser intrastromal lenticule scaffold provided better RPE characteristics and cilium structures. Also Ghiasi *et al*^[10] used decellularized SMLIE lenticule as a scaffold in combination with keratocyte conditional medium to differentiation of mesenchymal stem cells into human keratocytes. This recellularized tissue was implanted into the rabbit's cornea and showed that it integrated into the host stroma without any significant complication.

Xia *et al*^[98] investigated the optimum approach for long-term preservation of SMILE-derived lenticules using glycerol, a range of temperatures, and a variety of dehydration agents. In this study, fresh lenticules served as the control group, while other lenticules were divided into eight groups and stored at four different temperatures [room temperature (RT), 4°C, -20°C, and -80°C] with or without silica gel in anhydrous glycerol. Lenticular thickness increased markedly in all groups during a 3-month preservation period, specifically in samples stored at RT. Lenticules stored at -80°C with or without silica gel had a mean percentage transmittance that was most similar to fresh lenticules. Collagen fibers were found to be irregularly distributed and more dispersed in preserved lenticules than in fresh lenticules, especially in RT samples, according to hematoxylin and eosin staining. According to transmission electron microscopy, the fibril bundle densities in lenticules stored at RT were much lower than those stored at other temperatures. All preserved lenticules had no or decreased levels of CD45 and human leukocyte antigens compared to control samples according to immunohistochemistry tests. The preservation of SMILE-derived lenticules over 3mo was best achieved using the studied methods at -80°C with or without silica gel in anhydrous glycerol.

To summarize, decellularized SMILE-extracted lenticules have a good potential to act as a scaffold for pluripotent stem cells to produce corneal epithelial cells and RPE layers with minimal immunogenicity. They also have a significant therapeutic regenerative potential. It is also suggested to use recellularized SMILE-extracted lenticules with allogeneic pluripotent stem cells to enhance visual conditions in metabolic disorders or dystrophies caused by enzyme deficiencies, which cause RPE and photoreceptor damage or refractory corneal opacity. In addition, culturing human photoreceptors with RPE sheets in this recellularized scaffold can be a new way to treat retinal disorders with extensive damage to these cells. Table 3^[9,81,89,93,96-97] summarizes clinical studies regarding SMILE-extracted lenticule applications in corneal tissue engineering.

SMILE-extracted Lenticule Implantation for Refractive Error Correction For various reasons, surgical correction

Table 3 Published papers on SMILE's lenticule applications in corneal tissue engineering

Author (y)	Study design	n (eyes)	Follow-up (mo)	Outcome
Aghamollaei <i>et al</i> (2021) ^[9]	Prospective interventional	12	3	Excellent lenticule biointegration decellularized and recellularized with WJSCs groups; Higher number of keratocyte-specific markers in recellularized grafts; WJSCs are keratocyte progenitor cells that help maintain the cornea's structure and function.
Zhao <i>et al</i> (2020) ^[96]	Prospective interventional	6	24	Mild to moderate regression over time in corneal power; Disorganization of collagen fibers and decreased keratocytes in the embedded lenticules; Successfully increased corneal thickness while remaining stable during the follow-up period.
Zhao <i>et al</i> (2017) ^[81]	Prospective interventional	6	6	Corneal thickness increased effectively; Lenticules had successfully merged with the underlying tissue; Corneal nerves regenerated again at lenticules layers.
Qin <i>et al</i> (2019) ^[89]	Experimental	-	-	iPSCs and decellularized human stromal lenticules can provide a new source of expandable and bankable bioengineered cells, which provide great potential for repair of compromised corneal epithelia.
Chen <i>et al</i> (2019) ^[93]	Experimental	-	-	A comparison of fresh and decellularized SMILE lenticules revealed that both effectively enhance MSCs proliferation, but the decellularized group surpassed the fresh group in terms of inducing MSC differentiation into pure terminally corneal epithelial cells.
Ge <i>et al</i> (2019) ^[97]	Experimental	-	-	iPS-CM, in combination with FLI-lenticule scaffold, facilitates better RPE characteristics and cilium assembly.

SMILE: Small incision lenticule extraction; WJSCs: Wharton's Jelly stem cells; iPSCs: Induced pluripotent stem cells; MSCs: Mesenchymal stem cells; iPS-CM: Induced pluripotent stem-conditioned medium; FLI-lenticule: femtosecond laser intrastromal lenticule.

of hyperopia is more complex than myopia, and researchers have investigated various refractive procedures for treating hyperopia; however, each of these techniques has drawbacks and cannot be used in all patients^[99-103]. Regarding the limitations and challenges of LASIK surgery for hyperopic and presbyopic patients^[104-107], researchers have been interested in the possibility of using SMILE-extracted lenticules to treat presbyopia and hyperopia^[108-109].

Hyperopia treatment Wu *et al*^[110] compared the outcomes of two different surgical methods including SMILE-extracted lenticule implantation (transepithelial phototherapeutic keratectomy and femtosecond laser-assisted lenticule intrastromal keratoplasty (FS-LASIK) for correcting hyperopia ranging from +3.00 to +10.00 D. The results showed a significant increase in uncorrected distance visual acuity with no loss of one or more lines of CDVA. The postoperative spherical equivalent (SE) was within 0.50 D of the target in most eyes. the posterior corneal curvature was slightly steepened, and epithelial thickness showed the predicted doughnut pattern with a thinner epithelium thickness in the central zone. The study showed the potential feasibility of the lenticule implantation technique in correcting moderate to high hyperopia.

Zhao *et al*^[111] reported a case of hyperopic astigmatism correction with FS-LASIK after SMILE-extracted lenticule reimplantation. In this case report, a patient with a refraction of + 7.75/-1.25×5° mistakenly underwent SMILE surgery for myopic astigmatism (-8.50/-1.50×175°) in the left eye. Two years after FS-LASIK, the corneal tomography demonstrated no ectasia, the cornea remained clear, and the patient had a CDVA of 20/50 and refraction of -0.75/-0.25×165°. This study found that refractive lenticule reimplantation could help to restore corneal volume and thickness after improper SMILE

surgery, and FS-LASIK could correct residual refractive error following lenticule reimplantation; however, refractive predictability requires more research.

Li *et al*^[112] investigated microscopic morphological changes in the corneal architecture and nerves by *in vivo* confocal microscopy in five patients after hyperopia correction using FS-LASIK combined with autologous implantation of a SMILE-extracted lenticule. The results revealed the growth of nerve fibers into the implanted lenticules and partial morphological recovery of keratocytes during a one-year follow-up. These findings can ensure the long-term survival of implanted lenticule and the efficacy of this surgical approach for hyperopic correction.

Zheng *et al*^[113] performed an animal experimental study to assess the viability of acellular xenograft SMILE-extracted lenticule transplantation in treating hyperopia. In this study, a corneal matrix pouch was created on the right eyes of eight healthy New Zealand rabbits using a femto-laser, which was also used to perform SMILE on eight bovine corneas. A lenticule was treated acellular and placed into the matrix pouch of the right rabbit cornea. Retinoscopy two weeks after surgery revealed that all rabbit eyes achieved the expected refraction. The refraction drifted toward hyperopia and stabilized at eight weeks after surgery. At 24wk postoperatively, the refraction was approximately 1/3 of what it was before surgery, which could be due to corneal reshaping and improper gaze of rabbit eyes in retinoscopy and the subsequent off-axis of the lenticules. The transplanted lenticule and host cornea remained clear on the final examination, and the anterior segment OCT revealed a blurred lenticule edge indicating gradual fusion. In addition, histopathology examination showed that the corneal structure remained intact with the integration of the acellular corneal matrix lenticules and peripheral matrix and

no substantial cleft or infiltration of inflammatory cells. The results of this study demonstrated the safety and efficacy of acellular corneal lenticule transplants for surgical treatment of ametropia.

Li *et al*^[114] reported the safety and efficacy of the autologous implantation of SMILE-extracted lenticules for correcting hyperopia in five patients during a one-year follow-up. They continued their research by performing another interventional study in which they enrolled 10 patients (20 eyes) with myopia (SE -3.31 ± 1.73 D) in one eye and hyperopia (SE $+4.46 \pm 1.97$ D) in the contralateral eye. Each patient's myopic eye was treated with SMILE, and the lenticule was then re-implanted into the contralateral hyperopic eye. Seventeen months later, at the final visit, none of the eyes showed visual acuity loss and 60% of the implanted eyes were within the desired refractive target of ± 1.00 D. Furthermore, the corneal refractive power remained stable following autologous lenticule implantation, as evidenced by the lack of a statistically significant difference between keratometry readings one day postoperatively and any follow-up visit.

In summary, good visual outcomes, refraction, and stable long-term results of SMILE-extracted lenticule implantation may provide a potentially valuable modality for correcting moderate to high hyperopia.

Presbyopia treatment Presbyopia is the most common refractive error defined by a gradual difficulty in focusing on close objects affecting up to 85% of the individuals over 40 years old. It is expected to affect 2.1 billion people by 2030^[115-116]. Various surgical methods have been introduced and performed for presbyopia treatment, including monovision, multifocal intraocular lenses, conductive keratoplasty, and corneal inlays^[117-118]. However, no single method has been established as a standard method for the treatment of presbyopia. Synthetic or biological corneal inlays are becoming a popular therapeutic technique for presbyopia correction^[119-120]. Biological inlays derived from SMILE-extracted lenticules may have biocompatibility advantages over commercialized synthetic inlays^[119,121-122]. Jacob *et al*^[122] described an innovative method for treating presbyopia by using SMILE-extracted lenticules. They implanted a thin allogenic corneal inlay with a diameter of 1 mm prepared from SMILE-extracted lenticule under a femtosecond laser-created cap of 120 μm in the non-dominant eye [Presbyopic allogenic refractive lenticule inlay (PEARL)]. The results showed significant near vision improvement with no regression and no loss of CDVA over the 6-month follow-up period. None of the patients had night vision difficulties or other dysphotopic issues, and all patients were satisfied with the surgical outcome. The PEARL acted as a shape-changing inlay by increasing the central radius of the curvature, resulting in a hyperprolate corneal shape, and caused stable near vision

enhancement during the 6-month follow-up period. Unlike synthetic implants, this thin PEARL inlay allows unrestricted oxygen and nutrient flow and also has a very minimal risk of immunogenicity since the PEARL inlay implantation contains only stromal tissue. Furthermore, the use of allogenic PEARL tissue improves biocompatibility and integration into the host cornea, providing stable corneal conditions and reducing the possibility of corneal necrosis and melt in the long term.

Liu *et al*^[121] reported the safety and efficacy of autogenic, decellularized, xenogeneic SMILE-extracted lenticule implantation for managing presbyopia in non-human primates. The results showed effective central corneal steepening and hyper-prolate changes (asphericity Q values changed from 0.26 to 0.36) as well as anterior surface elevation without posterior corneal surface changes following thin lenticule implantation at the anterior one-fourth depth. According to the authors, autogenic, decellularized lenticules had excellent biocompatibility and great integration with the recipient cornea. The decellularization procedure reduced the risk of stromal rejection but could cause a transient lenticule tissue edema that resolved over time and did not affect therapeutic effectiveness.

Table 4^[110-114,121-122] summarizes clinical studies investigating SMILE-extracted lenticule applications for refractive error corrections.

CONCLUSION

As a novel, safe, practical, efficient, and cost-effective surgical technique, SMILE-extracted lenticule implantation effectively reconstructs corneal integrity after perforation or defect and restores normal corneal structures in patients with ectatic corneal disorders. Additionally, it is safe and effective for treating hyperopia and presbyopia. On the other hand, these lenticules are an ideal scaffold for tissue engineering, cell growth, and differentiation due to their low immunogenicity and minimal risk of infection. Decellularization and recellularization with mesenchymal stem cells may increase the potential use of lenticules for restoring corneal stroma without affecting the efficacy, decrease the graft complications by regional immunomodulation, and provide healthy keratocytes, resulting in minimized risk of rejection and infectious disease transmission. However, decellularized lenticules have some disadvantages including requiring specific laboratory equipment and experts. More extended follow-up periods with a larger number of patients are necessary to demonstrate the effectiveness and safety of this innovative treatment in the long term. Donor SMILE-extracted lenticules can be stored in eye banks for future use to overcome donor shortages for keratoplasty. In the future, eye banks have to provide a validated process for preparing, preserving, and making stromal lenticules with different shapes and refractive powers

Table 4 Published papers on SMILE's lenticule implantation for refractive error

Author (y)	Study design	Indication of surgery	n (eyes)	Follow-up (mo)	Outcome
Wu <i>et al</i> (2020) ^[110]	Case series	Hyperopic correction	10	8-13	No eyes lost one line or more of CDVA postoperatively, and six eyes had uncorrected distance visual acuity equal to or better than the preoperative CDVA; Post-operative spherical equivalent was within ± 0.50 D of the target for 9; The study shows a potentially useful modality of SMILE's lenticule for correcting moderate to high hyperopia.
Zhao <i>et al</i> (2019) ^[111]	Case report	Myopic overcorrection	1	24	Refractive lenticule implantation provides a potential solution for restoring corneal volume and thickness for refractive error correction with FS-LASIK.
Li <i>et al</i> (2018) ^[112]	Case series	Hyperopic correction	5	6-12	After autologous lenticule implantation, nerve fibers will regrow into the implanted lenticule. Keratocytes in lenticules gradually returned to normal morphology.
Zheng <i>et al</i> (2018) ^[113]	Experimental animal study	Hyperopic correction	8	6	Treated hyperopic eyes by acellular xenograft SMILE's lenticule transformed into myopia at early post-op. and gradually developed hyperopia over the follow-up period; Central corneal thickness stabilized four weeks after surgery; OCT imaging of the anterior segment revealed a distinct lenticule edge at the early post-operative stage and a blurred edge 24wk later, indicating progressive fusion with the host corneal matrix.
Li <i>et al</i> (2017) ^[114]	Prospective interventional	Hyperopic correction	10	17	Six eyes were within ± 1.00 D of the intended refractive target; Significant increase in the corneal anterior surface keratometry and stable posterior surface keratometry on post-op. keratometry; Autologous lenticule implantation could provide a reliable method of correcting hyperopia.
Jacob <i>et al</i> (2017) ^[122]	Case series	Presbyopia treatment	4	6	The PEARL corneal inlay improves near vision safely and effectively without impairing distance vision; Excellent biocompatibility and integration into the host cornea.
Liu <i>et al</i> (2018) ^[121]	Experimental	Presbyopia treatment	20	6	Decellularization procedure reduced the risk of stromal rejection but may result in transient lenticule tissue edema; Effective central corneal steepening (keratometric reading increased by 1.8-2.3 D); Central hyper-prolate changes (Q values changed by -0.26 to -0.36); Corneal anterior surface elevation (7.7-9.3 μm); No changes in the posterior corneal surface.

SMILE: Small incision lenticule extraction; CDVA: Corrected distance visual acuity; FS-LASIK: Femtosecond laser-assisted *in situ* keratomileusis; OCT: Optical coherence tomography; PEARL: Presbyopic allogenic refractive lenticule.

for keratoplasty and research purposes, which promotes the standardization and popularization of this technique, similar to the time when eye banks started to pre-cut and preload lamellar grafts.

Due to unique properties, it is expected that this lenticules will use in other treatment modality such as supporting cells in limbal stem cell deficiency, pigment carrier in corneal pigmentation, scaffold in cell therapy for corneal ectasia, carrier of drugs in drug delivery systems, or even as bandage contact lens.

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